Volume 18 · Número 1-2 · Jan.-Mar. · Abr.-Jun. 2023

REVISTA PORTUGUESA DE ENDOCRINOLOGIA, DIABETES E METABOLISMO

PORTUGUESE JOURNAL OF ENDOCRINOLOGY, DIABETES AND METABOLISM

SPEDM *Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo*

ISSN 1646-3439 E-ISSN 2183-9514

REVISTA PORTUGUESA DE ENDOCRINOLOGIA, DIABETES E METABOLISMO

PORTUGUESE JOURNAL OF ENDOCRINOLOGY, DIABETES AND METABOLISM

Orgão oficial / Affiliations:
Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo; Sociedade Portuguesa para o Estudo da Obesidade; Sociedade Portuguesa de Osteoporose e Doenças Ósseas Metabólicas; Sociedade Angolana de Endocrinologia, Diabetes e Metabolismo

SPEDM

ISSN: 1646-3439
E-ISSN: 2183-9514

A Revista está conforme os princípios e procedimentos ditados pelo Committee on Publication Ethics (COPE) http://www.publicationethics.org

Propriedade, Edição, Publicidade e Administração | *Property, Editing, Advertising and Management*
Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo
Rua Fernando Vicente Mendes, nº 1B - 1º Dto
1600-892 Lisboa - Portugal
http://www.spedm.pt/

Registo | Register
Isenta de registo por não estar à disposição do público em geral (Despacho da ERC em 05/12/2012)
Periodicidade | Periodicity
Trimestral (4 números por ano)
Tiragem | Edition
5000 exemplares
Impressa em papel ecológico e livre de cloro, papel não ácido/Printed in acid-free paper
Depósito Legal | Legal Deposit: 01020304/04

Normas de Publicação | Instructions for Authors
http://www.spedmjournal.com/

Preço por número | Price per number
Gratuito

E-mail para pedidos de subscrições da revista | Email for subscriptions:
geral@spedm.pt

Paginação | Publishing
Next Color – Porto

Indexada | Indexed in:
IndexRMP: Index Revistas Médicas Portuguesas
Latindex
Journal Following the ICMJE Recommendations (8/5/17)
Web of Science Core Collection

Informações sobre reprints | recompilações:
geral@spedm.pt

SPEDM

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Volume 18 • Número 1-2 • Janeiro / Março • Abril / Junho 2023

SUMÁRIO

SPEDM

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Volume 18 • Number 1-2 • January / March • April / June 2023

CONTENTS

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Editorial

Guidelines Luso-Brasileiras de Tratamento da Diabetes Tipo 2: Uma Referência para o Tratamento de Excelência

Luso-Brazilian Guidelines for the Treatment of Type 2 Diabetes: A Reference for Excellence in Care

João Jácome de Castro [a,*], João Filipe Raposo [a]

[a] *Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM), Lisboa, Portugal*

A diabetes é uma doença com uma elevada prevalência em Portugal e com um grande peso na saúde da nossa sociedade. Os dados do Observatório Nacional da Diabetes estimam que em Portugal mais de 1 em cada 8 adultos apresenta diabetes. O tratamento da diabetes envolve múltiplas especialidades médicas, várias classes profissionais não médicas e depende de múltiplos níveis de cuidado (cuidados de saúde primários, cuidados hospitalares e até abordagens de saúde pública) e um cada vez maior envolvimento das pessoas com diabetes, cuidadores e comunidade em geral nos processos de cuidados.

A última década revolucionou a forma como compreendemos o tratamento da diabetes tipo 2 indo cada vez mais longe do "simples" controlo glicémico. A avaliação rigorosa dos efeitos dos vários fármacos disponíveis para o tratamento da diabetes tipo 2 com ensaios clínicos aleatorizados de grande dimensão, permite-nos hoje definir com um elevado grau de segurança as melhores abordagens terapêuticas para cada doente. A aplicação prática deste conhecimento é essencial para melhorar o prognóstico das pessoas com diabetes tipo 2, para reduzir as complicações da diabetes e para permitir ganhos em saúde para toda a comunidade no longo prazo. A sistematização do conhecimento médico em *guidelines* permite uma harmonização da prática clínica e a garantia para cada doente que pode ter acesso às terapêuticas mais eficazes à data. Em 2020, pela primeira vez, a Sociedade Brasileira de Diabetes (SBD), Sociedade Brasileira de Endocrinologia e Metabologia (SBEM), Sociedade Portuguesa Diabetologia (SPD) e Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM) publicaram um documento de recomendações conjuntas para o tratamento da diabetes tipo 2 com o objetivo de harmonizar e melhorar o tratamento da diabetes tipo 2 em Portugal e no Brasil. A rápida evolução no conhecimento na área da diabetes tornou necessária a atualização destas recomendações. As novas *"Recomendações luso-brasileiras baseadas na evidência para a gestão da terapêutica antidiabética na diabetes tipo 2"* são mais do que uma revisão do que já tinha sido publicado em 2020, representando uma mudança de paradigma em relação às recomendações anteriores. As novas recomendações têm como ponto de partida central a necessidade de o tratamento da diabetes ir além do controlo glicémico, incluindo a perda de peso e a prevenção de complicações cardiorrenais. As abordagens não farmacológicas foram revistas, incluindo recomendações relacionadas com a duração do sono, com o sedentarismo e com o uso de monitorização contínua da glicose. Os algoritmos de tratamento foram revistos com importantes atualizações nos critérios de seleção da terapêutica médica tendo em consideração o risco cardiovascular, o peso, a função renal e a HbA1c de cada doente com diabetes tipo 2.

O desenvolvimento destas *guidelines* tendo como ponto de partida a perspetiva Portuguesa e Brasileira sobre a diabetes e o seu tratamento, tornam estas recomendações particularmente importantes para estes dois países unidos por ligações culturais e sociais tão profundas. A publicação simultânea destas recomendações na Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo, revista oficial da SPEDM, e na Revista Portuguesa de Diabetes, revista oficial da SPD, salientam a relevância que as duas sociedades dedicam a estas recomendações.

Acreditamos que estas recomendações vão ser muito úteis para todos os profissionais de saúde que na sua prática clínica acompanham as pessoas com diabetes. Este é também o momento para agradecer a dedicação e o trabalho dos membros da SPEDM e da SPD que em conjunto com os nossos colegas brasileiros contribuíram para a sua realização. Estamos certos que documentos

* Autor Correspondente/Corresponding Author:
Correio eletrónico: jjcastro@sapo.pt (João Jácome de Castro)
Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM),
Rua Fernando Vicente Mendes, Nº 1B, 1º Dto., 1600-892 Lisboa, Portugal

https://doi.org/10.26497/ed230040
Historial do artigo: Received/ Recebido: 2023-08-18 | Accepted/Aceite: 2023-08-21 | Publicado / Published: 2023-10-18

como este são ferramentas indispensáveis para um melhor tratamento da diabetes em Portugal com consequente redução da carga associada a esta doença com tanta relevância médica e social no nosso País.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio ou bolsa.
Proveniência e Revisão por Pares: Comissionado; sem revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Commissioned; without external peer review.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Sleep Quality in Caregivers of Pediatric Patients with Type 1 Diabetes Mellitus: The Impact of Flash Glucose Monitoring Systems with Alarms

Eulália Sousa [a,*], Telma Luís [b], Ana Cristina Santos [c,d,e], Conceição Lima [f], Maria Adriana Rangel [f], Rosa Arménia Campos [f], Ana Luísa Leite [f]

[a] *Department of Pediatrics, Centro Hospitalar Tâmega e Sousa*
[b] *Department of Pediatrics, Centro Hospitalar do Baixo Vouga*
[c] *EPIUnit, Institute of Public Health, University of Porto*
[d] *Laboratory for Integrative and Translational Research in Population Health (ITR)*
[e] *Department of Public Health and Forensic Sciences, and Medical Education, University of Porto Medical School*
[f] *Pediatric Endocrinology and Diabetology Unit, Department of Pediatrics, Centro Hospitalar de Vila Nova de Gaia/ Espinho*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-11-04
Accepted/Aceite: 2023-07-10
Publicado / Published: 2023-10-18

Keywords:
Blood Glucose Self-Monitoring;
Caregivers;
Child;
Diabetes Mellitus, Type 1/therapy;
Insulin/administration & dosage;
Insulin Infusion Systems.

Palavras-chave:
Automonitorização da Glicemia;
Criança;
Cuidadores; Diabetes Mellitus Tipo 1/tratamento;
Insulina/administração e dosagem;
Sistemas de Infusão de Insulina;
Sono.

A B S T R A C T

Introduction: Type 1 diabetes mellitus (T1DM) requires ongoing intensive management. Caregivers of pediatric patients assume a fundamental role in glucose monitoring, 24 hours per day, which may affect their sleep. We aimed to compare the sleep quality of principal caregivers of T1DM pediatric patients who use flash glucose monitoring system (FGMS) with and without alarms and assess its impact on metabolic control.
Methods: Observational and cross-sectional study of T1DM patients using an FGMS and a continuous subcutaneous insulin infusion device. The main caregiver's sleep quality was assessed through the Pittsburgh Sleep Quality Index (PSQI), and metabolic control was evaluated through the ambulatory glucose profile and HbA1c.
Results: Forty-two patients and their caregivers were included, 14 children and adolescents with an alarm and 28 controls. The PSQI score showed no significant differences in parental sleep quality between groups: a median of 6.5 (IQR 7) in the alarm group and 9 (IQR 5) in the control group, p=0.348. The characterization of metabolic control (adjusted for children's age and caregivers' educational qualifications) revealed mean values of time in range (TIR) 52.17% *vs* 42.60% (p=0.134), time below range (TBR) 1.56% *vs* 5.59% (p=0.014) and glucose coefficient of variation (CV) 35.36% *vs* 41.62% (p=0.004) in the group with and without alarm, respectively.
Conclusion: The use of alarms did not lead to a worse sleep quality or more nocturnal awakenings in caregivers of T1DM children. However, the alarms improved metabolic control by reducing TBR and glucose CV. Our results support using alarms in diabetes management without prejudice to the caregivers' sleep quality.

Qualidade do Sono dos Cuidadores de Doentes Pediátricos com Diabetes Mellitus Tipo 1: O Impacto dos Sistemas de Monitorização Flash da Glicose com Alarmes

R E S U M O

Introdução: A diabetes *mellitus* tipo 1 (DMT1) requer uma monitorização intensiva e contínua. Os cuidadores dos doentes pediátricos assumem um papel fundamental na monitorização da glicose, 24 horas por dia, o que pode afetar o seu sono. Este trabalho teve como objetivo comparar a qualidade do sono dos cuidadores de crianças e adolescentes com DMT1 que utilizam sistemas de monito-

* Autor Correspondente / Corresponding Author.
E-Mail: eulaliapatricia1@hotmail.com (Eulália Sousa)
Department of Pediatrics, Centro Hospitalar do Tâmega e Sousa
Avenida do Hospital Padre Américo, 4564-007 Penafiel, Portugal

https://doi.org/10.26497/ao220062

rização *flash* da glicose (MFG) com e sem alarmes, bem como avaliar o seu impacto no controlo metabólico.

Métodos: Estudo observacional, transversal e analítico de doentes pediátricos com DMT1 utilizadores de MFG e sob sistema de infusão subcutânea contínua de insulina. A qualidade do sono dos cuidadores principais foi avaliada através do *Pittsburgh Sleep Quality Index* (PSQI) traduzido e validado para português, e o controlo metabólico foi analisado através do perfil ambulatório de glicose e da HbA1c.

Resultados: Foram incluídos 42 doentes e respetivos cuidadores, 14 crianças e adolescentes com alarme e 28 controlos. O *score* total do PSQI não demonstrou diferenças significativas na qualidade do sono dos cuidadores entre os grupos: mediana de 6,5 (IQR 7) no grupo com alarmes e 9 (IQR 5) no grupo sem alarmes, p=0.348. A caracterização do controlo metabólico (ajustada para a idade dos doentes e habilitações literárias dos cuidadores) revelou valores médios de tempo no alvo de 52.17% *vs* 42.60% (p=0.134), tempo abaixo do alvo de 1.56% *vs* 5.59% (p=0.014) e coeficiente de variação de glicose de 35.36% *vs* 41.62% (p=0.004) no grupo com e sem alarmes, respetivamente.

Conclusão: A utilização de alarmes não condicionou mais despertares noturnos ou pior qualidade de sono dos cuidadores de crianças e adolescentes com DMT1. No entanto, a sua utilização associou-se a um melhor controlo metabólico, através da redução do tempo abaixo do alvo e do coeficiente de variação de glicose. Os nossos resultados apoiam a utilização de alarmes no tratamento e monitorização da DMT1, sem prejuízo da qualidade do sono dos cuidadores.

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic diseases in childhood and adolescence, and its incidence has increased worldwide.[1,2] These patients need lifelong insulin treatment and adequate metabolic control to avoid complications. The daily management of diabetes includes frequent glucose monitoring, insulin administration, adequate diet and physical activity. Consequently, this constitutes a challenge for both patients and their caregivers and may cause significant psychological stress and negatively impact the family´s quality of life.[1,3,4]

In order to decrease the burden of T1DM management and facilitate glucose monitoring, different technologies have been developed. The flash glucose monitoring system (flash GMS) continuously measures the glucose levels in the interstitial fluid, although the results are known and recorded only if the patient or the caregiver actively scans the sensor.[3,5] The flash GMS offers more than just a glucose measurement, it also indicates glucose tendencies (through trend arrows) and provides an ambulatory glucose profile (AGP) after transferring the data from the sensor to the reader.

Some flash GMS may have programmed alarms when hypoglycemia or hyperglycemia are detected.[5,6] In Portugal, at the time of the study, the National Health Service only subsidized one flash glucose monitoring system, the FreeStyle Libre 1®, which does not allow alarm programming.

The flash GMS makes glucose monitoring easier and allows caregivers to monitor the levels overnight with reduced interruption of the patients' sleep.[5]

Caregivers of T1DM patients commonly fear nocturnal hypoglycemia, leading to more frequent glucose monitoring during nighttime. This nocturnal vigilance could cause an interruption and shorter duration of the caregivers' sleep, impairing their daily activities and well-being.[3]

Recent studies revealed that a significant percentage of the caregivers of children and adolescents with T1DM have poor sleep quality or a sleep duration below the recommended amount, mainly due to nighttime glucose monitoring and fear of hypoglycemia.[1,7]

However, there is still scarce evidence on the impact of alarms associated with flash GMS on the caregivers' sleep quality.[8] A recent systematic review evaluated the patient and/or parents' sleep quality in seven studies on real-time continuous glucose monitoring use in youth. In contrast, the results from its literature review highlighted the lack of data on the quality of sleep in pediatric patients using flash GMS.[9]

The aim of this study was to compare the sleep quality of the main caregiver of T1DM pediatric patients who use flash GMS with and without programmed alarms. Therefore, we also intended to assess the alarms' impact on metabolic control.

Material and Methods

1. Participants

The potential participants were voluntarily recruited at their pediatric endocrinology appointment on pediatric endocrinology clinic from the north of Portugal.

The participants were children or adolescents with T1DM using a continuous subcutaneous insulin infusion (CSII) device and a flash GMS (FreeStyle Libre 1® or FreeStyle Libre 2®).

In Portugal, when the study was carried out, only FreeStyle Libre 1® was state-subsidized. Thus, most patients using flash GMS had FreeStyle Libre 1®, and only a few patients/caregivers had decided for FreeStyle Libre 2®.

FreeStyle Libre® has been approved for children aged four years and older. However, scientific evidence showed its safety and accuracy in younger children. For this reason, this study also included children under four years old.[10,11]

The following exclusion criteria were applied: diagnosis or alteration of the insulin delivery system in the previous three months, multiple daily insulin injections therapy, and the use of the flash GMS for less than one month or irregular use (patients did not use it at least 70% of the time).

The selected participants were divided into two groups: patients using flash GMS with programmed alarms (FreeStyle Libre 2®) and another group using flash GMS without alarms (FreeStyle Libre 1®), the control group. In the alarm group, patients had hypoglycemia alarms set to values <70 mg/dL; in patients who had hyperglycemia alarms, they were set to values > 250 mg/dL.

2. Study Design

An observational, cross-sectional, and analytical study was carried out in March 2021 at the Pediatric Endocrinology and Diabetology Unit of Centro Hospitalar de Vila Nova de Gaia/Espinho, a Portuguese tertiary hospital located in an urban environment.

After obtaining written informed consent, an online questionnaire was applied to the main caregiver, including socio-demographic data (sex, age, education level, and professional status) and questions regarding to the personal/subjective perception of glucose monitoring and programmed alarms; impact on individual sleep quality. The Pittsburgh Sleep Quality Index (PSQI - validated version in Portuguese) was also applied to all participants. The PSQI is a 19-item self-rated questionnaire that evaluates sleep quality over the previous month. The 19 questions are categorized into seven components, graded from 0 to 3. The PSQI score, ranging from 0 to 21, results from the sum of these seven components. A PSQI score equal to or lower than five corresponds to good sleep quality, while higher scores indicate poor sleep quality.[12]

The flash GMS data (AGP) from the previous four weeks was downloaded at the medical appointment on the same day the questionnaire was answered. When the patient did not have an appointment scheduled during the study period, caregivers made the discharge remotely and sent it. The collected AGP parameters were mean interstitial glucose, time in range (TIR, 70-180 mg/dL), time above range (TAR, >180 mg/dL), time below range (TBR, <70 mg/dL), coefficient of variation (CV), estimated HbA1c, percentage of time flash GMS is active, and the number of daily readings.

Patients' demographic and clinical data (sex, age, date of diagnosis, onset of CSII, and last HbA1c value) were collected from the corresponding clinical file after parental/legal guardians' consent.

3. Statistical Analysis

Statistical analysis was performed using SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA), and MPLUS for the latent class analysis. A value of $p<0.05$ was considered statistically significant.

Continuous variables were summarized as mean and standard deviation (SD) or as median and interquartile range (IQR), according to the normal or non-normal data distribution, and compared using the Student t-test or the Mann-Whitney U test, respectively. The categorical variables were described as counts and proportions and compared using the Chi-square test.

To study the association between using an alarm device and the metabolic variables, generalized linear models were computed to provide adjusted means and respective 95% confidence intervals (CI). The adjusted model included the age of the participants and their parental education.

Correlations between PSQI and metabolic variables were analyzed using Spearmans correlation.

4. Ethics

The study protocol was reviewed and approved by the ethics committee of our institution. Participants and their parents/legal guardians, as applicable, gave written informed consent to participate in the study.

Results

1. Sample Characteristics

At the time of the study, 136 pediatric patients with T1DM were followed-up in our hospital center, 105 were using CSII.

Forty-two (42) patients with T1DM fulfilled the inclusion criteria and accepted to participate in the study; 14 used flash GMS with associated alarms, and 28 used the same system without any alarm (Table 1). The youngest patient was two years old, and the oldest was 17 years (mean age 8.6 ± 4.2 years in the alarm group and 11.2 ± 4.2 years in the control group, p=0.061). The diabetes duration ranged from 0.4 to 13.6 years (median 1.9 years in the alarm group (IQR = 5.0) *vs* 4.4 years (IQR = 5.7), p=0.165). The median duration of treatment with CSII was 1.8 years (IQR = 3.9) in the alarm group and 3.2 years (IQR = 2.8) in the control group (p=0.298).

Table 1. Sample characteristics

	Alarm (n=14)	No alarm (n=28)	*p*-value
Diabetic child/adolescent characteristics			
Sex			
Female	8 (57%)	9 (32%)	0.221
Male	6 (43%)	19 (68%)	
Age, in years [mean ± SD]	8.6 ± 4.2	11.2 ± 4.2	
< 5 years	3 (21%)	2 (7%)	0.061
5-9 years	5 (36%)	7 (25%)	
≥ 10 years	6 (43%)	19 (68%)	
Duration of T1DM, in years [median (IQR)]	1.9 (5.0)	4.4 (5.7)	0.165
Duration of CSII, in years [median (IQR)]	1.8 (3.9)	3.2 (2.8)	0.298
Parents/caregivers characteristics			
Gender			
Female	11 (79%)	25 (89%)	0.383
Male	3 (21%)	3 (11%)	
Age, in years [mean ± SD]	42.1 ± 3.7	41.6 ± 5.5	0.796
Academic qualification			
4th Grade	0 (0%)	2 (7%)	
6th Grade	0 (0%)	2 (7%)	0.522
9th Grade	1 (7%)	5 (18%)	
Secondary education	5 (36%)	7 (25%)	
University education	8 (57%)	12 (43%)	
Professional situation			
Presential work	4 (29%)	9 (32%)	
Remote work	8 (57%)	6 (21%)	0.163
Unemployed	1 (7%)	8 (29%)	
Sick leave	0 (0%)	2 (7%)	
Other	1 (7%)	3 (11%)	

SD, standard deviation; IQR, interquartile range; T1DM, type 1 diabetes mellitus; CSII, continuous subcutaneous insulin infusion therapy.

The caregivers' age ranged from 30 to 52 years old, and 86% were female. In the alarm group, the mean caregivers' age was 42.1 ± 3.7 years *vs* 41.6 ± 5.5 (p=0.796), 57% had a bachelors degree *versus* 43% (p=0.522), and, by the time of the study, 57% were working remotely from home *versus* 21% (p=0.163). Therefore, there were no statistically significant differences in the characteristics of the caregivers between the two groups.

2. Sleep Characteristics and Qualification

Most caregivers self-evaluated their sleep quality as "bad" or "very bad" in both groups (Table 2). A number of awakenings equal to or greater than three times per night was reported by 36% caregivers in the alarm group and 43% in the control group (p=0.744). In the alarm group, 79% believed that alarms interfered with their sleep quality.

In both groups, most caregivers had a PSQI score above 5, which means poor sleep quality. The percentage of PSQI >5 was 57% *vs* 75% (p=0.298), and the PSQI median score was 6.5 (IQR

Table 2. Sleep characteristics and qualification

	Alarm (n=14)	No alarm (n=28)	*p*-value
Number of awakenings per night for GM			0.744
None	1 (7%)	3 (11%)	
1 to 2 times	8 (57%)	13 (46%)	
3 to 4 times	3 (21%)	10 (36%)	
5 or more times	2 (14%)	2 (7%)	
Sleep quality self-classification			0.264
Very good	1 (7%)	0 (0%)	
Good	5 (36%)	11 (39%)	
Bad	7 (50%)	10 (36%)	
Very bad	1 (7%)	7 (25%)	
Sleep quality classification			0.298
Good Sleep Quality (PSQI ≤ 5)	6 (43%)	7 (25%)	
Poor Sleep Quality (PSQI > 5)	8 (57%)	21 (75%)	

GM, glucose monitoring.

7.0) *vs* 9.0 (IQR 5.0) in the alarm and control group (p=0.348), respectively. There was a high agreement between the sleep quality self-classification and the PSQI score (p<0.001). There were no significant differences between the two groups regarding the number of awakenings per night for glucose monitoring, sleep quality self-classification, and global PSQI score.

3. Metabolic Control

The statistical analysis for the metabolic control is presented in Table 3.

Mean interstitial glucose adjusted for childrens age and caregivers' educational qualifications was 182.13 mg/dL (95% CI 162.80-201.45) in the alarm group and 193.44 mg/dL (95% CI 180.84-206.04) in the control group (p=0.360).

The adjusted mean for TIR was 52.17% (95% CI 42.06-62.27) in the alarm group and 42.60% (95% CI 36.1-49.19) in the control group (p=0.134). The adjusted mean for TBR was 1.56% (95% CI -0.96-4.08) in the alarm group and 5.59% (95% CI 3.95-7.24) in the control group (p=0.0014). The alarm group had a lower glucose coefficient of variation (p=0.004). HbA1c measured at the last medical appointment was 7.93% (95% CI 7.30-8.56) in the alarm group and 7.59% (95% CI 7.16-8.03) in the control group (p=0.393).

In both groups, there was no statistically significant correlation between the PSQI score and TIR (R=0.026; p=0.874), and the same occurred with PSQI and HbA1c (R=-0.199; p=0.207).

In the alarm group, 100% defined alarms for hypoglycemia and 93% for hyperglycemia too. When questioned about the reasons for acquiring alarm devices, 21% answered that they feared hypoglycemia; 36% wanted to improve metabolic control; 43% said they needed to feel more secure about the diabetes treatment of their children.

Discussion

Glucose monitoring systems have known benefits in metabolic control, although they may include alarms that could interfere in the sleep of patients and caregivers.[8]

In our study, most caregivers self-rated their sleep quality as "poor" or "very poor." When assessed by the PSQI, the majority of caregivers (69%) met poor sleep quality criteria. About 40% reported three or more awakenings per night to monitor glucose.

These results are consistent with the ones described in the literature. Several studies have shown poor quality or shorter sleep duration in caregivers of T1DM patients.[1,7,13,14] For this reason, we consider it is essential to understand the impact of alarms on the caregivers' sleep. Whether they can worsen sleep quality due to more frequent nocturnal awakenings and consequently greater fragmentation of sleep, or if, on the opposite, caregivers feel more comfortable knowing the alarms will alert them about hypo and hyperglycemia, leading to better a sleep quality.

Most caregivers (79%) in the alarm group believed that alarms interfered with their sleep quality, but we did not find significant differences in sleep quality or the number of nocturnal awakenings between the two groups.

These results are in accordance with those presented by Franceschi *et al*, who also showed that the alarms do not worsen the duration and the quality of sleep. However, in the study by Franceschi *et al*, patients used Freestyle Libre 2® only for 14 days, therefore the authors hypothesized that more prolonged alarms use could improve the sleep duration and quality.[8] In our study, the alarms were used for longer than one month. Even so, we did not find a significantly better sleep quality in the alarm group compared to the control group, which does not support their hypothesis.

Our results showed that alarms did not affect caregivers' sleep, as the alarms neither worsened nor improved their sleep quality. That probably occurred because the poor sleep quality in caregivers of diabetic patients has a multifactorial etiology.

Emotional stress is frequent among caregivers of patients with T1DM, especially concerning hypoglycemia.[4,15] In our cohort with alarms, 64% of the caregivers mentioned they chose to use alarms because they feared hypoglycemia or needed more confidence in diabetes treatment. There is evidence that continuous glucose monitoring improves the psychological well-being of children with T1DM and their parents by reducing worrisome and fear of hypoglycemia.[4,15] Franceschi et al also reported an improvement in the quality of life perceived by parents using flash GMS with alarms.[8]

Regarding to metabolic control, previous studies have demonstrated an improvement with flash GMS.[16,17] Franceschi *et al* also

Table 3. Metabolic control characterization

	Alarm (n=14)		No alarm (n=28)		*p*-value
	Adjusted mean[a]	95% CI	Adjusted meana	95% CI	
HbA1c (%)	7.93	7.30-8.56	7.59	7.16-8.03	0.393
Mean glucose (mg/dL)	182.13	162.80-201.45	193.44	180.84-206.04	0.360
TIR (%)	52.17	42.06-62.27	42.60	36.01-49.19	0.134
TAR (%)	46.11	35.79-56.43	51.81	45.08-58.54	0.378
TBR (%)	1.56	-0.96-4.08	5.59	3.95-7.24	**0.014**
Glucose CV (%)	35.36	31.97-38.75	41.62	39.41-43.83	**0.004**

[a] Adjusted means for the age of the participants and parental education; TIR, time in range; TAR, time above range; TBR, time below range; CV, coefficient of variation; CI, confidence interval.

found an improvement in metabolic control after switching from FreeStyle Libre 1® to FreeStyle Libre 2®, which increased TIR by about 5% and reduced TBR and glucose CV.[8]

Our results did not show a significantly better TIR or HbA1c in the alarm group than in the control group. Nonetheless, we found that using alarms was associated with a lower glucose CV and TBR. Decreasing the TBR is an essential target in diabetes management, and according to Battelino *et al*, the primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR.[18]

Thus, our study demonstrated that by reducing TBR, alarms are advantageous in glycemic control. These results are probably justified because all patients had established alarms for hypoglycemia and because of the younger age of this childrens group, which is usually associated with higher parental concern about hypoglycemia.

We hypothesized that the parents with the worst sleep quality were those more concerned and who frequently monitored glucose, and this could result in better metabolic control. Nevertheless, there was no significant correlation between the PSQI score and TIR or HbA1c.

Our study has the strengths of having a control group, using a validated questionnaire to assess sleep quality, and guaranteeing a simultaneous assessment of metabolic control and sleep quality. As previously mentioned, the use of FreeStyle Libre® in children under four years was based on scientific evidence of its safety and accuracy in this age group.[10,11]

However, this work also has some limitations, such as being a single-center study, having a small number of patients, assessing sleep and metabolic control only for one month, and not considering other factors like the use of psychotropic drugs or the existence of comorbidities/pathologies that may interfere with the caregivers' sleep quality. Besides, in the alarm group, sleep quality was not assessed before and after the alarm use onset in order to evaluate alarms' impact on sleep over time.

In Portugal, at the time of the study, only FreeStyle Libre 1® was state-subsidized, which justifies the small number of patients using alarms. The fact that FreeStyle Libre 2® was not subsidized is also a limitation, as it could be a confounding factor. Parents who purchased FreeStyle Libre 2® could be more concerned about preventing hypoglycemia and pursuing optimal glucose control, which could influence the metabolic control observed in the alarm group.

Longitudinal studies and a larger patient sample are needed to better understand the alarms' impact on sleep quality and metabolic control.

Conclusion

Our study showed that the alarms are not associated with worse sleep quality for caregivers, but they also did not improve sleep quality or reduce the number of nocturnal awakenings. On the other hand, the alarms improved metabolic control by significantly reducing the TBR and glucose CV. Therefore, our results support using alarms in diabetes management without prejudice to the caregivers; sleep quality.

Pediatric diabetes medical teams should be aware of caregivers' sleep disturbances to provide additional education and support in order to minimize this problem. Poor sleep quality has possibly a multifactorial cause, so other parameters, including emotional factors, must be considered and managed. This type of strategy will allow increasing caregivers' confidence and, at the same time, will promote the use of technological tools to improve glycemic control.

Contributorship Statement / Declaração de Contribuição:

ES and TL: Study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation.
ACS: Analysis and interpretation of results.
CL: Study conception and design, data collection.
MAR, RAC and ALL: Study conception and design, interpretation of results, supervision.
All authors reviewed and approved the final version of the manuscript.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Macaulay GC, Boucher SE, Yogarajah A, Galland BC, Wheeler BJ. Sleep and night-time caregiving in parents of children and adolescents with type 1 diabetes mellitus - a qualitative study. Behav Sleep Med. 2020;18:622-36. doi: 10.1080/15402002.2019.1647207.
2. Cohen A, Mok E, Simard M, Dubé M, Larocque I, Plante C, Legault L, Huot C, Wafa S, Rahme E, Nakhla M. Increasing Incidence of Type 1 and Type 2 Diabetes Among Canadian Children. Can J Diabetes. 2022;46:189-95. doi: 10.1016/j.jcjd.2021.08.006.
3. Schierloh U, Aguayo GA, Fichelle M, De Melo Dias C, Celebic A, Vaillant M, et al. Effect of predicted low suspend pump treatment on improving glycaemic control and quality of sleep in children with type 1 diabetes and their caregivers: the QUEST randomized crossover study. Trials. 2018;19:665. doi: 10.1186/s13063-018-3034-4.
4. Ng SM, Moore HS, Clemente MF, Pintus D, Soni A. Continuous glucose monitoring in children with type 1 diabetes improves well-being, alleviates worry and fear of hypoglycemia. Diabetes Technol Ther. 2019;21:133-7.

doi: 10.1089/dia.2018.0347.

5. Al Hayek AA, Al Dawish MA. Assessing diabetes distress and sleep quality in young adults with type 1 diabetes using freestyle libre: a prospective cohort study. Diabetes Ther. 2020;11:1551-62. doi: 10.1007/s13300-020-00849-3.
6. Young C, Grobelna A. Flash Glucose Monitoring Systems in Pediatric Populations with Diabetes. Ottawa: Canadian Agency for Drugs and Technologies in Health;2021.
7. Jaser SS, Foster NC, Nelson BA, Kittelsrud JM, DiMeglio LA, Quinn M, et al. Sleep in children with type 1 diabetes and their parents in the T1D Exchange. Sleep Med. 2017;39:108-15. doi: 10.1016/j.sleep.2017.07.005.
8. Franceschi R, Scotton C, Leonardi L, Cauvin V, Maines E, Angriman M, et al. Impact of intermittently scanned continuous glucose monitoring with alarms on sleep and metabolic outcomes in children and adolescents with type 1 diabetes. Acta Diabetol. 2022;59:911-9. doi: 10.1007/s00592-022-01882-3.
9. Franceschi R, Micheli F, Mozzillo E, Cauvin V, Liguori A, Soffiati M, et al. Intermittently scanned and continuous glucose monitor systems: a systematic review on psychological outcomes in pediatric patients. Front Pediatr. 2021; 9:660173. doi: 10.3389/fped.2021.660173.
10. Li Y, Cao B, Chen Q, Du M, Yan M, Chen Y, et al. Application of the FreeStyle® Libre Glucose Monitoring System in type 1 diabetes mellitus patients aged 1-4 years. Pediatr Diabetes. 2022;23:604-10.
11. Abulqasim J, Alotaibi F, Al Khalifah RA. Safety and user experience with off-label use of a flash glucose monitor (FreeStyle Libre® 1) among very young children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2023;36:119-25. doi: 10.1515/jpem-2022-0452.
12. Del Rio João KA, Becker NB, de Neves Jesus S, Isabel Santos Martins R. Validation of the Portuguese version of the Pittsburgh Sleep Quality Index (PSQI-PT). Psychiatry Res. 2017;247:225-9. doi: 10.1016/j.psychres.2016.11.042.
13. Barnard K, James J, Kerr D, Adolfsson P, Runion A, Serbedzija G. Impact of chronic sleep disturbance for people living with t1 diabetes. J Diabetes Sci Technol. 2016;10:762-7. doi: 10.1177/1932296815619181.
14. Feeley CA, Clougherty M, Siminerio L, Charron-Prochownik D, Allende AL, Chasens ER. Sleep in caregivers of children with type 1 diabetes. Diabetes Educ. 2019;45:80-6. doi: 10.1177/0145721718812484.
15. Polonsky WH, Fortmann AL. Impact of real-time CGM data sharing on quality of life in the caregivers of adults and children with type 1 diabetes. J Diabetes Sci Technol. 2022;16:97-105. doi: 10.1177/1932296820978423.
16. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42:1593-603. doi: 10.2337/dci19-0028.
17. Mohamed IAA, Talaat IM, Alghamdi HA, Allam G. Role of free style Libre-flash glucose monitoring: glycemic control of type-1 diabetes. Pak J Med Sci. 2021;37:1883-9. doi: 10.12669/pjms.37.7.4114.
18. Evans M, Welsh Z, Ells S, Seibold A. The impact of flash glucose monitoring on glycaemic control as measured by HbA1c: a meta-analysis of clinical trials and real-world observational studies. Diabetes Ther. 2020;11:83-95. doi: 10.1007/s13300-019-00720-0.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Gestational Diabetes Treatment and its Impact on Pregnancy and Neonatal Complications

Juliana Chen-Xu [a,*], Ângela Coelho [a]

[a] *Internal Medicine Department, Centro Hospitalar Póvoa de Varzim/Vila do Conde, Póvoa de Varzim, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-07-19
Accepted/Aceite: 2023-04-30
Publicado / Published: 2023-10-18

Keywords:
Pregnancy Complications;
Diabetes, Gestational/drug therapy;
Pregnancy Outcome.

A B S T R A C T

Introduction: The incidence of gestational diabetes (GD) has been increasing, mostly due to better diagnostic tools and recent diagnostic criteria, allowing early screening. This study aims to evaluate the impact of GD therapeutics on the occurrence of cesarean sections and pregnancy and neonatal complications.
Methods: This is a cohort study of GD pregnant women followed-up in various Portuguese hospitals and maternities, diagnosed between 2014 and 2018. Our sample was 15 089 pregnant women, divided in four groups, based on the therapeutics used to treat GD: diet and exercise, insulin, oral hypoglycemic drug (OHD) and insulin+OHD.
Results: The insulin group showed higher risk of caesarean section, neonatal hypoglycemia, neonatal hyperbilirubinemia and large for gestational age (LGA) newborns. Regarding the OHD group, there was higher probability for hydramnios and trauma at delivery and lesser risk for low birth weight and small for gestational age newborns (SGA). Lastly, the OHD+insulin group exhibited more likelihood to maternal and neonatal morbidity, like neonatal hypoglycemia, hyperbilirubinemia, trauma at delivery, and LGA newborns.
Conclusion: The simultaneous administration of insulin and OHD was more likely associated with pregnancy and neonatal complications. However, this group already had pre-conception characteristics that predisposed to complications (more advanced maternal age, higher previous BMI, familial history of diabetes, previous GD and/or macrosomia) and worse therapeutic adherence leading to a badly controlled glycemic profile. Therefore, these complications may be the result of the presence of previous characteristics and a glycemic profile that is difficult to control, rather than the use of insulin and OHD, *per se*.

Palavras-chave:
Complicações na Gravidez;
Diabetes Gestacional/tratamento farmacológico;
Resultado da Gravidez.

Tratamento da Diabetes Gestacional e o seu Impacto nas Complicações Obstétricas e Neonatais

R E S U M O

Introdução: A incidência da diabetes gestacional (DG) tem vindo a aumentar devido à melhoria da capacidade diagnóstica e à utilização de novos critérios de diagnóstico, possibilitando rastrear mais precocemente. Este estudo visa averiguar o impacto da terapêutica da DG quanto à ocorrência de complicações obstétricas e neonatais.
Material e Métodos: Estudo coorte de uma população de grávidas DG seguidas em hospitais e maternidades portuguesas, diagnosticadas entre 2014 e 2018. A amostra obtida foi de 15 089 grávidas, dividida em 4 grupos de terapêutica para controlo glicémico: dieta e exercício, insulina, antidiabéti-

* Autor Correspondente / Corresponding Author.
E-Mail: jchenxu@chpvvc.min-saude.pt (Juliana Chen-Xu)
Largo da Misericórdia, 4490-421 Póvoa de Varzim, Portugal

https://doi.org/10.26497/ao220051

cos orais (ADO) e ADO+insulina.

Resultados: O tratamento com insulina apresentou maior risco de cesariana, hipoglicemia e hiperbilirrubinemia neonatais e nascituros grandes para idade gestacional. Quanto ao grupo sob ADO demonstrou maior probabilidade de hidrâmnios e trauma no parto e menor risco de nascituros com baixo peso à nascença e leves para idade gestacional. O grupo com uso concomitante de ADO e insulina exibiu maior risco de morbilidades materna e neonatal, nomeadamente hipoglicemia, hiperbilirrubinemia neonatal, trauma no parto e recém-nascidos grandes para idade gestacional.

Conclusão: A co-utilização de insulina+ADO esteve associada a maior probabilidade de complicações. No entanto, este grupo já apresentava características pré-concepção que predispunham para complicações e um comportamento insuficiente durante a gestação com perfis glicémicos mais difíceis de controlar. Estas complicações podem ser resultado da presença de características prévias e um perfil glicémico de difícil controlo, mais do que da utilização de insulina e ADO, *per se*.

Introduction

Gestational diabetes (GD) is a metabolic alteration that occurs during pregnancy and is due to placental diabetogenic hormones that induce insulin resistance and pancreatic insufficiency.[1,2] When uncontrolled, this condition may lead to complications to the mother and to the fetus.[1-5]

The prevalence of GD has been increasing. It might be due to the new screening recommendations indicated by the conjoint effort of Portuguese national health department and International Association of Diabetes and Pregnancy Study Groups, since 2011, as well as the increased incidence of obesity in women at reproductive age.[6-8] According to these criteria, the diagnosis of GD is made through fasting glucose ≥92 mg/dL or by OGTT performed between the weeks of 24 and 28 (0' ≥ 92 mg/dL and/or 60' ≥ 180 mg/dL and/or 120' ≥ 153 mg/dL).[7,9]

GD has been associated to macrosomia, neonatal metabolic changes, neonatal hyperbilirubinemia, and disproportional growth, among other neonatal complications.[1,10-12] It also affects the course of pregnancy, sometimes causing the development of gestational hypertension, preeclampsia, hydramnios or even other maternal morbidities and mortality.[6,10-13]

In the majority of cases, it is possible to control GD by non-pharmacological means such as lifestyle intervention and adapted healthy diet.[1,14] As for the rest, it is necessary to use pharmacological therapy: oral hypoglycemic drugs (OHD) or insulin, isolated or in association.[14-17]

In our study, we aim to analyze the impact of the therapeutics used during pregnancy to reach glycemic control as for the occurrence of cesarean sections and maternal and neonatal complications.

Material and Methods

1. Study Design

This is a retrospective cohort study based on data from the National Registry of GD under the responsibility of Diabetes and Pregnancy Study Group initiated by the Portuguese Society of Diabetes and in which some maternities and hospitals of Portugal are represented, in digital format, as Microsoft Excel®. The data on the registry was acquired on interviews with the participants and from clinical reports on digital files.

The data comprised a total of 17 959 pregnant women followed-up from January 2014 to December 2018 (five years).

We excluded underaged participants (under 18 years-old), pregnant women with previous or de novo diabetes mellitus (fasting glucose or OGTT at 0' ≥ 126 mg/dL or occasional glycemia/OGTT at 60' or 120' ≥ 200 mg/dL), missing values (no information) regarding treatment used to control GD and multifetal pregnancies. We included the data of 15 089 pregnant women (18 years-old and over, GD women with hospital follow-up between 2014 and 2018, within hospital establishments taking part in the national registry record) and their newborns (Fig. 1).

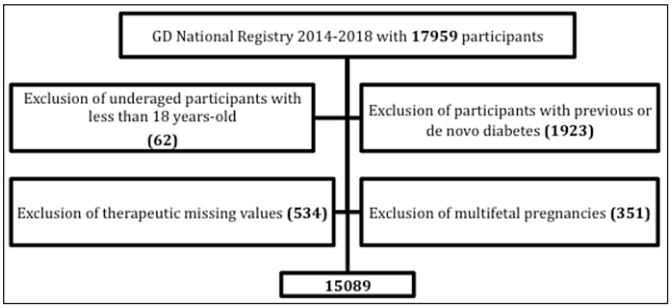


Figure 1. Flowchart of selection course for the final sample.

We considered the following maternal variables: maternal age, first-degree familial history of diabetes, previous macrosomia or GD, weight and height with estimated BMI, BMI categories following WHO guidelines, final gestational weight gain (GWG – difference between weight at delivery or at last appointment and pregestational weight), GWG groups according to the Institute of Medicine (IOM) guidelines, third trimester HbA1c (%), and treatment used for GD (lifestyle intervention and diet *vs* insulin *vs* OHD *vs* insulin + OHD).

According to the World Health Organization (WHO), the body mass index (BMI) categories are underweight (< 18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2) and obesity (≥ 30 kg/m^2).

GWG was grouped into adequate (A), insufficient (I) and excessive (E), within each BMI category, being considered adequate if between 12.5 – 18 kg for underweight, 11.5 – 16 kg for normal BMI, 7 – 11.5 kg for overweight and 5 – 9 kg for obese. It was considered insufficient or excessive when the presented values would be lower or higher, respectively, than the indicated range for each category.

Regarding the variables related to the delivery or the newborn, we analyzed the occurrence of dystocic delivery, specially, cesarean section, newborn weight and assortment by the Fenton and Portuguese growth charts (adequate, small or large for gestational age) depending on the percentile (P) of the newborn (small for gestational age < P10; large for gestational age > P90).

2. Study Groups

The data from the 15 089 mothers and their newborns were divided according to the therapy used to treat GD: control group

with lifestyle intervention and diet, insulin group, OHD group and OHD + insulin group.

Surveillance of glycemic control during pregnancy was done by self-vigilance, with at least four measurements of capillary glycemia per day. The defined targets were fasting glucose ≤ 95 mg/dL and post-prandial glucose ≤ 140 mg/dL (one hour after the beginning of the three main daily meals). When the targets were reached, the therapeutic approach was maintained until the end of pregnancy.

3. Neonatal and Obstetric Outcomes

The sample was divided into four groups regarding its treatment for GD and each was characterized by the variables mentioned above, with means and standard deviations or total number and frequency.

For obstetric outcomes, we analyzed maternal morbidity as primary outcome and secondary outcomes: abortion, fetal death, gestational hypertension (gHT; systolic BP > 140 mmHg or diastolic BP > 90 mmHg after 20 weeks of gestation and without proteinuria), preeclampsia (hypertension associated with proteinuria after week 20), hydramnios (amniotic liquid excess) and cesarean section.

As for neonatal outcomes, we investigated the occurrence of neonatal mortality and morbidity, the latter being a composite for macrosomia (birthweight ≥ 4000 g), low birthweight (< 2500 g), large for gestational age (LGA), small for gestational age (SGA) according to Fenton and Portuguese growth charts, premature (delivery with < 37 weeks of gestation), neonatal hypoglycemia (< 40 mg/dL within the first 48 hours of life), neonatal hyperbilirubinemia (> 18 mg/dL), respiratory distress syndrome (RDS), admission to neonatal intensive care unit (NICU), congenital abnormalities and trauma at delivery.

4. Statistical Analysis

The statistical analysis was done by Statistical Package for Social Sciences (SPSS) software, for Windows, 25.0 version. Continuous variables were characterized by means and SD whilst the qualitative variables were defined by total number and frequency. Considering our sample size, we checked histograms, symmetry, and kurtosis to assess normal distribution of continuous variables. To verify the variables relationship, we used the Kruskal-Wallis test in case of a continuous variable without normal distribution and categorical variable (non-parametric test) and χ^2 or Fisher's exact test for the comparison of categorical variables. We used binomial and multinomial logistic regression to calculate the odds ratio (OR) and verify the influence of the different treatment modes on the maternal and neonatal outcomes, adjusting in order to reduce the confounding effect of the variables. We established 95% confidence interval (CI) and considered statistically significant for p values < 0.05.

Adjustment was made through backward likelihood ratio method in binomial logistic regression and backward stepwise method in multinomial logistic regression for automatic selection of pre-selected covariates. Therefore, our outcomes were adjusted to maternal age, pregestational BMI, HbA1c, first-degree familial history of diabetes and number of weeks between diagnosis and first hospital appointment.

Results

As expected, most of the participants (nr = 9015) were able to control their glycemic values with diet and exercise or other lifestyle changes, leaving 40.3% (nr = 6074) requiring pharmacological therapy in order to control GD: 23.8% (nr = 3596) with insulin, 11% (nr = 1660) with OHD and 5.4% (nr = 818) with the association of OHD and insulin (Table 1).[1,11,14]

In our sample, 42.7% (nr = 6437) of pregnant women had first-degree familial history of diabetes, 12.4% (nr = 1877) had previous GD and 4.9% (nr = 737) previous macrosomia. Comparing the groups of pregnant women controlled with lifestyle intervention and those who needed pharmacological therapy, we observed a higher incidence of familial history of diabetes, previous GD and macrosomia in the second group, with statistical evidence (Table 1).[14,17-19]

The mothers that needed insulin and/or OHD therapy were older than the ones in the lifestyle intervention group (mean > 33.9 *vs* 32.8, p value<0.001).[17] They also exhibited a superior

Table 1. Sample characteristics of mothers and their newborns (nr = 15 089)

Characteristics	Diet and exercise nr= 9015 (59.7%)	Pharmacological treatment nr= 6074 (40.3%)∝	Insulin nr= 3596 (23.8%)	Oral hypoglycemic drug (OHD) nr= 1660 (11.0%)	Insulin + OHD nr= 818 (5.4%)	*p* value
Maternal age (years-old), mean ± SD	32.8 ± 5.3	34.0 ± 5.1	34.0 ± 5.1	33.9 ± 5.2	34.4 ± 5.2	**<0.001**
BMI (kg/m2), mean ± SD	26.0 ± 5.4	28.7 ± 6.2	28.1 ± 6.0	29.1 ± 6.2	31.0 ± 6.6	
Underweight, nr (%)	227 (2.5%)	62 (1.0%)	48 (1.3%)	9 (0.5%)	5 (0.6%)	
Normal, nr (%)	4152 (46.1%)	1779 (29.3%)	1191 (33.1%)	441 (26.6%)	147 (18.0%)	**<0.001**
Overweight, nr (%)	2528 (28.0%)	1840 (30.3%)	1073 (29.8%)	544 (32.8%)	223 (27.3%)	
Obesity, nr (%)	1754 (19.5%)	2181 (35.9%)	1174 (32.6%)	593 (35.7%)	414 (50.6%)	
1st degree familial history of diabetes, nr (%)	3532 (39.2%)	2905 (47.8%)	1723 (47.9%)	764 (46.0%)	418 (51.1%)	**<0.001**
Previous GD, nr (%)	871 (9.7%)	1006 (16.6%)	587 (16.3%)	249 (15.0%)	170 (20.8%)	**<0.001**
Previous macrosomia, nr (%)	344 (3.8%)	393 (6.5%)	231 (6.4%)	107 (6.4%)	55 (6.7%)	**<0.001**
GWG (kg), mean ± SD	11.1 ± 5.8	9.8 ± 5.9	9.6 ± 6.0	10.1 ± 5.7	9.6 ± 6.1	
Adequate, nr (%)	2578 (28.6%)	1708 (28.1%)	1024 (28.5%)	466 (28.1%)	218 (26.7%)	**<0.001**
Insufficient, nr (%)	3121 (34.6%)	2082 (34.3%)	1248 (34.7%)	558 (33.6%)	276 (33.7%)	
Excessive, nr (%)	2214 (24.6%)	1629 (26.8%)	903 (25.1%)	482 (29.0%)	244 (29.8%)	
HbA1c, mean ± SD	5.2 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.4 ± 0.4	**<0.001**
Newborn birthweight (g), Mean ± SD	3157.3 ± 501.0	3205.5 ± 493.4	3184.2 ± 496.1	3222.0 ± 477.9	3265.9 ± 507.0	**<0.001**

BMI: body mass index; GD: gestational diabetes; GWG: gestational weight gain; HbA1c: glycosylated hemoglobin; nr: number; OHD: oral hypoglycemic drug; SD: standard deviation.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

previous BMI (insulin 28.1 kg/m², OHD 29.1 kg/m² and OHD + insulin 31.0 kg/m² *vs* diet 26.0 kg/m²), and more than half of the patients in the group medicated with OHD + insulin were in the obese range (50.6%, nr = 414; Table 1).[11,14,17,20-23]

As for the GWG, the lifestyle intervention group presented a higher mean in comparison with the other groups (Table 1).[14,24] On the other hand, HbA1c value of the non-pharmacological group was the lowest of the four groups (diet 5.2%, insulin 5.3%, OHD 5.3% and OHD + insulin 5.4%).[14]

Regarding the newborn weight, it was lower in the group of pregnant women controlled with lifestyle intervention (diet 3157.3 g, insulin 3184.2 g, OHD 3222 g and OHD + insulin 3265.9 g; Table 1).[25]

When analyzing the implications of GD treatment on obstetric complications, it was possible to observe an association with statistical significance, in which mothers that required pharmacological therapy had higher risk of maternal morbidity (Table 2).[20,25] This statistical relationship was explored (supplementary Table 1) and, afterwards, was adjusted for maternal age, previous BMI, and third trimester HbA1c because these were the factors that demonstrated significant association in most of the pregnancy complications (Table 3).

There was a higher percentage of maternal complications within the group that needed concomitant use of OHD and insulin (23.8%; nr = 195; Table 2). We examined the associated risk to each of the therapy modes and compared to lifestyle intervention, in the development of complications.

Only the risk of cesarean section had statistical significance in the insulin group, with 17% more probability than the lifestyle intervention group, after adjustment (aOR 1.17; CI 95% 1.05-1.31; *p* value = 0.006) (supplementary Fig. 1; Table 3). The OHD group had 60% higher risk of hydramnios (aOR 1.60; CI 95% 1.07-2.39; *p* value = 0.023), whilst the other complications did not have statistical significance (supplementary Fig. 2; Table 3). As for the OHD and insulin group, only global maternal morbidity showed a 27% higher probability of occurring when compared to diet and exercise, with statistical significance (aOR 1.27; CI 95% 1.01-1.60; *p* value = 0.042) (Table 3).[20]

Overall, neonatal complications were more frequent within the pharmacological groups, especially the OHD and insulin association group, apart from low birthweight and SGA (Table 4). While various complications had statistical significance before adjustment (supplementary Table 2), only few retained significance after adjustment to maternal age, pregestational BMI, third trimester HbA1c, and first-degree familial history of diabetes (Table 5).[17]

In the insulin group, there was a higher probability of hypoglycemia (aOR 1.51; CI 95% 1.18-1.93; *p* value = 0.001) and hyperbilirubinemia (aOR 1.24; CI 95% 1.05-1.46; *p* value = 0.011) in the newborn by 51% and 24%, respectively, as well as an increase of 63% of LGA babies via Fenton charts (aOR 1.63; CI 95% 1.25-2.13; *p* value <0.001) and 25% via Portuguese charts (aOR 1.25; CI 95% 1.05-1.47; *p* value = 0.010) (supplementary Fig. 3, Table 5).[1,16,25]

Regarding the OHD group, only trauma at delivery was more likely to occur, with an increase of 76% over the lifestyle intervention group (aOR 1.76; CI 95% 1.12-2.76; *p* value = 0.014) and lower probability of low birthweight (aOR 0.57; CI 95% 0.41-0.81; *p* value = 0.001) and SGA (aOR 0.59; CI 95% 0.46-0.76; *p* value <0.001 Fenton charts; aOR 0.67; CI 95% 0.51-0.87; *p* value = 0.003 Portuguese charts) newborns (supplementary Fig. 4, Table 5).[25]

Table 2. Association between GD treatment and the development of obstetric complications

Obstetric complications	Diet and exercise nr= 9015	Pharmacological treatment nr= 6074 ∝	Insulin nr= 3596	Oral hypoglycemic drug (OHD) nr= 1660	Insulin + OHD nr= 818	*p* value
Maternal morbidity, nr (%)	1303 (14.5%)	1020 (16.8%)	542 (15.1%)	283 (17.0%)	195 (23.8%)	**<0.001**
Abortion, nr (%)	72 (0.8%)	25 (0.4%)	13 (0.4%)	9 (0.5%)	3 (0.4%)	**0.002**
Fetal death, nr (%)	28 (0.3%)	15 (0.2%)	7 (0.2%)	3 (0.2%)	5 (0.6%)	**<0.001**
gHT, nr (%)	348 (3.9%)	268 (4.4%)	139 (3.9%)	77 (4.6%)	52 (6.4%)	**<0.001**
Preeclampsia, nr (%)	225 (2.5%)	198 (3.3%)	111 (3.1%)	53 (3.2%)	34 (4.2%)	**0.038**
Hydramnios, nr (%)	158 (1.8%)	172 (2.8%)	90 (2.5%)	54 (3.3%)	28 (3.4%)	**<0.001**
Cesarean section, nr (%)	2705 (30.0%)	2152 (35.4%)	1259 (35.0%)	574 (34.6%)	319 (39.0%)	**<0.001**

GD: gestational diabetes; gHT: gestational hypertension; nr: number; OHD: oral hypoglycemic drug;.
∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Table 3. Adjusted correlation between GD therapy and the development of pregnancy complications.

Obstetric complications	Diet and exercise aOR (CI 95%)	Pharmacological treatment ∝ aOR (CI 95%)	*p* value	Insulin aOR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) aOR (CI 95%)	*p* value	Insulin + OHD aOR (CI 95%)	*p* value
Maternal morbidity	1.00	0.95 (0.84-1.08)	0.421	0.90 (0.78-1.04)	0.154	0.92 (0.75-1.12)	0.383	1.27 (1.01-1.60)	**0.042**
Abortions	1.00	1.10 (0.36-3.41)	0.869	0.93 (0.23-3.66)	0.912	1.43 (0.29-7.12)	0.661	1.27 (0.15-11.13)	0.827
gHT	1.00	0.92 (0.73-1.15)	0.457	0.83 (0.64-1.08)	0.171	0.96 (0.69-1.34)	0.828	1.10 (0.73-1.64)	0.655
Preeclampsia	1.00	1.08 (0.82-1.44)	0.584	1.14 (0.83-1.57)	0.415	0.92 (0.59-1.43)	0.706	1.14 (0.69-1.89)	0.599
Hydramnios	1.00	1.41 (1.06-1.89)	**0.018**	1.34 (0.97-1.86)	0.078	1.60 (1.07-2.39)	**0.023**	1.61 (0.98-2.66)	0.062
Cesarean section	1.00	1.10 (1.00-1.22)	0.053	1.17 (1.05-1.31)	**0.006**	0.98 (0.84-1.14)	0.766	1.05 (0.86-1.29)	0.637

aOR: adjusted odds ratio; CI 95%: confidence intervals at 95%; GD: gestational diabetes; gHT: gestational hypertension; OHD: oral hypoglycemic drug.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Adjusted for maternal age, pregestational BMI and HbA1c.

Table 4. Association between GD treatment and the development of obstetric complications.

Neonatal complications	Diet and exercise nr= 9015	Pharmacological treatment nr= 6074 ∝	Insulin nr= 3596	Oral hypoglycemic drug (OHD) nr= 1660	Insulin + OHD nr= 818	*p* value
Neonatal mortality, nr (%)	15 (0.2%)	13 (0.2%)	8 (0.2%)	3 (0.2%)	2 (0.2%)	**<0.001**
Neonatal morbidity, nr (%)	1541 (17.1%)	1217 (20.0%)	703 (19.5%)	321 (19.3%)	193 (23.6%)	**<0.001**
Hypoglycemia, nr (%)	317 (3.5%)	313 (5.2%)	181 (5.0%)	82 (4.9%)	50 (6.1%)	**<0.001**
Hyperbilirubinemia, nr (%)	893 (9.9%)	737 (12.1%)	418 (11.6%)	186 (11.2%)	133 (16.3%)	**<0.001**
RDS, nr (%)	274 (3.0%)	186 (3.1%)	104 (2.9%)	53 (3.2%)	29 (3.5%)	**<0.001**
Admission to NICU, nr (%)	640 (7.1%)	410 (6.8%)	233 (6.5%)	119 (7.2%)	58 (7.1%)	**<0.001**
Prematurity, nr (%)	641 (7.1%)	419 (6.9%)	256 (7.1%)	99 (6.0%)	64 (7.8%)	0.283
Macrosomia, nr (%)	310 (3.4%)	269 (4.4%)	159 (4.4%)	63 (3.8%)	47 (5.7%)	**<0.001**
Low birthweight, nr (%)	728 (8.1%)	389 (6.4%)	256 (7.1%)	83 (5.0%)	50 (6.1%)	
Fenton charts, nr (%)						
LGA	265 (2.9%)	340 (5.6%)	199 (5.5%)	77 (4.6%)	64 (7.8%)	**<0.001**
SGA	1171 (13.0%)	573 (9.4%)	374 (10.4%)	130 (7.8%)	69 (8.4%)	
Portuguese charts, nr (%)						
LGA	806 (8.9%)	819 (13.5%)	459 (12.8%)	216 (13.0%)	144 (17.6%)	**<0.001**
SGA	990 (11.0%)	507 (8.3%)	333 (9.3%)	114 (6.9%)	60 (7.3%)	
Congenital abnormalities, nr (%)	338 (3.7%)	224 (3.7%)	126 (3.5%)	55 (3.3%)	43 (5.3%)	**<0.001**
Trauma at delivery, nr (%)	122 (1.4%)	104 (1.7%)	46 (1.3%)	40 (2.4%)	18 (2.2%)	**0.004**

GD: gestational diabetes; LGA: large for gestational age; OHD: oral hypoglycemic drug; NICU: neonatal intensive care unit; nr: number; RDS: respiratory distress syndrome; SGA: small for gestational age.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Table 5. Adjusted correlation between GD therapy and the development of neonatal complications.

Neonatal complications	Diet and exercise aOR (CI 95%)	Pharmacological treatment ∝ aOR (CI 95%)	*p* value	Insulin aOR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) aOR (CI 95%)	*p* value	Insulin + OHD aOR (CI 95%)	*p* value
Neonatal mortality	1.00	1.25 (0.42-3.73)	0.691	1.49 (0.46-4.83)	0.509	0.68 (0.08-5.65)	0.719	1.27 (0.14-11.14)	0.831
Neonatal morbidity	1.00	1.14 (1.02-1.28)	**0.025**	1.14 (0.999-1.30)	0.052	1.02 (0.85-1.22)	0.869	1.46 (1.17-1.82)	**0.001**
Hypoglycemia	1.00	1.41 (1.13-1.76)	**0.003**	1.51 (1.18-1.93)	**0.001**	1.06 (0.74-1.52)	0.756	1.74 (1.18-2.59)	**0.006**
Hyperbilirubinemia	1.00	1.28 (1.11-1.47)	**<0.001**	1.24 (1.05-1.46)	**0.011**	1.15 (0.92-1.43)	0.212	1.73 (1.33-2.24)	**<0.001**
RDS	1.00	0.82 (0.63-1.06)	0.133	0.87 (0.64-1.18)	0.365	0.73 (0.47-1.12)	0.152	0.88 (0.52-1.48)	0.619
Admission to NICU	1.00	0.92 (0.77-1.10)	0.357	1.02 (0.83-1.25)	0.854	0.82 (0.62-1.09)	0.176	0.77 (0.53-1.13)	0.180
Macrosomia	1.00	0.98 (0.78-1.24)	0.881	1.09 (0.84-1.43)	0.525	0.83 (0.57-1.21)	0.321	1.05 (0.69-1.60)	0.825
Low birthweight	1.00	0.80 (0.67-0.96)	**0.017**	0.92 (0.75-1.13)	0.411	0.57 (0.41-0.81)	**0.001**	0.81 (0.545-1.21)	0.307
Fenton charts									
LGA	1.00	1.62 (1.28-2.05)	**<0.001**	1.63 (1.25-2.13)	**<0.001**	1.38 (0.97-1.96)	0.070	1.89 (1.29-2.78)	**0.001**
SGA	1.00	0.79 (0.69-0.91)	**<0.001**	0.88 (0.75-1.03)	0.116	0.59 (0.46-0.76)	**<0.001**	0.83 (0.61-1.15)	0.262
Portuguese charts									
LGA	1.00	1.27 (1.10-1.47)	**0.001**	1.25 (1.05-1.47)	**0.010**	1.24 (0.998-1.54)	0.052	1.58 (1.22-2.05)	<0.001
SGA	1.00	0.86 (0.74-0.995)	**0.043**	0.95 (0.80-1.12)	0.533	0.67 (0.51-0.87)	**0.003**	0.94 (0.67-1.31)	0.704
Prematurity	1.00	0.97 (0.80-1.17)	0.717	1.03 (0.83-1.27)	0.808	0.78 (0.57-1.09)	0.142	1.16 (0.80-1.69)	0.436
Congenital abnormalities	1.00	1.17 (0.92-1.50)	0.211	1.30 (0.99-1.70)	0.062	0.77 (0.50-1.18)	0.226	1.38 (0.88-2.16)	0.157
Trauma at delivery	1.00	1.25 (0.89-1.75)	0.204	0.93 (0.60-1.43)	0.724	1.76 (1.12-2.76)	**0.014**	2.13 (1.23-3.68)	**0.007**

aOR: adjusted odds ratio; CI 95%: confidence intervals at 95%; GD: gestational diabetes; LGA: large for gestational age; OHD: oral hypoglycemic drug; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; SGA: small for gestational age.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Adjusted for maternal age, pregestational BMI, HbA1c, weeks between diagnosis and first hospital appointment and first-degree familial history of diabetes.

Lastly, there was a higher risk, of about 46%, for neonatal morbidity (aOR 1.46; CI 95% 1.17-1.82; *p* value = 0.001), particularly neonatal hypoglycemia (aOR 1.74; CI 95% 1.18-2.59; *p* value = 0.006) and hyperbilirubinemia (aOR 1.73; CI 95% 1.33-2.24; *p* value <0.001) within the group with OHD and insulin. In this group there was also 113% higher odds of developing trauma at delivery (aOR 2.13; CI 95% 1.23-3.68; *p* value = 0.007) and higher probability of mothers giving birth to LGA newborns (aOR 1.89; CI 95% 1.29-2.78; *p* value = 0.001 Fenton charts and aOR 1.58; CI 95% 1.22-2.05; *p* value < 0.001 Portuguese charts) (supplementary Fig. 5, Table 5).[1,16,25]

Supplementary Table 1. Crude correlation between Gestational Diabetes treatment and the development of pregnancy complications.

Obstetric complications	Diet and exercise OR (CI 95%)	Pharmacological treatment ∝ OR (CI 95%)	*p* value	Insulin OR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) OR (CI 95%)	*p* value	Insulin + OHD OR (CI 95%)	*p* value
Maternal morbidity	1.00	1.21 (1.10-1.32)	**<0.001**	1.06 (0.95-1.18)	0.341	1.23 (1.07-1.42)	**0.005**	1.92 (1.61-2.28)	**<0.001**
Abortions	1.00	0.52 (0.33-0.81)	**0.004**	0.45 (0.25-0.82)	**0.009**	0.68 (0.34-1.35)	0.269	0.46 (0.14-1.45)	0.184
Fetal death	1.00	0.81 (0.43-1.51)	0.498	0.64 (0.28-1.47)	0.292	0.58 (0.18-1.91)	0.372	1.97 (0.76-5.11)	0.164
gHT	1.00	1.18 (0.998-1.38)	0.053	1.02 (0.83-1.25)	0.861	1.22 (0.95-1.57)	0.121	1.82 (1.35-2.46)	**<0.001**
Preeclampsia	1.00	1.32 (1.09-1.60)	**0.005**	1.25 (0.99-1.57)	0.060	1.28 (0.95-1.74)	0.107	1.68 (1.17-2.43)	**0.005**
Hydramnios	1.00	1.64 (1.32.2.04)	**<0.001**	1.45 (1.11-1.88)	**0.006**	1.88 (1.38-2.58)	**<0.001**	1.97 (1.31-2.97)	**0.001**
Caesarean section	1.00	1.27 (1.18-1.37)	**<0.001**	1.24 (1.14-1.36)	**<0.001**	1.24 (1.10-1.39)	**<0.001**	1.49 (1.27-1.74)	**<0.001**

CI 95%: confidence intervals at 95%; gHT: gestational hypertension;

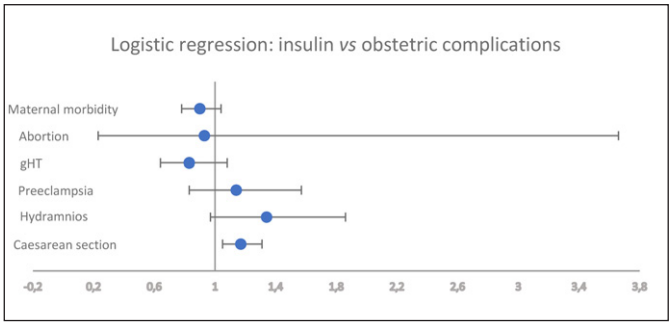
∝ types of pharmacological treatment: insulin, oral hypoglycemic drug (OHD) or association of OHD and insulin.

Supplementary Table 2. Crude correlation between GD treatment and the development of neonatal complications.

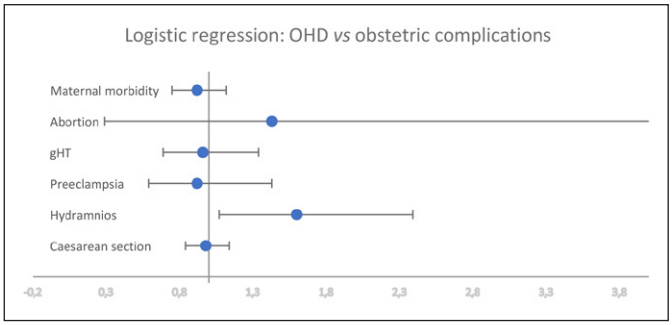
Neonatal complications	Diet and exercise OR (CI 95%)	Pharmacological treatment ∝ OR (CI 95%)	*p* value	Insulin OR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) OR (CI 95%)	*p* value	Insulin + OHD OR (CI 95%)	*p* value
Neonatal mortality	1.00	1.32 (0.63-2.78)	0.463	1.40 (0.59-3.31)	0.440	1.08 (0.31-3.72)	0.909	1.49 (0.34-6.52)	0.598
Neonatal morbidity	1.00	1.23 (1.13-1.34)	**<0.001**	1.21 (1.09-1.33)	**<0.001**	1.16 (1.01-1.33)	0.030	1.51 (1.27-1.79)	**<0.001**
Hypoglycaemia	1.00	1.54 (1.32-1.81)	**<0.001**	1.55 (1.28-1.87)	**<0.001**	1.41 (1.10-1.80)	**0.007**	1.82 (1.34-2.48)	**<0.001**
Hyperbilirubinemia	1.00	1.30 (1.17-1.44)	**<0.001**	1.26 (1.12-1.43)	**<0.001**	1.13 (0.96-1.34)	0.153	1.80 (1.48-2.20)	**<0.001**
RDS	1.00	1.04 (0.86-1.25)	0.720	0.998 (0.79-1.26)	0.989	1.04 (0.77-1.40)	0.818	1.19 (0.81-1.76)	0.377
Admission to NICU	1.00	0.97 (0.86-1.11)	0.667	0.95 (0.81-1.11)	0.530	0.996 (0.81-1.22)	0.973	1.01 (0.76-1.34)	0.942
Macrosomia	1.00	1.28 (1.08-1.51)	**0.004**	1.29 (1.06-1.56)	**0.012**	1.07 (0.81-1.41)	0.628	1.68 (1.22-2.30)	**0.001**
Low birthweight	1.00	0.79 (0.69-0.89)	**<0.001**	0.88 (0.76-1.02)	0.096	0.60 (0.48-0.76)	**<0.001**	0.76 (0.57-1.02)	0.069
Fenton charts									
LGA	1.00	1.88 (1.59-2.22)	**<0.001**	1.87 (1.55-2.26)	**<0.001**	1.51 (1.17-1.96)	**0.002**	2.68 (2.02-3.57)	**<0.001**
SGA	1.00	0.72 (0.64-0.80)	**<0.001**	0.80 (0.70-0.90)	**<0.001**	0.58 (0.48-0.70)	**<0.001**	0.65 (0.51-0.85)	**0.001**
Portuguese charts									
LGA	1.00	1.54 (1.39-1.71)	**<0.001**	1.46 (1.29-1.65)	**<0.001**	1.46 (1.24-1.71)	**<0.001**	2.12 (1.74-2.58)	**<0.001**
SGA	1.00	0.78 (0.69-0.87)	**<0.001**	0.86 (0.76-0.99)	**0.029**	0.63 (0.51-0.77)	**<0.001**	0.72 (0.55-0.95)	**0.018**
Prematurity	1.00	0.97 (0.85-1.10)	0.617	1.00 (0.86-1.16)	0.986	0.83 (0.67-1.03)	0.091	1.11 (0.85-1.45)	0.449
Congenital abnormalities	1.00	1.03 (0.87-1.23)	0.727	1.03 (0.83-1.26)	0.813	0.86 (0.64-1.14)	0.293	1.43 (1.03-1.98)	**0.032**
Trauma at delivery	1.00	1.33 (1.02-1.73)	**0.035**	1.02 (0.73-1.44)	0.903	1.78 (1.24-2.56)	**0.002**	1.67 (1.01-2.75)	**0.045**

CI 95%: confidence intervals at 95%; GD: gestational diabetes; LGA: large for gestational age; NICU: neonatal intensive care unit; OHD: oral hypoglycemic drug; OR: odds ratio; RDS: respiratory distress syndrome; SGA: small for gestational age.

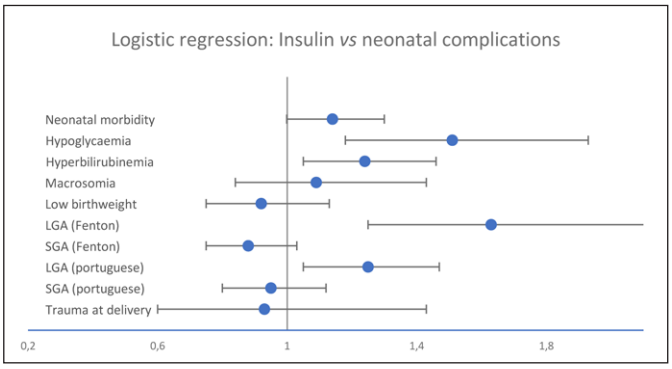
∝ types of pharmacological treatment: insulin, oral hypoglycemic drug (OHD) or association of OHD and insulin.



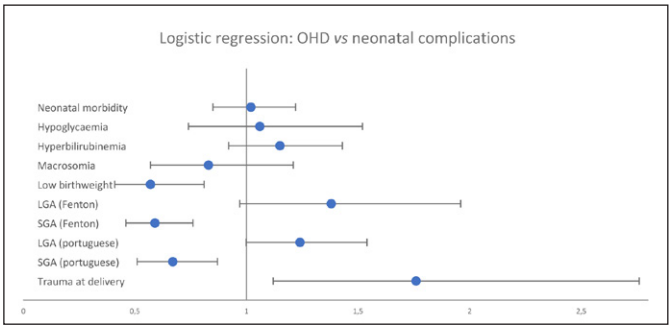
Supplementary Figure 1. Logistic regression of insulin therapy in the development of obstetric complications.



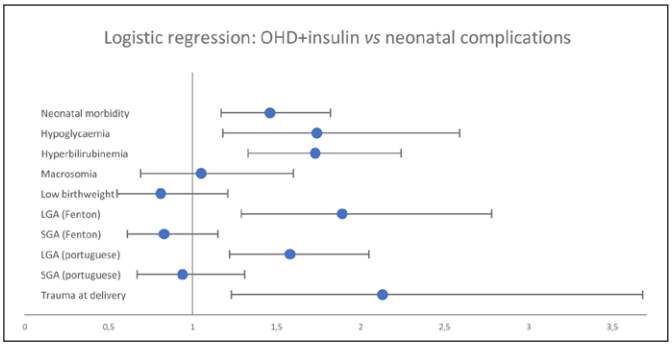
Supplementary Figure 2. Logistic regression of OHD in the development of maternal complications.



Supplementary Figure 3. Logistic regression of insulin in the development of neonatal complications.



Supplementary Figure 4. Logistic regression of OHD in the development of neonatal complications.



Supplementary Figure 5. Logistic regression of OHD+insulin in the development of neonatal complications.

Discussion

GD therapy differs from patient to patient and is conditioned by many pregestational risk factors, being that its administration might have an impact in the development of maternal and neonatal complications.

Only a few pregnancy complications showed statistically significant differences within the different therapeutic groups, such as maternal morbidity, hydramnios and cesarean section,[20] when unadjusted. After adjustment to maternal age, pregestational BMI and third trimester HbA1c, some lost the association evidence, demonstrating the presence of confounding variables. Nonetheless, it was possible to verify that the need for pharmacological treatment, in particular insulin and OHD association, was connected to an increased probability of obstetric complications,[1] although not statistically significant, which shows the need for a bigger sample to reach statistical evidence.

As for neonatal complications, those also ceased to have statistical significance after adjustment to maternal age, pregestational BMI, third trimester HbA1c, and family history of diabetes, demonstrating confounding. However, the use of medical therapy for GD may be related to increased occurrence of complications, particularly for the ones with simultaneous use of OHD and insulin, whose glycemic profile is much more difficult to control and with higher risk for neonatal hypoglycemia, hyperbilirubinemia and LGA newborns which leads to trauma during delivery.[1,16,20,25] Additionally, this particular group demonstrated a synergistic effect on the risk that either OHD or insulin alone were associated with.

Despite that, it is important to take into account the fact that mothers that required medical treatment, had previous pregestational characteristics which predisposed to complications, like advanced maternal age, superior pregestational BMI, history of familial diabetes, previous GD and macrosomia.[1,26-29] They also featured glycemic profiles that were more difficult to control, greater third trimester HbA1c values, requiring pharmacological treatment.[14] Therefore, the simultaneous use of OHD and insulin may not be directly related to complications *per se*, but it might reflect the difficulty to control glycemic profile that favors the development of complications.[14,16,28]

This study presented various limitations. The national registry of GD is a database fulfilled by health professionals that previously volunteered to take part in the registration. This results in lack of total national representation because many peripheral hospitals are not represented and those, who miss the deadlines and do not deliver the patients data, may also be out of the registry. Consequently, this results in selection by participation bias. Moreover, some filling criteria are sometimes subjective, leading to lack of uniformity, high variability, and many missing data, causing an information bias due to variability of the observer and interviewer.

At last, there is also another bias of information due to measuring error, memory, and social desirability when the information is the result of self-report recollection.

Although there are many significant biases, some may be reduced through training and establishing action protocols for the information acquisition and filling methods. Additionally, prospective studies may also avoid some of these limitations.

Conclusion

It is essential for pregnant women, after being diagnosed with GD, to have precocious and regular hospital appointments, allowing the institution of lifestyle intervention strategies and pharmacological therapy as soon as possible, in order to rapidly reach glycemic control.

In this retrospective study, in some pregnant women with the need for pharmacological therapy a stricter surveillance, with more frequent appointments and immediate and adequate therapeutic adjustments, might have lacked.

Equally, we should take into account the importance of pregestational risk factors, like advanced maternal age, high pregestational BMI, history of familial diabetes, previous GD and/or macrosomia, that affects the gestational course and augment the probability of future pharmacological requirements, sometimes more than one medical therapy and therefore increasing the risk for maternal and neonatal complications.

In conclusion, it is crucial to provide frequent hospital appointments as well as preconception follow-up to pregnant women so to avoid complications.

Acknowledgement

To all the elements that contributed to the construction of the national registry of GD.

Contributorship Statement / Declaração de Contribuição:

JCX: Contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article and giving the final approval of the version to be published.
AC: Contributed to conception and design, acquisition of data, revising the article and providing the final approval of the version to be published.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.
Data Availability Statement: The data that support the findings of this study are available from the Diabetes and Pregnancy Study Group initiated by the Portuguese Society of Diabetes, but restrictions apply to the availability of these data, that is not publicly accessible. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable.

References / Referências

1. Silva AL, Amaral AR, Oliveira DS, Martins L, Silva MR, Silva JC. Neonatal outcomes according to diferent therapies for gestational diabetes mellitus. J Pediatr. 2007; 93: 87-93. http://dx.doi.org/10.1016/j.jped.2016.04.004.
2. Burks ML, Cozzi GD, Wang L, Jagasia SM, Chakkalakal RJ. Socioeconomic status and care metrics for women diagnosed with gestational diabetes mellitus. Clin Diabetes. 2017;35:217-26. doi: 10.2337/cd16-0064.
3. Marques JB, Reynolds A.Distócia de ombros – uma emergência obstétrica. Acta Med Port. 2011; 24: 613-20.
4. Agudelo-Espitia V, Parra-Sosa BE, Restrepo-Mesa SL. Factors associated with fetal macrosomia. Rev Saude Publica. 2019; 53:100. doi: 10.11606/s1518-8787.2019053001269.
5. Gonçalves CV, Mendoza-Sassi RA, Cesar JA, Castro NB, Bortolomedi AP. Índice de massa corporal e ganho de peso gestacional como fatores preditores de complicações e do desfecho da gravidez. Rev Bras Ginecol Obstet. 2012;34:304-9. doi: 10.1590/S0100-72032012000700003.
6. Mimoso G, Oliveira G. Morbilidade neonatal e diabetes gestacional. Acta Med Port. 2017;30: 589-98. doi: 10.20344/amp.8033.
7. Sociedade Portuguesa de Endocrinologia Diabetes e Metabolismo, Sociedade Portuguesa de Diabetologia, Sociedade Portuguesa de Obstetrícia e Medicina Materno-Fetal, Secção de Neonatologia da Sociedade Portuguesa de Pediatria. Relatório de Consenso sobre Diabetes e Gravidez. Lisboa: SPEDM, SPD, SPOMMF, Secção de Neonatologia da Sociedade Portuguesa de Pediatria; 2011.
8. Alves JM, Stollmeier A, Leite IG, Pilger CG, Detsch JC, Radominski RB, et al. Postpartum Reclassification of Glycemic Status in Women with Gestational Diabetes Mellitus and Associated Risk Factors. Rev Bras Ginecol Obstet. 2016;38:381-90. doi: 10.1055/s-0036-1588008. .
9. Megia A, Näf S, Herranz L, Serrat N, Yañez RE, Simón I, et al. The usefulness of HbA1c in postpartum reclassification of gestational diabetes. BJOG. 2012;119:891-4. doi: 10.1111/j.1471-0528.2012.03325.x.
10. Silva JC, Bertini AM, Ribeiro TE, Carvalho LS, Melo MM, Neto LB. Fatores relacionados à presença de recém-nascidos grandes para a idade gestacional em gestantes com diabetes mellitus gestacional. Rev Brasil Ginecol Obstet. 2009; 31. doi:10.1590/S0100-72032009000100002.
11. Simões AB, Robalo R, Gomes G, Aleixo F, Amaral N, Guerra S. Diabetes Gestacional nos anos 2000 e 2010: Retrato de uma sociedade?. Rev Port Endocrinol Diabetes Metabol. 2013;8: 21-4. doi: 10.1016/j.rpedm.2012.09.001.
12. Carocha A, Rijo C, Amaral N, Aleixo F, Rocha T. Diabetes gestacional – rastreio pós-parto. Acta Med Port. 2012; 25:165-8. PMID:
13. Pongcharoen T, Gowachirapant S, Wecharak P, Sangket N, Winichagoon P. Pre-pregnancy body mass index and gestational weight gain in Thai pregnant women as risks for low birth weight and macrosomia. Asia Pac J Clin Nutr. 2016;25: 810-7. doi: 10.6133/apjcn.092015.41.
14. Bianchi C, de Gennaro G, Romano M, Aragona M, Battini L, Del Prato S, et al. Pre-pregnancy obesity, gestational diabetes or gestational weight gain: Which is the strongest predictor of pregnancy outcomes? Diabetes Res Clin Pract. 2018144:286-93. doi: 10.1016/j.diabres.2018.08.019.
15. Martis R, Crowther CA, Shepherd E, Alsweiler J, Downie MR, Brown J .Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2018; 8: CD012327. doi: 10.1002/14651858.CD012327.pub2.
16. Kong L, Nilsson IAK, Gissler M, Lavebratt C. Associations of Maternal Diabetes and Body Mass Index With Offspring Birth Weight and Prematurity. JAMA Pediatr. 2019;173:371–8. doi:10.1001/jamapediatrics.2018.5541.
17. Ouzounian JG, Rosenheck R, Lee RH, Yedigarova L, Walden CL, Korst LM. One-hour post-glucola results and pre-pregnancy body mass index are associated with the need for insulin therapy in women with gestational diabetes. J Matern Fetal Neonatal Med. 2011;24:718-22. doi:10.3109/14767058.2010.521869.
18. Miranda A, Fernandes V, Marques M, Castro L, Fernandes O, Pereira ML. Diabetes Gestacional: Avaliação dos Desfechos Maternos, Fetais e Neonatais. Revista Portuguesa de Endocrinologia, Diabetes e Metab. 2017;12:36-44. do: 10.1016/j.rpedm.2015.10.030.
19. Collier A, Abraham EC, Armstrong J, Godwin J, Monteath K, Lindsay R. Reported prevalence of gestational diabetes in Scotland: The relationship with obesity, age, socioeconomic status, smoking and macrosomia, and how many are we missing? J Diabetes Investig. 2017;8:161-7. doi:10.1111/jdi.12552.
20. Freitas ICS, Hintz MC, Orth LC, Rosa TGD, Iser BM, Psendziuk C.Comparison of Maternal and Fetal Outcomes in Parturients With and Without a Diagnosis of Gestational Diabetes. Rev Bras Ginecol Obstet. 2019; 41: 647-53. doi:10.1055/s-0039-1696947.
21. Ribeiro AMC, Nogueira-Silva C, Melo-Rocha G, Pereira ML, Rocha A. Diabetes gestacional: determinação de fatores de risco para diabetes mellitus. Rev Port Endocrinol Diabetes Metab. 2015;10: 8–13. doi:

10.1016/j.rpedm.2014.05.004.
22. Bouvier D, Forest JC, Dion-Buteau E, Bernard N, Bujold E, Pereira B, et al. Association of Maternal Weight and Gestational Weight Gain with Maternal and Neonate Outcomes: A Prospective Cohort Study. J Clin Med. 2019;8:2074. doi: 10.3390/jcm8122074. .
23. Megia A, Vendrell J, Gutierrez C, Sabaté M, Broch M, Fernández-Real JM, et al. Insulin sensitivity and resistin levels in gestational diabetes mellitus and after parturition. Eur J Endocrinol. 2008;158:173-8. doi: 10.1530/EJE-07-0671.
24. Simmons D, Devlieger R, van Assche A, Galjaard S, Corcoy R, Adelantado JM, et al. Association between Gestational Weight Gain, Gestational Diabetes Risk, and Obstetric Outcomes: A Randomized Controlled Trial Post Hoc Analysis. Nutrients. 2018;10:1568. doi: 10.3390/nu10111568. .
25. Martis R, Crowther CA, Shepherd E, Alsweiler J, Downie MR, Brown J. Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev.2018; 8: CD012327. doi: 10.1002/14651858.CD012327.pub2.
26. Aydın H, Çelik Ö, Yazıcı D, Altunok Ç, Tarçın Ö, Deyneli O, et al. Prevalence and predictors of gestational diabetes mellitus: a nationwide multicentre prospective study. Diabet Med. 2019;36:221-7. doi: 10.1111/dme.13857.
27. Macrì F, Pitocco D, di Pasquo E, Salvi S, Rizzi A, Di Leo M, et al. Gestational weight gain as an independent risk factor for adverse pregnancy outcomes in women with gestational diabetes. Eur Rev Med Pharmacol Sci. 2018;22:4403-10. doi: 10.26355/eurrev_201807_15490 .
28. Hosseini E, Janghorbani M, Shahshahan Z. Comparison of risk factors and pregnancy outcomes of gestational diabetes mellitus diagnosed during early and late pregnancy. Midwifery. 2018;66:64-69. doi: 10.1016/j.midw.2018.07.017.
29. Xu X, Liu Y, Liu D, Li X, Rao Y, Sharma M, et al. Prevalence and Determinants of Gestational Diabetes Mellitus: A Cross-Sectional Study in China. Int J Environ Res Public Health. 2017;14:1532. doi: 10.3390/ijerph14121532.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Síndrome do Ovário Poliquístico em Adolescentes: Impacto da Terapêutica no Perfil Clínico e Analítico

Ana Luísa Duarte [a], Olinda Marques [b], Sofia Martins [c], Ana Antunes [c], Maria Miguel Gomes [a,c,*]

[a] *Escola de Medicina da Universidade do Minho, Braga, Portugal*
[b] *Serviço de Endocrinologia, Hospital de Braga, Braga, Portugal*
[c] *Unidade de Endocrinologia e Diabetologia Pediátrica, Serviço de Pediatria, Hospital de Braga, Braga, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-06-07
Accepted/Aceite: 2023-06-14
Publicado / Published: 2023-10-18

Palavras-chave:
Adolescente;
Síndrome do Ovário Poliquístico/diagnóstico;
Síndrome do Ovário Poliquístico/tratamento.

R E S U M O

Introdução: A síndrome do ovário poliquístico (SOP) é um distúrbio endócrino que pode afetar 3% a 11% das adolescentes estando associada ao desenvolvimento de complicações reprodutivas, metabólicas e psicológicas. O seu diagnóstico requer pelo menos 2 de 3 critérios: disfunção ovulatória, hiperandrogenismo e ovários poliquísticos. A base do tratamento assenta em medidas de estilo de vida (MEV), e a terapêutica farmacológica pode envolver fármacos insulinossensibilizantes, anti-androgénicos e contracetivos orais combinados (COC).
O nosso objetivo foi avaliar o impacto da terapêutica no perfil clínico e analítico de uma população adolescente com SOP.
Métodos: Foram incluídas 84 doentes com primeira consulta entre 01/01/2012 e 01/07/2019. Avaliou-se disfunção ovulatória, hiperandrogenismo clínico e analítico, insulinorresistência, perfil lipídico e índice de massa corporal (IMC), assim como as terapêuticas utilizadas. Foi realizada análise de associação entre a instituição de tratamento e os resultados clínicos e analíticos.
Resultados: Nesta coorte averiguou-se 79,8% de disfunção ovulatória, 100% de hiperandrogenismo clínico/analítico, 67,9% excesso de peso/obesidade, 42,9% insulinorresistência clínica e 23,8% dislipidemia. Verificou-se regularização dos ciclos menstruais nas adolescentes que faziam terapêutica farmacológica (p=0,014), sobretudo quando usado COC (p<0,001) e relacionou-se maior eficácia com maior duração de tratamento (p=0,005). No entanto, o COC foi associado a evolução desfavorável do perfil lipídico e IMC. Constatou-se que o tratamento dirigido ao hiperandrogenismo promoveu diminuição significativa dos valores de sulfato de dihidroepiandrosterona (p=0,004). O HOMA-IR evoluiu favoravelmente com o uso de MEV (p=0,026) e metformina (p=0,013). As MEV promoveram melhoria do IMC (p=0,007).
Conclusão: A correta caracterização dos critérios clínicos e analíticos da SOP, assim como uma minuciosa avaliação metabólica, permitem melhorar as estratégias terapêuticas a adotar. Existe a necessidade de criar protocolos de diagnóstico, terapêutica e seguimento de adolescentes com SOP.

Keywords:
Adolescent;
Polycystic Ovary Syndrome/diagnosis;
Polycystic Ovary Syndrome/therapy.

Polycystic Ovary Syndrome in Adolescents: Impact of Therapy on Clinical and Analytical Profile

A B S T R A C T

Introduction: Polycystic ovary syndrome (PCOS) is an endocrine disorder that can affect 3% to 11% of adolescents and is associated with the development of reproductive, metabolic, and psychological complications. Diagnosis of PCOS requires at least 2 of 3 criteria: ovulatory dysfunction, hyperandrogenism and polycystic ovaries. The basis of treatment is lifestyle measures (LSM), and

* Autor Correspondente / Corresponding Author.
E-Mail: mariamiguelsagomes@gmail.com (Maria Miguel Gomes)
Sete Fontes - São Victor. 4710-243 Braga, Portugal

https://doi.org/10.26497/ao220031

pharmacological therapy may involve insulin-sensitizing drugs, anti-androgens and combined oral contraceptives (COC) Our aim was to assess the impact of therapy on the clinical and analytical profile of an adolescent population with PCOS.

Methods: In this study were included 84 adolescents with their first appointment between 01/01/2012 and 1/07/2019. The variables analysed were ovulatory dysfunction, clinical and analytical hyperandrogenism, insulin resistance, lipid profile and body mass index (BMI), as well as the therapies used. An analysis of association was performed between treatment and clinical/analytical results.

Results: In this cohort, we found 79.8% of ovulatory dysfunction, 100% of clinical/analytical hyperandrogenism, 67.9% of overweight/obesity, 42.9% of clinical insulin resistance and 23.8% of dyslipidaemia. There was regularization of the menstrual cycles in the adolescents who were undergoing pharmacological therapy (p=0.014), especially when using COC (p<0.001) and greater efficacy was associated with longer duration of treatment (p=0.005). However, COC was associated with a worse evolution of the lipid profile and BMI. Treatment directed to hyperandrogenism promoted a significant decrease in the values of dehydroepiandrosterone sulfate (p=0.004). The HOMA-IR evolved favorably with the use of LSM (p=0.026) and metformin (p=0.013). The LSM promoted an improvement in the BMI (p=0.007).

Conclusion: The correct characterization of the clinical and analytical criteria of PCOS, as well as a thorough metabolic assessment, allow for the improvement of the therapeutic strategies to be adopted. There is a need to create protocols regarding diagnosis, therapy, and follow-up for adolescents with PCOS.

Introdução

A síndrome do ovário poliquístico (SOP) é um distúrbio endócrino, frequente na população feminina. A sua prevalência pode alcançar até 20% das mulheres em idade reprodutiva, e os estudos na população adolescente evidenciam um intervalo semelhante, entre 3% e 11%.[1]

A SOP tem uma etiologia multifatorial e que não está totalmente esclarecida, envolvendo fatores hereditários, genéticos, hormonais e ambientais.[1]

Para o diagnóstico desta entidade, são frequentemente aplicados os critérios de Roterdão, que englobam 3 parâmetros:

1. Disfunção ovulatória (irregularidades menstruais, com ciclos de duração inferior a 21 dias ou superior a 35 dias);
2. Hiperandrogenismo clínico (acne, hirsutismo e/ou alopécia) e/ou analítico (elevação dos androgénios como a testosterona total, 4-androestenediona e/ou sulfato de dihidroepiandrosterona (DHEA-S));
3. Morfologia ovárica poliquística em ecografia (presença de mais de 12 folículos por ovário com dimensões entre 2 e 9 mm ou volume ovárico superior a 10 mm).

O diagnóstico de SOP implica a presença de, pelo menos, 2 destes 3 critérios.[2,3]

As diferentes conjugações dos critérios permitem classificar a SOP em quatro fenótipos:

A. Disfunção ovulatória, hiperandrogenismo e morfologia ovárica poliquística;
B. Disfunção ovulatória e hiperandrogenismo;
C. Hiperandrogenismo e morfologia ovárica poliquística;
D. Disfunção ovulatória e morfologia ovárica poliquística.[2,4]

A prevalência de cada fenótipo varia consoante a população em estudo, dependendo se a análise é realizada em populações não selecionadas ou em populações em seguimento por SOP.[4,5]

Estima-se que o fenótipo A esteja presente em 19% das populações não selecionadas, sendo mais prevalente em populações em seguimento, estando presente em até 50%.[5]

Contrariamente, para os fenótipos B e C a prevalência estimada para as populações em seguimento é inferior às populações não selecionadas (13% *vs* 25% e 14% *vs* 34%, respetivamente).[5]

Relativamente ao fenótipo D, a prevalência é semelhante em ambas as populações (17% *vs* 19%).[5] Um estudo realizado em 2020 na população pediátrica do Hospital de Braga (HB) com SOP corrobora estes dados.[6]

Na adolescência existem aspetos particulares que dificultam o diagnóstico de SOP, nomeadamente a presença fisiológica de hiperandrogenismo, oligo-anovulação e insulinorresistência, que são frequentes nos primeiros 2-3 anos após a menarca.[1]

Por esse motivo, têm sido feitos vários estudos na população pediátrica para identificar critérios de diagnóstico mais concretos, e recentemente, tem-se colocado em questão o uso da ecografia pélvica para diagnóstico de SOP nesta faixa etária.[7]

Esta entidade tem diferentes implicações a longo prazo, nomeadamente na função reprodutora (risco de anovulação e subfertilidade/infertilidade), no impacto psicológico (alterações da qualidade de vida e risco de depressão e/ou ansiedade) e no impacto metabólico (risco de excesso de peso/obesidade, diabetes *mellitus* tipo 2 (DM2), insulinorresistência e dislipidemia).[2]

Assim, o diagnóstico precoce de SOP torna-se fundamental para prevenir e controlar os fatores de risco supramencionados.[8]

Por outro lado, o diagnóstico incerto e precipitado acarreta ansiedade e gera *stress*, podendo, ainda, conduzir a tratamentos que condicionam custos e riscos desnecessários.[9]

O tratamento depende das características clínicas e analíticas e pretende minimizar as complicações a longo prazo.[10]

A base do tratamento assenta em medidas de estilo de vida (MEV) como perda ponderal, hábitos alimentares saudáveis e exercício físico regular.[9] A terapêutica farmacológica envolve fármacos insulinossensibilizantes (metformina), antiandrogénicos (espironolactona, citrato de ciproterona, flutamida ou finasterida) e/ou estroprogestativos como os contraceptivos orais combinados (COC).[10]

Os tratamentos sistémicos podem ser complementados com tratamentos tópicos ou mecânicos com alvo no hiperandrogenismo clínico. Para o hirsutismo pode ser aplicada depilação laser, a cera ou lâmina e cremes com eflornitina, no caso de hirsutismo facial. Tratamentos cosméticos tópicos ou isotretinoína podem ser utilizados no caso de acne.[8]

A correta caracterização clínica e analítica das adolescentes tem como objetivo adotar terapêuticas dirigidas e individualizadas, de acordo com o controlo de sinais e sintomas, prevenindo potenciais complicações.[10] Torna-se fundamental existirem recomendações concretas para que se possa tratar e monitorizar adequadamente esta população.

A pertinência deste estudo prende-se com a descrição da apresentação clínica e analítica das adolescentes diagnosticadas com

SOP, na avaliação das estratégias terapêuticas adotadas e na interpretação do seu impacto clínico e analítico.

Material e Métodos

Tipo de Estudo

Estudo retrospetivo, observacional, descritivo e analítico.

População e Amostra

Doentes do sexo feminino, com idade entre 12 e 18 anos, seguidas em consulta de Endocrinologia Pediátrica do HB, com diagnóstico de SOP, de acordo com os critérios de Roterdão.

Foram selecionadas as doentes que cumprissem os seguintes critérios de inclusão:

Diagnóstico de SOP (≥2 de 3 critérios de diagnóstico), pelo menos 2 anos após a menarca, e cuja primeira consulta decorreu entre 01/01/2012 e 01/07/2019.

Foram excluídas as doentes que apresentassem os seguintes critérios: ausência de dados necessários (por inexistência de registos clínicos ou perda de seguimento); realização de terapêutica prévia à primeira consulta; presença de doenças que pudessem mimetizar as características clínicas de SOP, nomeadamente, patologia da tiróide, hiperprolactinemia, hiperplasia congénita da suprarrenal ou síndrome de Cushing; consumo de fármacos que pudessem mimetizar as características clínicas da SOP, nomeadamente, a administração exógena de androgénios ou esteróides.

De uma amostra inicial de 99 doentes com diagnóstico de SOP no processo clínico, foram excluídos 15 casos: 4 doentes por terapêutica prévia à primeira avaliação, 2 adolescentes por apresentarem condições mimetizantes (hiperprolactinemia), 6 casos por terem apenas 1 consulta registada, e 3 casos por perda de seguimento. Desta forma, foram incluídas neste estudo 84 doentes.

Recolha de Dados

Os dados necessários para a caracterização do perfil clínico e analítico foram recolhidos através da consulta dos processos clínicos da população-alvo, informatizados no processo clínico eletrónico. Os parâmetros/variáveis avaliados foram os seguintes: 1) variáveis demográficas - idade da menarca, idade da primeira consulta, história familiar de SOP, comorbilidades prévias (diabetes *mellitus* tipo 2, hipertensão e dislipidemia), insulinorresistência (HOMA-IR e acantose nigricans), classificação do fenótipo de SOP e índice de massa corporal; 2) variáveis clínicas e analíticas na primeira consulta - disfunção ovulatória, hiperandrogenismo clínico (acne, hirsutismo pelo *score* de Ferriman-Gallwey (*score* FG) e alopecia) ou analítico (testosterona total, 4-androstenedione e DHEA-S), e ecografia; 3) variáveis clínicas e analíticas na consulta de seguimento aos 12 meses disfunção ovulatória, hiperandrogenismo clínico (acne, hirsutismo pelo *score* de Ferriman-Gallwey e alopecia) ou analítico (testosterona total, 4-androstenediona e DHEA-S), insulinorresistência (HOMA-IR e acantose nigricans), perfil lipídico e índice de massa corporal.

Considerações para as Variáveis em Estudo

A apresentação clínica de hiperandrogenismo foi avaliada pela presença de acne, alopécia e/ou hirsutismo (para a população mediterrânea, de acordo com o *score* FG, considerou-se hirsutismo para valores ≥9).[11] A evolução foi classificada como favorável se melhoria, ou desfavorável no caso de manutenção ou agravamento.

Relativamente ao hiperandrogenismo analítico, foram seguidos os seguintes valores de referência: Testosterona total 20,0-38,0 ng/dL, DHEA-S 44,0-248 µg/dL e 4 androstenediona 0,80-2,40 ng/dL.[12]

O padrão ecográfico de ovários poliquísticos foi estabelecido pela presença de mais de 12 folículos por ovário com dimensões entre 2 e 9 mm ou volume ovárico superior a 10 mm (sendo suficiente um ovário com este padrão para ser diagnóstico).[4]

Os parâmetros do perfil lipídico (colesterol total (CLT), *high density lipoprotein* (HDL), *low density lipoprotein* (LDL) e triglicerídeos (TG)) foram interpretados tendo em conta os valores definidos no Programa Nacional de Saúde Infantil e Juvenil.[13] Os valores definidos foram os seguintes: CLT: normal (<170 mg/dL), *borderline* (170-199 mg/dL) e elevado (≥200 mg/dL); HDL: normal (35,0 mg/dL) e baixo (<35,0 mg/dL); LDL: normal (<110 mg/dL), *borderline* (110-130 mg/dL) e elevado (≥130 mg/dL); TG: normal (150 mg/dL) e elevado (>150 mg/dL).

O percentil e Z-*score* de IMC foram definidos segundo a Organização Mundial de Saúde (OMS).[14]

O valor de *cut-off* para alterações glicídicas seguiu o estabelecido nas *guidelines* da ISPAD (International Society for Pediatric and Adolescent Diabetes) em que se considera anomalia da glicose em jejum um valor de glicemia ≥ 100 mg/dL.[15,16]

Foram consideradas valores de pré-hipertensão (HTA) quando ≥120/80 mmHg.[13]

Para os valores de HOMA-IR, considerou-se existir insulinorresistência se >3 em adolescentes normoponderais e >3,42 em adolescentes com excesso de peso/ obesidade. A resistência à insulina foi, ainda, avaliada pela presença ou ausência de acantose nigricans.[17]

Foram consideradas como tratamento não farmacológico as MEV saudáveis, com dieta e exercício, quando utilizadas em exclusividade.

Como tratamento dirigido ao hiperandrogenismo englobaram-se os tratamentos tópicos ou cosméticos com alvo dos casos de acne e hirsutismo e, ainda, os fármacos anti-androgénicos.

Em SOP é frequente o uso de tratamento combinado. No entanto, no contexto deste estudo apenas foram considerados os tratamentos individualmente, pelo que cada doente pode apresentar mais do que um tratamento.

Análise Estatística

A análise estatística foi realizada com recurso ao programa *Statistical Package for the Social Science*® (SPSS®), versão 28, e foi estabelecido um nível de significância estatística para $p<0,050$.[18-21]

Resultados

Caraterização da Amostra

Das 84 adolescentes analisadas, verificou-se que a mediana de idade da menarca foi de 11,0 anos (AIQ=1,00) e a mediana da idade da primeira consulta de 15,0 anos (AIQ=2,00). Existia história familiar de SOP em 10,7% (n=9).

A média do Z-*score* do IMC foi de 1,60 (DP=1,00), variando entre -1,00 e +3,50. Nesta amostra 32,1% das adolescentes eram normoponderais, 19,1% apresentavam excesso de peso e 48,8% apresentavam obesidade.

À admissão, nenhuma adolescente apresentava alterações do metabolismo glicídico, 25,0% (n=21) tinham pré-HTA, não se encontrando nenhuma sob medicação anti-hipertensora. Relativa-

mente ao perfil lipídico, 23,8% (n=20) apresentavam dislipidemia e 15,5% (n=13) apresentavam valores borderline, no entanto, nenhuma adolescente se encontrava sob medicação.

No que concerne à insulinorresistência, 42,9% (n=36) apresentavam acantose nigricans e das 63 doentes em que foi avaliado o HOMA-IR, 41,3% (n=26) tinham critérios de resistência à insulina.

A mediana do HOMA-IR foi 1,45 (AIQ=1,17) em adolescentes normoponderais e de 3,38 (AIQ=1,69) nas que apresentavam excesso de peso/obesidade, com diferenças significativas entre estes grupos (t(61)=3,72, p<0,001).

Em relação à apresentação fenotípica: 45,2% pertenciam ao fenótipo A, 34,5% ao fenótipo B e 20,2% ao fenótipo C.

Relativamente à disfunção ovulatória, 79,8% (n=67) das adolescentes tinham ciclos menstruais irregulares. No que diz respeito ao hiperandrogenismo, foram avaliadas as suas vertentes clínica e analítica. Em relação a critérios clínicos: 66,7% (n=56) apresentavam acne, 1,20% (n=1) alopecia e 51,2% (n=43) hirsutismo, sendo a mediana do *score* FG de 12,0 (AIQ=6,00). Quanto a critérios analíticos: de um universo de 76 doentes, 86,8% (n=66) apresentavam elevação da testosterona total, sendo o seu valor médio de 61,0 ng/dL (DP=23,1). Não se verificou existir associação entre os valores de testosterona superiores a 40,0 ng/dL (χ^2 =2,66; p=0,191; Φ=0,187), 50,0 ng/dL (χ^2 =1,02; p=0,448; Φ=0,116) ou 60,0 ng/dL (χ^2 =0,84; p=0,491; Φ=0,105) e a presença de hirsutismo. Segundo a curva ROC (Fig. 1), o ponto de corte é de 55,0 ng/dL. No entanto, a área sob a curva (ASC) é de 0,542 (IC 95%, [0,41;0,68], p=0,530), pelo que se demonstrou que os valores de testosterona total não são um bom preditor para a presença de hirsutismo.

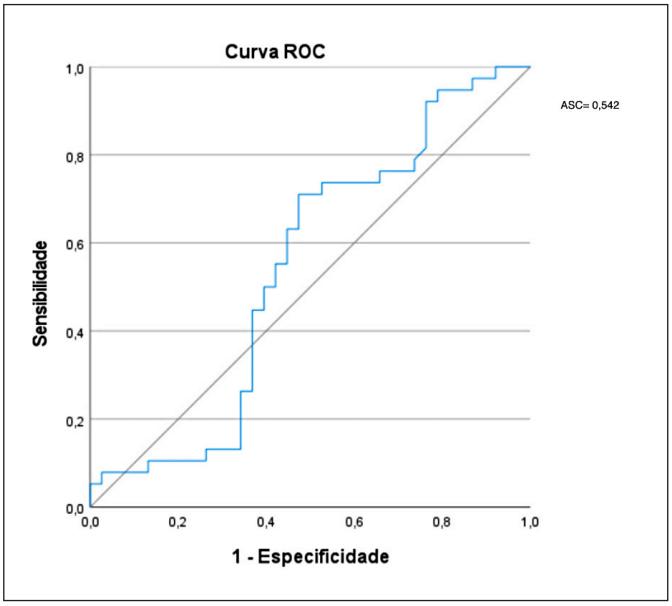


Figura 1. Representação gráfica da curva receiver operating characteristic (ROC) de testosterona total para hirsutismo.

ASC - área sob a curva.

De 67 doentes, 88,1% (n=59) apresentavam elevação da 4-androstenediona, sendo a sua mediana 3,90 ng/mL (AIQ=2,1). De um total de 72 adolescentes, a média do valor de DHEA-S foi 274,5 µg/dL (DP=107,6), correspondendo a critério de hiperandrogenismo em 62,5% (n=45).

Quanto à avaliação ecográfica, das 80 adolescentes que realizaram este exame, 68,8% (n=55) apresentavam morfologia ovárica poliquística.

Caracterização dos Tratamentos Instituídos

Na primeira consulta foram aplicados diferentes tratamentos às adolescentes como representado na Fig. 2A.

Das 84 doentes em estudo, 21,4% (n=18) realizaram apenas tratamento não farmacológico. Das adolescentes a realizar terapêutica farmacológica, 62,1% (n=41) realizaram COC, 40,9% (n=27) metformina e 28,8% (n=19) faziam terapêutica dirigida ao hiperandrogenismo.

De referir que 34,8% (n=23) das doentes sob terapêutica, faziam-na de forma combinada.

A terapêutica utilizada segundo o perfil fenotípico encontra-se representada na Fig. 2B.

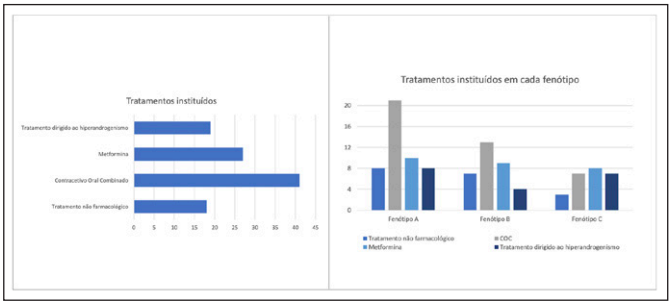


Figura 2. Representação gráfica dos tratamentos instituídos (esquerda) e distribuição dos diferentes tratamentos instituídos de acordo com o fenótipo da síndrome do ovário poliquístico (direita).

COC - contraceptivo oral combinado

Nota: No contexto deste estudo apenas foram considerados os tratamentos individualmente, pelo que cada doente pode apresentar mais do que um tratamento. Tratamento dirigido ao hiperandrogenismo inclui fármacos anti-androgénicos e tratamentos tópicos/cosméticos com alvo no acne ou hirsutismo; Medidas não farmacológicas corresponde à implementação de medidas de estilo de vida de forma exclusiva.

Avaliação do Impacto do Tratamento no Perfil Clínico e Analítico

Disfunção Ovulatória

Na consulta dos 12 meses, 2,38% (n=2) das adolescentes apresentaram irregularidades menstruais de novo, assim 82,1% (n=69) das doentes foram avaliadas para irregularidades menstruais, e destas, 79,7% (n=55) iniciaram tratamento farmacológico. Como detalhado na Tabela 1, verificou-se associação entre as medidas farmacológicas e a regularização do ciclo menstrual (χ^2 =6,739, p=0,014, Φ=-0,313), nomeadamente com o uso de COC (χ^2=14,486, p<0,001, Φ=0,458).

Das adolescentes sem regularização dos ciclos, 20,8% (n=5) realizavam COC, com boa adesão e sem efeitos laterais do tratamento, tendo-o iniciado, em média, há 5 meses (DP=2,3).

Entre as adolescentes que realizavam COC, as que apresentaram evolução favorável, tinham uma média de duração de tratamento (M=9,77; DP=4,73) superior às doentes com evolução desfavorável (M=5,00; DP=2,34), sendo esta diferença significativa (t(10,4)=-3,54, p=0,005, d=1,056).

Hiperandrogenismo

Acne

Foram avaliadas para a evolução da acne 69,0% (n=58) das adolescentes, sendo que destas 3,4% (n=2) apresentaram acne de

Tabela 1. Relação da evolução da disfunção ovulatória com os diferentes tratamentos instituídos.

Total (n=69)		Disfunção Ovulatória						
		Evolução Desfavorável		Evolução Favorável		Qui-quadrado	*p*	Phi
		n	%	N	%			
Tratamento não farmacológico	**sim**	**9**	**37,5%**	**5**	**11,1%**	**6,739**	**0,014**	**-0,313**
	não	**15**	**62,5%**	**40**	**88,9%**			
Contracetivo Oral Combinado	**sim**	**5**	**20,8%**	**31**	**68,9%**	**14,486**	**<0,001**	**0,458**
	não	**19**	**79,2%**	**14**	**31,1%**			
Metformina	sim	7	29,2%	14	31,1%	0,028	>0.999	0,020
	não	17	70,8%	31	68,9%			
Tratamento dirigido ao hiperandrogenismo	sim	5	20,8%	8	17,8%	[a]	0,756	-0,037
	não	19	79,2%	37	82,2%			

[a] Foi utilizado o Teste exato de Fisher quando a contagem esperada era menor que 5 em mais do que 20% das células. Foi realizado um CrossTabs para obter o valor de qui-quadrado, *p* e Phi. Apresenta-se a **negrito** as varáveis em que $p<0,05$.

Nota: No contexto deste estudo apenas foram considerados os tratamentos individualmente, pelo que cada doente pode apresentar mais do que um tratamento. Tratamento dirigido ao hiperandrogenismo inclui fármacos anti-androgénicos e tratamentos tópicos/cosméticos com alvo no acne ou hirsutismo; Medidas não farmacológicas corresponde à implementação de medidas de estilo de vida de forma exclusiva.

Tabela 2. Relação da evolução de acne, da variação do *Score* de Ferriman-Gallwey (*Score* FG), Testosterona Total, 4-androstenediona e sulfato de Dihidroepiandrosterona (DHEA-S) com os diferentes tratamentos instituídos.

Total (n=58)		Acne						
		Evolução Desfavorável		Evolução Favorável		Qui-quadrado	*p*	Phi
		n	%	N	%			
Tratamento não farmacológico	Sim	6	18,8%	3	11,5%	[a]	0,495	-0,099
	Não	26	81,3%	23	88,5%			
Contracetivo Oral Combinado	Sim	15	46,9%	17	65,4%	1,987	0,191	0,185
	Não	17	53,1%	9	34,6%			
Metformina	Sim	9	28,1%	10	38,5%	0,696	0,574	0,110
	Não	23	71,9%	16	61,5%			
Tratamento dirigido ao hiperandrogenismo	Sim	11	34,4%	5	19,2%	1,647	0,246	-0,169
	não	21	65,6%	21	80,8%			

Total (n=61)	Variação do *Score* FG								
	sim	não	Diferença entre médias	BCa IC 95%		t	gl	*p*	d
				Inferior	Superior				
Tratamento não farmacológico	-1,00 (2,35)	-1,56 (2,48)	-0,559	-1,950	1,290	-0,608	41	0,550	-0,228
Contracetivo Oral Combinado	-1,67 (2,68)	-1,16 (2,12)	0,509	-0,930	1,900	0,677	41	0,502	0,208
Metformina	-1,09 (1,45)	-1,56 (2,70)	-0,472	-1,608	0,565	-0,550	41	0,585	-0,192
Tratamento dirigido ao hiperandrogenismo	-1,71 (2,10)	-1,31 (2,61)	0,404	-1,580	1,928	0,506	41	0,616	0,163

Total (n=41)	Variação da testosterona total						
	sim	não	Diferença entre médias	t	gl	*p*	d
Tratamento não farmacológico	-6,70 (33,7)	-16,9 (29,9)	-10,230	-0,911	39	0,368	-0,331
Contracetivo Oral Combinado	-16,9 (33,1)	-12,0 (29,0)	4,893	0,504	39	0,617	0,157
Metformina	-11,3 (27,5)	-15,9 (32,6)	-4,588	-0,439	39	0,663	-0,147
Tratamento dirigido ao hiperandrogenismo	-12,8 (15,5)	-14,8 (33,7)	-2,035	-0,166	39	0,869	-0,065

Tabela 2. Relação da evolução de acne, da variação do *Score* de Ferriman-Gallwey (*Score* FG), Testosterona Total, 4-androstenediona e sulfato de Dihidroepiandrosterona (DHEA-S) com os diferentes tratamentos instituídos. (Continuação)

Total (n=35)	Variação da 4-androstenediona								
	sim	não	Diferença entre médias	BCa IC 95%		t	gl	*p*	d
				Inferior	Superior				
Tratamento não farmacológico	-0,640 (1,53)	1,87 (16,4)	2,51	-1,51	9,33	0,453	33	0,474	0,175
Contracetivo Oral Combinado	-1,44 (2,40)	3,22 (18,6)	4,66	-0,324	12,8	0,962	33	0,436	0,329
Metformina	6,12 (23,9)	-1,33 (2,07)	-7,45	-25,4	0,484	-1,08	11,1	0,455	-0,536
Tratamento dirigido ao hiperandrogenismo	-1,56 (0,984)	2,05 (16,1)	3,61	-0,169	10,8	0,628	33	0,445	0,253

Total (n=34)	Variação da DHEA-S						
	sim	não	Diferença entre médias	t	gl	*p*	d
Tratamento não farmacológico	21,8 (83,3)	5,59 (88,8)	-16,2	-0,478	32	0,636	-0,186
Contracetivo Oral Combinado	24,4 (97,3)	-1,61 (77,6)	-26,1	-0,870	32	0,391	-0,300
Metformina	16,2 (94,8)	7,26 (84,7)	-8,94	-0,271	32	0,788	-0,102
Tratamento dirigido ao hiperandrogenismo	**-26,1 (29,0)**	**19,2 (94,0)**	**45,4**	**2,15**	**30,7**	**0,040**	**0,529**

Acne: [a] Foi utilizado o Teste exato de Fisher quando a contagem esperada era menor que 5 em mais do que 20% das células. Foi realizado um *crosstabs* para obter o valor de qui-quadrado, *p* e Phi.

Variação do *Score* FG/ testosterona total/ 4-androstenediona/ DHEA-S: A variação do *Score* FG apresenta-se sob a forma de média (desvio padrão). Foi utilizado o teste t-*student* para obter o valor de t e *p*, o d de Cohen foi calculado através da média e desvio padrão dos grupos; viés corrigido e acelerado (BCa); graus de liberdade (gl).

Apresenta-se a **negrito** as varáveis em que $p<0,050$.

Nota: No contexto deste estudo apenas foram considerados os tratamentos individualmente, pelo que cada doente pode apresentar mais do que um tratamento. Tratamento dirigido ao hiperandrogenismo inclui fármacos anti-androgénicos e tratamentos tópicos/cosméticos com alvo no acne ou hirsutismo; Medidas não farmacológicas corresponde à implementação de medidas de estilo de vida de forma exclusiva.

novo. Verificou-se uma evolução favorável em 44,8% (n=26), não se identificando associação significativa com o tratamento instituído, como reportado na Tabela 2.

Hirsutismo

Na consulta de seguimento, das 43 adolescentes com diagnóstico de hirsutismo à admissão, 11,6% (n=5) deixaram de ter critérios de hirsutismo e 39,5% (n=17) baixaram a pontuação do *score* FG entre os momentos pré e pós tratamento, com variação mínima de -10 e máxima de 2. Não se identificou associação significativa com o tratamento instituído, como reportado na Tabela 2.

Testosterona Total

A variação da testosterona total foi avaliada em 41 adolescentes. Verificou-se uma melhoria em 68,3% (n=28), sendo a variação média de -14,4 (DP=30,8). Não se obtiveram diferenças significativas em relação à variação média da testosterona entre os tratamentos realizados, como representado na Tabela 2.

4-androstenediona

A variação da 4-androstenediona foi avaliada em 35 adolescentes, das quais 65,7% (n=23) apresentaram melhoria. A mediana desta variação foi de -0,820 (AIQ=2,26). A média da variação da 4-androstenediona não diferiu significativamente com os diferentes tratamentos instituídos, como detalhado na Tabela 2.

Sulfato de Dihidroepiandrosterona

Na consulta de seguimento, a DHEA-S foi avaliada em 34 adolescentes, tendo-se verificado evolução desfavorável em 50,0% (n=17). A média da diferença entre os momentos pré e pós tratamento foi de 9,89 (DP=86,4), o que traduz agravamento deste parâmetro. Como descrito na Tabela 2, a média da variação da DHEA-S nas adolescentes que realizaram tratamento dirigido ao hiperandroginismo (M=-26,1, DP=29,0) traduz melhoria e é significativamente diferente daquelas que não realizaram este tratamento (M=19,2,DP=94,0) (t(30,7)=2,15, p=0,040, d=0,529).

Insulinorresistência

Das 37 adolescentes com avaliação da acantose nigricans aos 12 meses, 27,0% (n=10) apresentavam evolução favorável, não se identificando associação significativa com o tratamento instituído, como representado na Tabela 3.

Foram avaliadas 37 adolescentes quanto à evolução do índice HOMA-IR. Destas, 40,5% (n=15) apresentavam insulinorresistência prévia, sendo que 66,7% (n=10) mantiveram critérios de insulinorresistência. Das doentes avaliadas, 8,11% (n=3) apresentavam insulinorresistência de novo. A mediana da variação deste índice foi de -0,101 (AIQ=1,19).

Tal como representado na Tabela 3, o uso de tratamento farmacológico (M=-0,515, DP=1,68) demonstrou uma melhoria significativamente superior comparativamente ao uso de medidas não farmacológicas (M=0,760, DP=1,41) (Bca IC 95% [-2,35; -0,280], t(35)=2,05, p=0,026, d=-0,785). Destaca-se uma melhoria significativa com o uso de metformina (M=-1,42, DP=1,91) (Bca IC 95% [0,761; 2,94], t(35)=3,46, p=0,013, d=1,22).

Tabela 3. Relação da evolução da acantose nigricans, variação do HOMA-IR, perfil lipídico e média do z-score do Índice de Massa Corporal (IMC) com os diferentes tratamentos instituídos.

Total (n=37)		Acantose nigricans						
		Evolução Desfavorável		Evolução Favorável		Qui-quadrado	*p*	Phi
		n	%	N	%			
Tratamento não farmacológico	sim	7	25,9%	2	20,0%	[a]	>0,999	-0,061
	não	20	74,1%	8	80,0%			
Contracetivo Oral Combinado	sim	10	37,0%	4	40,0%	[a]	>0,999	0,027
	não	17	63,0%	6	60,0%			
Metformina	sim	10	37,0%	6	60,0%	[a]	0,274	0,206
	não	17	63,0%	4	40,0%			
Tratamento dirigido ao hiperandrogenismo	sim	3	11,1%	3	30,0%	[a]	0,313	0,228
	não	24	88,9%	7	70,0%			

Total (n=35)	HOMA-IR							
	sim	não	Diferença entre médias	BCa IC 95%		t	gl	*p*	d
				Inferior	Superior				
Tratamento não farmacológico	**0,760 (1,41)**	**-0,515 (1,68)**	**-1,27**	**-2,35**	**-0,280**	**-2,05**	**35**	**0,026**	**-0,785**
Contracetivo Oral Combinado	-0,267 (1,58)	-0,151 (1,82)	0,116	-0,967	1,21	0,205	35	0,854	0,067
Metformina	**-1,42 (1,91)**	**0,380 (1,24)**	**1,80**	**0,761**	**2,94**	**3,46**	**35**	**0,013**	**1,22**
Tratamento dirigido ao hiperandrogenismo	0,153 (1,10)	-0,303 (1,83)	-0,457	-1,56	0,516	-0,670	35	0,375	-0,268

Total (n=51)		Perfil Lipídico						
		Evolução Desfavorável		Evolução Favorável		Qui-quadrado	*p*	Phi
		n	%	N	%			
Tratamento não farmacológico	sim	9	22,0%	2	20,0%	[a]	>0,999	
	não	32	78,0%	8	80,0%			-0,019
Contracetivo Oral Combinado	sim	**24**	**58,5%**	**2**	**20,0%**	[a]	**0,038**	**-0,306**
	não	**17**	**41,5%**	**8**	**80,0%**			
Metformina	sim	12	29,3%	4	40,0%	[a]	0,705	0,092
	não	29	70,7%	6	60,0%			
Tratamento dirigido ao hiperandrogenismo	sim	9	22,0%	3	30,0%	[a]	0,682	0,075
	não	32	78,0%	7	70,0%			

Total (n=84)	Variação da média do z-*score* do IMC						
	sim	não	Diferença entre médias	t	gl	*p*	d
Tratamento não farmacológico	**-0,315 (0,352)**	**-0,086 (0,303)**	**0,229**	**2,740**	**82**	**0,007**	**0,729**
Contracetivo Oral Combinado	**-0,064 (0,327)**	**-0,203 (0,314)**	**-0,139**	**-1,99**	**82**	**0,049**	**-0,435**
Metformina	-0,155 (0,234)	-0,126 (0,363)	0,029	0,377	82	0,707	0,088
Tratamento dirigido ao hiperandrogenismo	-0,041 (0,225)	-0,163 (0,347)	-0,122	-1,44	82	0,153	-0,376

Acantose nigricans e Perfil lipídico: a Foi utilizado o Teste exato de Fisher quando a contagem esperada era menor que 5 em mais do que 20% das células. Foi realizado um *crosstabs* para obter o valor de qui-quadrado, *p* e Phi.

Variação do HOMA-IR e variação da média do z-*score* do IMC: apresenta-se sob a forma de média (desvio padrão). Foi utilizado o teste t-*student* para obter o valor de t e *p*, o d de Cohen foi calculado através da média e desvio padrão dos grupos; viés corrigido e acelerado (BCa); graus de liberdade (gl).

Apresenta-se a **negrito** as varáveis em que $p<0,050$.

Nota: No contexto deste estudo apenas foram considerados os tratamentos individualmente, pelo que cada doente pode apresentar mais do que um tratamento. Tratamento dirigido ao hiperandrogenismo inclui fármacos anti-androgénicos e tratamentos tópicos/cosméticos com alvo no acne ou hirsutismo; Medidas não farmacológicas corresponde à implementação de medidas de estilo de vida de forma exclusiva.

A diferença do HOMA-IR entre o valor aos 12 meses e da admissão foi, em média, de 0,230±1,63 no fenótipo A, -0,740±2,02 no fenótipo B e -0,204±1,05 no fenótipo C. Isto é, o valor deste *score* aumentou, em média, no fenótipo A e as meninas com fenótipo B e C pontuaram menos no *score* do HOMA-IR na consulta dos 12 meses. No entanto não se encontrou correlação entre o HOMA-IR e o fenótipo apresentado.

Perfil Lipídico

A evolução do perfil lipídico foi avaliada em 51 adolescentes, sendo que apenas 19,6% (n=10) apresentaram evolução favorável. Como detalhado na Tabela 3, as adolescentes que realizaram COC têm uma evolução desfavorável (TEF, p=0,038, Φ=-0,306).

Índice de Massa Corporal

A variação da média do *z-score* do IMC foi -0,135 (DP=0,326), o que corresponde a uma melhoria média do percentil do IMC. Como explanado na Tabela 3, esta melhoria foi significativa com o uso de tratamento não farmacológico (M=-0,315, DP=0,352), em comparação com o uso de fármacos (M=-0,086, DP=0,303) (t(82)=2,740, p=0,007, d=0,729). Demonstrou-se ainda uma melhoria significativa sem o uso de COC (M=-0,203, DP=0,314) (t(82)=-1,99, p=0,049, d=-0,435).

Discussão

Análise Crítica dos Dados Demográficos e Apresentação Clínica e Analítica

A SOP encontra-se ainda pouco estudada na população pediátrica, o que levanta várias questões no seu diagnóstico e abordagem.

A distribuição etária da primeira consulta e idade da menarca são concordantes com as descritas noutros estudos sobre SOP, reforçando o atraso entre o aparecimento dos sintomas, o diagnóstico e instituição de tratamento.[22] Contudo, a história familiar de SOP foi inferior à verificada na literatura.[23]

Relativamente às comorbilidades prévias, nesta amostra não foi identificada nenhuma menina com anomalia da tolerância à glicose ou DM2, contrariamente ao descrito na literatura de 25%-40%.[4,9,24] No entanto, tendo em conta a fisiopatologia da SOP, é expectável que nos próximos anos se verifique um perfil metabólico alterado nestas doentes.[2,9] Em concordância, nesta amostra foram identificadas, na primeira consulta, 25% de doentes com pré-HTA e 23,8% com dislipidemia e cerca de 40% com insulinorresistência.

Neste estudo, verificou-se uma elevada prevalência de excesso de peso/obesidade, o que apesar de preocupante, está de acordo com o descrito na literatura. A média do Z-*score* do IMC foi de 1,60, dado tratar-se de uma variável que segue a curva normal, este Z-*score* equivale ao percentil 95, o que também é concordante com o descrito.[1,8,22]

Estudos demonstraram que a apresentação mais comum de SOP, presente em 80% dos casos, é o hiperandrogenismo, manifestado sobretudo sob a forma de hirsutismo.[25,26] Este facto também se verificou na amostra deste estudo, uma vez que todas as adolescentes se apresentaram com hiperandrogenismo clínico e/ou analítico, não sendo identificada nenhuma adolescente com o fenótipo D (caracterizado por disfunção ovulatória e ovários poliquísticos). A distribuição da prevalência dos restantes fenótipos encontra-se de acordo com o esperado para populações com diagnóstico de SOP.[5] A falta de representatividade do fenótipo D poderá ser justificada por subdiagnóstico, pelo facto de exigir um meio complementar de diagnóstico nem sempre disponível, e por ser mais frequente nas mulheres em idade reprodutiva que recorrem à consulta no contexto de infertilidade. Não obstante, nesta amostra quase a totalidade das doentes realizaram este exame e 68,8% apresentavam critérios diagnósticos de SOP, uma vez mais concordante com o estudo de Fitzgerald *et al*.[22]

Tendencialmente os interlúnios tornam-se regulares cerca de um ano após a menarca.[4] Nesta amostra populacional, avaliada mais de 2 anos após a menarca, 79,8% das adolescentes tinham ciclos menstruais irregulares, tal como esperado em doentes com SOP.

Como já referido, o hiperandrogenismo afeta a grande maioria das adolescentes com SOP, podendo manifestar-se clinicamente, sob a forma de hirsutismo, acne e/ou alopecia. Das adolescentes analisadas, apenas 1,19% (n=1) apresentava alopecia, o que é consistente com uma menor expressão nesta faixa etária.[11] Em relação à acne, neste estudo a sua prevalência foi de 66,7% e a literatura mostra uma prevalência de 35%-90% na população geral e de 15%-25% na população com SOP.[23] A literatura refere que se deve considerar associado a hiperandrogenismo se a acne for classificada como: 1) inflamatória moderada (> 10 lesões faciais), 2) inflamatória grave, ou 3) moderada a grave, persistente, com fraca resposta ao tratamento tópico ou oral. Neste estudo foi apenas considerada a presença de "acne" nos registos (dado que a classificação esteve sempre ausente), o que pode constituir um viés.[27]

Como esperado, o hirsutismo foi a manifestação mais comum.[24] Analiticamente, valores diagnósticos de hiperandrogenismo estiveram também presentes na maioria das doentes estudadas. Não se verificou existir associação entre os valores de testosterona superiores a 40, 50 ou 60 ng/dL e a presença de hirsutismo, o que constitui um ponto de debate em vários estudos internacionais. A curva ROC mostrou um ponto de corte de testosterona total de 55,0 ng/dL, o que está de acordo com os valores de referência, contudo não se comprovou ser um bom preditor.[8,28-30]

Análise Crítica dos Tratamentos Instituídos

A base do tratamento de SOP assenta em MEV, nomeadamente alimentação equilibrada e exercício físico regular.[9,31,32] Estas recomendações foram transmitidas a todas as adolescentes, sendo que 21,4% as mantiveram de forma isolada, sem iniciar terapêutica farmacológica.

Apesar de existirem ainda poucos estudos em adolescentes com SOP, os COC representam a primeira linha de tratamento farmacológico para irregularidades menstruais e/ou hiperandrogenismo.[8,10,28-30] Deve ser privilegiada a combinação com progestativos com maior atividade antiandrogénica, e deve ser tido em consideração se a adolescente já iniciou atividade sexual e se necessita de contraceção, para evitar gravidez na adolescência. Tal como o esperado, das adolescentes a realizar terapêutica farmacológica, 62,1% realizavam COC.

O hiperandrogenismo tem expressão clínica e analítica, pelo que se utilizam tratamentos tópicos/cosméticos e fármacos anti-androgénicos, sendo que 28,8% das adolescentes realizavam terapêutica dirigida ao hiperandroginismo.[33] Os anti-androgénicos devem ser sempre utilizados em associação com COC devido ao seu potencial teratogénico e a decisão de iniciar estes fármacos depende da severidade dos sintomas.[8]

Segundo a literatura, o fármaco insulinossensibilizante mais utilizado é a metformina, o que está de acordo com esta amostra,

com 40,9% das adolescentes medicadas realizarem este fármaco.[10]

Uma vez que a SOP tem diferentes características clínicas com objetivos de tratamento diferentes, é frequente o uso de terapêutica combinada de forma a atuar nas diferentes manifestações. Assim, nesta amostra 34,8% das adolescentes sob terapêutica, faziam-na de forma combinada.

Análise Crítica do Seguimento e Evolução dos Perfis Clínico e Analítico

Disfunção Ovulatória

Têm sido reportadas associações entre MEV e a regularização dos ciclos menstruais. No entanto, nesta amostra esse efeito não se verificou, o que poderá ser explicado pelo reduzido número de doentes sob estas medidas de forma isolada.[9]

Detetou-se uma relação entre o tratamento farmacológico e a regularização do ciclo menstrual. Dentro destas medidas farmacológicas destaca-se a interdependência entre o uso de COC e a regularização dos interlúnios, tal como seria expectável e que reforça a adesão e cumprimento terapêutico desta população.[9] No entanto, nem todas as doentes que realizavam COC obtiveram regularização dos interlúnios. Este facto pode ser explicado pela curta duração do tratamento, uma vez que estas doentes o realizavam, em média, há menos tempo (M=5,00), diferindo significativamente das doentes que obtiveram melhoria (M=9,77). É expectável que com o tratamento continuado se verifique uma melhoria nestas doentes. De salientar que não foram avaliados outros fatores que podem contribuir para a existência de hemorragia ou spotting, como o uso correto de COC com toma regular, alterações do trânsito intestinal ou tabagismo.

Hiperandrogenismo

Das adolescentes em estudo, 44,8% obtiveram melhoria da acne ao longo do seguimento. No entanto, contrariamente ao esperado, neste estudo não se verificou associação significativa de evolução favorável do acne com os tratamentos instituídos, o que poderá ser explicado pelo reduzido número da amostra e pela ausência de classificação da acne.[24]

Como esperado, não foram constados mais casos de alopecia para além do inicialmente reportado nem alterações da sua apresentação.[11]

Apesar de se ter verificado uma evolução favorável em quase 40% das doentes com hirsutismo, apenas 5 adolescentes deixaram de ter critérios.

Na literatura está reportada a associação do uso prolongado destes fármacos com a diminuição dos valores de 4-androstenediona e DHEA-S, o que não se verificou neste estudo e que pode ser explicado pelo curto tempo de *follow-up*.[28]

Relativamente à DHEA-S, metade da amostra evoluiu de forma desfavorável, e a média da diferença entre os momentos pré e pós tratamento revelou agravamento deste parâmetro. No entanto, como referido previamente, não foi constatado agravamento do hirsutismo, acne ou alopecia, e assim a elevação da DHEA-S poderá estar associada a um aumento fisiológico próprio da puberdade, sem tradução clínica.

O tratamento dirigido ao hiperandrogenismo promoveu uma melhoria significativa dos valores de DHEA-S, tendo esta relação um efeito alto, tal como o descrito noutros estudos internacionais.[9]

Insulinorresistência

Não se verificou melhoria significativa da acantose nigricans com nenhum dos tratamentos, tal como seria expectável, uma vez que o tempo de *follow-up* é curto e esta alteração cutânea é de muito difícil resolução.[34]

A mediana da variação do HOMA-IR foi de -0,101, o que traduz uma melhoria ligeira deste parâmetro.

O tratamento farmacológico associou-se a melhoria significativa do HOMA-IR e, tal como descrito no estudo de Khalifah *et al*, o uso de metformina traduziu uma melhoria significativamente superior aos restantes tratamentos.[24]

Perfil Lipídico

Existiu uma evolução favorável do perfil lipídico em apenas 19,6% das adolescentes. No entanto, a maioria apresentou uma evolução desfavorável, sobretudo quando as adolescentes realizaram COC, o que corrobora o reportado por outros estudos.[9] De salientar que os novos progestativos têm um perfil cardiovascular mais seguro sem alterações do perfil lipoproteico.

Índice de Massa Corporal

A variação do *z-score* do IMC traduziu uma melhoria do IMC, tendo evoluído para um *z-score* de 1,45 que, dado tratar-se de uma variável que segue a curva normal, equivale ao percentil 92.

Esta variação foi superior nas doentes que faziam tratamento não farmacológico, o que seria expectável com a combinação de exercício físico e uma alimentação equilibrada. Penã *et al* descreveram que as MEV excediam os tratamentos farmacológicos isolados e podiam potenciar os seus efeitos quando usados em combinação.[27] Neste estudo constatou-se que o uso isolado de MEV foi superior ao tratamento farmacológico, o que pode ser explicado pelo empenho da população e pela ausência da ideia de que os fármacos irão resolver isoladamente o problema. Também se constatou melhoria significativa sem o uso de COC, tal como já descrito noutros estudos. De referir que os métodos contracetivos (exceto o acetato de medroxiprogesterona) não provocam alterações de peso, sendo este um dos mitos e receios que leva à não adesão terapêutica e risco de gravidez na adolescência.

Forças e Limitações do Estudo

A amostra analisada é constituída por 84 doentes com diagnóstico de SOP sendo reduzida e com risco de não ser representativa da população. No entanto, tratando-se de uma síndrome que afeta, na população pediátrica, até 11,0% das adolescentes, é justificável obter-se uma amostra reduzida.

Os critérios de diagnóstico na população pediátrica são controversos e tem mudado ao longo dos anos.

Uma outra limitação é o tipo de estudo realizado – retrospetivo, estando dependente dos registos clínicos, os quais, nem sempre são completos e detalhados. De referir que as variáveis acantose nigricans e acne não estavam classificadas de acordo com escalas de avaliação, dificultando a sua análise. A classificação do hirsutismo foi feita com base no *score* FG que para além de ser subjetivo, é dependente do observador e de difícil aplicação uma vez que a maioria das adolescentes quando recorre à consulta já fez tratamento estético.

Neste estudo apenas foram considerados os tratamentos individualmente, estando algumas doentes sob combinações de diferentes tratamentos, sendo este um fator confundidor.

Salienta-se que existem poucos estudos sobre SOP na população pediátrica, nomeadamente em Portugal e a grande maioria da literatura utilizada sobre o tema diz respeito à população adulta internacional.

Conclusão

Nesta amostra constatou-se uma percentagem considerável de pacientes com excesso de peso/obesidade, insulinorresistência e alterações metabólicas, e a presença destes fatores de risco em idade pediátrica alerta para a necessidade de uma intervenção precoce e atempada por forma a evitar complicações futuras.

Foram encontradas associações importantes que reforçam o conhecimento da literatura, nomeadamente regularização dos ciclos menstruais com o uso prolongado de COC, reforço das MEV e relação positiva entre MEV e o uso de metformina com a melhoria do perfil metabólico. Deve ser feita monitorização do IMC e perfil lípidico pelo risco aumentado de síndrome metabólico e consequências futuras.

Demonstrou-se também que o tratamento não farmacológico foi o que afetou mais positivamente o IMC, dai a necessidade de reforçar os programas nutricionais e de exercício físico.

No entanto, devido ao reduzido tamanho amostral, não se conseguiram obter indicações robustas sobre qual o tipo de tratamento mais adequado a cada fenótipo de SOP.

Salienta-se a importância do estabelecimento de planos de acompanhamento específicos e individualizados para garantir uma maior adesão e eficácia terapêutica.

Assim, será importante uma ampliação deste estudo, por exemplo, através de uma análise multicêntrica nacional, a fim de estabelecer melhor o paradigma da SOP em idade pediátrica em Portugal. Seria também importante avaliar o impacto psicológico de SOP nas adolescentes em estudos prospetivos futuros.

Contributorship Statement / Declaração de Contribuição:

ALD e MMG: Foram responsáveis pela conceção e desenho do estudo, interpretação dos dados e redação do artigo.
ALD: Foi responsável pela recolha e análise dos dados.
OM, SM, AA: Foram responsáveis pelo conteúdo intelectual importante. .
MM: Foi responsável pela revisão crítica do conteúdo.
Todos os autores aprovaram a versão final a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Louwers YV, Laven JSE. Characteristics of polycystic ovary syndrome throughout life. Ther Adv Reprod Health. 2020;14:2633494120911038. doi: 10.1177/2633494120911038.
2. Azziz R. Polycystic Ovary Syndrome. Obstet Gynecol. 2018;132:321-36. doi: 10.1097/AOG.0000000000002698.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19:41-7. doi: 10.1093/humrep/deh098.
4. Neven ACH, Laven J, Teede HJ, Boyle JA. A Summary on Polycystic Ovary Syndrome: Diagnostic Criteria, Prevalence, Clinical Manifestations, and Management According to the Latest International Guidelines. Semin Reprod Med. 2018;36:5-12. doi: 10.1055/s-0038-1668085.
5. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106:6-15. doi: 10.1016/j.fertnstert.2016.05.003.
6. Nogueira-Lima I. Síndrome do ovário poliquístico na adolescência: perfil metabólico e qualidade de vida de diferentes fenótipos clínicos [Mestrado Integrado em Medicina]. Porto: Universidade do Porto;2020.
7. Senaldi L, Gopi RP, Milla S, Shah B. Is ultrasound useful in the diagnosis of adolescents with polycystic ovary syndrome? J Pediatr Endocrinol Metab. 201;28:605-12. doi: 10.1515/jpem-2014-0307.
8. Trent M, Gordon CM. Diagnosis and Management of Polycystic Ovary Syndrome in Adolescents. Pediatrics. 2020;145:S210-8. doi: 10.1542/peds.2019-2056J.
9. Ibáñez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm Res Paediatr. 2017;88:371-95. doi: 10.1159/000479371.
10. Conlon JL, Malcolm S, Monaghan M. Diagnosis and treatment of polycystic ovary syndrome in adolescents. JAAPA. 2021;34:15-22. doi: 10.1097/01.JAA.0000791468.37054.5d.
11. Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibáñez L, Pena A, Horikawa R, Gomez-Lobo V, Joel D, Tfayli H, Arslanian S, Dabadghao P, Garcia Rudaz C, Lee PA. The Diagnosis of Polycystic Ovary Syndrome during Adolescence. Horm Res Paediatr. 2015; 1. doi: 10.1159/000375530.
12. Hancock M. Endocrinology expected values and S.I. unit conversion tables. 2016
13. Direção Geral da Saúde. Programa Nacional de Saúde Infantil e Juvenil. Lisboa: DGS; 2013.
14. World Health Organiztion. Growth Reference data for 5 to 19 years. BMI for age. Geneve: WHO; 2007.
15. Tagi VM, Giannini C, Chiarelli F. Insulin Resistance in Children. Front Endocrinol. 2019;10:342. doi: 10.3389/fendo.2019.00342.
16. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2018;19:7-19. doi: 10.1111/pedi.12773.
17. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53:251-60. doi: 10.1007/s00592-015-0782-4.
18. Discovering Statistics Using IBM SPSS Statistics. 5th ed. London: SAGE Publications Ltd; 2018.
19. Kotrlik JW, Williams HA, Jabor MK. Reporting and interpreting effect size in quantitative agricultural education research. J Agricultural Educ.

2011;52:132-42. doi:10.5032/jae.2011.01132.
20. Sawilowsky S. New effect size rules of thumb. J Modern Applied Statist Methods. 2009;8:597-99. doi:10.22237/jmasm/1257035100.
21. Hoo ZH, Candlish J, Teare D. What is an ROC curve?. Emerg Med J.2017; 34:357–59. doi:10.1136/emermed-2017-206735
22. Fitzgerald S, Stamoulis C, Gooding HC, DiVasta AD. Characteristics of Adolescents with Differing Polycystic Ovary Syndrome Phenotypes. J Pediatr Adolesc Gynecol. 2020;33:697-702. doi: 10.1016/j.jpag.2020.08.015.
23. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91:4237-45. doi: 10.1210/jc.2006-0178.
24.. Al Khalifah RA, Florez ID, Dennis B, Thabane L, Bassilious E. Metformin or Oral Contraceptives for Adolescents With Polycystic Ovarian Syndrome: A Meta-analysis. Pediatrics. 2016;137:e20154089. doi: 10.1542/peds.2015-4089.
25. Emans SI. Androgen Abnormalities in the Adolescent Girl., Emans SI, editor.. Pediatric and Adolescent Gynecology. Philadelphia: Wolters Kluwer; 2005.
26. Rosenfield RL. The Diagnosis of Polycystic Ovary Syndrome in Adolescents. Pediatrics. 2015;136:1154-65. doi: 10.1542/peds.2015-1430.
27. Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020;18:72. doi: 10.1186/s12916-020-01516-x.
28. Teede H, Misso M, Costello M, Dokras A, Laven J, Moran L,et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome.[accessed Dez 2020] Available from: http://repositorio.uchile.cl/handle/2250/167630
29. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98:4565-92. doi: 10.1210/jc.2013-2350. Erratum in: J Clin Endocrinol Metab. 2021;106:e2462.
30. Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Pract Res Clin Obstet Gynaecol. 2018;48:103-14. doi: 10.1016/j.bpobgyn.2017.08.008.
31. DiVall S, Merjaneh L. Adolescent Polycystic Ovary Syndrome: An Update. Pediatr Ann. 2019;48:e304-10. doi: 10.3928/19382359-20190729-01.
32. Pasquali R, Gambineri A, Cavazza C, Ibarra Gasparini D, Ciampaglia W, Cognigni GE, et al. Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. Eur J Endocrinol. 2011;164:53-60. doi: 10.1530/EJE-10-0692.
33. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014;171:P1-29. doi: 10.1530/EJE-14-0253.
34. Videira-Silva A, Albuquerque C, Fonseca H. Acanthosis nigricans as a clinical marker of insulin resistance among overweight adolescents. Ann Pediatr Endocrinol Metab. 2019;24:99-103. doi: 10.6065/apem.2019.24.2.99.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Pregnancy Outcomes After Bariatric Surgery: Should We Favour Restrictive Procedures in Women of Reproductive Age?

Bárbara Araújo [a,*,#], Ana Carreira [a,#], Mariana Lavrador [a,b], Inês Vieira [a,b], Dírcea Rodrigues [a,b], Sandra Paiva [a], Miguel Melo [a,b], Isabel Paiva [a]

[a] *Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[b] *Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[#] *Joint first authors / Co-primeiros autores*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2023-01-26
Accepted/Aceite: 2023-07-03
Publicado / Published: 2023-10-18

Keywords:
Bariatric Surgery;
Micronutrients/deficiency;
Nutritional Status;
Pregnancy;
Pregnancy Complications;
Pregnancy Outcome.

A B S T R A C T

Introduction: Bariatric surgery (BS) is frequently performed in women of reproductive age, and is often associated with nutritional deficiencies and increased risk of adverse outcomes during pregnancy, such as small for gestational age (SGA) neonates. Whether we should favour restrictive procedures in this population, to minimize these risks, is still uncertain. Our aim was to evaluate the impact of the type of BS procedure on micronutrient deficiencies and on maternal and foetal outcomes during pregnancy.
Methods: Single centre retrospective study, including a cohort of 47 pregnancies after BS, with follow up between 2008-2020. Neonates were classified as SGA if birth weight was <10th percentile. Data collection included type of surgery, body mass index (BMI) before surgery and before pregnancy, micronutrient levels and supplementation, and pregnancy outcomes (anaemia, preeclampsia, gestational diabetes, caesarean delivery, abortion, pre-term delivery, SGA).
Results: The more frequently performed procedures were gastric bypass (36.2%) and sleeve gastrectomy (36.2%), followed by adjustable gastric banding (23.4%) and biliopancreatic diversion (4.2%). BMI mean reduction from surgery to pregnancy was higher in malabsorptive procedures. The BS-to-conception interval did not differ between surgery types. Micronutrient deficiencies were frequent during pregnancy (vitamin D: 75.9%, calcium: 43.8%, vitamin B12: 23.5%, folic acid: 8.7%, iron: 77.8%), despite multivitamin supplementation in most women. The prevalence of SGA neonates was elevated (26.3%). There were no differences considering micronutrient deficiencies or pregnancy outcomes between surgical procedures. The prevalence of SGA neonates was increased in the presence of vitamin B12 deficiency in the first trimester of pregnancy (33.3 *vs* 0.0%, p=0.027) and in pregnant women not supplemented with iron in addition to multivitamins (46.2% *vs* 14.8%, p=0.052).
Conclusion: Micronutrient deficiencies were frequent, despite multivitamin supplementation. Micronutrient deficiencies and pregnancy outcomes were similar between BS procedure types. Our results suggest that in lieu of favouring restrictive procedures in women of reproductive age, the procedure decision should be based on individual characteristics. Following BS, women should be monitored and supplemented using a close individualized approach during pre-conception and pregnancy.

Palavras-chave:
Cirurgia Bariátrica;
Complicação na Gravidez;
Estado Nutricional;
Gravidez;
Micronutrientes/deficiência;
Resultado da Gravidez.

Resultados da Gravidez Após Cirurgia Bariátrica: Devemos Preferir Procedimentos Restritivos em Mulheres em Idade Fértil?

R E S U M O

Introdução: A cirurgia bariátrica (CB) é frequentemente realizada em mulheres em idade fértil, estando associada a uma elevada prevalência de défices nutricionais na gestação e a risco aumentado de desfechos neonatais adversos, como recém-nascidos leves para a idade gestacional (LIG). Os procedimentos malabsortivos parecem estar associados a um risco superior, contudo, ainda não é

* Autor Correspondente / Corresponding Author.
E-Mail: barbarafilipaca@gmail.com (Bárbara Araújo)
Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra
Praceta Prof. Mota Pinto 3000-075 Coimbra, Portugal

https://doi.org/10.26497/ao230007

claro se deve haver uma preferência por estas técnicas nesta população. O nosso objetivo foi avaliar o impacto do tipo de procedimento cirúrgico no risco de défices de micronutrientes e resultados materno-fetais da gravidez.

Métodos: Estudo retrospetivo unicêntrico, que incluiu uma coorte de 47 gestações após CB, com seguimento entre 2008-2020. Foram classificados como LIG os recém-nascidos cujo peso ao nascimento fosse <percentil 10. Recolhidos dados acerca do tipo de procedimento cirúrgico; índice de massa corporal (IMC) antes da CB e antes da gestação; doseamentos de micronutrientes e dados da suplementação; desfechos materno-fetais (anemia, pré-eclâmpsia, diabetes gestacional, parto por cesariana, abortamento, prematuridade e LIG).

Resultados: Os procedimentos mais frequentes foram o *bypass* gástrico (36,2%) e gastrectomia em sleeve (36,2%), seguidos da banda gástrica ajustável (23,4%) e derivação biliopancreática (4,2%). A redução média de IMC entre a CB e a gravidez foi superior nos procedimentos malabsortivos. O intervalo de tempo entre a CB e a gravidez foi semelhante em ambos os tipos de cirurgias, a idade materna era inferior nos procedimentos restritivos. Os défices de micronutrientes foram frequentes durante a gravidez (vitamina D: 75,9%, cálcio: 43,8%, vitamina B12: 23,5%, ácido fólico: 8,7%, ferro: 77,8%), apesar da suplementação multivitamínica na maioria dos casos. A prevalência de recém-nascidos LIG foi elevada (26,3%). Não se registaram diferenças entre os procedimentos cirúrgicos quanto ao risco de défices de micronutrientes ou desfechos materno-fetais. A prevalência de recém-nascidos LIG foi superior na presença de défice de vitamina B12 no primeiro trimestre (33,3 *vs* 0,0%, *p*=0,027), e nas grávidas que não foram suplementadas com ferro em adição ao multivitamínico (46,2% *vs* 14,8%, *p*=0,052).

Conclusão: Os défices de micronutrientes foram prevalentes, apesar da suplementação vitamínica. Os défices vitamínicos e os desfechos materno-fetais da gravidez foram semelhantes entre os tipos de procedimento. Os nossos resultados sugerem que, ao invés de se favorecer procedimentos restritivos em mulheres em idade fértil, a decisão do tipo de procedimento deve ser fundamentada em características individuais da doente. Após CB, as mulheres devem ser monitorizadas e suplementadas de forma individualizada, quer no período pré-concecional, quer durante a gravidez.

Introduction

Overweight and obesity among women of reproductive age has reached a worrying prevalence across many European countries and continues to increase.[1] Obesity is a common cause of anovulation and infertility. In pregnancy, obesity increases the risk of miscarriage, gestational diabetes, hypertensive disorders, cesarean delivery, stillbirth and large for gestational age (LGA) neonates.[2,3] Bariatric surgery (BS) is on the rise as a treatment for severe obesity among women of reproductive age.[4,5] BS comprises restrictive and malabsorptive procedures: sleeve gastrectomy and adjustable gastric banding are examples of purely restrictive procedures, whilst Roux-en-Y gastric bypass and biliopancreatic diversion are also malabsorptive. Sleeve gastrectomy and Roux-en-Y gastric bypass are the most performed procedures worldwide.[6] BS improves factors related to anovulation and reduces obesity-related comorbidities in pregnancy; however, it increases the risk of nutritional deficiencies, that may be further aggravated by physiological changes of pregnancy. Furthermore, pregnancies after BS have been associated with increased risk of some adverse perinatal outcomes, such as small for gestational age (SGA) neonates and preterm births.[7-9] SGA is defined as birth weight of less than the 10th percentile for gestational age,[10] and may be a marker of foetal growth restriction, which is associated with increased perinatal morbidity and mortality.[11] Moreover, SGA neonates are at higher risk of developing metabolic disease later in life.[12] Micronutrient deficiencies can occur in both restrictive and malabsorptive procedures; therefore, adequate supplementation with multivitamins and minerals is recommended regardless of procedure type.[13,14] Still, these deficiencies are generally more pronounced and more extensive in malabsorptive procedures, usually requiring larger doses of supplements.[13] Currently, there is limited evidence and no consensus regarding the optimal nutritional monitoring and supplementation in pregnancies after BS. Some recommendations advocate that daily vitamin and mineral supplements should be initiated at least 3-6 months prior to conception and contain the following at a minimum: copper (1-2 mg), zinc (8-22 mg), selenium (50-60 µg), calcium (1200-2400 mg), folic acid (0.4 mg or 4-5 mg if obesity or diabetes), iron (45-60 mg), thiamine (>12 mg), vitamin D (>1000-3000 IU), vitamin B12 (1 mg oral or 1 mg depot injection every 3 months), vitamin E (15 mg), beta-carotene (vitamin A, 5000 IU) and vitamin K (300 µg if malabsorptive procedures). Micronutrient levels should be monitored throughout pregnancy, at least once every trimester, and supplementation should be adjusted to maintain concentrations within normal limits.[14,15]

The potential for malnutrition after BS has been linked to the increased risk of adverse perinatal outcomes in these patients, with several studies suggesting an association between micronutrient deficiencies, inadequate weight gain and SGA.[16,17] Studies comparing micronutrient deficiencies and SGA risk between different BS procedures have shown conflicting results, with some reporting a higher risk following malabsorptive procedures[7,16,18,19] and others reporting no significant differences.[20,21] Thus, the question whether we should favour restrictive procedures in female patients of reproductive age remains unanswered, as there is still no solid scientific evidence to guide clinicians on the most appropriate type of procedure in this population.[13] Understanding the factors associated with increased risk of adverse outcomes in pregnancies after BS is essential to adjust and improve the periconceptional counselling and pregnancy surveillance. Therefore, the aim of our study was to evaluate the impact of malabsorptive and restrictive bariatric surgery procedures on micronutrient deficiencies during pregnancy and on maternal and perinatal outcomes.

Material and Methods

Study Design and Participants

We performed a retrospective cohort study of pregnant women with a history of bariatric surgery, that were followed in the obstetrics department in a University Hospital Centre in Portugal,

between 2008-2020. We included all singleton pregnancies that were followed from the first trimester of pregnancy by our multidisciplinary team. Multiple pregnancies and pregnancies without birth data were excluded. The multidisciplinary team included obstetricians, endocrinologists, and dietitians, and follow-up was performed at least once every trimester, or more frequently if needed. Our approach consisted in prescribing multivitamin supplements specifically designed for pregnancy, monitoring for nutritional deficiencies at every visit and adding and adjusting specific micronutrient supplements (such as calcium, vitamin D, vitamin B12, iron and folic acid), according to individual needs. Screening for gestational diabetes was performed in the first trimester, by fasting plasma glucose ≥ 92 mg/dL, and repeated, if negative, in the second trimester (between 24-28 weeks of gestation), through capillary blood glucose monitoring 4 times a day during one week (diagnosis if fasting capillary glucose ≥ 95 mg/dL or ≥ 140 mg/dL 1 hour after meals).

Bariatric surgery procedures comprised adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion. These procedures were performed from 2005 to 2018. Data collection on age, demographics, comorbidities, type and date of bariatric surgery, pre-gestational body mass index (BMI) and BMI before surgery, gestational weight gain, micronutrient deficiencies and pregnancy outcomes was obtained from electronic health records.

Gestational weight gain was defined according to the pre-gestational BMI, and classified as adequate for weight gains of 11.5-16.0 kg (BMI 18.5-24.9 kg/m^2), 7.0-11.5 kg (BMI 25.0-29.9 kg/m^2) or 5.0-9.0 kg (BMI ≥30 kg/m^2), based on the 2009 Institute of Medicine (IOM) guidelines for pregnancy.[22] Weight gain inferior or superior to the recommended values was classified as insufficient or excessive, respectively.

Exposures and Outcomes

The exposure of interest was the type of bariatric surgery procedure. Sleeve gastrectomy and adjustable gastric banding were included as restrictive procedures and Roux-en-Y gastric bypass and biliopancreatic diversion as malabsorptive procedures. The outcomes of interest were the prevalence of micronutrient deficiencies and maternal and perinatal outcomes: preeclampsia, gestational diabetes, maternal anaemia, caesarean delivery, abortion, preterm delivery, SGA and LGA. Micronutrients were assessed through the levels of ferritin, folate, vitamin B12, vitamin D, calcium and magnesium; deficiencies were considered if present in one or more trimesters of pregnancy. Deficiencies were classified according to our hospital centre laboratory reference values for iron (ferritin < 30 ng/mL), folate (<3.5 ng/mL), vitamin B12 (<187 pg/mL), total calcium corrected to albumin (<8.8 mg/dL) and magnesium (<1.9 mg/dL). Vitamin D deficiency was defined as a level of 25(OH)D <20 ng/dL, according to the recommendations from the Endocrine Society, and classified as severe if <10 ng/dL.[23] Maternal anaemia was defined according to World Health Organization (WHO) as haemoglobin <11.0 g/dL in the first and third trimesters or <10.5 g/dL in the second trimester. SGA and LGA were defined as birth weight inferior to the 10th percentile and above the 90th percentile, respectively, according to the WHO growth charts in term births, or Fenton curves in preterm births. Preterm births were defined as births occurring before 37 completed weeks of gestation, and classified according to WHO as extremely preterm if birth occurred before 28 weeks, very preterm from 28-32 weeks and moderate to late preterm from 32-37 weeks.

Statistical Analysis

Analyses were performed with the use of IBM SPSS Statistics 26.0. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges (IQR) for variables with skewed distributions. The means or medians of continuous variables were compared between patient groups using the Student's T-test for independent samples or the Mann Whitney test, respectively. Associations between categorical variables were assessed using the Chi-square test. All reported *p* values are two-tailed, with a *p* value of less than 0.05 indicating statistical significance.

Results

Baseline Pregestational Characteristics

Our study included 47 singleton pregnancies after bariatric surgery. Most were spontaneous pregnancies, but in three women pregnancy was achieved through medically assisted reproduction. Mean maternal age was 34.3±4.5 years and mean BMI at conception was 30.2±5.5 kg/m^2. The most performed procedures were Roux-en-Y gastric bypass (N=17, 36.2%) and sleeve gastrectomy (N=17, 36.2%), followed by adjustable gastric banding (N=11, 23.4%) and biliopancreatic diversion (N=2, 4.2%). Pregnant women submitted to restrictive procedures were younger than those submitted to malabsorptive procedures (33.1±4.4 *vs* 35.9±4.2, *p*=0.038).

Mean BMI reduction from surgery to conception was 14.4±7.1 kg/m^2; leading to a normal BMI at conception in 19.5% of the women, overweight in 29.3% and obesity in 51.2% (34.1% class I, 12.2% class II and 4.9% class III). Other comorbidities included hypothyroidism in 10.6%, arterial hypertension in 8.5%, type 2 diabetes in 8.5% and thrombophilia (antiphospholipid syndrome or factor V Leiden mutation) in 6.4%.

Median bariatric surgery-to-conception interval was 36 months, ranging from a minimum of 4 to a maximum of 144 months.

Weight Loss Before Pregnancy and Gestational Weight Gain

Pregestational BMI was similar in women submitted to malabsorptive and restrictive procedures, but those submitted to malabsorptive procedures had a higher BMI before surgery [42.0 (IQR 40.4-46.5) *vs* 46.4 (IQR 43.5-50.0), *p*=0.044] and higher BMI reduction from surgery to conception (16.8±5.9 *vs* 12.8±7.6, *p*=0.042). BMI mean reduction was highest for biliopancreatic diversion (26.5±3.9 kg/m^2), intermediate for Roux-en-Y gastric bypass (14.6±4.7 kg/m^2) and sleeve gastrectomy (12.9±7.9 kg/m2) and lowest for adjustable gastric banding (9.8±5.3 kg/m^2). BMI reduction showed no correlation with maternal age (*p*=0.252) or surgery-to-conception interval (*p*=0.190), and the association between malabsorptive procedures and BMI reduction was sustained after adjusting for maternal age (β=5.5; *p*=0.023).

Gestational weight gain (GWG) and adequacy of GWG were similar between procedure types. Adequate weight gain was achieved in 21.7% of pregnant women in the restrictive group and 36.8% in the malabsorptive group (*p*=0.309), as shown in Table 1. There was insufficient weigh gain or weight loss in 6 women in each group (26.1% *vs* 31.6%, *p*=0.510). There was no association between maternal age and GWG.

Table 1. Baseline characteristics, maternal and neonatal outcomes and micronutrient deficiencies in restrictive and malabsorptive procedures.

Characteristics	Total (N=47)	Restrictive (N=28)	Malabsorptive (N=19)	*p* value
Pregestational characteristics				
Age (years)	34.3±4.5	33.1±4.4	35.9±4.2	0.038
Time from surgery to conception (months)	36.0 (24.0-72.0)	36.0 (24.0-66.0)	58.0 (22.0-96.0)	0.245
BMI at conception (kg/m2)	30.2±5.5	30.6±5.8	29.6±5.2	0.575
BMI reduction from surgery to conception (kg/m2)	14.4±7.1	12.8±7.6	16.8±5.9	0.042
Pregestational obesity	22 (46.8%)	12 (42.9%)	10 (52.6%)	0.976
Class I	15 (31.9%)	8 (28.6%)	7 (36.8%)	0.439
Class II	5 (10.6%)	2 (7.1%)	3 (15.8%)	0.923
Class III	2 (4.3%)	2 (7.1%)	0 (0.0%)	0.200
Arterial hypertension	4 (8.5%)	3 (10.7%)	1 (5.3%)	0.638
Type 2 diabetes	4 (8.5%)	3 (10.7%)	1 (5.3%)	0.638
Abortion or foetal loss	5.0 (10.6%)	5.0 (17.9%)	0.0 (0.0%)	0.072
Maternal/neonatal outcomes[a]				
Gestational weight gain (kg)*	9.1±8.3	9.1±9.2	9.1±7.5	0.973
Insufficient [b]*	12 (28.6%)	6 (26.1%)	6 (31.6%)	0.510
Adequate [b]*	12 (28.6%)	5 (21.7%)	7 (36.8%)	0.309
Excessive [b]*	15 (35.7%)	10 (43.5%)	5 (26.3%)	0.411
Maternal anaemia*	12 (36.4%)	5 (31.3%)	7 (41.2%)	0.554
Gestational diabetes	8.0 (19.0%)	4 (17.4%)	4 (21.1%)	0.764
Caesarean delivery	13.0 (31.0%)	7 (30.4%)	6 (31.6%)	0.257
Preeclampsia	1.0 (2.4%)	1 (4.3%)	0.0 (0.0%)	0.370
Pre-term delivery	3 (7.1%)	3 (13.0%)	0.0 (0.0%)	0.102
SGA	10 (23.8%)	7 (30.4%)	3 (15.8%)	0.267
Multivitamin supplementation [a]	31 (73.8%)	15 (65.2%)	16 (84.2%)	0.119
Micronutrient deficiencies [ac]				
Iron*	21 (77.8%)	11 (73.3%)	10 (83.3%)	0.535
Vitamin B12*	8 (23.5%)	3 (15.8%)	5 (33.3%)	0.231
Folic acid*	2 (8.7%)	2 (14.3%)	0 (0.0%)	0.235
Vitamin D*	22 (75.9%)	11 (78.6%)	11 (73.3%)	0.742
Calcium*	14 (43.8%)	7 (38.9%)	7 (50.0%)	0.530
Magnesium*	8 (32.0%)	4 (28.6%)	4 (36.4%)	0.678

Continuous data are presented as mean ± SD or median (interquartile range); categorical data are presented as frequencies (percentages). BMI – body mass index.

[a] Excluding cases of spontaneous abortion or foetal loss: N=42, restrictive=23 and malabsorptive=19.

[b] Adequacy of gestational weight gain according to the IOM recommendations (2009).

[c] Considered if present in one or more trimesters of pregnancy.

*Missing values: 2 for gestational weight gain [2 for restrictive (R), 0 for malabsorptive (M) procedures], 3 for adequacy of gestational weight gain (2R, 1M), 9 for anaemia (7R, 2M), 15 for iron (8R, 7M), 8 for vitamin B12 (4R, 4M), 19 for folic acid (9R, 10M), 13 for vitamin D (9R, 4M), 10 for calcium (5R, 5M), 17 for magnesium (9R, 8M).

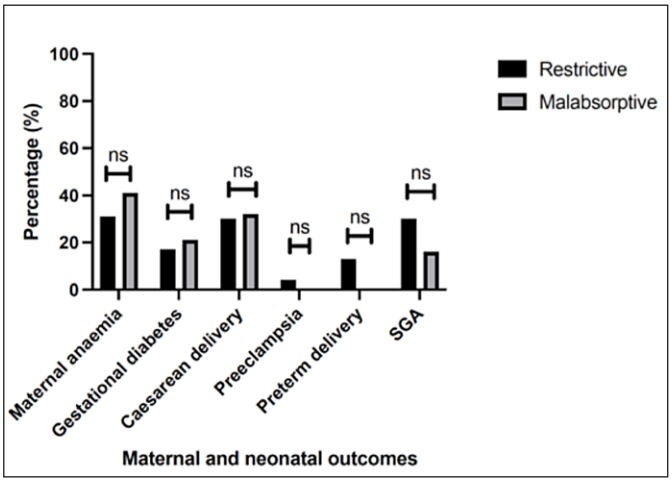


Figure 1. Maternal and neonatal outcomes in restrictive versus malabsorptive procedures.

*ns, non-significant; SGA, small for gestational age

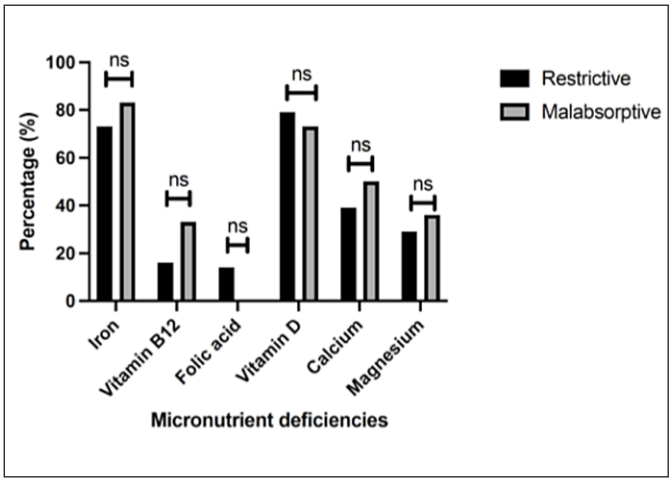


Figure 2. Micronutrient deficiencies in restrictive versus malabsorptive procedures.

*ns, non-significant;

Maternal and Neonatal Outcomes and Micronutrient Deficiencies

From the total of 47 pregnancies, four (8.5%) resulted in first trimester spontaneous abortion and one (2.1%) in foetal demise at 30 weeks. One of the abortions and the foetal demise occurred in women with sleeve gastrectomy and diagnosed thrombophilia; the other three spontaneous abortions occurred in women with adjustable gastric banding. The remaining 42 pregnancies resulted in 39 term births and 3 preterm births (7.1%): one extremely preterm and 2 moderate to late preterm.

Median foetal birth weight was 3103 g (IQR 2780-3361 g), with a prevalence of SGA of 23.8% (10 neonates) and LGA of 2.4% (one neonate). A percentage of 90% of SGA neonates were born at term, with median gestational age of 38 weeks (IQR 38-39 weeks) and mean birth weight of 2498±233 g. Most neonates (83.3%) had birth weight inferior to the 50th percentile (P): 23.8% inferior to P10, 19.0% between P10-P25 and 40.5% between P25-P50; 11.9% had birth weight between P50-P75, 2.4% between P75-P90 and 2.4% above P90. Considering maternal outcomes (N=42), eight women (19.0%) were diagnosed with gestational diabetes; 13 (31.0%) had a caesarean delivery; one (2,4%) had preeclampsia; and 12 (36.4%) had anaemia, mostly due to iron deficiency. Pregnant women with gestational diabetes were significantly older (38.9±2.4 *vs* 33.2±4.1, p=0.001). Supplementation with multivitamins with general formulation for pregnancy was carried out by 73.8% of all pregnant women, with a slightly higher prevalence in the group of malabsorptive procedures (84.2% *vs* 65.2%, p=0.119). Additionally, individualised supplementation with folic acid, iron, calcium, and vitamin D was also prescribed, according to measured analytes: 27 patients (64.3%) were supplemented with iron, 24 (57.1%) with folic acid beyond the first trimester of pregnancy, 16 (38.1%) with calcium, 15 (35.7%) with vitamin D, 5 (11.9%) with vitamin B12 and 5 (11.9%) with magnesium. There was no association between bariatric procedure type and the analysed maternal or foetal outcomes. Older maternal age increased the risk of gestational diabetes (odds ratio: 1.78; confidence interval 1.16-2.73) but showed no association with the other analysed outcomes. The prevalence of vitamin D deficiency was 75.9% (severe in 24.1%), calcium deficiency 43.8%; vitamin B12 deficiency 23.5% and folic acid deficiency 8.7%. Iron deficiency was found in 77.8% of pregnancies, with 33.3% requiring supplementation with intravenous iron (31.5% corresponding to malabsorptive and 30.4% to restrictive procedures, p=0.972). The prevalence of micronutrient deficiencies did not differ significantly between restrictive and malabsorptive procedures.

Analysing the possible association of micronutrient deficiencies and SGA, we found a higher prevalence of SGA neonates in pregnant women with vitamin B12 deficiency in the first trimester (33.3 *vs* 0.0%, p=0.027); and no associations between other vitamin deficiencies and SGA. Even though no association was found between iron deficiency and SGA, there was a trend towards a higher prevalence of SGA in patients not taking individualised iron supplements (46.2% *vs* 14.8%, p=0.052). Regarding the possible association between gestational weight gain and SGA, there was a higher prevalence of SGA neonates in pregnancies with insufficient and excessive weight gain than in those with adequate weight gain, but this difference did not reach statistical significance (33.3% and 26.7% *vs* 8.3%, p=0.32). Moreover, 44.4% of all SGA were born from mothers with insufficient weight gain (*vs* 55.6% from mothers with adequate or excessive weight gain, p=0.238).

There was no record of other pregnancy complications, such as dumping syndrome, internal hernias or other complications requiring surgery.

Discussion

In the analysed cohort, micronutrient deficiencies were highly prevalent in pregnancies after both types of BS, despite supplementation with multivitamins in most patients. Even though there was significant weight loss after BS, most women had pregestational obesity. Nonetheless, obesity-related pregnancy complications such as LGA or preeclampsia were uncommon. The prevalence of SGA in our study was more than double that of the reported in the Portuguese population (23.8% *vs* 8.9%).[24,25] We found no significant differences in the prevalence of micronutrient deficiencies, preeclampsia, gestational diabetes, maternal anaemia, caesarean delivery, preterm delivery, SGA and LGA between restrictive and malabsorptive bariatric procedures. Spontaneous abortion occurred only in pregnancies following restrictive procedures, but the small number of cases and the high prevalence of significant additional risk factors such as thrombophilia does not allow for a reliable comparison between surgical procedure types. Pregnant women submitted to malabsorptive procedures were older, had a higher BMI before surgery and a more pronounced weight loss from surgery to conception, but showed no difference in weight gain during pregnancy. We also found a higher prevalence of SGA in pregnancies with vitamin B12 deficiency in the first trimester, in those not supplemented with iron in addition to usual multivitamins and in the presence of insufficient gestational weight gain.

To date, few studies have focused on maternal vitamin deficiencies following BS and its association to neonatal outcomes. Recently, some authors described an association between levels of vitamins B9, B12, calcium, iron and birth weight[19,26]; others reported that women receiving nutritional advice were significantly less likely to have an SGA neonate.[16] In the latter – the AURORA prospective case-control study,[16] the authors describe that pregnant women with SGA neonates had slightly lower levels of iron and vitamin B12 when compared to women giving birth to adequate for gestational age neonates, but did not find an association between serum levels of micronutrients and the risk of SGA. Nevertheless, their analysis was limited by the amount of missing data (10%-72%) on nutritional levels.

Currently, guidelines on pregnancy after BS recommend individualised supplementation with multivitamins and minerals in both types of procedures, that should ideally be optimized 3-6 months prior to conception and adjusted during pregnancy based on serum levels of nutrients.[13,14] It is known that malabsorptive procedures may lead to more pronounced micronutrient deficiencies and some studies suggest that these may impair gestational weight gain and influence the risk of adverse perinatal outcomes. Most studies that associate malabsorptive procedures with increased risk of lower birth weight, SGA and other adverse foetal outcomes, hypothesize that the reason behind this may be the increased prevalence of micronutrient deficiencies, but lack information on patient's multivitamin supplementation and measured analytes.[7,16,18,19,27,28]

In our cohort, micronutrient deficiencies did not differ between surgery type, which may explain our results regarding pregnancy outcomes. Similar to our study, Hazart *et al*[20] analysed pregnancies with an elevated prevalence of multivitamin supplementation (77.8% to 100.0%) after both types of procedures, and found no significant difference on micronutrient deficiencies and pregnancy outcomes between BS types; Ducarme *et al*[29] performed a prospective study of 87 women with comparable nutritional supplementation and found that serum micronutrient levels

of zinc, selenium, vitamins A1, B1, B6, C, and E were similar in pregnancies after Roux-en-Y gastric bypass and sleeve gastrectomy, as were maternal and neonatal outcomes. In the latter, almost all the included women had at least one micronutrient deficiency during pregnancy. Watanabe and colleagues[27] also described that birth weight in pregnancies after malabsorptive procedures without anaemia was similar to that of pregnancies after restrictive procedures, and Mead *et al*[30] found no significant differences in iron, vitamin B12 or calcium deficiencies between biliopancreatic diversion, Roux-en-Y gastric bypass and sleeve gastrectomy in women following nutritional supplement guidelines before and during pregnancy. Additionally, a higher prevalence of supplementation of women submitted to malabsorptive versus restrictive procedures was also found in the studies by Hazart *et al*[20] and by Akhter *et al*,[16] in the first trimester of pregnancy. The elevated prevalence of SGA and the low prevalence of adequate weigh gain in our analysis were also consistent with previous studies.[16,20] In our analysis, and in line with the results from the AURORA study, 44% of mothers of SGA had insufficient weight gain, but in our study this difference did not reach statistical significance.

Our study is important, as it shows the elevated risk of micronutrient deficiencies in our population of pregnant women submitted to BS. Moreover, it emphasises that the risk of micronutrient deficiencies is present in both malabsorptive and restrictive procedures, and reinforces the importance of adequate, intensive and individualized supplementation, starting before conception, in both types of BS. In line with this, our results suggest that, in daily clinical practice, the decision between BS procedures in women of reproductive age should be based on individual characteristics, such as baseline BMI and comorbidities, apart from possible future pregnancies. Therefore, it is our opinion that we should not favour restrictive procedures in women of reproductive age as a general rule, but individualize our choice and adjust follow-up and supplementation accordingly.

Nonetheless, we recognize that micronutrient deficiencies are just one in several factors that may influence foetal birth weight, and that foetal growth is also largely dictated by macronutrient availability. In turn, macro and micronutrient availability is dependent on maternal nutritional intake during preconception and pregnancy, and on the ability of the placenta to transport these nutrients to the foetus. Adequate nutritional counselling and close foetal monitoring are, therefore, also of unneglectable importance.

Strengths of our study include data collection on multivitamin supplementation, micronutrient assessments in each trimester and sample homogeneity between groups. Additionally, the diversity of bariatric procedures and the similarity in multivitamin supplementation in restrictive and malabsorptive procedures, as recommended in the guidelines, reinforced our results. Weaknesses of our study include its retrospective nature and small sample size, which precludes the generalization of the results. It should be noted that the small sample size may have biased the evaluation of uncommon pregnancy outcomes. Additionally, given the low number of biliopancreatic diversion surgeries in our cohort, our results are not representative for this procedure. Similar to some previous studies, we must also point out the significant amount of missing data on micronutrient deficiencies, that limited our analysis; and the fact that the only available analytes were calcium, magnesium, iron and vitamins D, B9 and B12. Venous blood glucose assessment was mostly inaccessible retrospectively; therefore, the prevalence of hypoglycaemia in both types of surgical procedures could not be compared and a possible association with adverse neonatal outcomes could not be assessed. Macronutrients were also not assessed, and would be a relevant complement to our analysis.

Prospective studies with a greater sample size are needed for a better assessment of the risk factors for adverse pregnancy outcomes in women submitted to BS. Future studies should focus not only in gestational weight gain and micronutrient deficiencies, but also in other factors that might influence perinatal outcomes, such as maternal weight loss trajectories, exercise and food intake behaviors, placental function, microbiome profiles and macronutrient and energy status. This evidence will be crucial for the development of more comprehensive follow-up programs and counselling.

Conclusion

Our study showed an elevated prevalence of micronutrient deficiencies, insufficient gestational weight gain and SGA neonates in pregnancies after both types of BS. Malabsorptive procedures were associated with greater weight reduction, but showed no significant differences in the prevalence of micronutrient deficiencies and maternal and foetal outcomes, when compared to restrictive procedures. We hypothesise that the careful management of pregnant women with history of BS, with frequent follow-up, generalised multivitamin supplementation, and additional individualised supplementation according to measured analytes during pregnancy might have mitigated the expected differences between malabsorptive and restrictive procedures. However, other factors besides micronutrient supplementation were not assessed in this study and might have also influenced maternal and neonatal outcomes.

Finally, our results suggest that there may be no benefit in favouring restrictive procedures in women of reproductive age on a routine basis, but studies with a greater sample size are needed to validate this hypothesis. Our analysis also highlights the importance of adequate supplementation and regular follow-up to minimize adverse pregnancy outcomes in both types of BS.

Contributorship Statement / Declaração de Contribuição:

BA and AC: Contributed equally to this study and were responsible for the study conception and design, data collection, data analysis and interpretation and drafting the article.
ML and IV: Were responsible for data collection.
SP: Was responsible for study conception and design.
MM: Was responsible for study conception and design and for critical revision of the manuscript.
DR and IP: Were responsible for critical revision and for important intellectual content.
All authors approved the final version to be published.

BA e AC: Contribuíram igualmente para este estudo e foram responsáveis pela conceção e desenho do estudo, recolha de dados, análise e interpretação dos dados e redação do artigo.
ML e IV: Foram responsáveis pela recolha de dados.
SP: Foi responsável pela conceção e desenho do estudo.
MM: Foi responsável pela conceção e desenho do estudo, pela revisão crítica do conteúdo.
DR e IP: Foram responsáveis pela revisão crítica e pelo conteúdo intelectual importante.
Todos os autores aprovaram a versão final a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Esta investigação não recebeu qualquer subsídio específico de qualquer agência de financiamento do sector público, comercial ou sem fins lucrativos. Recebeu um subsídio da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo para apresentação no Congresso Europeu de Obesidade (maio/2022).
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Os autores obtiveram o consentimento informado dos pacientes e/ou sujeitos mencionados no artigo.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. It received a grant from the Portuguese Society of Endocrinology, Diabetes and Metabolism for presentation in the European Congress on Obesity (may/2022).
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
The authors have obtained the informed consent of the patients and/or subjects mentioned in the article.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. World Health Organization. WHO European Regional Obesity Report 2022. Geneva:WHO; 2022.
2. ACOG Practice Bulletin No 156: Obesity in Pregnancy. Obstet Gynecol. 2015;126:e112-e26.
3. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev. 2015;16:621-38. doi: 10.1111/obr.12288.
4. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, et al. Pregnancy and fertility following bariatric surgery: a systematic review. JAMA. 2008;300:2286-96. doi: 10.1001/jama.2008.641.
5. Edison E, Whyte M, van Vlymen J, Jones S, Gatenby P, de Lusignan S, et al. Bariatric Surgery in Obese Women of Reproductive Age Improves Conditions That Underlie Fertility and Pregnancy Outcomes: Retrospective Cohort Study of UK National Bariatric Surgery Registry (NBSR). Obes Surg. 2016;26:2837-42. doi: 10.1007/s11695-016-2202-4.
6. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. Obes Surg. 2019;29:782-95. doi: 10.1007/s11695-018-3593-1.
7. Akhter Z, Rankin J, Ceulemans D, Ngongalah L, Ackroyd R, Devlieger R, et al. Pregnancy after bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. PLoS Med. 2019;16:e1002866. doi: 10.1371/journal.pmed.1002866.
8. Johansson K, Cnattingius S, Näslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015;372:814-24. doi: 10.1056/NEJMoa1405789.
9. Carreau AM, Nadeau M, Marceau S, Marceau P, Weisnagel SJ. Pregnancy after bariatric surgery: balancing risks and benefits. Can J Diabetes. 2017;41:432-8. doi: 10.1016/j.jcjd.2016.09.005.
10. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71:159-63.
11. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56:298-312. doi: 10.1002/uog.22134.
12. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocr Rev. 2007;28:219-51. doi: 10.1210/er.2006-0039.
13. Ciangura C, Coupaye M, Deruelle P, Gascoin G, Calabrese D, Cosson E, et al. Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery. Obes Surg. 2019;29:3722-34. doi: 10.1007/s11695-019-04093-y.
14. Shawe J, Ceulemans D, Akhter Z, Neff K, Hart K, Heslehurst N, et al. Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care. Obes Rev. 2019;20:1507-22. doi: 10.1111/obr.12927.
15. Vanheule G, Ceulemans D, Vynckier AK, De Mulder P, Van Den Driessche M, Devlieger R. Micronutrient supplementation in pregnancies following bariatric surgery: a practical review for clinicians. Obes Surg. 2021;31:4542-54. doi: 10.1007/s11695-021-05546-z.
16. Akhter Z, Heslehurst N, Ceulemans D, Rankin J, Ackroyd R, Devlieger R. Pregnancy after Bariatric Surgery: A Nested Case-Control Study of Risk Factors for Small for Gestational Age Babies in AURORA. Nutrients. 2021;13:1699. doi: 10.3390/nu13051699.
17. Heusschen L, Krabbendam I, van der Velde JM, Deden LN, Aarts EO, Merién AER, et al. A Matter of Timing-Pregnancy After Bariatric Surgery. Obes Surg. 2021;31:2072-9. doi: 10.1007/s11695-021-05546-z.
18. Kwong W, Tomlinson G, Feig DS. Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks? Am J Obstet Gynecol. 2018;218:573-80. doi: 10.1016/j.ajog.2018.02.003.
19. Yu Y, Groth SW. Risk factors of lower birth weight, small-for-gestational-age infants, and preterm birth in pregnancies following bariatric surgery: a scoping review. Arch Gynecol Obstet. 2023;307:343-78. doi: 10.1007/s00404-022-06480-w.
20. Hazart J, Le Guennec D, Accoceberry M, Lemery D, Mulliez A, Farigon N, et al. Maternal Nutritional Deficiencies and Small-for-Gestational-Age Neonates at Birth of Women Who Have Undergone Bariatric Surgery. J Pregnancy. 2017;2017:4168541. doi: 10.1155/2017/4168541.
21. Ducarme G, Parisio L, Santulli P, Carbillon L, Mandelbrot L, Luton D. Neonatal outcomes in pregnancies after bariatric surgery: a retrospective multi-centric cohort study in three French referral centers. J Matern Fetal Neonatal Med. 2013;26:275-8. doi: 10.3109/14767058.2012.735723.
22. Institute of Medicine and National Research Council Committee to Reexamine IOMPWG. The National Academies Collection: Reports funded by National Institutes of Health. In: Rasmussen KM, Yaktine AL, editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington: National Academies Press; 2009
23. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74:1498-513. doi: 10.1038/s41430-020-0558-y.
24. Raposo J. Diabetes: Fatos e Números. Revista Portuguesa de Diabetes. 2020.15(1):19-27.
25. National Institute of Statistics (INE). Live births in Portugal (2017-2021) [database on the Internet]. [accessed on December 2022]. Available from: http://www.ine.pt
26. Faintuch J, Dias MC, de Souza Fazio E, de Oliveira FC, Nomura RM, Zugaib M, et al. Pregnancy nutritional indices and birth weight after Roux-en-Y gastric bypass. Obes Surg. 2009;19:583-9.
27. Watanabe A, Seki Y, Haruta H, Kikkawa E, Kasama K. Maternal impacts and perinatal outcomes after three types of bariatric surgery at a single

institution. Arch Gynecol Obstet. 2019;300:145-52. doi: 10.1007/s00404-019-05195-9.
28. Chevrot A, Kayem G, Coupaye M, Lesage N, Msika S, Mandelbrot L. Impact of bariatric surgery on fetal growth restriction: experience of a perinatal and bariatric surgery center. Am J Obstet Gynecol. 2016;214:655.e1-7. doi: 10.1016/j.ajog.2015.11.017.
29. Ducarme G, Planche L, Abet E, Desroys du Roure V, Ducet-Boiffard A. A Prospective Study of Association of Micronutrients Deficiencies during Pregnancy and Neonatal Outcome among Women after Bariatric Surgery. J Clin Med. 2021;10:204. doi: 10.3390/jcm10020204. .
30. Mead NC, Sakkatos P, Sakellaropoulos GC, Adonakis GL, Alexandrides TK, Kalfarentzos F. Pregnancy outcomes and nutritional indices after 3 types of bariatric surgery performed at a single institution. Surg Obes Relat Dis. 2014;10:1166-73. doi: 10.1016/j.soard.2014.02.011.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo
www.spedmjournal.com

Artigo Original

FIB-4 Index should Guide the Referral of Patients with Metabolic Syndrome to Gastroenterology: The Perspective of a Portuguese Cohort

Marta Borges-Canha [a], Rodrigo Liberal [b], Ana Rita Leite [a], Joana Correia-Chaves [c], Inês Mariana Lourenço [c], Madalena von Hafe [c], João Sérgio Neves [a], Mariana Fragão-Marques [a], Catarina Vale [c], Pedro Pimentel-Nunes [c], Adelino Leite-Moreira [c], Davide Carvalho [d], Paula Freitas [a]

[a] *Serviço de Endocrinologia, Diabetes e Metabolismo / Centro Hospitalar Universitário de São João, Porto, Portugal*
[b] *Serviço de Gastrenterologia e Hepatologia / Centro Hospitalar Universitário de São João, Porto, Portugal*
[c] *Departamento de Cirurgia e Fisiologia / Faculdade de Medicina da Universidade do Porto, Porto, Portugal*
[d] *Instituto de Investigação e Inovação em Saúde (i3s) / Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2023-04-21
Accepted/Aceite: 2023-07-10
Publicado / Published: 2023-10-18

Keywords:
Metabolic Syndrome;
Non-alcoholic Fatty Liver Disease.

A B S T R A C T

Introduction: Data regarding the referral of patients with metabolic syndrome (MetS) to hepatologists is scarce. Most authors agree that at-risk patients (including the ones with diabetes or MetS) should be screened for non-alcoholic fatty liver disease (NAFLD) and referred to hepatologists when needed. Existing data highlights that referral of patients with NAFLD to specialists remain low among endocrinologists.
Our aim was to evaluate a Portuguese cohort of patients with MetS followed in Endocrinology outpatient setting regarding their need to referral to hepatologists.
Methods: Secondary analysis including the patients from microDHNA cohort (adult patients with MetS followed for any cause in Endocrinology outpatient setting). The recruitment includes anamnesis, physical examination, blood drawing for several predefined analyses and hepatic elastography. Our main outcome was referral to gastroenterology due to hepatic fibrosis (every patient with a median value on elastography ³7kPa was referred). We tested the discriminatory accuracy of hepatic biochemical parameters and indexes [FLI (Fatty Liver Index) score, a predictor of hepatic steatosis; and BARD (Body Mass Index, AST/ALT Ratio, and Diabetes), APRI (Aspartate Aminotransferase to Platelet Ratio Index), NFS (NAFLD Fibrosis Score) and FIB-4 (Fibrosis-4 Index) scores, predictors of hepatic fibrosis] for the need to referral of patients using ROC curve analyses.
Results: We included a total of 65 participants; of those, 53.8% were female and the average age was 61.2±9.6 years old. Eight patients (12.3%) were referred to gastroenterology after performing hepatic elastography, none of which was already referred. Our analysis showed that the best parameter in this cohort was FIB-4 index. A cut-off value of 2.11 associates to an area under the curve of 0.80 and has a sensitivity of 62% and specificity of 98% for predicting the need for referral.
Conclusion: Our results highlight that the use of scores as the FIB-4 index should be included in the evaluation of patients with MetS in the Endocrinology outpatient setting. Further studies are needed to validate FIB-4 best cut-off value in our population.

Palavras-chave:
Doença Hepática Não Alcoólica;
Síndrome Metabólica.

O Índice FIB-4 deve Orientar a Referenciação de Doentes com Síndrome Metabólica para a Gastrenterologia: A Perspetiva de uma Coorte Portuguesa

R E S U M O

Introdução: Os dados sobre a necessidade de referenciação dos doentes com síndrome metabólica (SM) para a consulta de Hepatologia são escassos. A maioria dos autores concorda que os doentes

* Autor Correspondente / Corresponding Author.
E-Mail: marta.canha@gmail.com (Marta Borges Canha)
Serviço de Endocrinologia, Diabetes e Metabolismo / Centro Hospitalar Universitário de São João
Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

https://doi.org/10.26497/ao230023

de risco (incluindo doentes com diabetes ou SM) devem ser rastreados para doença hepática não alcoólica (DHNA) e referenciados para a consulta de Hepatologia/ Gastroenterologia sempre que necessário. A evidência atual reporta uma baixa taxa de referenciação dos doentes com DHNA para hepatologistas. O nosso objetivo foi fazer uma avaliação de uma coorte de doentes com SM seguidos em consulta externa de Endocrinologia relativamente à necessidade da sua referenciação para Hepatologia/ Gastroenterologia.

Métodos: Análise secundária incluindo os doentes da coorte microDHNA (adultos com SM seguidos em consulta externa de Endocrinologia por qualquer causa). O recrutamento inclui anamnese, exame objetivo, estudo analítico e elastografia hepática. O resultado principal desta análise foi a necessidade referenciação para Gastroenterologia por fibrose hepática (todos os doentes com um valor ³7kPa na elastografia hepática foram referenciados). Foi testada a capacidade discriminatória de vários parâmetros bioquímicos e índices ([FLI (*Fatty Liver Index*), preditor de esteatose hepática; BARD (*Body Mass Index*, AST/ALT *Ratio, and Diabetes*), APRI (*Aspartate Aminotransferase to Platelet Ratio Index*), NFS (NAFLD *Fibrosis Score*) e FIB-4 (*Fibrosis-4 Index*), preditores de fibrose hepática]) relativamente à predição da necessidade de referenciação dos doentes, utilizando análises de curvas ROC.

Resultados: Foram incluídos no total 65 doentes, sendo 53,8% do sexo feminino e a média de idade de 61,2±9,6 anos. Oito (12,3%) doentes tinham critérios de referenciação para a consulta de Gastroenterologia após realização de elastografia hepática, nenhum dos quais tinha sido previamente referenciado. A nossa análise mostrou que o melhor parâmetro para predizer a tomada de decisão de referenciação dos doentes com SM foi o índice FIB-4. Um valor limiar de FIB-4 de 2,11 associou-se a uma área sob a curva de 0,80, sensibilidade de 62% e especificidade de 98%, como preditor da necessidade de referenciação.

Conclusão: Os nossos resultados demonstram que a utilização de índices como o FIB-4 deve ser incluída na avaliação dos doentes com SM, nas consultas de Endocrinologia. São necessários mais estudos para validar o limiar de FIB4 que deve guiar.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the primary cause of chronic liver disease. It comprehends a wide spectrum from simple steatosis to steatohepatitis (NASH) and fibrosis, which may lead to cirrhosis and hepatocarcinoma.[1] It has been termed a "barometer of metabolic health" due to its metabolic recognized origins.[2] Many epidemiological studies show an association between NAFLD and metabolic syndrome (MetS).[3,4] Although traditionally NAFLD is considered as the hepatic counterpart of MetS, growing evidence supports a bidirectional relationship between the two, being insulin resistance the common central pathophysiological process.[5,6]

Endocrinologists frequently follow people with MetS at risk of NAFLD, namely in its severest forms and should, therefore, be aware and promptly refer patients at high-risk of cirrhosis to the hepatologist to achieve a timely diagnosis and treatment.[7]

NAFLD is typically asymptomatic at initial stages. The biochemical evaluation of liver enzymes and its usage in predictive scores is of paramount importance at this time. There are several scores which can be easily used to predict hepatic steatosis and fibrosis, each with acknowledged strengths and limitations.[8]

There are no firm recommendations regarding which individuals should be screened for NAFLD. Most authors agree that at-risk patients (including the ones with diabetes or MetS)[9-12] should be screened, but also disclose that there are no cost-effectiveness studies to support this decision.[10]

Data regarding MetS patient's referral to hepatologists is scarce, namely in tertiary Portuguese patients' cohorts. Existing data highlights that referral of patients with NAFLD to specialists remain low among endocrinologists.[13,14] In this analysis, we aimed to evaluate a Portuguese well defined cohort of patients with MetS, followed in Endocrinology outpatient setting, regarding their need to referral to hepatologists and draw attention to this imminent need.

Methods

This study was reviewed and approved by the ethical committee of Centro Hospitalar Universitário de São João, Porto, Portugal. Written informed consent for participation was obtained from each patient included. Privacy of the included patients was preserved throughout the study.

1. Study Design

This is a secondary analysis including the patients from microDHNA cohort. This is a cohort of adult patients with MetS followed in Endocrinology outpatient setting for any cause. In brief, the inclusion criteria are: 1) being diagnosed with MetS; 2) being 18 to 75 years old. The exclusion criterion was not being able to consent. The recruitment includes anamnesis, filling of quality-of-life questionnaires (Short-Form Health Survey, SF-36, and Chronic Liver Disease Questionnaire), physical examination (including anthropometric and blood pressure evaluation), blood drawing for several predefined analyses and hepatic elastography (performed by the same operator, in 58 from the total 65 individuals). After these steps, all results are reviewed by the authors and patients with hepatic fibrosis (defined as a median value on elastography ³7kPa[15-17] [are referred to the hepatology clinic. We included all 65 patients from microDHNA cohort in this analysis.

2. Clinical Definitions

We used FLI (Fatty Liver Index) score as a predictor of hepatic steatosis and BARD (Body Mass Index, AST/ALT Ratio, and Diabetes), APRI (Aspartate Aminotransferase to Platelet Ratio Index), NFS (NAFLD Fibrosis Score) and FIB-4 (Fibrosis-4 Index) scores as predictors of hepatic fibrosis. These were built based on the following formulas:

1) **FLI score:** FLI = ey/(1+ ey) x 100, where y = 0.953 x ln (triglycerides, mg/dL) + 0.139 x BMI, kg/m^2 + 0.718 x ln (GGT, U/L) + 0.053 x waist circumference, cm – 15.745.

FLI scores <30 indicate low risk of hepatic steatosis, 30 to 60 intermediate risk and ≥60 high risk.[18]

2) **BARD score:** BMI≥28 = 1 point; AST/ALT ratio≥0.8 = 2 points, presence of diabetes = 1 point. Low fibrosis risk patients are scored 0 to 1 points and higher risk patients are scored 2 to 4 points.[19]
3) **APRI score:** (AST/AST upper limit normal)/(platelet count [10^9/L]) × 100[20];
4) **NFS score:** 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × diabetes (yes = 1, no = 0) + (0.99 × AST/ALT ratio) (0.013 × platelet [×10^9/L]) (0.66 × albumin [g/dL]).[21]
5) **FIB-4:** (age [years] × AST [U/L])/([platelets (10^9/L)] × ÖALT [U/L]).[22]

3. Outcomes and Statistical Analysis

Continuous variables are presented as mean (standard deviation, SD), if normally distributed, or as median (25^{th} to 75^{th} percentiles), if non-normally distributed. Variables with skewed distribution were transformed to their natural logarithm. Categorical variables are presented as absolute and relative frequencies.

Our primary outcome was patients' referral to gastroenterology due to hepatic fibrosis (defined as a median value on elastography ³7kPa).

Logistic regression analyses were performed to evaluate the associations of hepatic biochemical parameters and hepatic steatosis and fibrosis indexes with our main outcome.

The diagnostic accuracy of each hepatic biochemical parameter or index in discriminating between the referral of patients was evaluated using ROC curve analysis calculating the optimal cut-off value (based on Liu index[23]), and the AUC, specificity, and sensitivity at the estimated optimal cut-off value.

Statistical analyses were conducted using Stata software, version 14.1 (StataCorp). We considered a two-sided *p* value less than 0.05 to be statistically significant.

Results

1. Baseline Population Characteristics

Table 1 shows the demographic and clinical characteristics of the included population (total n=65) per group (referred versus not referred to gastroenterology). A total of 8 patients (12.3%) were referred to gastroenterology after performing hepatic elastography, none of which was already referenced.

The groups are significantly different considering GGT, total and direct bilirubin levels, FLI, NFS, APRI and FIB-4 indexes, controlled attenuation parameter, and, as expected, regarding hepatic elastography median (our group defining variable).

2. Logistic Regression Analyses

Table 2 displays the logistic regression models for hepatic biochemical parameters and for hepatic steatosis and fibrosis predictor indexes, regarding our main outcome (patient referral to gastroenterology). Patients with higher total bilirubin levels, and higher APRI and FIB-4 scores had higher odds of being referred to gastroenterology.

3. ROC Curve Analyses

Table 3 displays the ROC curve analysis testing the discriminatory ability of each parameter to patients' referral. Considering such analysis, one should note that a FIB-4 value of 2.11 associates to an area under the curve of 0.80 and has a sensitivity of 62% and specificity of 98% at this cut-off point.

Table 4 shows ROC curve analysis for other FIB-4 cut points previously addressed in the literature. The usage of 3.25 denotes a specificity of 100%, at the expense of a 25% sensibility. The lower

Table 1. Clinical and demographic characteristics of the population included (n=65).

	Not referred (n=57)	Referred (n=8)	*p* value
Age, years	61.8 ± 9.6	62.1 ± 10.4	0.82
Female sex, n (%)	31 (54.4)	4 (50.0)	0.94
Body Mass Index, kg/m²	29.5 ± 5.3	32.9 ± 7.0	0.11
Waist circumference, cm	102.3 ± 12.5	110.4 ± 16.1	0.10
Waist-to-Hip Ratio	0.96 ± 0.09	0.98 ± 0.08	0.46
Systolic blood pressure, mmHg	141.2 ± 20.8	137.6 ± 16.1	0.65
Diastolic blood pressure, mmHg	75.2 ± 13.6	74.1 ± 13.1	0.84
Glycated haemoglobin, %	7.0 ± 1.4	7.0 ± 0.6	0.96
AST, U/L	23.0 [19.0, 30.0]	26 [15.5, 44.0]	0.88
ALT, U/L	24.0 [18.0, 31.0]	20.5 [14.0, 31.0]	0.51
GGT, U/L	25.0 [17.5, 43.0]	58.0 [28.5, 247.5]	**0.029**
Total bilirubin, mg/dL	0.55 [0.44, 0.71]	0.83 [0.54, 1.73]	**0.06**
Total cholesterol, mg/dL	165.5 ± 49.4	145.8 ± 35.9	0.28
HDL cholesterol, mg/dL	49.9 ± 10.4	42.2 ± 8.4	**0.05**
LDL cholesterol, mg/dL	83.0 [66.0, 101.0]	68.5 [49.0, 103.0]	0.32
Triglycerides, mg/dL	117.5 [85.0, 180.0]	136.5 [97.8, 175.5]	0.69
FLI	69.2 [47.0, 82.8]	93.7 [74.0, 96.9]	**0.039**
BARD	3.0 [3.0, 4.0]	4.0 [2.5, 4.0]	0.57
NFS	-0.9 [-2.0, -0.3]	0.3 [-1.5, 1.6]	**0.046**
APRI	0.4 [0.3, 0.5]	0.6 [0.3, 0.9]	**0.07**
FIB-4	1.2 ± 0.5	2.1 ± 1.4	**<0.001**
CAP, dBm	274.4 ± 56.8	315.6 ± 44.4	**0.06**
IQR/median	15.0 [12.0, 21.0]	21.5 [18.5, 26.5]	**0.019**
Elastography median, kPa	5.2 ± 1.6	12.8 ± 4.8	**<0.001**
IQR/median	29.0 [22.0, 49.0]	29.5 [26.0, 39.0]	0.97

Values are shown as mean ± standard deviation or as median [percentile 25 – percentile 75]. AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; BARD, body mass index, AST/ALT ratio, and diabetes; NFS, NAFLD fibrosis score; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 index; CAP, controlled attenuation parameter; IQR, interquartile range.

Table 2. Logistic regression analyses for the main outcome (referral to gastroenterology).

	Odds ratio	95% confidence interval	*p* value
AST, U/L	1.02	0.97, 1.07	0.477
ALT, U/L	0.99	0.94, 1.04	0.630
GGT, U/L	0.02	0.01, 0.03	**0.007**
Total bilirubin, mg/dL	7.53	1.30, 43.5	**0.024**
FLI	0.03	-0.01, 0.07	0.125
BARD	1.12	0.51, 2.45	0.786
NFS	0.80	0.06, 1.53	**0.034**
APRI	4.51	0.91, 8.11	**0.014**
FIB-4	1.36	0.34, 2.39	**0.029**

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; BARD, Body Mass Index, AST/ALT Ratio, and Diabetes; NFS, NAFLD Fibrosis Score; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

Table 3. ROC curve analyses for the main outcome (referral to gastroenterology).

	Empirical optimal cut point	Sensitivity/ specificity at cut point*	AUC at cut point*
AST, U/L	37	0.38 (0.09, 0.76) / 0.89 (0.77, 0.96)	0.63 (0.45, 0.82)
ALT, U/L	29.5	0.38 (0.09, 0.76) / 0.72 (0.58, 0.84)	0.55 (0.36, 0.74)
GGT, U/L	52	0.62 (0.25, 0.92) / 0.85 (0.72, 0.93)	0.74 (0.55, 0.92)
Total bilirubin, mg/dL	0.665	0.71 (0.29, 0.96) / 0.69 (0.55, 0.90)	0.70 (0.51, 0.90)
FLI	84.1	0.75 (0.35, 0.97) / 0.77 (0.63, 0.88)	0.76 (0.59, 0.93)
BARD	3.5	0.62 (0.25, 0.92) / 0.56 (0.41, 0.69)	0.59 (0.40, 0.78)
NFS	-0.21	0.71 (0.29, 0.96) / 0.79 (0.64, 0.90)	0.75 (0.56, 0.94)
APRI	0.73	0.50 (0.16, 0.84) / 0.96 (0.87, 0.99)	0.73 (0.54, 0.92)
FIB-4	**2.11**	**0.62 (0.25, 0.92) / 0.98 (0.9, 1.0)**	**0.80 (0.62, 0.98)**

* Values are shown as value (95% confidence interval).

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, Fatty Liver Index; BARD, Body Mass Index, AST/ALT Ratio, and Diabetes; NFS, NAFLD Fibrosis Score; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

Table 4. ROC curve analyses for different FIB-4 (Fibrosis-4 Index) cut points.

Cut point	Sensitivity/ specificity at cut point*	AUC at cut point*
1.30	0.63 (0.25, 0.92) / 0.58 (0.43, 0.71)	0.60 (0.41, 0.79)
1.45	0.63 (0.25, 0.92) / 0.67 (0.53, 0.80)	0.65 (0.46, 0.84)
2.11	0.62 (0.25, 0.92) / 0.98 (0.9, 1.0)	0.80 (0.62, 0.98)
3.25	0.25 (0.03, 0.65) / 1.00 (0.93, 1.00)	0.62 (0.46, 0.79)

* Values are shown as value (95% confidence interval).

cut points of 1.3 and 1.45 just slightly augment the sensibility to 63%, at the expense of bearing a lower specificity.

Discussion

This is a secondary analysis of a Portuguese well defined cohort of patients with MetS followed in Endocrinology outpatient setting regarding their need to referral to hepatologists. Data on this subject is scarce and needed. We showed that around 13% of patients were referred to gastroenterology due to hepatic stiffness (none of which had already been referenced), and that FIB-4 was the better predictor of referral among the studied parameters.

Current literature is scarce and not consensual. The American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings states that clinicians must screen patients with features of MetS for NAFLD and advanced fibrosis.[24] These authors agreed that a FIB-4 score >1.3 should lead to further workup, for example, hepatic elastography.[24]

The clinical practice guidelines for NAFLD/NASH from the joint committee of Japanese Society of Gastroenterology and the Japanese Society of Hepatology (2020) propose a screening method for NAFLD with hepatic fibrosis by a general physician and, if liver fibrosis is indicated, referral for gastroenterology specialist should be considered.[25] Regarding FIB-4, these authors consider that a value of <1.3 do not need further assessment and that values above this should undertake elastography.[25]

On the other hand, the Practice guidance from the American Association for the Study of Liver Diseases (2016) considered that patients with a FIB-4 score <1.45 are unlikely and that those with values above 3.25 are likely to have advanced fibrosis.[1,26]

In our study, we show that a FIB-4 value of ≥ 2.11 has a specificity of 98% for significant liver stiffness, suggesting that these range of FIB-4 values warrant urgent gastroenterology referral. In our population, the lower cut points of 1.3 and 1.45 just slightly augment the sensibility but considerably diminishes the specificity. The usage of 3.25 denotes a specificity of 100%, at the expense of a 25% sensibility.

FIB-4 has been validated in ethnically different NAFLD populations, with consistent results.[11,24] FIB-4 score seems to be better than BARD and APRI for predicting advanced fibrosis in patients with biopsy-proven NAFLD.[1,27] This index has been shown to predict overall mortality, cardiovascular and liver-related mortality.[11] The performance of such index is dependent on the population studied, being better at hepatology clinics, where pretest probability of liver fibrosis is higher.[24] Of note, this it is not a perfect surrogate marker and physicians must be aware of its weaknesses when interpreting it. For instance, age is one of the factors included in the index and, as such, higher index values in older individuals do not necessarily mean true liver stiffness.[25]

This study has limitations that must be acknowledged. Firstly, the low number of participants may be a drawback given the lack of power to detect small differences. Also, this is a retrospective secondary analysis, and we may have missing confounders. Finally, we used hepatic elastography as our group defining variable and we do not have histological diagnosis of either hepatic steatosis or fibrosis. However, to the best of our knowledge, this is the first study on a tertiary Portuguese cohort, and we believe that the importance of our results fairly overcome the limitations.

Our results highlight that the use of FIB-4 index should be included in the evaluation of patients with MetS in Endocrinology outpatient setting, which are high risk patients for liver fibrosis. It is worth to think about including it as an automatic calculated result when ordering AST, ALT and platelets. Timely patients' referral is of paramount importance to avoid progression of NAFLD to cirrhosis. Further studies are needed to validate FIB-4 best cut-off value in our population.

Contributorship Statement / Declaração de Contribuição:

MBC, JSN, ARL, MvH and CV: Responsible for the study conception and design.
MBC, RL, ARL, JCC, IML and MvH: Contributed to data collection.

MBC, JSN and ARL: Responsible for data analysis and interpretation, and statistical analysis.
MBC prepared the first version of the article.
All authors provided critical revision and approved the final version to be published.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328-57.
2. Sookoian S, Pirola CJ. Personalizing care for nonalcoholic fatty liver disease patients: what are the research priorities? Per Med. 2014;11:735-43.
3. Cortez-Pinto H, Camilo ME, Baptista A, De Oliveira AG, De Moura MC. Non-alcoholic fatty liver: another feature of the metabolic syndrome? Clin Nutr. 1999;18:353-8.
4. Souza MR, Diniz Mde F, Medeiros-Filho JE, Araujo MS. Metabolic syndrome and risk factors for non-alcoholic fatty liver disease. Arq Gastroenterol. 2012;49:89-96.
5. Zhang Y, Zhang T, Zhang C, Tang F, Zhong N, Li H, et al. Identification of reciprocal causality between non-alcoholic fatty liver disease and metabolic syndrome by a simplified Bayesian network in a Chinese population. BMJ Open. 2015;5:e008204. doi: 10.1136/bmjopen-2015-008204.
6. Wainwright P, Byrne CD. Bidirectional relationships and disconnects between nafld and features of the metabolic syndrome. Int J Mol Sci. 2016;17:367. doi: 10.3390/ijms17030367.
7. Belfort-DeAguiar R, Lomonaco R, Cusi K. Approach to the patient with nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2023;108:483-95. doi: 10.1210/clinem/dgac624. .
8. Borges-Canha M, Neves JS, Mendonca F, Silva MM, Costa C, Cabral PM, et al. The impact of bariatric surgery on hepatic function and predictors of liver steatosis and fibrosis. Obes Surg. 2020;30:2935-41. doi: 10.1007/s11695-020-04622-0.
9. Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. Hepatol Res. 2021;51:1013-25. doi: 10.1111/hepr.13688.
10. Aller R, Fernandez-Rodriguez C, Lo Iacono O, Banares R, Abad J, Carrion JA, et al. Consensus document. Management of non-alcoholic fatty liver disease (NAFLD). Clinical practice guideline. Gastroenterol Hepatol. 2018;41:328-49. doi: 10.1016/j.gastrohep.2017.12.003.
11. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388-402. doi: 10.1016/j.jhep.2015.11.004.
12. Kanwal F, Shubrook JH, Younossi Z, Natarajan Y, Bugianesi E, Rinella ME, et al. Preparing for the NASH epidemic: A call to action. Gastroenterology. 2021;161:1030-42.e8. doi: 10.1053/j.gastro.2021.04.074.
13. Kanwal F, Shubrook JH, Younossi Z, Natarajan Y, Bugianesi E, Rinella ME, et al. Preparing for the NASH Epidemic: A Call to Action. Diabetes Care. 2021;44:2162-72. doi: 10.2337/dci21-0020.
14. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, et al: Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021;161:1657-69. doi: 10.1053/j.gastro.2021.07.049.
15. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51:454-62.
16. Berends MA, Snoek J, de Jong EM, Van Krieken JH, de Knegt RJ, van Oijen MG, et al. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver fibrosis. Liver Int. 2007;27:639-45. doi: 10.1111/j.1478-3231.2007.01489.x.
17. Torbator K, Poo S, Al-Rubaye T, Mapara L, Punjabi S, Al-Rubaye A, et al. Whether screening for non-alcoholic fatty liver disease in patients with psoriasis is necessary: a pilot quality improvement project. Cureus. 2022;14:e24714. doi: 10.7759/cureus.24714.
18. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33. doi: 10.1186/1471-230X-6-33.
19. Cheah MC, McCullough AJ, Goh GB. Current Modalities of Fibrosis Assessment in Non-alcoholic Fatty Liver Disease. J Clin Transl Hepatol. 2017;5:261-71. doi: 10.14218/JCTH.2017.00009.
20. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38:518-26.
21. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45:846-54.
22. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
23. Liu X: Classification accuracy and cut point selection. Stat Med 2012, 31(23):2676-2686.
24. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022;28:528-62. doi: 10.1016/j.eprac.2022.03.010.
25. Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol. 2021;56:951-63. doi: 10.1007/s00535-021-01796-x.
26. Kaswala DH, Lai M, Afdhal NH. Fibrosis assessment in nonalcoholic fatty liver disease (NAFLD) in 2016. Dig Dis Sci. 2016;61:1356-64.
27. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology. 2016;150:626-37.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Revisão

Redução Gradual até à Suspensão da Corticoterapia Oral e a Avaliação do Eixo Hipotálamo-Hipófise-Suprarrenal

Sara Correia [a], José Diogo Silva [a], Gustavo Melo Rocha [a], Maria João Oliveira [a]

[a] *Serviço de Endocrinologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-07-11
Accepted/Aceite: 2023-01-25
Ahead of Print: 2023-04-19
Publicado / Published: 2023-10-18

Palavras-chave:
Glucocorticoides;
Insuficiência Adrenal/induzida quimicamente;
Síndrome de Abstinência a Substâncias;
Sistema Hipófise-Suprarrenal.

Keywords:
Adrenal Insufficiency/chemically induced;
Glucocorticoids;
Pituitary-Adrenal System;
Substance Withdrawal Syndrome.

R E S U M O

Os glucocorticoides orais são muito utilizados na prática clínica e representam a base para o tratamento de inúmeras doenças inflamatórias, autoimunes e respiratórias. Porém, as suas ações terapêuticas são contrabalançadas por efeitos colaterais, dos quais fazem parte, o risco de desenvolver insuficiência cortico-suprarrenal. A potência, a dose e a duração do glucocorticoide são preditores importantes, mas imperfeitos, da supressão do eixo hipotálamo-hipófise-suprarrenal. De uma forma geral, quanto maior o tempo de tratamento com glucocorticoide e maior a sua potência, maior o risco de supressão. Nestas circunstâncias, é necessário que a redução da dose seja gradual e o eixo hipotálamo-hipófise-suprarrenal seja testado ao longo do processo de redução da dose e suspensão. Não existe atualmente nenhuma orientação clínica definida pelas sociedades científicas para a redução da dose do glucocorticoide, existindo diferentes esquemas propostos na literatura. Este artigo pretende assim apresentar uma revisão atualizada e prática de como efetuar de forma segura a suspensão da corticoterapia.

Oral Glucocorticoid Withdrawal and Assessment of the Hypothalamic-Pituitary-Adrenal Axis

A B S T R A C T

Oral glucocorticoids are widely used in clinical practice and represent the basis for the treatment of numerous inflammatory, autoimmune and respiratory diseases. However, its therapeutic actions are counterbalanced by side effects, which include the risk of developing cortico-adrenal insufficiency. Glucocorticoid potency, dose, and duration are important but imperfect predictors of hypothalamic-pituitary-adrenal axis suppression. In general, the longer the treatment time with glucocorticoid and the greater its potency, the greater the risk of suppression. In these circumstances, it is necessary that the dose reduction be gradual and the hypothalamic-pituitary-adrenal axis be tested throughout the process of dose reduction and withdrawal. There is currently no clinical guideline defined by scientific societies for reducing the dose of glucocorticoid, with different schemes proposed in the literature. This article therefore intends to present an up-to-date and practical review of how to safely discontinue corticosteroid therapy.

* Autor Correspondente / Corresponding Author.
E-Mail: saracostacorreia@live.com.pt (Sara Correia)
Rua Conceição Fernandes S/N, 4434-502 Vila Nova de Gaia, Portugal

https://doi.org/10.26497/ar220048

Introdução

Os glucocorticoides (GC) orais são muito utilizados na prática clínica e representam a base para o tratamento de inúmeras doenças inflamatórias, autoimunes e respiratórias. Atualmente, cerca de 1%-3% da população mundial está em tratamento crónico com GC, o que pode causar uma ISR secundária.[1-5]

Após absorção para a circulação sistémica, os GC sintéticos, que resistem ao metabolismo hepático de primeira passagem (como a hidrocortisona, a prednisolona e a betametasona), exercem um mecanismo de retrocontrolo negativo sobre o eixo hipotálamo-hipófise-suprarrenal (HHS), suprimindo a produção da hormona libertadora de corticotropina (CRH) e da hormona adrenocorticotrópica (ACTH).[2,5-7] Uma secreção de ACTH insuficiente prolongada (mais de 3-6 semanas) leva a uma hipoplasia e atrofia da zona fasciculada das glândulas suprarrenais, com redução da capacidade secretora de cortisol.[2,5-7] A supressão pode ser parcial ou total.[1] Existem vários fatores que aumentam o risco de desenvolvimento da ISR induzida por GC: o horário da toma, a dose e a potência do GC, a duração da terapêutica, a via e o esquema de administração, a idade do doente, a doença de base, a toma simultânea com outros fármacos que interferem no seu metabolismo e a variabilidade interindividual na sensibilidade do eixo HHS a GC exógenos.[8]

Habitualmente, a administração de GC orais, a longo prazo e em altas doses, pode originar uma insuficiência suprarrenal (ISR) induzida por GC. De uma forma geral, quando os GC são usados por um período inferior a 3 semanas, o eixo recupera rapidamente e não há necessidade de uma redução gradual na dose do corticoide, podendo este ser interrompido de imediato.[2,5,6] No caso de um período de exposição superior, o risco de supressão do eixo HHS aumenta.[2,5-7] Nestes casos, perante a interrupção de forma abrupta ou uma redução demasiado rápida do GC, podem desenvolver-se sintomas de ISR (Tabela 1) ou ocorrer uma ISR aguda com sintomas gastrointestinais graves, choque cardiovascular, hipoglicemia, convulsões e, eventualmente, coma.[3,8] Recomenda-se assim uma redução paulatina do GC e a avaliação da integridade do eixo.[9,10] Na prática clínica, as provas que avaliam a recuperação do eixo HHS são realizadas raramente.[2,7,8] Após a remoção do GC, as funções hipotalâmica e hipofisária são as primeiras a recuperar, seguida da função cortico-suprarrenal. A recuperação completa da função suprarrenal pode levar meses e até um ano, especialmente em casos que realizaram terapêutica prolongada com altas doses de GC.[3,4,11] A prevalência da ISR induzida por GC é difícil de determinar dada a heterogeneidade dos vários estudos e as conclusões são limitadas.[5,12] Porém, acredita-se que a ISR induzida por GC está claramente subdiagnosticada na prática clínica.[12,13]

Tabela 1. Manifestações da insuficiência suprarrenal

Sintomas/sinais sugestivos de ISR crónica
Mal-estar geral
Fadiga
Astenia
Tonturas
Sintomas gastrointestinais (náuseas, vómitos, diarreia, dor abdominal, anorexia)
Perda ponderal
Palidez cutânea
Hipotensão (sobretudo, hipotensão postural)
Cefaleias (usualmente matinais)
Artralgias (especialmente, afetando as articulações das mãos)
Mialgias
Infeções respiratórias recorrentes com uma recuperação lenta
Hipoglicemia (mais frequente em crianças)
Linfocitose e eosinofilia
Hiponatremia

ISR- insuficiência suprarrenal

Fatores de Risco para ISR Induzida por GC

Existem vários fatores que aumentam o risco de desenvolvimento da ISR induzida por GC: o horário da toma, a dose e a potência do GC, a duração, a via e o esquema de administração, a idade do doente, a doença de base, a associação com outros fármacos que interferem na sua ação e a variabilidade individual (Tabela 2).[1]

Tabela 2. Fatores de risco para insuficiência suprarrenal induzida por glucocorticoides

Duração da terapêutica	A supressão do eixo pelo GC, mesmo que em dose supra-fisiológica, por um curto período (até 3 semanas) não persiste quando este é suspenso e é improvável que tenha qualquer consequência clínica. No caso de um período de exposição superior (>3 semanas), há uma maior probabilidade de supressão do eixo.[2]
Potência do GC	Os corticoides podem ser divididos em três grupos de acordo com a duração da supressão da ACTH causada por uma dose padrão (equivalente a 50 mg de prednisolona): os de curta duração (hidrocortisona, cortisona, deflazacort), que suprimem a ACTH por menos de 36 horas; os de ação intermédia (prednisona, prednisolona, metilprednisolona) que suprimem cerca de 48 horas e os de ação prolongada (dexametasona, betametasona) que suprimem a ACTH por mais de 48 horas.[1] O uso de formulações com uma semivida biológica tecidular mais longa como a dexametasona e com maior potência (ou seja, com uma ligação mais forte ao recetor GC) predispõem a uma supressão suprarrenal mais pronunciada, dado o seu efeito contínuo sobre o eixo.[3,5]
Dose do GC	A supressão do eixo é incomum com doses de prednisolona inferior a 5 mg/dia, embora alguns estudos tenham demonstrado a sua supressão com esta dosagem.[8]
Horário da toma	A toma noturna do GC ou várias tomas ao longo do dia, aumenta a probabilidade de afetar a secreção circadiana de ACTH, comprometendo o funcionamento do eixo HHS.[4,5]
Via e esquema de administração	A administração por via sistémica (oral, parentérica ou intra-muscular) tem um maior risco de ISR, dada a maior concentração sanguínea atingida.[1,3,5,11,14,15]
Uso simultâneo de fármacos que interferem na ação do GC	O uso concomitante de fármacos inibidores do CYP3A4, como por exemplo, o cetaconazol, o itraconazol ou os inibidores da protease usados na terapêutica anti-retroviral, aumenta a exposição sistémica aos GC (como a dexametasona e a prednisolona, que são metabolizados por este citocromo) e aumenta também o risco de ISR.[5,11]
Idade	Na população idosa, a semivida dos GC é mais prolongada, ocorrendo um maior risco de desenvolver ISR.[5,14]
Doença de base	Numa revisão sistemática, o risco absoluto de ISR induzida por GC orais foi de 48,7%, com maior risco em indivíduos com doenças hematológicas malignas (60%), seguidos por doentes com antecedentes de transplante renal (56,2%), doença inflamatória intestinal (52,2%) e distúrbios reumatológicos (39,4%), doentes que habitualmente necessitam de terapêutica com GC durante um longo período.[5]
Suscetibilidade individual	Existe uma variabilidade inter-individual importante.[4,12] Diferenças a nível da sensibilidade ao GC, da concentração plasmática das proteínas transportadoras, da depuração e variações genéticas na regulação da atividade do recetor do GC parecem estar envolvidas no risco de supressão.[12,16] Indivíduos que evidenciam características cushingóides provavelmente também apresentam supressão do eixo HHS.[5,14]
Depuração do GC	A diminuição da depuração do GC foi observada em indivíduos com hepatopatias, nefropatias, uso de estrógenios, cetoconazol e anti-inflamatórios e o aumento da depuração, em doentes sob uso de fenitoína, fenobarbital e rifampicina.[1]

ACTH - hormona adrenocorticotrópica, GC- glucocorticoide, HHS - hipotálamo-hipófise-suprarrenal, ISR- insuficiência suprarrenal.

Para além disso, os GC sintéticos possuem uma afinidade muito baixa à CBG; sendo que 2/3 ligam-se fracamente à albumina e 1/3 circula sob a forma livre.[14] Deste modo, os GC sintéticos apresentam uma elevada afinidade pelos seus recetores, exercendo os seus efeitos.[14] Nos indivíduos com doença hepática crónica com hipoalbuminemia, a fração livre do GC sintético é superior e, portanto, mesmo sob uma dose baixa, pode resultar no desenvolvimento de uma síndrome de Cushing iatrogénica.[11]

Classificação dos Doentes Segundo o Risco de ISR Induzida por GC

Os doentes podem ser classificados em não suprimidos, suprimidos ou com supressão incerta/indeterminada do eixo HHS, com base no histórico de uso do GC (a dose e a duração) e na presença ou ausência de características cushingóides. De acordo com esse risco, é sugerida a suspensão imediata ou uma redução gradual da dose do GC até à suspensão.[2,7,8]

O risco de supressão do eixo HHS é improvável em doentes com (Tabela 3):

Tabela 3. Doentes sob corticoterapia com supressão do eixo HHS improvável.

• Toma de GC (qualquer dose) por um período <3 semanas • Terapêutica em dias alternados, com uma dose de prednisolona <10 mg ou equivalente • Toma matinal < 5 mg/dia de prednisolona ou equivalente por qualquer período de tempo	**Suspender, sem redução gradual**

AGC- glucocorticoide, HHS- hipotálamo-hipófise-suprarrenal.

Adaptado de: Pelewicz K, *et al*. Glucocorticoid Withdrawal-An Overview on When and How to Diagnose Adrenal Insufficiency in Clinical Practice. Diagnostics. 2021; 11:728.[8]

No caso de se proceder à suspensão da terapêutica, doentes sob estes esquemas, podem interromper o GC de imediato, sem uma redução gradual, desde que não apresentem sintomas clínicos de ISR.[2,7] Todavia, perante um individuo frágil, pode optar-se por agir com maior cuidado e realizar uma redução gradual do GC.[17] Para além disso, alguns estudos recentes revelam que mesmo o uso de GC num curto período (<4 semanas) ou em baixa dose (<5 mg de prednisolona/dia ou equivalente) pode alterar a função do eixo HHS.[8]

É provável que exista supressão do eixo HHS nos seguintes casos (Tabela 4):

Tabela 4. Doentes sob corticoterapia com supressão do eixo hipotálamo-hipófise-suprarrenal provável.

• Terapêutica com alta dose sistémica de corticóide (≥ 20 mg/dia de prednisolona ou equivalente) por um período > 3 semanas. • Terapêutica com corticóide ≥ 5 mg/dia de prednisolona ou equivalente, administrada à noite, durante ≥ 3 semanas. • Doente com características cushingóides – face em "lua cheia", pescoço de búfalo e obesidade central.	**Redução gradual do GC**

GC- glucocorticoide.

Adaptado de: Pelewicz K, *et al*. Glucocorticoid Withdrawal-An Overview on When and How to Diagnose Adrenal Insufficiency in Clinical Practice. Diagnostics. 2021; 11:728.[8]

É indeterminado ou incerto, o risco de supressão suprarrenal com (Tabela 5):

Tabela 5. Doentes sob corticoterapia com supressão do eixo hipotálamo-hipófise-suprarrenal indeterminada/incerta.

• Toma de 5-20 mg de prednisolona/dia ou equivalente durante > 3 semanas (desde que não seja tomada em dose única à noite). • Terapêutica de curta duração (< 3 semanas) no intervalo de um ano após interrupção de terapêutica prolongada com GC, sem que tenha sido realizado a avaliação do eixo HHS.	**Redução gradual do GC**

GC- glucocorticoide.

Adaptado de: Pelewicz K, *et al*. Glucocorticoid Withdrawal-An Overview on When and How to Diagnose Adrenal Insufficiency in Clinical Practice. Diagnostics. 2021; 11:728.[8]

Recomendações para Reduzir o Risco de Insuficiência Adrenal Induzida por GC

Não existe atualmente nenhuma orientação clínica definida pelas sociedades científicas para a redução da dose do GC.[11] Dada a variabilidade inter-individual, torna-se difícil elaborar um esquema ideal para todos os indivíduos e diferentes esquemas são propostos na literatura.[4] Existe também uma considerável variabilidade inter-individual na recuperação do eixo, com alguns indivíduos a serem capazes de tolerar a redução do GC mais rapidamente do que outros.[4,12] Os principais objetivos ao longo da redução do GC incluem: evitar a recorrência da doença de base, o desenvolvimento de ISR secundária e a síndrome de abstinência dos esteróides.[2,18] No caso de recrudescimento da doença de base, é necessário o ajuste da dose do GC, de acordo com as limitações da doença e a decisão deve ser partilhada entre o endocrinologista e o médico assistente.[1] Os doentes devem ser instruídos a estar atentos a possíveis sintomas/sinais sugestivos de ISR e, caso se manifestem, devem informar o médico, que deve prolongar o esquema de redução. Em situações que requerem um aumento da secreção de cortisol, como em casos de doença associada a febre ou infeção e outras situações de *stress*, os doentes e os familiares próximos devem ser informados quanto à necessidade de duplicar/triplicar a dose do GC.[5,8] Em caso de trauma, doença grave ou vómitos persistentes (via oral comprometida) ou diarreia persistente, o doente deve procurar assistência médica e a reposição do GC deve ser administrada por via endovenosa. Num procedimento cirúrgico há também necessidade de ajuste da dose, de acordo com a magnitude do *stress* cirúrgico.[1] Por sua vez, perante um indivíduo sob terapêutica prolongada, é aconselhável fornecer um cartão que reconheça o fato de estar sob terapêutica com GC e toda a informação deve ser fornecida por escrito.[11,13] Em doentes com alto risco de desenvolverem uma ISR aguda, os doentes e familiares devem ainda aprender a reconhecer os sinais e sintomas e como administrar a hidrocortisona (100 mg intramuscular).[5] De realçar, que existem duas situações que requerem a cessação imediata dos GC ou uma redução rápida significativa, ao invés de uma retirada gradual: na psicose aguda induzida por esteroides que não responde aos antipsicóticos e no caso de uma úlcera da córnea por vírus herpes, que pode levar rapidamente à perfuração da córnea e possível cegueira.[2]

Esquema de Redução do Corticóide Proposto

Em indivíduos com GC em alta dose (prednisolona > 20 mg/dia), propõe-se uma fase inicial de redução "rápida", seguida de uma fase de redução "lenta"[5] (Tabelas 6 e 7). Por sua vez, indivíduos sob prednisolona ≤ 20 mg/dia, sugere-se apenas a fase de redução "lenta" (Tabela 7). No caso do doente estar medicado com dexametasona, esta deverá ser substituída por uma dose

Tabela 6. Fase de redução "rápida"

Redução "rápida" inicial de GC Para doentes com uma dose diária média de GC de:	
PED > 40 mg/dia	Reduzir a dose diária de GC em 5-10 mg/semana, até PED 20 mg/dia
PED 20-40 mg/dia	Reduzir a dose diária de GC em 5 mg/semana, até PED 20 mg/dia
PED 10-20 mg/ dia	Seguir as recomendações de redução lenta dos GC

GC- glucocorticoides, PED- prednisolona.

Adaptado de: Prete A, *et al*. Glucocorticoid induced adrenal insufficiency. BMJ. 2021;374:n1380. doi: 10.1136/bmj.n1380.[5]

Tabela 7. Fase de redução "lenta"

Redução "lenta" do GC Para doentes com uma dose diária média de PED≤ 20 mg/dia:	
PED 10-20 mg/dia	Reduzir a dose diária do GC em 1-2,5 mg/semana, até 10 mg/dia. (Se SAG grave, considerar decréscimos bimensais)
PED 5-10 mg/dia	Reduzir em 1 mg semanalmente até 5 mg/dia. (Se SAG grave, considerar decréscimos bimestrais ou mensais)
PED 5 mg/dia	Não suspender ou reduzir o GC até que a recuperação do eixo HHS seja documentada. Considerar alterar para hidrocortisona 20 mg (15 ao acordar, 5 mg a meio da tarde), se recuperação tardia do eixo

HHS- hipotálamo-hipófise-suprarrenal, GC- glucocorticoides, PED- prednisolona, SAG- síndrome de abstinência dos glucocorticoides.

Adaptado de: Prete A, *et al*. Glucocorticoid induced adrenal insufficiency. BMJ. 2021;374:n1380. doi: 10.1136/bmj.n1380.[5]

equivalente de prednisolona. A substituição de um GC com longa duração de ação para um GC com uma semivida intermédia irá possibilitar a recuperação mais rápida do eixo HHS. Caso o doente esteja a fazer duas tomas ou uma toma noturna de prednisolona, esta deverá ser substituída por uma única toma de manhã.[5] É ainda provável que a recuperação do HHS ocorra mais rapidamente se o doente estiver sob hidrocortisona (GC com curta duração de ação) em oposição à prednisolona, dada a sua menor semivida.[5] A evidência científica quanto à redução gradual dos GC num esquema de dias alternados, não é consensual na literatura e há doentes que não toleram o dia de não tomar o corticóide.[5,14] Recomenda-se sempre uma abordagem individualizada sobre os sintomas e sinais apresentados pelo doente.[8]

Avaliação da Recuperação do Eixo HHS

É recomendável avaliar a função do eixo HHS nos indivíduos com supressão provável ou incerta, antes da suspensão do GC, dado o risco de ISR.[1,7,8,16] O diagnóstico de ISR induzida por GC é estabelecido pela deteção de um cortisol sérico basal e/ou estimulado baixo (Tabela 8).[8, 11]

Quando se alcança a dose de prednisolona ≤ 5 mg/dia ou hidrocortisona ≤ 20 mg/dia, durante pelo menos um período de 1-4 semanas, nesse momento deverá ser doseado o cortisol sérico matinal e a ACTH.[5] A Fig. 1 apresenta de uma forma sucinta o esquema de gestão sugerido para um doente sob terapêutica com GC e os passos a seguir na avaliação do eixo HHS.

Doseamento do Cortisol Matinal e da ACTH

O doseamento deve realizar-se em jejum entre as 8 e as 9 horas da manhã, pelo menos 24 horas após a última toma do GC (incluindo, se este for a hidrocortisona).[16] O doente não deverá estar a tomar um GC de longa duração de ação, como a dexametasona.[5] Os níveis plasmáticos de ACTH são geralmente baixos ou inapropriadamente normais em indivíduos sob terapêutica com GC, pelo que têm um valor limitado na avaliação da recuperação do eixo.[19] Um nível de ACTH muito elevado (>100 pg/mL) pode ser útil para excluir a ISR induzida por GC, pois é uma característica da ISR primária.[8] Quanto ao valor do cortisol sérico total, se este for < 3 µg/dL, considera-se que o eixo está suprimido e é necessário manter a reposição do corticóide.[8,20] Caso o cortisol tenha um valor intermédio entre 3-15 µg/dL é necessário realizar adicionalmente uma prova dinâmica. Se o cortisol for > 15 µg/dL, considera-se que o eixo está recuperado e pode suspender-se o GC de imediato.[8,20,21] De realçar que o valor de corte de 15 µg/dL não é consensual na literatura, existindo diferentes estudos que consideram valores de corte distintos de 12,7/ 13/ 14,91/ 16,3 ou 18,3 µg/dL.[8,16,19,22] Num estudo realizado em 2016, foram propostos valores de cortisol sérico matinal que prediziam uma resposta

Tabela 8. Formas de avaliação do eixo hipotálamo-hipófise-suprarrenal

Provas hormonais basais	**Doseamento do cortisol sérico matinal e ACTH**
Provas hormonais dinâmicas	• Prova de hipoglicemia insulínica e a prova da metirapona - permitem avaliar o eixo completo; • Prova da CRH e a prova de glucagon – permite avaliar o subsistema hipófise-córtex suprarrenal; • Prova do tetracosactídeo - permite avaliar diretamente o córtex suprarrenal.

ACTH- hormona adrenocorticotrópica, CRH- hormona libertadora de corticotropina.

Adaptado de: Pelewicz K, *et al*. Glucocorticoid Withdrawal-An Overview on When and How to Diagnose Adrenal Insufficiency in Clinical Practice. Diagnostics. 2021; 11:728.[8]; Pokrzywa A, Ambroziak U, *et al*. Detecting adrenal insufficiency in patients with immunoglobulin A nephropathy, lupus nephritis, and transplant recipients qualified for glucocorticoid withdrawal. Pol Arch Intern Med. 2019;129:874-82.[16]

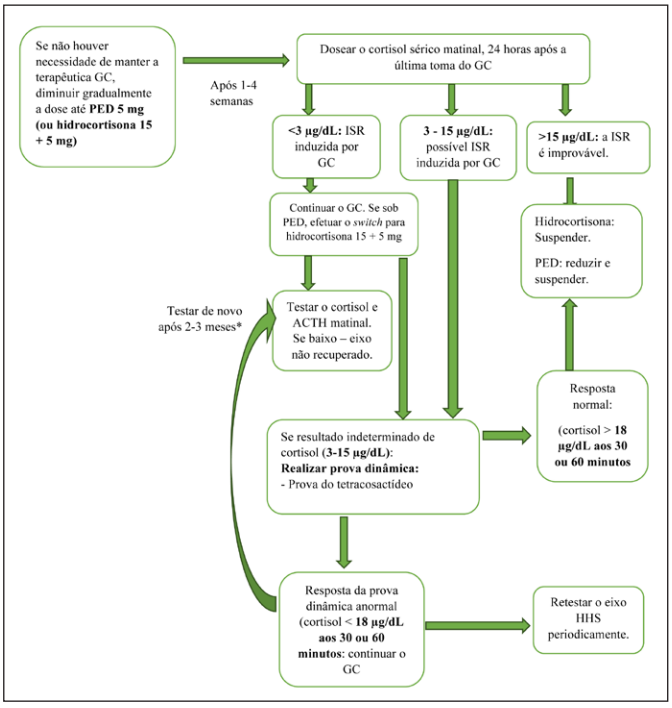


Figura 1. Gestão da terapêutica com GC e avaliação do eixo hipotálamo-hipófise-suprarrenal. (Este é apenas um guia – A gestão deve ser adaptada individualmente.)

* Se o eixo HHS não se recuperar por 1-2 anos, considerar reavaliar a cada 3-6 meses.
ACTH - hormona adrenocorticotrópica; GC - glucocorticóides; HHS - hipotálamo-hipófise-suprarrenal; ISR - insuficiência suprarrenal; PED - prednisolona. Dados: Esquema adaptado a partir dos artigos 5 e 8.

adequada na prova do tetracosactídeo, com uma especificidade de 100%, consoante o método de doseamento utilizado: para a Advia Centaur (Siemens) foi definido como > 13 µg/dL, para a Abbott Architect i -2000 como >12,2 µg/dL e para a Roche *Modular System* como > 18,3 µg/dL.[22]

Por outro lado, o doseamento do cortisol total pode ter várias interferências que devem ser tidas em consideração na interpretação dos resultados obtidos. O cortisol pode ser mais elevado em mulheres sob terapêutica com estrogénios ou na gravidez, dado o aumento dos níveis da globulina de ligação aos corticosteroides (CBG) que originam. A CBG representa a principal proteína de transporte (60%-80%).[19] Uma das recomendações inclui assim a suspensão da toma de estrogénios, pelo menos 6 semanas antes de efetuar este doseamento.[22] Em contraste, o cortisol pode encontrar-se diminuído em doentes com CBG e albumina baixas (albumina ≤ 2,5 g/dL), como na cirrose hepática ou na doença crítica.[5,19] Na ausência de patologia que condicione alterações das proteínas de ligação, o doseamento do cortisol sérico total é considerado na maioria dos casos, confiável.[19] Contudo, o julgamento clínico continua a ser essencial para decidir quando confiar totalmente nesse doseamento.[22] O doseamento do cortisol sérico livre irá trazer vantagens, não sendo influenciado pela variação das proteínas de ligação, porém ainda não se encontra disponível por rotina.[19]

Prova do Tetracosactídeo

Embora a prova de hipoglicemia insulínica seja considerado o "padrão de ouro" para avaliação do eixo HHS, dado ser contraindicado em indivíduos idosos, com antecedentes de epilepsia ou patologia cardíaca e dada a conveniência, a segurança e a ampla disponibilidade demonstradas pela prova do tetracosactídeo, este é habitualmente o método preferido para avaliar a função suprarrenal e o mais utilizado na prática clínica.[11] A prova do tetracosactídeo é realizado quando o valor de cortisol basal obtido tem um resultado intermédio, entre os 3-15 µg/dL.[1]

A prova com alta dose de ACTH é realizado da seguinte forma: após a suspensão da corticoterapia por pelo menos 24 horas, determina-se o cortisol sérico basal entre 8-9 horas, administra-se de seguida 250 µg de ACTH sintética via endovenosa e, após 30 e 60 minutos, repete-se o doseamento do cortisol sérico.[1] Um nível de cortisol ≥18 µg/dL aos 30 ou 60 minutos, prevê uma reserva adequada e a terapêutica com o GC pode ser descontinuada.[2] Caso o cortisol pós-estímulo seja <18 µg/dL, o eixo ainda não está recuperado, sendo necessário uma redução mais lenta do GC.[11] De salientar uma vez mais que o ponto de corte diagnóstico depende do método de doseamento utilizado.[23] Um estudo propôs diferentes níveis de cortisol para se considerar uma resposta adequada à prova do tetracosactídeo, consoante o método de doseamento utilizado: para a Advia Centaur (Siemens) foi definida como > 16,3 µg/dL, para a Abbott Architect i -2000 *immunoassay analyser* como >15,6 µg/dL e para o Roche *Modular System* como > 19,9 µg/dL.[22]

Embora a prova do tetracosactídeo não forneça informações sobre a integridade completa do eixo, considera-se que dado que o córtex suprarrenal retoma a sua atividade mais tardiamente que a função hipotálamo-hipofisária, uma resposta adequada nesta prova, indica que todo o eixo HHS está a funcionar adequadamente.[11,24] Esta prova é extremamente útil na maioria dos casos e tem demonstrado resultados equivalentes à hipoglicemia insulínica (padrão de ouro).[7,22] Os estudos têm demonstrado resultados semelhantes no uso da prova de alta dose de ACTH (250 µg) e de baixa dose (1µ). Como as ampolas de ACTH disponíveis contêm 250 µg, torna-se mais exequível a prova de alta dose, não implicando a necessidade de diluição.[25] Todavia, a prova de tetracosactídeo tem custos inerentes, nomeadamente o preço da ampola e a necessidade de uma equipa de enfermagem e/ou médica obrigatória na supervisão ao longo da realização da prova.[22] No caso de não ser possível a sua realização, considera-se que o doente que fez uso prolongado de corticoide esteja sob risco de ISR até 1 ano após a sua suspensão.[1]

Limitações das Provas de Avaliação do Eixo HHS

Uma das principais dificuldades inerente às provas de avaliação da função suprarrenal prende-se como anteriormente mencionado, com o uso de diferentes métodos de doseamento para a mensuração do cortisol e diferentes valores de corte para a interpretação dos resultados das provas.[22,24] Os resultados devem ser interpretados de acordo com o contexto clínico e ter em consideração, que existem possíveis interferências.[24] Os valores de corte para a ISR secundária ainda não estão claramente definidos na literatura.[16,22] Quando os resultados das provas de estimulação com ACTH são equívocos ou quando a prova é negativa num caso de alta suspeita clínica, então deve realizar-se uma prova adicional, como a prova de hipoglicemia insulínica ou a prova de metirapona.[22,24] Dado o ponto de corte do cortisol ≥ 18 µg/dL ser amplamente aceite na prática clínica como exclusão da ISR, consideramos prudente que em indivíduos que obtiveram um valor de cortisol basal intermédio entre os 15-18 µg/dL e que suspenderam o GC, em caso de doença crítica, devam ser avaliados através de uma prova dinâmica ou senão for possível, devem iniciar reposição de GC em dose de *stress*.

A frequência da avaliação do eixo HHS deve realizar-se habitualmente a cada 2-3 meses, caso o eixo não se encontre recuperado. Caso não ocorra ao fim de 1-2 anos, a reavaliação deve passar a cada 3-6 meses.[5] A ISR pode durar até 2-4 anos após a retirada do GC, uma vez que a atrofia suprarrenal é lentamente reversível e 2%-7% podem nunca readquirir a função suprarrenal. Caso a ISR persista após 4 anos é improvável que ocorra a sua recuperação.[5,6,8,23]

Síndrome de Abstinência dos GC

A síndrome de abstinência dos esteroides é uma entidade pouco compreendida e caracteriza-se por sintomas que sugerem ISR, mas com o eixo HHS analiticamente íntegro.[11,14] Pode-se dever a um estado de "insuficiência suprarrenal relativa" dos tecidos, que estavam expostos anteriormente a níveis elevados de GC.[11,14] Trata-se de uma situação habitualmente temporária, com uma duração de 6-10 meses.[1] devendo-se aumentar a dose de GC até resolução dos sintomas seguindo-se uma redução gradual da dose. Pode coexistir dependência psicológica à toma do GC, manifestando-se por mudanças do humor e labilidade emocional (mais comuns), delírio e estados psicóticos.[1,14]

Uso do Cortisol Salivar, da Cortisolúria 24 Horas e do Sulfato de Hidroepiandrosterona na Avaliação do Eixo HHS

O cortisol salivar e o cortisol livre na urina das 24 horas não estão válidos para avaliar a recuperação do eixo HHS.[1,23] Evidências recentes sugerem que o sulfato dehidroepiandrosterona (DHEA-S) é um bom marcador para avaliar a integridade da função suprarrenal, juntamente com o cortisol e se o seu nível estiver

adequado para a idade e sexo normal prevê uma função adequada do eixo HHS com uma sensibilidade de 87,1%, especificidade de 86,7% e valor preditivo positivo de 93,1%.[8,25]

Conclusão

Os GC orais são muito utilizados na prática clínica e representam uma das principais causas de ISR secundária. O seu diagnóstico e o tratamento permanecem um desafio. Não existe atualmente nenhuma orientação clínica definida pelas sociedades científicas para a redução da dose do GC e existem vários esquemas propostos na literatura. A interrupção da terapêutica crónica com GC requer uma abordagem individual, levando em consideração o risco de supressão do eixo HHS. Em indivíduos com supressão provável ou incerta é importante avaliar a função do eixo HHS antes da suspensão do GC. Os doentes e familiares devem ser instruídos para a possibilidade de sintomatologia sugestiva de ISR, aprender a reconhecer uma ISR aguda e contactar a equipa médica de imediato.

Contributorship Statement / Declaração de Contribuição:

SC: Pesquisa de literatura e escrita do texto.
JDS: Revisão crítica.
GR e MJO: Revisão crítica e aprovação final.
Todos os autores aprovaram a versão final.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Alves C, Robazzi TV, Mendonça M. Retirada da corticoterapia: recomendações para a prática clínica. J Pediatr. 2008; 84: 192-202. doi: 10.2223/JPED.1773.
2. Furst DE, Saag KG. Glucocorticoid Withdrawal. 2021 [consultado 2022 Maio]. Disponível em: https://www.uptodate.com/contents/glucocorticoid-withdrawal.
3. Paragliola RM, Papi G, Pontecorvi A, Corsello SM. Treatment with Synthetic Glucocorticoids and the Hypothalamus-Pituitary-Adrenal Axis. Int J Mol Sci. 2017;18:2201. doi: 10.3390/ijms18102201.
4. Richter B, Neises G, Clar C. Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. Endocrinol Metab Clin North Am. 2002;31:751-78. doi: 10.1016/s0889-8529(02)00008-7.
5. Prete A, Bancos I. Glucocorticoid induced adrenal insufficiency. BMJ. 2021;374:n1380. doi: 10.1136/bmj.n1380. Erratum in: BMJ. 2021;374:n1936.
6. Vilar L. Endocrinologia Clínica. 7ª ed. São Paulo: Guanabara Koogan; 2020
7. Joseph RM, Hunter AL, Ray DW, Dixon WG. Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Semin Arthritis Rheum. 2016;46:133-41. doi: 10.1016/j.semarthrit.2016.03.001.
8. Pelewicz K, Miskiewicz P. Glucocorticoid withdrawal-an overview on when and how to diagnose adrenal insufficiency in clinical practice. Diagnostics. 2021;11:728. doi: 10.3390/diagnostics11040728.
9. Younes AK, Younes NK. Recovery of steroid induced adrenal insufficiency. Transl Pediatr. 2017;6:269-73. doi: 10.21037/tp.2017.10.01.
10. Salem MA, Tantawy AA, El Sedfy HH, El Laboudy MA, Toaima DN, Mahmoud NH, et al. A prospective study of the hypothalamic-pituitary-adrenal axis in children with acute lymphoblastic leukemia receiving chemotherapy. Hematology. 2015; 20: 320-7. doi: 10.1179/1607845414Y.0000000208.
11. Igaz P, Rácz K, Tóth M, Gláz E, Tulassay Z. Treatment of iatrogenic Cushing syndrome: questions of glucocorticoid withdrawal. Orvosi Hetilap. 2007; 148:195-202. doi: 10.1556/OH.2007.27964.
12. Dinsen S, Baslund B, Klose M, Rasmussen AK, Friis-Hansen L, Hilsted L, et al. Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. Eur J Intern Med. 2013;24:714-20. doi: 10.1016/j.ejim.2013.05.014. Erratum in: Eur J Intern Med. 2014;25:781-3.
13. Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. BMJ. 2012;345:e6333. doi: 10.1136/bmj.e6333.
14. Romanholi DJ, Salgado LR. Síndrome de Cushing exógena e retirada de glicocorticóides. Arq Brasil Endocrinol Metabol. 2007; 51: 1280-92. doi: 10.1590/S0004-27302007000800014.
15. Broersen LH, Pereira AM, Jørgensen JO, Dekkers OM. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015;100:2171-80. doi: 10.1210/jc.2015-1218.
16. Pokrzywa A, Ambroziak U, Foroncewicz B, Macech M, Paczek L, Florczak M, et al. Detecting adrenal insufficiency in patients with immunoglobulin A nephropathy, lupus nephritis, and transplant recipients qualified for glucocorticoid withdrawal. Pol Arch Intern Med. 2019;129:874-82. doi: 10.20452/pamw.15091.
17. Hamrahian AH, Roman S, Milan S. The management of the surgical patient taking glucocorticoids. 2022 [consultado 2022 Maio]. Disponível em: https://www.uptodate.com/contents/the-management-of-the-surgical-patient-taking-glucocorticoids.
18. Insuficiência Suprarrenal Associada a Corticoterapia. 2019 [consultado 2022 Abril]. Disponível em: http://hdl.handle.net/10400.6/8701.
19. Al-Aridi R, Abdelmannan D, Arafah BM. Biochemical diagnosis of adrenal insufficiency: the added value of dehydroepiandrosterone sulfate measurements. Endocr Pract. 2011;17:261-70. doi: 10.4158/EP10262.RA.
20. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888-921. doi: 10.1210/jc.2016-2118.
21. Ahluwalia R, Swords F, Gorick S. Joint Trust Guideline for the Management of Adult Patients with Suspected Adrenal Suppression Due to Long Term Steroids. [consultado 2022 Jan]. Disponível em: https://www.nnuh.nhs.uk
22. Sbardella E, Isidori AM, Woods CP, Argese N, Tomlinson JW, Shine B, et al. Baseline morning cortisol level as a predictor of pituitary-adrenal reserve: a comparison across three assays. Clin Endocrinol. 2017;86:177-84. doi: 10.1111/cen.13232.
23. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3:216-26. doi: 10.1016/S2213-8587(14)70142-1.
24. Ospina NS, Nofal AA, Bancos I, Javed A, Benkhadra K, Kapoor E, et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2016; 101:427-34. doi: 10.1210/jc.2015-1700.
25. Charoensri S, Chailurkit L, Muntham D, Bunnag P. Serum dehydroepiandrosterone sulfate in assessing the integrity of the hypothalamic-pituitary-adrenal axis. J Clin Transl Endocrinol. 2017;7:42-6. doi: 10.1016/j.jcte.2017.01.001.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Revisão

José Luís Medina Vieira: um Exemplo na Endocrinologia Portuguesa

Marta Filipa Correia Barbosa [a,*], Amélia Assunção Beira Ricon Ferraz [a], Davide Maurício Costa Carvalho [b]

[a] *Faculty of Medicine University of Porto, Porto, Portugal*
[b] *Endocrinology Department, Oporto Medical School, Core Researcher i3S, Porto, Portugal*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2023-04-10
Accepted/Aceite: 2023-07-06
Publicado / Published: 2023-10-18

Palavras-chave:
Endocrinologia/história;
História do Século 20;
Portugal.

R E S U M O

José Luís Medina Vieira traçou um percurso ímpar, assente em três pilares: docência, investigação e prática clínica, ocupando cargos de destaque em todos estes domínios. O objetivo da presente dissertação é homenagear a vida e obra do Professor José Luís Medina.
Nascido no Porto a 9 de maio de 1940, licenciou-se em Medicina em 1965 e concluiu o doutoramento em 1988. Começou a sua carreira docente como Assistente de Química Fisiológica, tendo também sido assistente de Clínica Média, Propedêutica Médica, Medicina I e II e Endocrinologia. Tornou-se Professor Associado em 1990, Professor Associado com agregação em 1996 e Professor Catedrático em 2000. Foi membro da Direção da Faculdade de Medicina da Universidade do Porto e Diretor do Laboratório de Endocrinologia da mesma. Ocupou vários cargos de relevo no âmbito da Endocrinologia. Foi Diretor do Serviço de Endocrinologia do Centro Hospitalar Universitário de São João, presidente de inúmeras Sociedades Científicas, membro do Colégio da Especialidade de Medicina Interna da Ordem dos Médicos e integrou a direção do Colégio de Endocrinologia e Nutrição. Exerceu ainda funções de consultor na Direção Geral de Saúde. Foi agraciado com a Medalha de Ouro de serviços distintos do Ministério da Saúde e a Medalha de Mérito da Ordem dos Médicos, em 2016.
É recordado pelo seu apurado raciocínio clínico e pela sua notável dedicação aos doentes e à medicina clínica, à formação e à investigação.
É uma referência na Medicina Portuguesa e um exemplo a seguir na área da Endocrinologia, com um legado notável a nível nacional e internacional.

Keywords:
Endocrinology/history;
History, 20th Century;
Portugal.

José Luís Medina Vieira: A Reference in Portuguese Endocrinology

A B S T R A C T

José Luís Medina Vieira had a unique career based on three pillars: teaching, research and clinical practice, holding prominent positions in all these areas. This dissertation pretends to honor the life and work of Professor José Luís Medina.
Born in Porto on May 9, 1940, he graduated in Medicine in 1965 and completed his PhD in 1988. He began his teaching career as an Assistant in Physiological Chemistry, also serving as Assistant in Medical Clinic, Medical Propaedeutics, Medicine I and II and Endocrinology. He became an Associate Professor in 1990, Associate Professor with aggregation in 1996 and Full Professor in 2000. He was a member of Faculdade de Medicina da Universidade do Porto Directorate and Director of its Endocrinology Laboratory. He held several prominent positions in the field of Endocrinology. He was Director of Endocrinology Service of Centro Hospitalar Universitário de São João, president of numerous Scientific Societies, a member of Specialty College of Internal Medicine of Ordem dos

* Autor Correspondente / Corresponding Author.
E-Mail: martafcbarbosa@gmail.com (Marta Filipa Correia Barbosa)
Alameda Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

https://doi.org/10.26497/ar230019

Médicos and served on the board of College of Endocrinology and Nutrition. He also served as a consultant in Direção Geral de Saúde. He was awarded the Gold Medal for Distinguished Services from Ministério da Saúde and the Medal of Merit from Ordem dos Médicos in 2016.
He is remembered for his keen clinical reasoning and remarkable dedication to patients and clinical medicine, education and research.
He is a reference in Portuguese Medicine and an example to follow in the field of Endocrinology, with a remarkable legacy, not only nationally but also internationally.

Introdução

A presente dissertação partiu de uma conversa com a Professora Amélia Ricon Ferraz, que sugeriu o nome do Professor José Luís Medina como uma personalidade de grande importância na área da Endocrinologia. Após uma rápida pesquisa, apercebi-me facilmente do seu percurso notável.

É no futuro que abrimos novas portas e traçamos novos caminhos, mas é no passado que encontramos os alicerces que nos permitem avançar. É importante relembrar e manter vivo na memória de todos, os feitos grandiosos dos nossos antepassados e o percurso insigne de inúmeras personalidades, particularmente as que se dedicam à Ciência e Arte que abraçamos.

O objetivo deste trabalho é homenagear a carreira excecional do Professor José Luís Medina. Assim, serão abordados os tempos até à faculdade e a vida estudantil. Sucede-se uma descrição da sua atividade como docente e clínico, sobretudo na área da Endocrinologia, e ainda, uma análise do seu contributo na Investigação Científica. O Serviço Militar na Guerra Colonial será, igualmente, alvo de particular atenção. Paralelamente, houve a vontade de dar a conhecer o Homem para além do Professor.

Nasceu no Porto a 9 de maio de 1940 e licenciou-se pela Faculdade de Medicina da Universidade do Porto (FMUP), onde iniciou a sua carreira académica como Assistente de Química Fisiológica. Foi detentor de um percurso ímpar que assentou, sobretudo em três pilares: docência, investigação e prática clínica.

Figura 1. A Infância do Professor José Luís Medina Vieira. Fotografia tirada no estúdio Gualtieri, Porto, 5 de dezembro de 1946 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

1. Dos Primeiros Anos até ao Ensino Universitário

Nasceu a 8 de maio de 1940 no Porto e aqui viveu toda a sua vida.

Teve uma infância feliz e tranquila. Costumava brincar na rua, jogar à bola, ao pião, à "carica" e fazer os seus próprios brinquedos.

A sua infância foi marcada por uma forte influência espanhola, por intermédio do seu avô materno, nascido em Zamora. Costumava passar as férias em Espanha, na casa dos primos, recordadas como recheadas de histórias e aventuras. As suas maiores referências são os avós maternos (Lucinda e Zenon), a mãe e o seu tio Luiz. (ANEXO A - Figura A.1)

Frequentou o Liceu D. Manuel II, no Porto, no qual fez grandes amigos, com os quais sempre manteve relação. Costumavam encontrar-se regularmente e trocar mensagens.

A Medicina sempre se destacou como a principal área de interesse, apesar de não existir tradição de médicos na família. Como estudante sempre foi muito curioso e apaixonado pelo que aprendia.

2. A Vida Estudantil

José Luís Medina Vieira foi aprovado no exame de admissão à FMUP no ano letivo de 1957/1958.1 (ANEXO A- Figura A.2)

Sempre foi muito bom aluno e, nos últimos anos da faculdade, conciliava o estudo com o trabalho na indústria farmacêutica. Desempenhou funções como Delegado de Informação Médica na Ferraz Lynce.

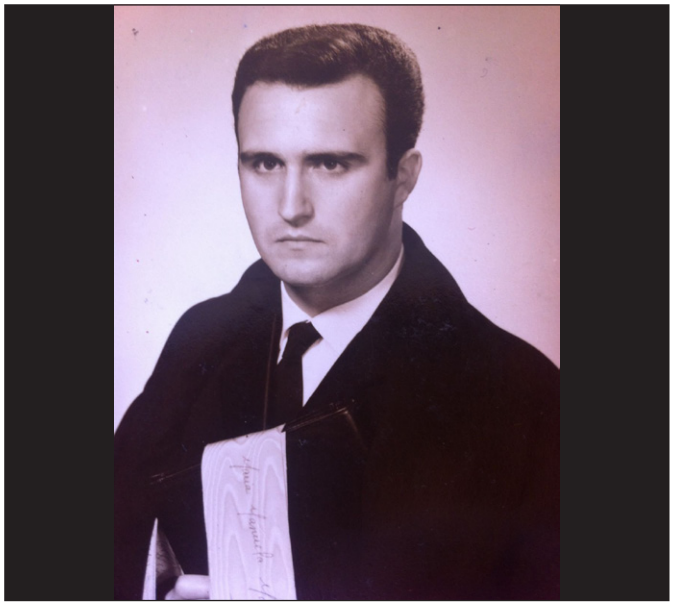


Figura 2. O estudante da Faculdade de Medicina da Universidade do Porto José Luís Medina Vieira (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

Foi um membro ativo na tuna académica e jogava futebol, ocupando a posição de guarda-redes, na equipa do Centro de Desporto da Universidade do Porto. (ANEXO A- Figura A.3)

Licenciou-se a 21 de outubro de 1965, com a classificação final de 16 valores, após defesa da Tese de Licenciatura com o tema "Sobre algumas parasitoses hepatobiliares (Ascaris lumbricoides, Echinococcus granulosus, Fasciola hepatica)", com a classificação de 19 valores. Esta tese foi realizada no Serviço de Propedêutica Cirúrgica, sob a orientação do Professor Joaquim Bastos.[2]

Como comemoração do fim da licenciatura, realizou uma visita de estudo à Suíça e Itália, junto dos colegas de curso. Foram acompanhados por um professor da faculdade e pela sua esposa. (ANEXO A- Figura A.4)

3. A Carreira Académica

O Professor teve uma vasta carreira como docente, ao nível do ensino pré e pós-graduado.

A convite do Professor Sobrinho Simões, ocupou o cargo de Assistente Eventual de Química Fisiológica da FMUP, tendo iniciado funções em dezembro de 1969.[3,4] (ANEXO A- Figura A.5 e Figura A.7) Em 1972 passou a ocupar a função de Assistente.[4,5] (ANEXO A- Figura A.6 e Figura A.8). Foi encarregue das aulas práticas e colaborou nas provas de avaliação final dos alunos.[1]

No ano letivo de 1972/1973 fez parte da redação do Boletim Informativo da faculdade.[1]

Desempenhou funções como Monitor e Assistente de Clínica Médica, a convite do Professor Ferraz Júnior e Professor Manuel Hargreaves, de 2 de janeiro de 1975 até 31 de outubro de 1975, data em que pediu exoneração de funções, que retomou a 12 de agosto de 1977 até 1 de agosto de 1982.[4] (ANEXO A- Figura A.9) Foi responsável por aulas práticas e teóricas de Medicina Interna e Endocrinologia e colaborou nos exames de avaliação.[1]

A 2 de Agosto de 1982, iniciou funções como Assistente Convidado a 30% de Propedêutica Médica 4 (ANEXO A- Figura A.10) e passou a Assistente Convidado a 40% a 18 de novembro de 1985. Procurou estimular os alunos à frequência das enfermarias, realçando a importância do contacto frequente com o doente e da experiência adquirida na prática clínica.[1]

Em 1983 colaborou com a Associação de Estudantes da FMUP no programa de intercâmbio com outros países, tendo acompanhado estudantes estrangeiros, no serviço hospitalar.[1]

A Dissertação de Candidatura ao grau de Doutor foi apresentada à FMUP em 1987, com o tema "Contribuição para o estudo da lesão do sistema nervoso autónomo em diabéticos", sob a orientação do Professor Manuel Hargreaves.[6]

Em 1988 ocupou o cargo de Professor Auxiliar de Medicina e, em 1990, de Professor Associado de Medicina.[7]

Colaborou com o Professor Lopes Vaz no ensino da Medicina I, no ano letivo de 1991/1992 e foi responsável pelo ensino da Endocrinologia do 4º. ano da FMUP.[7]

Nos anos de 1991/1992 a 1994/1995, a convite do Professor Mário Cerqueira Gomes, participou no ensino da Medicina II.[7]

José Luís Medina desempenhou um papel preponderante na FMUP, tendo integrado inúmeras vezes a Assembleia de Representantes e o Conselho Pedagógico da mesma, nomeadamente nos anos de 1978,1980, de 1982 a 1987 e nos biénios de 1992/1993, 1994/1995 e 1996/1997.[1,7] Foi vogal do Conselho Diretivo da mesma faculdade, de 1991 a 1993, sendo o Professor Tomé Ribeiro o presidente. Foi Diretor do Laboratório de Endocrinologia (Laboratório Nobre). Em 1994 foi diretor do Serviço de Endocrinologia da FMUP, por designação do Conselho Diretivo e foi ainda Diretor do Departamento de Medicina da FMUP.

Em 1995 realizou a candidatura ao título de Professor Agregado da Faculdade de Medicina do Porto com os trabalhos: "Relatório de índole pedagógica sobre o ensino da Endocrinologia" e "Sumário Pormenorizado da Lição Síntese - Lesão do sistema nervoso autónomo cardiovascular em doentes diabéticos. 8 Prestou provas de Agregação em janeiro de 1996, obtendo o título de Professor Associado com agregação em Medicina.[1]

Em 2000 tornou-se Professor Catedrático na FMUP.

Teve uma relevante participação em diversas ações pedagógicas de pós-graduação, nomeadamente em júris de exame de especialidade,[1] cursos de mestrado e de medicina do trabalho, como orientador e coorientador de dissertações de doutoramento, como arguente em provas académicas.[7] Foi ainda membro de vários júris Académicos tanto em Portugal como em Espanha.

No dia 25 de maio de 2010, na Aula Magna da FMUP, proferiu a "Lição de Jubilação", intitulada "Stress e vida quotidiana: o desafio do século XXI", tornando-se Professor Catedrático Jubilado.[9]

Figura 3. O Professor José Luís Medina Vieira após apresentar a "Lição de Jubilação", intitulada "Stress e vida quotidiana: o desafio do século XXI", na Aula Magna da FMUP, a 25 de maio de 2010 (Fotografia gentilmente cedida pela esposa, Drª. Luísa Pádua Ramos)

4. A Carreira Médica

A sua atividade clínica iniciou-se a 29 de novembro de 1965, como Estagiário Voluntário do Serviço de Propedêutica do Hospital Escolar de São João, adquirindo treino básico cirúrgico. Concomitantemente foi admitido como médico do Posto Clínico de Vizela dos Serviços Médico-Sociais, desde novembro de 1965 até agosto de 1966.[1]

A 31 de março de 1966 foi admitido no Internato Geral do Centro Hospitalar Universitário de São João (CHUSJ), permanecendo em funções no Serviço de Propedêutica Cirúrgica, sob a direção do Professor Joaquim Bastos. Interrompeu o Internato Geral a 12 de setembro de 1966 para cumprir o Serviço Militar obrigatório. Quando foi desmobilizado a 30 de novembro de 1969, foi readmitido no Serviço de Propedêutica Médica, sob a direção do Professor Emídio Ribeiro. Fez o exame de saída do Internato Geral, com provas públicas, a 28 de fevereiro de 1970, sendo classificado com Muito Bom (56/60 pontos).[1]

A 8 de junho de 1970 como não havia internato de Endocrinologia, concorreu e foi admitido no Internato Complementar de Medi-

cina Interna, no Serviço de Clínica Médica, sob a direção do Professor Ferraz Júnior, tendo iniciado a 8 de junho. Havia uma Secção de Endocrinologia, sob a orientação do Professor Manuel Hargreaves, onde fez estágio. O contacto com a Medicina Interna deu-lhe uma visão mais alargada, não se confinando à Endocrinologia.[1]

De 1971 a 1983, primeiro como estagiário e ulteriormente especialista encarregado de uma parte da consulta de Endocrinologia, desempenhou funções no Hospital Central Especializado de Crianças de Maria Pia, do Porto. Adquiriu uma vasta experiência neste campo, sob orientação do Professor Manuel Hargreaves e da Drª. Luísa Vila-Cova.[1]

Prestou provas públicas no exame final do Internato Complementar de Medicina, o qual concluiu a 19 de dezembro de 1973, com a classificação de Muito Bom, com distinção e louvor.[1] Em 1974, foi autorizado pela Direcção-Geral dos Hospitais a fazer exame equivalente ao do Internato Complementar de Endocrinologia, tendo obtido a classificação máxima de Muito Bom.[10] Passou a médico eventual com especialidade a 1 de janeiro de 1974.[11] Inscreveu-se na Ordem dos Médicos nas Especialidades de Medicina Interna e Endocrinologia Nutrição.

A 21 de janeiro de 1976 fez o exame de Medicina do "Educational Comission for Foreign Medical Graduates", tendo obtido os "scores scaled 75, standard 305" (passing scaled score 75, passing standard score 290).

Em 1976 fez concurso para Assistente Hospitalar de Endocrinologia do CHUSJ, tendo sido classificado com Muito Bom.[1] A 13 de dezembro de 1977 foi distribuído no mapa do pessoal médico como especialista de Endocrinologia. Nesta altura, o chefe de clínica de Endocrinologia era o Professor Manuel Hargreaves.[11]

A 17 de março de 1978 fez concurso para Chefe de Serviço de Endocrinologia do quadro pessoal médico do CHUSJ, tendo obtido a classificação de 16 valores, o que lhe deu acesso ao grau. A partir desta data passou a Assistente Graduado.[1] Desde 1978 foi responsável da Consulta de Endocrinologia da Administração Regional de Saúde (ARS) do Porto e foi, mais tarde, nomeado Coordenador da Unidade de Endocrinologia e de Medicina de Apoio a Doentes Asmáticos, da ARS do Porto.[1]

A 1 de Novembro de 1980 fez concurso para Especialista de Endocrinologia do Quadro do Pessoal do CHUSJ e ficou aprovado. A 12 de julho de 1982 tomou posse definitiva como Especialista de Endocrinologia do CHUSJ.[1]

A 28 de dezembro de 1987 tomou posse do cargo de Assistente Hospitalar Letra C[11]. Passou a ser abonado com Letra B a partir de 1 de janeiro de 1989: "*O Professor José Luís Medina Vieira tem desenvolvido no Serviço de Medicina IV uma atividade da mais elevada categoria, tanto do ponto de vista assistencial como investigacional e docente. São de realçar as suas inexcedíveis qualidades humanas de lealdade e correção no seu relacionamento com todos os elementos do serviço e no atendimento dos doentes*."[11]

Em 1991, com o falecimento do Professor Manuel Hargreaves, foi nomeado pelo Conselho de Administração, presidido pelo Professor Levi Guerra, para responsável da Unidade de Endocrinologia do CHUSJ.

De 1990 a 1992 foi Presidente do Colégio de Endocrinologia da Ordem dos Médicos.

A 25 de março de 1993 foi nomeado para Chefe de Serviço de Endocrinologia pelo Conselho de Administração, sendo o Diretor do hospital o Professor Fleming Torrinha. Ocupou este cargo até à sua aposentação em 2010.[11]

A 07 de fevereiro de 1996 foi nomeado adjunto do Professor Fleming Torrinha, competindo-lhe a coordenação das Comissões do Plano de Investimento e da Telemática, mais tarde substituída pela Comissão de Informática, da qual foi Presidente. Cabia-lhe dar parecer sobre pedidos de equipamento e respetivas prioridades e fazer o inventário e gestão de espaços livres no hospital.[11]

Realizou outras atividades na Ordem dos Médicos, nomeadamente como presidente do Colégio da Especialidade de Medicina Interna e membro de vários júris da carreira hospitalar.

A 20 de julho de 2000, foi admitido como presidente da Comissão da Hormona do Crescimento (Ministério da Saúde), sendo o Diretor Clínico à data o Dr. Luís Manuel Ribeiro. No mesmo ano, fez parte da Comissão do Departamento de Medicina do CHUSJ, com o Dr. Jaime Duarte na direção.[11]

Fez parte do grupo de trabalho para a elaboração do "Programa Nacional de Combate à Obesidade", tendo participado em várias reuniões em Lisboa, nomeadamente a 16 de março de 2004 e a 14 e 24 de janeiro de 2005.[11]

A 4 de abril de 2006 foi aprovada a proposta de nomeação para os diretores dos Serviços que integravam a Unidade Autónoma de Gestão de Medicina. Foi nomeado para o Serviço de Endocrinologia, sendo o Diretor Clínico o Professor António Ferreira.[11]

De 2011 a 2013 e de 2014 a 2016 foi Vice-Presidente da Mesa da Assembleia Regional da Secção Regional do Norte da Ordem dos Médicos.

José Luís Medina foi agraciado com a Medalha de Ouro de serviços distintos do Ministério da Saúde e a Medalha de Mérito da Ordem dos Médicos, ambas atribuídas em 2016.

Foi eleito para o Conselho Superior da Ordem dos Médicos, tendo sido vogal deste conselho de 2017 a 2019.

Paralelamente à atividade hospitalar exerceu clínica privada, como endocrinologista: primeiro num consultório na Rua de Gonçalo Cristóvão, mais tarde, na Rua de Sá da Bandeira, onde seguiu doentes ao longo de toda a sua vida. Entre o final da década de 60 e o início da década de 70, durante o mês de agosto, fazia acompanhamento clínico nas Termas de Monfortinho.

Fez estágios no Hospital da Universidade de Minnesota (agosto de 1990), no Hvidovre Hospital da Universidade de Copenhaga e no Hospital da Cruz Roja (Madrid).

Figura 4. José Luís Medina, enquanto diretor do Serviço de Endocrinologia (Fotografia gentilmente cedida pela esposa, Drª. Luísa Pádua Ramos)

5. O Serviço Militar

Interrompeu o Internato Geral a 12 de setembro de 1966 para cumprir o Serviço Militar obrigatório, primeiro na Escola Prática de Infantaria (Mafra) e, posteriormente, com a frequência do curso de especialização no Hospital Militar Principal (Lisboa).[1]

No final deste, foi transferido para a Força Aérea, sendo colocado como Médico da Base Aérea n°. 7 em São Jacinto (Aveiro). Em junho de 1966 foi mobilizado para uma Comissão de Serviço no Ultramar como Alferes Médico Miliciano no Batalhão de Caçadores Paraquedistas n°. 31 (BCP 31), com sede na Beira (Moçambique).[1] O BCP 31 foi condecorado com a Cruz de Guerra de 1ª. classe, a 12 de junho de 1969, pelo grau de excelência atingido na atividade operacional. Como médico deste Batalhão acompanhou as companhias às zonas operacionais no Norte, onde teve oportunidade de pôr em prática o que aprendeu, particularmente no tratamento de feridos em combate, quer no mato, quer na enfermaria de Sector de Moeda.[1] A sua atividade, como médico do Batalhão, foi considerada "extraordinária, relevante e distinta", em louvor atribuído pelo General Comandante da 3ª. Região Aérea.[1] Recebeu a medalha comemorativa das Campanhas das Forças Armadas de Moçambique (1969). Foi desmobilizado a 30 de novembro de 1969. Por despacho do Secretário de Estado da Aeronáutica foi condecorado com a Medalha de Prata de Serviços Distintos com Palma, no dia 10 de junho de 1970.[1] (ANEXO A- Figura A.11)

Figura 5. José Luís Medina durante o Serviço Militar Obrigatório como médico do Batalhão de Caçadores Paraquedistas, 1966-1969 (Fotografia gentilmente cedida pela esposa, Drª. Luísa Pádua Ramos)

6. A Dedicação à Investigação Científica

O Professor tem um notável legado na investigação científica, com mais de 200 trabalhos publicados, em revistas nacionais e internacionais.

Enquanto docente de Química Fisiológica, esteve inserido de 1971 a 1973 no Projeto de Investigação 74-P CM-2. O seu plano de trabalho incluía o estudo das mucopolissacaridoses, tendo iniciado a separação e doseamento de mucopolissacarídeos na urina e a separação eletroforética dos mesmos, sob a orientação do Professor Sobrinho Simões.[7]

Enquanto docente de Clínica Médica dedicou-se ao estudo das lipoproteínas, sob orientação do Professor Manuel Hargreaves, tendo montado a técnica de eletroforese em Cellogel.[7] O Professor Manuel Hargreaves foi um grande mestre para si, tendo alguns trabalhos publicados com o mesmo.

Foi investigador do Centro de Cardiologia da FMUP, e após a sua extinção, continuou a ser investigador da Unidade de Investigação e Desenvolvimento Cardiovascular do Porto, sob coordenação do Professor Mário Cerqueira Gomes.[7]

Dedicou-se à área da Endocrinologia de uma forma transversal, tendo publicado sobre diabetes mellitus, patologia da tiroide, paratiroides e suprarrenal, disfunção gonadal, obesidade e dislipidemia, tumores neuroendócrinos, patologia da hipófise.

Nos primeiros anos, algumas das pessoas com quem mais publicou foram a Drª. Maria Luísa Vila Cova, o Professor Manuel Hargreaves, a Drª. Helena Ramos, o Professor Amândio Tavares e a Drª. Lídia Monteiro.

Nas décadas de 80 e 90, a temática diabetes *mellitus* continuou a destacar-se, tendo publicações sobre o diagnóstico, tratamento, complicações microvasculares e macrovasculares, e ainda, a correlação com outras patologias. A década de 90 foi o período com mais publicações, com um número superior a 80. A Drª. Maria Fernanda Guerra foi uma das pessoas com quem mais publicou nesta fase, com mais de 20 publicações em comum, especialmente sobre diabetes *mellitus*, dislipidemias e patologia da suprarrenal. Acompanhou-o em inúmeros trabalhos desde 1984 até 2010.

Em 1987 colaborou no projeto CNP1 do Serviço de Patologia Médica (com o Professor Mário Cerqueira Gomes como Diretor), no âmbito do estudo da lesão do sistema nervoso autónomo em diabéticos, tendo sido este o tema da sua dissertação de candidatura ao grau de Doutor.[6] Tem várias publicações em comum com o mesmo, principalmente sobre diabetes *mellitus*.

A partir do final da década de 90, destaque para o Professor Davide Carvalho, com o qual trabalhou em mais de 80 publicações, assim como o Dr. Celestino Neves, com mais de 60 trabalhos em comum.

A partir de 2009, começou a publicar com o Professor Martin Buysschaert do departamento de Endocrinologia e Diabetologia da University Clinic Saint-Luc, Université Catholique de Louvain de Bruxelas e com o Professor Michael Bergman da NYU School of Medicine, de Nova York. Trabalharam em conjunto até ao final da sua vida.

De 2010 até 2019 publicou sobretudo sobre diabetes *mellitus*, patologia da tiroide e obesidade.

As suas últimas publicações incidiram essencialmente na temática da diabetes mellitus, tendo trabalhado em colaboração com o Dr. João Sérgio Neves, Professor Martin Buysschaert, Professor Michael Bergman, Dr. Celestino Neves, Drª. Oksana Sokhatska, Doutor Luís Delgado, Dr. Miguel Pereira, entre os principais. (ANEXO B - Publicações Científicas)

Tornou-se membro de inúmeras comissões, pertenceu aos corpos editoriais ou conselho científico de variadas revistas médicas e teve um papel preponderante em inúmeras sociedades científicas.[1,11] Relativamente à Sociedade Portuguesa de Diabetologia, foi o Primeiro Secretário-Geral de 1987 a 1992, de 2011 a 2017 foi Presidente e, ainda, fundador e coordenador do GRENEDI (Grupo de estudos de Neuropatia Diabética). Tornou-se sócio da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo em 1972. Em 1998 foi fundador e coordenador do GREDIS (Grupo de estudos de dislipidemias) e foi presidente da mesma de 2003 a 2008.

Figura 6. Fotografia exposta na Galeria da Sociedade Portuguesa de Diabetologia, 2014 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

ANEXO A. Imagens Complementares.

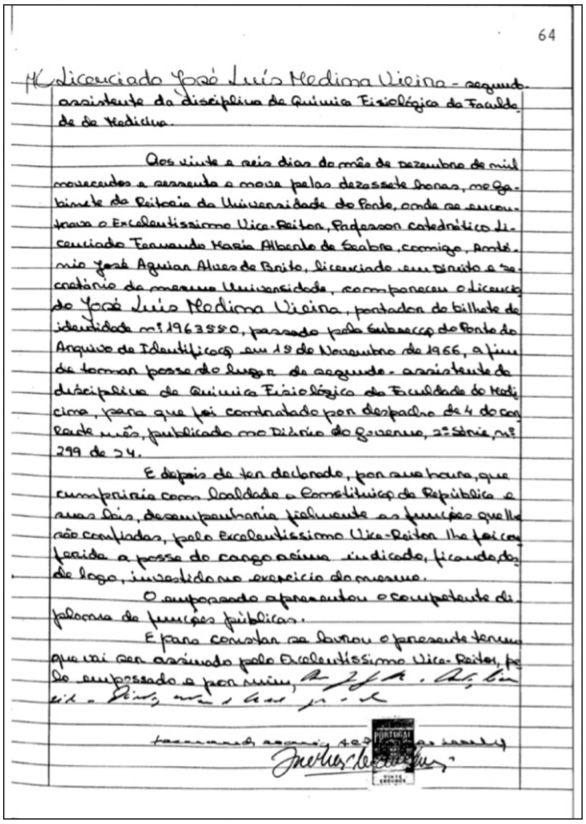
Figura A.1. José Luís Medina Vieira com o avô materno Zénon Medina Antón, na Baixa do Porto, 1944 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

Figura A.2. O cartão de identidade do aluno José Luís Medina Vieira, da Faculdade de Medicina do Porto, 1958 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

Figura A.3 José Luís Medina Vieira como Guarda-Redes na Equipa de Futebol do Centro de Desporto da Universidade do Porto, 1963 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

Figura A.4 José Luís Medina Vieira na viagem de Curso a Itália e Suíça, 1964 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

ANEXO A. Imagens Complementares. (Continuação)



64

Licenciado José Luís Medina Vieira - segundo assistente da disciplina de Química Fisiológica da Faculdade de Medicina.

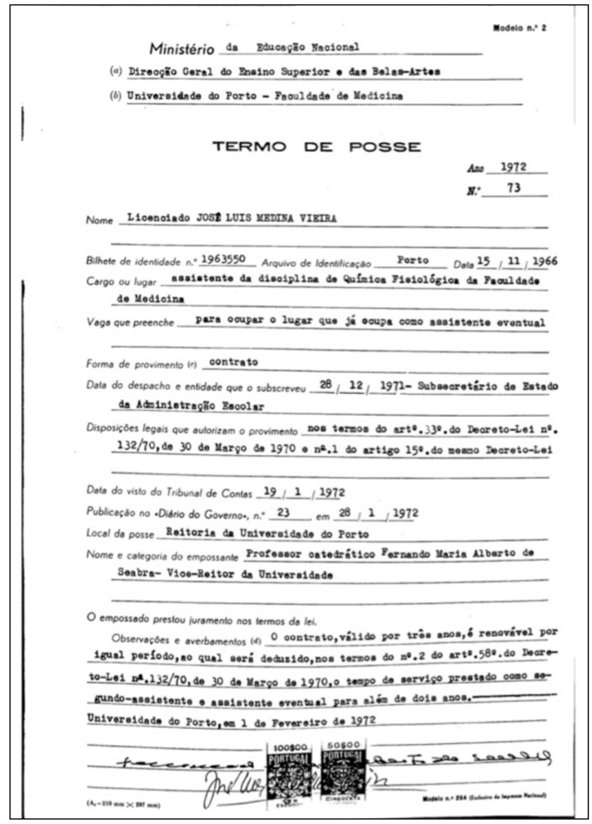
Aos vinte e seis dias do mês de Dezembro de mil novecentos e sessenta e nove pelas dezassete horas, no gabinete da Reitoria da Universidade do Porto, onde se encontrava o Excelentíssimo Vice-Reitor, Professor catedrático licenciado Fernando Maria Alberto de Seabra, comigo, António José Aguiar Alves de Brito, licenciado em Direito e secretário da mesma Universidade, compareceu o licenciado José Luís Medina Vieira, portador do bilhete de identidade nº 1963550, passado pela Subsecção do Porto do Arquivo de Identificação em 15 de Novembro de 1966, a fim de tomar posse do lugar de segundo-assistente da disciplina de Química Fisiológica da Faculdade de Medicina, para que foi contratado por despacho de 4 do corrente mês, publicado no Diário do Governo, 2ª Série, nº 299 de 24.

E depois de ter declarado, por sua honra, que cumpriria com lealdade a Constituição da República e suas leis, desempenharia fielmente as funções que lhe são confiadas, pelo Excelentíssimo Vice-Reitor lhe foi conferida a posse do cargo acima indicado, ficando desde logo, investido no exercício do mesmo.

O empossado apresentou o competente diploma de funções públicas.

E para constar se lavrou o presente termo que vai ser assinado pelo Excelentíssimo Vice-Reitor, pelo empossado e por mim, [illegible]

Figura A.5. Livros de Termos de posse e de aceitação de nomeação de pessoal docente e não docente (1914-1973) – Termo de posse de 1969 do lugar de 2º. Assistente de Química Fisiológica



Modelo n.º 2

Ministério da Educação Nacional
(a) Direcção Geral do Ensino Superior e das Belas-Artes
(b) Universidade do Porto - Faculdade de Medicina

TERMO DE POSSE

Ano 1972
N.º 73

Nome Licenciado JOSÉ LUIS MEDINA VIEIRA

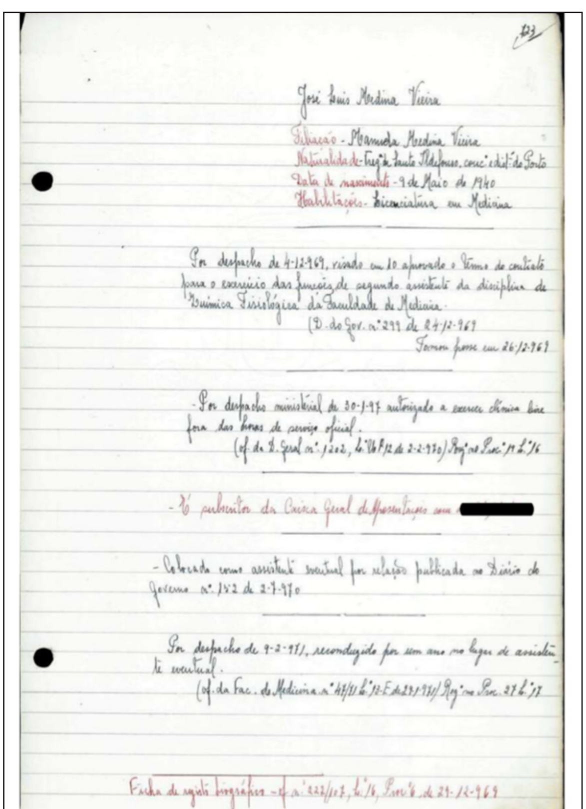
Bilhete de identidade n.º 1963550 Arquivo de Identificação Porto Data 15 / 11 / 1966
Cargo ou lugar assistente da disciplina de Química Fisiológica da Faculdade de Medicina
Vaga que preenche para ocupar o lugar que já ocupa como assistente eventual
Forma de provimento (c) contrato
Data do despacho e entidade que o subscreveu 28 / 12 / 1971- Subsecretário de Estado da Administração Escolar
Disposições legais que autorizam o provimento nos termos do artº.33º.do Decreto-Lei nº. 132/70,de 30 de Março de 1970 e nº.1 do artigo 15º.do mesmo Decreto-Lei
Data do visto do Tribunal de Contas 19 / 1 / 1972
Publicação no «Diário do Governo», n.º 23 em 28 / 1 / 1972
Local da posse Reitoria da Universidade do Porto
Nome e categoria do empossante Professor catedrático Fernando Maria Alberto de Seabra- Vice-Reitor da Universidade

O empossado prestou juramento nos termos da lei.
Observações e averbamentos (d) O contrato,válido por três anos,é renovável por igual período,ao qual será deduzido,nos termos do nº.2 do artº.58º.do Decreto-Lei nº.132/70,de 30 de Março de 1970,o tempo de serviço prestado como segundo-assistente e assistente eventual para além de dois anos.
Universidade do Porto,em 1 de Fevereiro de 1972

100$00 PORTUGAL 50$00 PORTUGAL

(A4 - 210 mm × 297 mm) Modelo n.º 264 (Exclusivo da Imprensa Nacional)

Figura A.6. Livros de Termos de posse e de aceitação de nomeação de pessoal docente e não docente (1914-1973) – Termo de posse de 1972 do lugar de 2º. Assistente de Química Fisiológica



123

José Luís Medina Vieira
Filiação - Manuela Medina Vieira
Naturalidade - Freg. de Santo Ildefonso, conc.º e dist.º do Porto
Data de nascimento - 9 de Maio de 1940
Habilitações - Licenciatura em Medicina

Por despacho de 4-12-969, visado em 10 aprovado o termo de contrato para o exercício das funções de segundo assistente da disciplina de Química Fisiológica da Faculdade de Medicina.
(D. do Gov. nº 299 de 24-12-969
Tomou posse em 26-12-969

- Por despacho ministerial de 30-1-97[illegible] autorizado a exercer clínica livre fora das horas de serviço oficial.
(of. da D. Geral nº 1202, [illegible] de 2-2-970) [illegible]

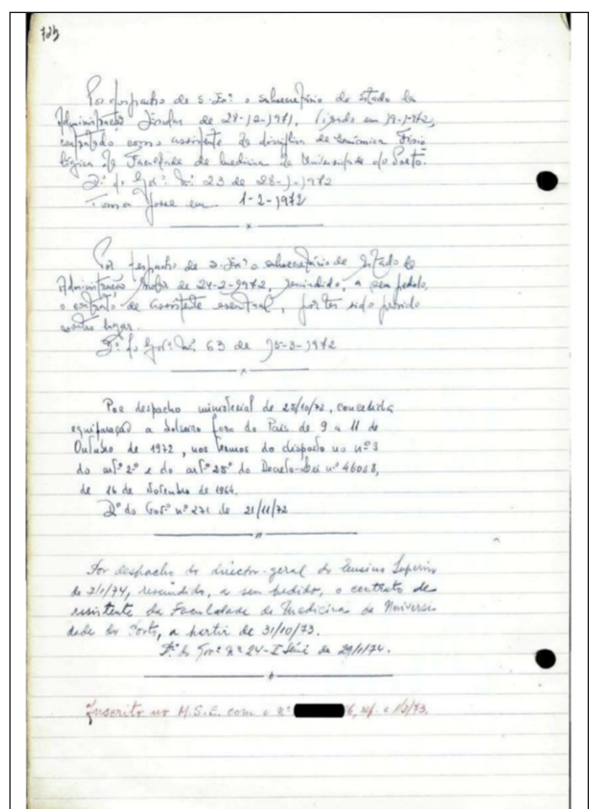
- É subscritor da Caixa Geral de Aposentações com [redacted]

- Colocado como assistente eventual por relação publicada no Diário do Governo nº 152 de 2-7-970

Por despacho de 9-2-971, recondusido por um ano no lugar de assistente eventual.
(of. da Fac. de Medicina nº [illegible] de 2[illegible]-1-971) [illegible]

Ficha de registo biográfico - [illegible] de 29-12-969

Figura A.7. Série Livros de cadastro de pessoal- Percurso Profissional na Universidade do Porto do Professor José Luís Medina Vieira



123

Por despacho de S. Exª o Subsecretário de Estado da Administração Escolar de 28-12-1971, visado em 19-1-1972, contratado como assistente da disciplina de Química Fisiológica da Faculdade de Medicina da Universidade do Porto.
D.º do Gov.º nº 23 de 28-1-1972
Tomou posse em 1-2-1972

Por despacho de S. Exª o Subsecretário de Estado da Administração Escolar de 24-2-1972, rescindido, a seu pedido, o contrato de assistente eventual, por ter sido provido noutro lugar.
D.º do Gov.º nº 63 de 15-3-1972

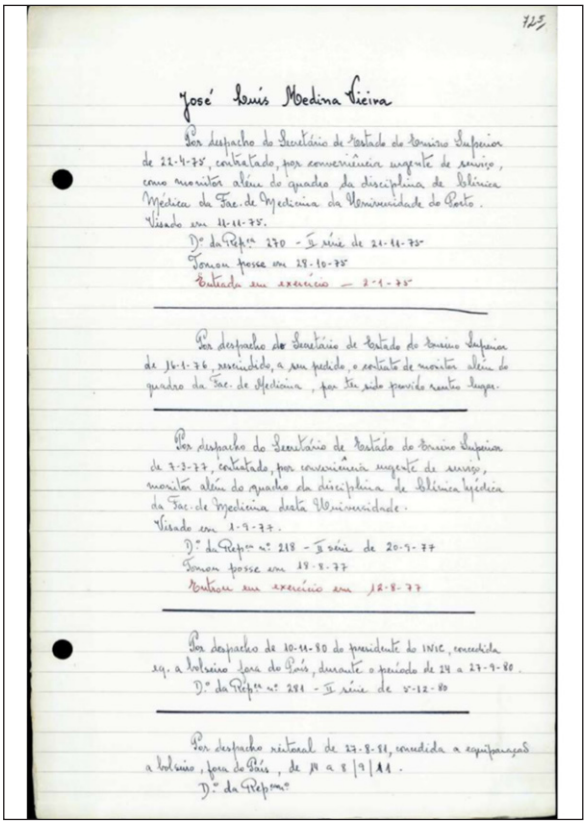
Por despacho ministerial de 25/10/72, concedida equiparação a bolseiro fora do País de 9 a 11 de Outubro de 1972, nos termos do disposto no nº 3 do artº 2º e do artº 25º do Decreto-Lei nº 46031, de 16 de Setembro de 1964.
D.º do Gov.º nº 271 de 21/11/72

Por despacho do director-geral do Ensino Superior de 7/1/74, rescindido, a seu pedido, o contrato de assistente da Faculdade de Medicina da Universidade do Porto, a partir de 31/10/73.
D.º do Gov.º nº 24 - I Série de 29/1/74.

Inscrito no M.S.E. com o nº [redacted]6, of. de 1/3/73.

Figura A.8. Série Livros de cadastro de pessoal- Percurso Profissional na Universidade do Porto do Professor José Luís Medina Vieira

ANEXO A. Imagens Complementares. (Continuação)



José Luís Medina Vieira

Por despacho do Secretário de Estado do Ensino Superior de 22-4-75, contratado, por conveniência urgente de serviço, como monitor além do quadro da disciplina de Clínica Médica da Fac. de Medicina da Universidade do Porto. Visado em 11-11-75.
D.º da Repº nº 270 - II série de 21-11-75
Tomou posse em 29-10-75
Entrado em exercício — 2-1-75

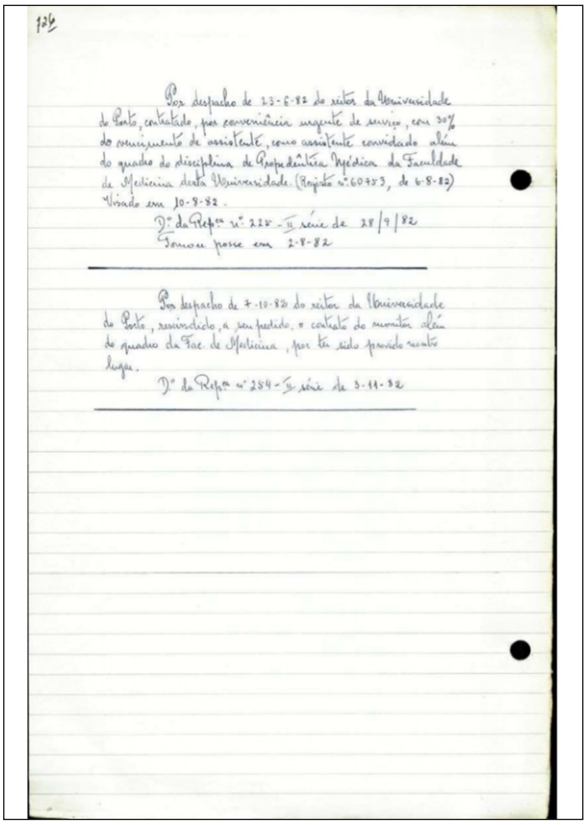
Por despacho do Secretário de Estado do Ensino Superior de 16-1-76, rescindido, a seu pedido, o contrato de monitor além do quadro da Fac. de Medicina, por tem sido provido outro lugar.

Por despacho do Secretário de Estado do Ensino Superior de 7-3-77, contratado, por conveniência urgente de serviço, monitor além do quadro da disciplina de Clínica Médica da Fac. de Medicina desta Universidade.
Visado em 1-9-77.
D.º da Repº nº 218 - II série de 20-9-77
Tomou posse em 19-8-77
Entrou em exercício em 18-8-77

Por despacho de 10-11-80 do presidente do INIC, concedida eq. a bolseiro fora do País, durante o período de 29 a 27-9-80.
D.º da Repº nº 281 - II série de 5-12-80

Por despacho ministerial de 27-8-81, concedida a equiparação a bolseiro, fora do País, de 29 a 8/9/81.
D.º da Repº

Figura A.9. Série Livros de cadastro de pessoal- Percurso Profissional na Universidade do Porto do Professor José Luís Medina Vieira



Por despacho de 23-6-82 do reitor da Universidade do Porto, contratado, por conveniência urgente de serviço, com 30% do vencimento de assistente, como assistente convidado além do quadro da disciplina de Propedêutica Médica da Faculdade de Medicina desta Universidade (Registo nº 60753, de 6-8-82)
Visado em 10-8-82.
D.º da Repº nº 228 - II série de 28/9/82
Tomou posse em 2-8-82

Por despacho de 7-10-82 do reitor da Universidade do Porto, rescindido, a seu pedido, o contrato de monitor além do quadro da Fac. de Medicina, por tem sido provido outro lugar.
D.º da Repº nº 284 - II série de 3-11-82

Figura A.10. Série Livros de cadastro de pessoal- Percurso Profissional na Universidade do Porto do Professor José Luís Medina Vieira

Figura A.11 Condecoração do Professor José Luís Medina Vieira com a Medalha de Prata de Serviços Distintos com Palma, Avenida dos Aliados, Porto, 10 de junho de 1970 (Fotografia gentilmente cedida pela filha, Drª. Susana Medina)

ANEXO B. Publicações Científicas.

Ano de Publicação	Título	Fonte	Autores
1973	Síndrome de Cushing. Revisão de casos clínicos	Jornal do Médico	J. L. Medina, M. P. Hargreaves, M. L. Vila-Cova, E. Peres.
1977	Hipotiroidismo na criança	Revista Portuguesa de Pediatria 8:152-161	M. L. Vila-Cova, J. L. Medina, Lídia P. Monteiro
1977	Síndroma de Klinefelter. Dois casos de diagnóstico pré-puberal	Revista Portuguesa de Pediatria, 8:354-363	M. L. Vila-Cova, J. L. Medina, Lídia P. Monteiro, Amândio S. Tavares
1977	Hiperlipoproteinemias. Da bioquímica à terapêutica	Jornal do Médico, 45:501-507	J. L. Medina, M. P. Hargreaves, L. Marques, M. Helena Ramos.
1977	Obesidade, atraso mental, anomalia cromossómica (18r) e alteração da IgA	Jornal do Médico, 45:501-507	J. L. Medina, M. Helena Ramos, Alda S. Soares, L. Marques, Amândio S. Tavares
1978	Endocrinologia e Doenças do Metabolismo. Reflexões sobre um Programa para o Internato da Especialidade	O Médico, 87:363-365	J. L. Medina
1978	Tiróide sub-lingual, hipotiroidismo e mongoloidismo. Considerações sobre um caso clínico	O Médico, 87:451-453	J. L. Medina, M. Helena Ramos, L. Marques, Alda S. Soares, M. I. Varela, M. P. Hargreaves
1978	Acromegalia. Revisão de casos clínicos	O Médico, 89:241-247	J. L. Medina, B. Faria, M. Portocarrero, A. Ferreira da Silva, A. Ferreira, J. Teixeira.
1981	Terapêutica da obesidade	Reumatologia Multidisciplinar, 1:18-22	J. L. Medina, M. H. Ramos, M. Fontoura, L. Meneses.
1982	Obesidade na criança	Jornal do Médico, 109:929-934	J. L. Medina, M. L. Vila-Cova
1983	Hipertiroidismo na criança	Jornal do Médico, 112:49-54	Lídia P. Monteiro, J. L. Medina, M. I. Varela
1984	Síndrome de insensibilidade androgénica completa (Síndrome de feminização testicular). Considerações sobre um caso clínico	Jornal do Médico, 115:60-64	J. L. Medina, P. Soares, Lídia P. Monteiro, J. Vaz Saleiro, M. Emília Paiva, A. Pimenta, M. Melo, M. Fernanda Guerra
1984	Hirsutismo. Etiologia, clínica e terapêutica	O Médico, 111:325-330	M. Dulce Madeira, J. L. Medina.
1984	Autovigilância da glicosúria por diabéticos. Avaliação de novo teste	O Médico, 111:846-851	P. Soares, M. Ribeiro, F. Guerra, J. L. Medina.
1985	Avaliação do grau de compensação da diabetes mellitus. Breve revisão crítica dos parâmetros mais usados	O Médico, 113:330-339	J. L. Medina, J. L. Castedo, M. D. Madeira.
1986	Bócio no Concelho de Paredes de Coura. Nota preliminar	O Médico, 114:206-213	A. M. Medina, M. I. Ramos, J. L. Medina, M. I. Gramaxo, M. J. Pinheiro, M. M. Pinto
1986	Atraso de crescimento, dente incisivo central único do maxilar superior e hipoplasia da sela turca	O Médico, 114:557-563	J. L. Medina, M. F. Guerra, M. P. Tavares
1986	Autovigilância dos doentes diabéticos. Estudo comparativo de duas tiras-teste para avaliação de glicemia capilar	O Médico, 115:58-61	M. Ribeiro, P. Soares, M. F. Guerra, J. L. Medina
1986	Reflexões e conselhos práticos sobre a diabetes mellitus na 3ª idade	O Médico, 115:622-630	J. L. Medina, M. F. Guerra, M. C. Gouveia
1986	Lesão do sistema nervoso autónomo cardiovascular em diabéticos. Avaliação de resultados dos 5 testes usados. Correlação com alguns parâmetros clínicos e laboratoriais	Revista Portuguesa Cardiologia, 5:157-165	J. L. Medina, M. F. Guerra, M. A. Cruz, F. Brandão, M. D. Madeira, J. L. Castedo, J. Maia, M. P. Hargreaves, M. polónia-Gomes
1986	Alguns progressos na terapêutica da diabetes mellitus. Actualização para os Clínicos Gerais	Jornal do Médico, 121:587-600	J. L. Medina, M. F. Guerra, C. Gouveia, C. Arteiro, M. F. Correia.
1986	Retinopatia diabética. Classificação, prevalência e correlação com as lesões do sistema nervoso periférico e autónomo e com alguns factores de risco. Resultados preliminares	Revista Sociedade Portuguesa Oftalmologia, XII:27-46	J. L. Medina, J. Castro-Correia, A. Brandão, J. Araújo, J. Borges, V. Rosas, M. F. Coutinho, M. F. Guerra, M. A. Cruz, F. Brandão, R. polonia, M. Assunção, J. Maia, M. P. Hargreaves, M. Cerqueira-Gomes.
1986	Nesidioblastosis and insulinoma. An infrequent association	Acta Medica Portuguesa	Madeira MD, Reis L, Medina JL, Sambade C, Carneiro F, de Oliveira C.
1987	Obesidade na criança. Alguns dados sobre um inquérito alimentar	Centro de Estudos de Nutrição,11:22-26	M. F. Guerra, J. L. Medina, C. Gouveia
1989	Pharmacological treatment of hyperlipidemias	Arquivos de Medicina	Medina, J.L., Brandão, F., Guerra, M.F.
1990	Drug therapy and other treatment methods in obesity	Arquivos de Medicina	Medina, J.L., Torres,I.
1991	Glomerular hyperfiltration in insulin-dependent diabetes mellitus: No evidence for enhanced activity of the renin-angiotensin aldosterone system	Journal of Diabetic Complications	Carvalho Braga,D., Almeida,R., Azevedo,M., Amaral,I., Medina,J., Hargreaves,M.
1992	Insulinomas: dificuldades de diagnóstico e de terapêutica	Arquivos de Medicina 6 (supl. 1): 80	Neves C, Vinha E, Carvalho D, Marques L, Fonseca E, Teixeira M, Medina JL
1992	Colelitíase e obesidade. Que relações?	Arquivos de Medicina 6 (supl. 1): 65,	Pinheiro D, Lima Reis JP, Carvalho D, Cardoso de Oliveira M, Medina J.
1992	Obesidade. resultados da terapêutica	Arquivos de Medicina 6 (supl. 1): 65	Ribeiro L, Lima Reis JP, Castedo JL, Medina JL.
1992	Tumor feminizante da supra-renal: a propósito de um caso clínico	Arquivos de Medicina 6 (supl. 1): 69	Vinha E, Neves C, Marques L, Pignatelli D, Teixeira M, Ramos U, Medina JL
1992	Insuficiência suprarrenal primária em doente com SIDA.	Arquivos de Medicina 6 (supl. 1): 70	Carvalho D, Marques R, Miranda M, Vinha E, Lecour H, Medina JL.
1992	Hipoparatiroidismo - apresentação de 2 casos clínicos em 2 irmãos	Arquivos de Medicina 6 (supl. 1): 83	Pereira Monteiro L, Carvalho D, Neves C, Medina JL.
1992	Os níveis de Lp(a) correlacionam-se com a área de gordura total quantificada por TAC e não se associam a padrão específico de distribuição de gordura corporal	Arquivos de Medicina 6 (supl. 1): 64	Von Hafe, A Pérez, JL Medina
1992	Obesidade Androide e Ginóide Avaliada por Tomografia Computorizada Relação com as Lipoproteínas, Insulina e Hábitos Tabágicos. II Congresso Nacional de Medicina Interna	Livro de Resumos, p. 86	Von Hafe, A Pérez, JP Nunes, J Polónia, JL Medina, FR Gonçalves, M Cerqueira Gome

ANEXO B. Publicações Científicas. (Continuação)

Ano de Publicação	Título	Fonte	Autores
1992	Lipoproteína (a): revisão breve	Endocrinologia, Metabolismo e Nutrição 1: 28-32	Medina JL, Figueiredo S, Torres 1, Guerra F, Cruz C, Magalhães A, Alvarez D
1992	Equilíbrio glicémico - beneficios e potenciais riscos	Livro de homenagem ao Professor Cerqueira Magro. Ed. H Lecour. Porto	Hargreaves MP, Medina JL
1992	Obesidade e dislipidemia. Recomendações da Associação Europeia de Aterosclerose	Revista Portuguesa Nutrição 4:22-30	Cruz MC, Torres I, Guerra F, Magalhães A, Figueiredo S, Alvarez D, Von Haffe P. Rocha-Gonçalves F, Cerqueira-Gomes M, Medina JL
1992	Dados antropométricos e impedância bioelétrica. Correlações	Endocrinologia, Metabolismo e Nutrição, 1:283-291	Monteiro I, Lima Reis JP, Carvalho D, Medina JL
1992	Insulinemia is Correlated with Subcutaneous Fat Area Quantified by Computed Tomography	Abstract Book: 82	Von Haffe, A Pérez, JP Nunes, J Polónia, F Brandão, JL Medina, FR Gonçalves, M Cerqueira Gomes.
1992	Comparation between cough test and other tests used to assess cardiovascular autonomic function in diabetes	Abstract Book (P-11.03.098) 9th International Congress of Endocrinology. Nice, 1992.	Medina JL, Guerra F, Torres I, Figueiredo S, Cruz C, Alvarez D, Magalhães A, Brandão F, Polónia J, Cerqueira-Gomes.
1992	Osteoporosis risk factors in menopausal women in the North of Portugal	Abstract Book (P-06.01.036) 9th International Congress of Endocrinology. Nice, 1992.	Pignatelli D, Pereira-Monteiro L, Coimbra-Peixoto A, Medina JL.
1992	Smoking is Associated with Intraabdominal Fat Accumulation	Abstract Book: 111	Von Hafe, A Pérez, JP Nunes, J Polónia, F Brandão, JL Medina, FR Gonçalves, M Cerqueira Gomes.
1993	Comparação entre o teste da tosse e outros testes usados para avaliar a função autónoma cardiovascular em doentes diabéticos	Arquivos de Medicina 5: 273-274	Guerra F, Torres I, Figueiredo S, Cruz C, Alvarez D, Magalhães A, Medina JL. Brandão F, Polónia J, Maia J, Cerqueira Gomes M
1993	Estudo comparativo de dois métodos de doseamento de apolipoproteínas AI e B	Arquivos de Medicina 4: 217-218	Figueiredo S, Magalhães A, Cruz C, Alvarez D, Guerra F, Torres I, Nascimento F, Sá L, Portocarrero C, Maia J, Medina JL
1993	Regressão da aterosclerose - revisão de estudos	Arquivos de Medicina 7 (supl 7): 375-383	Medina JL
1993	24 h ambulatory blood pressure monitoring in acromegaly	Arquivos de Medicina 7 (supl. 6): 16	Carvalho D, Monteiro A, Baldaque-Faria A, Medina JL, Falcão de Freitas A.
1993	Xantelasma	Arquivos de Medicina 7 (supl. 5): 8-9	Medina JL, Guerra MF
1993	Acidose láctica	Arquivos de Medicina 7 (supl. 5): 2-3	Guerra F, Medina JL
1993	Efeito do conteúdo em gordura da dieta na distribuição anatómica do tecido adiposo em indivíduos obesos do sexo feminino	Arquivos de Medicina 1: 18-23	Monteiro I, Lima Reis JP, Carvalho D, Medina JL
1993	Guia prático para controlo dos factores de risco de doença coronária. Adaptação às realidades portuguesas	Sociedade Portuguesa de Aterosclerose, 53	Miguel JP, Medina JL, Saldanha MF, Galvão Teles A
1993	Acromegalia: a propósito de um caso de diabetes mellitus de difícil compensação	Livro de resumos.	Silva D, Craveiro M, Neves C, Vinha E, Medina JL
1993	Neuropatia diabética. Epidemiologia, factores de risco, etiopatogenia	Endocrinologia Metabolismo e Nutrição, 2: 87-90	Medina JL
1993	Terapêutica farmacológica da obesidade e outras formas de tratamento. In Manual sobre Obesidade na Clínica Geral	Arquivos de Medicina 7 (supl 4): 158-163	Medina JL, Torres I.
1993	High fat diet is associated with android adipose tissue distribution	Abstract book	
	Reis L, Monteiro I, Carvalho D, Medina JL		
1993	Auditory studies in young type 1 (insulin dependent) diabetics	XV World Congress of Otorhinolaryngology, Head and Neck Surgery, Istanbul	Carvalho D, Nunes R, Santos M, Oliveira V, Tsou R, Teixeira Santos N, Medina JL, Pais Clemente M
1994	Obesidade: factor de risco para osteoartrose	Endocrinologia, Metabolismo e Nutrição, 3: 31	Silva F, Neves C, Nóvoa T, Ventura F, Rodrigues E, Lima Reis JP, Medina JL,
1994	Carcinoma oculto de manifestação hipofisária	Endocrinologia Metabolismo e Nutrição, 3: 26	Barbosa AP, Carvalho D, Rodrigues E, Carvalho-Braga D, Machado-Carvalho A, Batista A, Monteiro M, Serrano A, Barroca H, Baldaque Faria A, Cruz C, Medina JL.
1994	Resultados da terapêutica de prolactinomas com bromocriptina injectável de acção prolongada	Endocrinologia, Metabolismo e Nutrição 3 : 24	Carvalho D, Neves C, Barbosa A, Rodrigues E, Baldaque-Faria A, Lima T, Medina JL
1994	Os níveis de Cortisol Plasmático estão relacionados com os hábitos tabágicos	Livro de resumos, 171	Von Hafe, P. Fernando, MJ Andrade, JL Medina, F Brandão, M Cerqueira Gomes
1994	Obesidade, hiperinsulinemia e hipertensão arterial	Livro de resumos.	Coimbra-Peixoto A, Pignatelli D, Lima Reis JP, Medina JL
1994	Dyslipidemia and diabetes mellitus	Arquivos de Medicina	Medina, J.L., Marques,L., Reis,L., Monteiro,L., Faria,B.
1994	Diabetic foot	Arquivos de Medicina	Vinha,E., Marques,L., Medina,J.L.
1994	Reflexões sobre a situação da Diabetologia em Portugal	Arquivos de Medicina 8 (supl1): 13-14	Medina JL.
1994	The role of modified lipoproteins in the development of arterial disease in diabetes	Dialogue 4: 11-15	Medina JL.
1994	Relationship of Plasmatic Renin Activity and Aldosterone to Body Fat Distribution Indexes Quantified by Computed Tomography in Hypertensives	Abstract Book: 66, 1994.	Von Hafe, A Pérez, J Polónia, JL Medina, FR Gonçalves, M Cerqueira Gomes
1994	Effects of imipramine on plasma levels of catecholamines and metabolites in normal subjects and in diabetics	Journal of Autonomic Pharmacology, 14(1): 22	Medina JL, Polónia J, Brandão F, Vaz-da-Silva M, Pinto A, Magalhães D. Campelo M.
1994	Cushing Syndrome in ACTH-producing pulmonary tumor	European Journal of Endocrinology. 130 (supl. 2): 230 (P.3.165)	Cernadas P, Cruz C, Mendes S, Carvalho D, Medina JL, Pimenta A, Cardoso V.
1994	Petrosal sinus catheterization in the differential diagnosis of Cushing syndrome with negative pituitary imaging	European Journal of Endocrinology. 130 (supl. 2): 208 (P.3.075)	Carvalho D, Cruz J, Machado-Carvalho, Portocarrero MC, Barbosa A, Rodrigues E, Neves C, Baldaque-Faria A, Cruz C, Medina JL

ANEXO B. Publicações Científicas. (Continuação)

Ano de Publicação	Título	Fonte	Autores
1995	Feocromocitoma	Arquivos de Medicina 9: 32-35	Alvarez D, Vinha E, Monteiro L, Guerra F, Pignatelli D, Castedo JL, Marques L, Medina JL.
1995	Pé diabético - um exemplo de consulta	Endocrinologia Metabolismo e Nutrição 3 (5): 261-63	Vinha E, Marques L, Medina JL
1995	Hipertrigliceridemia - factor de risco cardiovascular	Endocrinologia Metabolismo e Nutrição 3 (6): 353-55	Medina JL, Ramalhão C, Rodrigues E.
1995	Osteoporose e doenças endócrinas	Revista Portuguesa de Reumatologia 6 (52): 1307-1310	Medina JL, Rodrigues E.
1995	Interrelações obesidade e colelitíase	Endocrinologia Metabolismo e Nutrição 3 (6): 307-17	D Pinheiro, D Carvalho, JP Lima Reis, M Cardoso Oliveira. JL Medina
1995	Insulino-resistência, dislipidemia e aterosclerose	Endocrinologia Metabolismo e Nutrição 4 (6): 19-23	Medina JL, Rodrigues E
1995	QTc interval and autonomic neuropathy in diabetic patients	Abstract Book	Rodrigues E, Medina JL, Freitas P, Barbosa AP, Neves C, Polónia J, Cerqueira Gomes M
1995	Reevaluation of autonomic neuropathy in diabetic patients	Abstract Book	Barbosa AP, Medina JL, Neves C, Rodrigues E, Freitas P, Guerra MF, Cruz MC, Torres I, Alvarez D, Figueiredo S, Magalhães A, Polónia J, Cerqueira-Gomes M
1995	Autonomic nervous function evaluation after cardiac transplantation in man	Abstract Book	Neves C, Medina JL, Barbosa AP, Rodrigues E, Freitas P, Polónia J, Cerqueira-Gomes M, Torres P, Rodrigues Gomes M.
1995	Diabetes Educators Formation Course Report	Abstract Book International Symposium "News in Diabetes Management".	Pereira Monteiro L, Carvalho D, Vila-Cova MIL, Correia F, Correia A, Guerra MF, Brandão I, Palha P, Sampaio M, Medina JL
1995	Update Metformina	Abstract Book	Medina JL
1995	Factors influencing the immediate and late outcome of Cushing's-disease treated by transsphenoidal surgery - a retrospective study by the European Cushing's-disease survey group	Journal of Clinical Endocrinology and Metabolism	Bochicchio, D losa, M; Buchfelder, M; Stevenaert, A; Beckers, A; Hagen, C; Bjerre, P ; Kruse, A; Lindholm, J ;Fahlbusch, R; Muller, OA; Vonwerder, K; Ambrosi, B; Faglia, G; Giovanelli, M; Angeli, A; Maira, G; Pieters, GFFM; Carvalho, D; Medina, JL; Costa, C; Teles, AG; Guerreiro, L; Ruas, M; Salcedo, I; Dolenc, V; Jezernik, M; Vazquez, JA; Gaztambide, S; Webb, SM; Halperin, I; Vilardell, E ; Vidal, O; Sanchezfranco, F; Astorga, R; Lealcerro, A ; Luna,PPG; Torres, E ; Thoren, M; Werner, S; Landolt, AM; Atkinson, AB; Mccance, DR; Gordon, DS; Hadden, DR; Kennedy, L; Scanlon, MF;Cruickshanks, G;Teasdale, GM;
1996	Diabetes and surgery	Arquivos de Medicina	Neves,C., Pereira-Monteiro,L., Medina,J.L.
1996	Five -years follow-up of cardiovascular autonomic neuropathy in diabetic patients	Avances en Diabetologia 12: 159-64	Barbosa AP, Medina JL, Neves C, Rodrigues E, Freitas P, Polónia J, Cerqueira-Gomes M, Maia J
1996	Feocromocitoma maligno: a propósito de um caso clínico	Arquivos de Medicina 10(1): 43-47,	Barbosa AP, Marques L, Pinto J, Amado P, Figueiredo J, Nogueira R, Lopes Vaz A, Medina JL
1996	Rastreio de bócio e cancro da tiroide no concelho de Lousada	Arquivos de Medicina 10(2): 92-95	Torres I, Barbosa AP, Marques L, Lima Reis JP, Milheiro L, Matos Lima L, Medina JL.
1996	Importância do doseamento de PTHrP no diagnóstico da hipercalcemia tumoral maligna: resultados preliminares	Arquivos de Medicina 10(4): 253-256	Neves C, Pereira-Monteiro L, Carvalho D, Pimentel FL, Portocarrero MC, Limas I, Lopes Vaz A, Medina JL
1996	Nutrição no idoso. Considerações gerais	Revista Portuguesa de Geriatria, IX (88): 9-11	Medina JL
1996	Interesse da variabilidade da frequência cardíaca na avaliação da neuropatia autonómica diabética	Revista Portuguesa de Cardiologia 15 (supl. III): 78	Campelo M, Medina JL, Polónia J, Rodrigues E, Santos A, Van varezeller P. Cerqueira-Gomes M
1996	Apresentação atípica de feocromocitoma - um caso de acidentaloma	Endocrinologia, Metabolismo e Nutrição 5(supl. 1): 53	Rodrigues E, Vinha E, Guerra MF, Carvalho-Braga D, Cruz C, Matos Lima L, Lopes IM. Medina JL
1996	Pseudo-hiperaldosteronismo tipo II: a propósito de um caso clínico	Endocrinologia, Metabolismo e Nutrição 5 (supl 1): 5	Freitas P, Braga D, Lima Reis JP, Pereira Monteiro L, Medina JL
1996	Adrenal incidentaloma: an unusual case of pheochromocytoma	Book of Abstracts, pg 321	Rodrigues E, Vinha E, Guerra MF, Carvalho-Braga D, Cruz C, Matos Lima L, Lopes JM, Medina JL.
1996	Bone remodeling markers in acromegaly	Book of Abstracts, pg 266.	Freitas P, Carvalho D, Barbosa AP, Lima Reis JP, Medina JL.
1996	Acromegaly is associated with an increased albumin excretion rate	Book of Abstracts, pg 270.	Carvalho D, Carvalho A, Baldaque A, Cruz C, Medina JL.
1996	Reevaluation of cardiovascular autonomic neuropathy in diabetic patients	Book of Abstracts, pg. 74.	Barbosa AP, Medina JIL, Neves C, Rodrigues E, Freitas P, Guerra MF, Cruz MC, Torres I, Alvarez D, Figueiredo S, Magalhães A, Polónia J, Cerqueira-Gomes M.
1996	Blunting of night-time blood pressure fall in diabetic hypertensive patients with severe autonomic neuropathy	American Journal Hypertension 9(4), part II: 112A	Medina JL, Polónia J, Rodrigues E, Barbosa A, Neves C, Santos A.
1996	Resposta da prolactina e da somatotrofina no teste GRF	Endocrinologia Metabolismo e Nutrição 5: 42	Neves C, Carvalho D, Carvalho A, Portocarrero M, Baldaque A, Cruz C, Medina JL.
1996	Preoperative octreotide treatment of acromegaly	Journal of Endocrinological Investigation 19:12	Carvalho D, Barbosa AP, Freitas P, Carvalho A, Baldaque A, Cruz J, Pina R, Cruz C, Medina JL.
1996	Cytokines response to CRF stimulation in Cushing's syndrome	Journal of Endocrinological Investigation. 5:19	Carvalho D., Barbosa A.P., Delgado J.L., Bodas A., Cruz J., Carvalho A, Baldaque A., Cruz C., Medina J.L..
1996	Retinopatia diabética na acromegalia. Que papel para a somatotrofina?	JAMA (ed Port.) 3: 86	Carvalho D, Rosas V, Baldaque A, Castro-Correia J, Medina JL.

ANEXO B. Publicações Científicas. (Continuação)

Ano de Publicação	Título	Fonte	Autores
1998	Medical aspects of Nephrolithiasis	Acta Medica Portuguesa	Barbosa AP, Medina JL.
1998	Diabetic Ketoacidosis, diagnostic and therapeutic strategies	Arquivos de Medicina	Neves,C., Rodrigues,E.,Varela,A, Medina,J.L.
1999	Inefficiency of the anticoagulant therapy in the regression of the radiation-induced optic neuropathy in Cushing's disease	Journal of Endocrinological Investigation	Barbosa AP, Carvalho D, Marques L, Monteiro M, Castro Neves A, Machado Carvalho A, Cruz J, Medina JL.
1999	Subacute thyroiditis	Arquivos de Medicina	Pereira, M.L., Carvalho-Braga,D., Medina,J.L.
1999	Sheehan's Syndrome	Arquivos de Medicina	Pereira,M.L., Braga,D.C., Marques,L., Medina, J.L.
1999	Administration of combined solutions of glucose-insulin-potassium (GIK) versus glucose and insulin in separate solutions (GISS) in diabetic patients submitted to cardiac surgery	Arquivos de Mecicina	Neves, C., Paula Barbosa,A., Carvalho, D., Pereira--Monteiro,L., Basto,P., Medina,J.L.
1999	Hormone replacement therapy and the selective-estrogen response modulators (SERMs) as a promising alternative	Arquivos de Medicina	Pereira,M.L., Pignateli,D., Braga,D.C., Medina,J,L.
2000	Male hypogonadism	Arquivos de Medicina	Pereira,M.L., Braga,D.C., Neves,C., Medina,J.L.
2000	Quality of health care	Acta Médica Portuguesa	Medina, J.L., De Melo,P.C.
2001	Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13	Nature Genetics	Magré J, Delépine M, Khallouf E, Gedde-Dahl T Jr, Van Maldergem L, Sobel E, Papp J, Meier M, Mégarbané A, Bachy A, Verloes A, d'Abronzo FH, Seemanova E, Assan R, Baudic N, Bourut C, Czernichow P, Huet F, Grigorescu F, de Kerdanet M, Lacombe D, Labrune P, Lanza M, Loret H, Matsuda F, Navarro J, Nivelon-Chevalier A, Polak M, Robert JJ, Tric P, Tubiana-Rufi N, Vigouroux C, Weissenbach J, Savasta S, Maassen JA, Trygstad O, Bogalho P, Freitas P, Medina JL, Bonnicci F, Joffe BI, Loyson G, Panz VR, Raal FJ, O'Rahilly S, Stephenson T, Kahn CR, Lathrop M, Capeau J; BSCL Working Group.
2001	Prevalence and risk factors of clinical diabetic polyneuropathy in a Portuguese primary health care population	Diabetes and Metabolism	Barbosa AP, Medina JL, Ramos EP, Barros HP.
2002	Craniopharyngiomas. Clinicopathological aspects in different age groups	Acta Medica Portuguesa	Barbosa AP, Varela A, Carvalho D, Cerejo A, Pereira J, Castro L, Vinha E, Monteiro M, Cruz J, Vaz R, Medina JL.
2002	Thyroid diseases during pregnancy	Acta Medica Portuguesa	Medina JL, Neves C, Magalhães A, Pereira-Monteiro L, Marques L.
2002	Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy	Journal of Medical Genetics	Van Maldergem, L; Magre, J; Khallouf, TE ;Gedde-Dahl, T ; Delepine, M; Trygstad, O; Seemanova, E; Stephenson, T ; Albott, CS; Bonnici, F; Panz,VR; Medina, JL; Bogalho, P; Huet, F; Savasta, S; Verloes, A; Robert, JJ; Loret, H; de Kerdanet, M;Tubiana-Rufi, N; Megarbane, A; Maassen, J; Polak, M; Lacombe, D; Kahn, CR; Silveira, EL; D'Abronzo, FH; Grigorescu, F; Lathrop, M; Capeau, J; O'Rahilly, S
2002	Polycystic ovary syndrome	Arquivos de Medicina	Cunha, M., Carvalho, D.; Freitas,P., Costa, A.R., Bernardes,J.,Cunha,H., Nunes,A.,Limas,T., Ramos,J.,Medina,J.L., Oliveira,A.M.
2002	Mauriac's Syndrome	Arquivos de Medicina	Freitas,P., Melo,P.C, Marinho,R., Vinha,E., Guerra,F., Lima Reis, J.P., Medina,J.L.
2003	Inhibins A and B: Physiologic characterization in long menstrual cycles	Arquivos de Medicina	Freitas, P., Cunha,M., Carvalho, D., Ramos,J.P., Lima,T., Martinez-Oliveira, A., Medina, J.L.
2004	Circadian energy intake evaluation of a group of office workers in Porto	Acta Medica Portuguesa	Setas CD, Pinhão SC, Carvalho DM, Correia FC, Medina JL.
2004	Androgens and the aging male	Arquivos de Medicina	Monteiro, S., Castedo, J.L., Medina, J.L.
2006	Prevalence of the metabolic syndrome: comparison between ATPIII and IDF criteria in a feminine population with severe obesity	Acta Medica Portuguesa	Correia F, Poínhos R, Freitas P, Pinhão S, Maia A, Carvalho D, Medina JL.
2007	Endocrine alterations and imuno-modulation on pregnancy	Arquivos de Medicina	Neves,C., Medina,J.L., Delgado, J.L.
2007	Craniopharyngioma: Same dangers, different age	Endocrinologia y Nutricion	Queirós, J., Magalhaes, A., Medina,J.L.
2008	Reduction of the cut-off of waist circumference does not seem to modify the prevalence of metabolic syndrome in a population with morbid obesity	International Journal of Obesity	Souto, S; Mesquita; Oliveira, A; Freitas, P; Correia, F; Varela, A; Carvalho, D; Braga, D;Medina, JL.
2008	Serum levels of aminotransferases and gamma-GT in obese patients	International Journal of Obesity	Mesquita, J; Souto, S; Oliveira; Freitas, P; Varela, A; Correia, F; Carvalho, D; Medina, JL.
2008	Social desirability and barriers to the accomplishment of the dietary treatment in overweight women	Acta Medica Portuguesa	Poínhos R, Correia F, Faneca M, Ferreira J, Gonçalves C, Pinhão S, Medina JL.
2008	Thyroid diseases, dyslipidemia and cardiovascular pathology	Revista Portuguesa de Cardiologia	Neves C, Alves M, Medina JL, Delgado JL
2008	Graves' Disease	Arquivos de Medicina	Neves,C., Alves,M., Delgado,J.L., Medina,J.L.
2009	Psychological characteristics in an obese population assessed using psychometric self-evaluation	Obesity and Metabolismo-Milan	Correia, F; Poinhos, R; Pinhao, S; De Oliveira, BMPM; Coelho, R; De Almeida, MDV; Medina, JL; Galvao-Teles, A;
2009	Post-partum thyroiditis	Acta Medica Portuguesa	Neves C, Alves M, Delgado L, Medina JL.
2009	Obstacles in dietary treatment of obesity	Obesity and Metabolism-Milan	Correia, F; Pinhao, S; Poinhos, R; de Oliveira, BMPM; de Almeida, MDV (Vaz de Almeida, Maria Daniel);Medina, JL (Medina, Jose Luis); Galvao-Teles, A (Galvao-Teles, Alberto)

ANEXO B. Publicações Científicas. (Continuação)

Ano de Publicação	Título	Fonte	Autores
2009	A randomized double-blind study comparing the efficacy and safety of orlistat versus placebo in obese patients with mild to moderate hypercholesterolemia	Revista Portuguesa de Cardiologia	de Castro JJ, Dias T, Chambel P, Carvalheiro M, Correia LG, Guerreiro L, Marques O, Medina JL, Nobre E, Nunes JS, Pereiraa MC, Polónia J, Portugal J, Raimundo A, Ruas A, da Silva PM, Vasconcelos C, Reis JL, Teles AG.
2009	Is glycemic optimization sufficient to prevent macroangiopathy in type 2 diabetics?	Louvain Medical Conference Paper	Buysschaert,M., Medina, J.L.
2010	Laboratorial diagnosis of Cushing's syndrome	Acta Medica Portuguesa	Alves M, Neves C, Medina JL.
2010	Interrelations between insulin resistance, lipid profile, and inflammation in patients with autoimmune thyroiditis	Endocrine Journal	Neves, C; Alves, M; Pereira, M; Ramalho, R; Palmares, C; Guimaraes, C; Ramos, JP; Carvalho, D; Delgado, L; Medina, JL;
2010	Thyroid function and cardiovascular risk factors in patients with autoimmune thyroiditis	Endocrine Journal	Neves, C; Alves, M; Pereira, M; Ramalho, R; Palmares, C; Guimaraes, C; Carvalho, D; Delgado, L; Medina, JL;
2010	Diabetic ketoacidosis: Retrospective study of the patients admitted to the Endocrinology Departmentof Sao Joao Hospital	Endocrine Journal	Mesquita, JM ; Alves, ML; Varela, AM; Rodrigues, EG; Neves, C; Guerra, MF;Medina, JL;
2010	Casuistic revision of Wolfram Syndrome in Sao Joao Hospital, Portugal	Endocrine Journal	Alves, ML; Campos, T; Loureiro, I; Espinheira, C; Costa, C; Correia, C; Neves, C; Fontoura, M; Medina, JL;
2010	Symptomatic primary hyperparathyroidism associated with ectopic parathyroid glands	Endocrine Journal	Alves, M; Neves, C; Carvalho-Braga, D; Medina, JL;
2010	Hydatidiform mole and hyperthyroidism	Endocrine Journal	Alves, M; Neves, C; Carvalho-Braga, D; Medina, JL
2010	Fat mass ratio: an objective tool to define lipodystrophy in HIV--infected patients under antiretroviral therapy	Journal of Clinical Densitometry	Freitas P, Santos AC, Carvalho D, Pereira J, Marques R, Martinez E, Sarmento A, Medina JL.
2010	Thyroid Function, Lipid Profile, Insulin Resistance, Homocysteine and High Sensitivity C-Reactive Protein in Patients with Autoimmune Thyroid Disease	Endrocine Reviews	Neves, C; Ramalho, R; Guimaraes, C; Beltrao, M; Alves, M; Pereira, M; Carvalho, E; Pimentel, I; Palmares, C; Ramos, JP; Carvalho, D; Delgado, L; Medina, JL
2010	Nitrogen balance assessment in burn patients	Acta Medica Portuguesa	Beça A, Egipto P, Carvalho D, Correia F, Oliveira B, Rodrigues A, Amarante J, Medina JL.
2010	Dyslipidemia in renal disease: causes, consequences and treatment	Endocrinologia y Nutricion	Mesquita J, carvalho A, Medina JL.
2010	Trauma and the endocrine system	Endocrinologia y Nutricion	Mesquita J, Varela A, Medina JL.
2010	Diagnosis and Treatment of late-onset Hypogonadism	Arquivos de Medicina	Alves,M., Neves,C., Medina,J.L.
2010	Diabetes, insulin and cancer	Louvain Medical Conference Paper	Buysschaert,M., Medina, J.L.
2011	Prevention and current onset delay approaches of type 2 diabetes mellitus (T2DM)	European Journal of Clinical Pharmacology	Souto SB, Souto EB, Braga DC, Medina JL.
2011	Intra-gastric and safe balloon but there are indications and contraindications	Acta Medica Portuguesa	Medina, JL (Medina, Jose Luis)
2011	Impact of Lipodystrophy on the prevalence and components of metabolic syndrome in HIV-infected patients	BMC Infectious Diseases	Freitas, P; Carvalho, D; Souto, S; Santos, AC; Xerinda, S; Marques, R; Martinez, E; Sarmento, A; Medina, JL;
2011	Assessment of body fat composition disturbances by bioimpedance analysis in HIV-infected adults	Journal of Endocrinological Investigation	Freitas P, Carvalho D, Santos AC, Mesquita J, Correia F, Xerinda S, Marques R, Martinez E, Sarmento A, Medina JL.
2011	Thyroid associated orbitopathy	Acta Medica Portuguesa	Alves M, Neves C, Carvalho D, Medina JL.
2011	Continuous subcutaneous insulin infusion	Acta Medica Portuguesa	Balsa AM, Neves C, Alves M, Pereira M, Carvalho D, Medina JL.
2012	Lipodystrophy defined by Fat Mass Ratio in HIV-infected patients is associated with a high prevalence of glucose disturbances and insulin resistance	BMC Infectious Diseases	Freitas P, Carvalho D, Santos AC, Mesquita J, Matos MJ, Madureira AJ, Martinez E, Sarmento A, Medina JL
2012	Central/Peripheral Fat Mass Ratio Is Associated with Increased Risk of Hypertension in HIV-Infected Patients	Journal of Clinical Hypertension	Freitas P, Carvalho D, Santos AC, Madureira AJ, Xerinda S, Martinez E, Pereira J, Sarmento A, Medina JL.
2012	Prevalence of obesity and its relationship to clinical lipodystrophy in HIV-infected adults on anti-retroviral therapy	Journal of Endocrinological Investigation	Freitas P, Carvalho D, Santos AC, Matos MJ, Madureira AJ, Marques R, Martinez E, Sarmento A, Medina JL
2014	Diagnosis and Definition	Global Health Perspectives in Prediabetes and Diabetes Prevention Book Chapter	Buysschaert, M., Preumont,V., Medina, J.L., Bergman, M.
2014	Graves' Disease and Cardiovascular Risk Factors	Endocrine Reviews	Neves, C; Esteves, CM; Sokhatska, O; Palmares, C; Medina, JL; Delgado, L; Carvalho, D;
2014	Autoimmune Thyroiditis, Subclinical Hypothyroidism and Cardiovascular Risk Factors	Endocrine Reviews	Neves, C; Esteves, CM; Sokhatska, O; Palmares, C; Medina, JL; Delgado, L; Carvalho, D;
2014	Adipokines, hormones related to body composition, and insulin resistance in HIV fat redistribution syndrome	BMC Infectious Diseases	Freitas P, Carvalho D, Santos AC, Madureira AJ, Martinez E, Pereira J, Sarmento A, Medina JL.
2014	Carotid intima media thickness is associated with body fat abnormalities in HIV-infected patients	BMC Infectious Diseases	Freitas P, Carvalho D, Santos AC, Madureira AJ, Martinez E, Pereira J, Sarmento A, Medina JL.
2015	Prediabetes and associated disorders	Endocrine	Buysschaert M, Medina JL, Bergman M, Shah A, Lonier J.
2015	Subclinical Hypothyroidism, autoimmune thyroiditis and cardiovascular risk factor	Arquivos de Medicina	Pereira, T.A., Neves,C., Esteves,C., Carvalho,D., Delgado,L.,Medina, J.L.
2015	Postpartum thyroiditis	Arquivos de Medicina	Barreira, J.F, Neves., C., Esteves, C., Delgado, L., Medina, J.L.,Carvalho, D.
2015	Immunological changes and tyroid function during pregnancy and potpartum period	Arquivos de Medicina	Barreira, J.F, Neves., C., Esteves, C., Delgado, L., Medina, J.L.,Carvalho, D.

ANEXO B. Publicações Científicas. (Continuação)

Ano de Publicação	Título	Fonte	Autores
2015	Do hypoglycemic treatments show collateral cardiovascular effects? The state of the art as of March 2015?	Louvain Medical	Buysschaert M, Medina JL,
2016	Definitions (and Current Controversies) of Diabetes and Prediabetes	Current Diabetes Reviews	Buysschaert M, Medina JL, Buysschaert B, Bergman M.
2017	Reducing the prevalence of dysglycemia: is the time ripe to test the effectiveness of intervention in high-risk individuals with elevated 1 h post-load glucose levels?	Endocrine	Bergman M, Jagannathan R, Buysschaert M, Medina JL, Sevick MA, Katz K, Dorcely B, Roth J, Chetrit A, Dankner R.
2017	Evaluation of the Interrelationships between Thyroid Function, Autoimmunity, Insulin Resistance and Lipid Profile in Graves' Disease	Revista Portuguesa de Endocrinologia Diabetes e Metabolismo	Carujo, A; Neves, C; Neves, JS; Oliveira, SC; Sokhatska, O; Esteves, C; Pereira, M; Medina, JL; Delgado, L; Carvalho, D;
2017	Cardiovascular Risk Factors in Patients with Autoimmune Thyroiditis	Revista Portuguesa de Endocrinologia Diabetes e Metabolismo	Cunha, CA; Neves, C; Neves, JS; Oliveira, SC; Sokhatska, O; Dias, C; Esteves, C; Pereira, M; Medina, JL; Delgado, L; Carvalho, D;
2018	The 1-h post-load plasma glucose as a novel biomarker for diagnosing dysglycemia	Acta Diabetologica	Jagannathan R, Buysschaert M, Medina JL, Katz K, Musleh S, Dorcely B, Bergman M.
2018	Lessons learned from the 1-hour post-load glucose level during OGTT: Current screening recommendations for dysglycaemia should be revised	Diabetes/Metabolism Research and Reviews	Bergman M, Jagannathan R, Buysschaert M, Pareek M, Olsen MH, Nilsson PM, Medina JL, Roth J, Chetrit A, Groop L, Dankner R.
2018	Petition to replace current OGTT criteria for diagnosing prediabetes with the 1-hour post-load plasma glucose ≥ 155 mg/dl (8.6 mmol/L)	Diabetes Research and Clinical Practice	Bergman M, Manco M, Sesti G, Dankner R, Pareek M, Jagannathan R, Chetrit A, Abdul-Ghani M, Buysschaert M, Olsen MH, Nilsson PM, Medina JL, Roth J, Groop L, Del Prato S, Raz I, Ceriello A.
2020	Review of methods for detecting glycemic disorders	Diabetes Research and Clinical Practice	Bergman M, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, Fiorentino TV, Ceriello A, Rhee M, Phillips LS, Chung S, Cravalho C, Jagannathan R, Monnier L, Colette C, Owens D, Bianchi C, Del Prato S, Monteiro MP, Neves JS, Medina JL, Macedo MP, Ribeiro RT, Filipe Raposo J, Dorcely B, Ibrahim N, Buysschaert M.
2020	Pitfalls of HbA1c in the Diagnosis of Diabetes	The Journal of Clinical Endocrinology and Metabolism	Bergman M, Abdul-Ghani M, Neves JS, Monteiro MP, Medina JL, Dorcely B, Buysschaert M.
2020	Cardiovascular Risk factors, Autoimmunity, and Insulin Resistance in Graves' disease	Revista Portuguesa de Endocrinologia Diabetes e Metabolismo	Ferreira, CT; Neves, C; Neves, JS; Oliveira, SC; Sokhatska, O; Pereira, M; Oliveira, A; Medina, JL; Delgado, L; Carvalho, D;
2020	Lipid Profile, Insulin Resistance and Cytokines Evaluation in Autoimmune Thyroiditis Patients	Revista Portuguesa de Endocrinologia Diabetes e Metabolismo	Goncalves, JR; Neves, C; Pego, F; Neves, JS; Oliveira, SC; Sokhatska, O; Pereira, M; Oliveira, A; Medina, JL; Delgado, L; Carvalho, D;
2020	Metabolic Footprint towards understanding type 2 diabetes beyond glycemia	Journal of Clinical Medicine	Pina, A.F, Patarrão; R.S,Ribeiro; R.T., Penha-Gonçalves; C.,Raposo; J.F., Gardete-Correia,L.; Duarte,R.; Boavida,J.M.; Medina,J.L.; Henriques,R.; Macedo,M.P.
2021	Loss of postprandial insulin clearance control by Insulin-degrading enzyme drives dysmetabolism traits	Metabolism: Clinical and Experimental	Borges DO, Patarrão RS, Ribeiro RT, de Oliveira RM, Duarte N, Belew GD, Martins M, Andrade R, Costa J, Correia I, Boavida JM, Duarte R, Gardete-Correia L, Medina JL, Raposo JF, Jones JG, Penha-Gonçalves C, Macedo MP.
2022	Prediabetes blunts DPP4 genetic control of postprandial glycaemia and insulin secretion	Diabetologia	Patarrão RS, Duarte N, Coelho I, Ward J, Ribeiro RT, Meneses MJ, Andrade R, Costa J, Correia I, Boavida JM, Duarte R, Gardete-Correia L, Medina JL, Pell J, Petrie J, Raposo JF, Macedo MP, Penha-Gonçalves C.
2022	Remission of T2DM requires early diagnosis and substantial weight reduction	Nature Reviews Endocrinology	Bergman M, Buysschaert M, Medina JL, Tuomilehto J.
2022	Management of dyslipidemia and atherosclerotic cardiovascular risk in prediabetes	Diabetes Research and Clinical Practice	Neves JS, Newman C, Bostrom JA, Buysschaert M, Newman JD, Medina JL, Goldberg IJ, Bergman M

Foi presidente da Sociedade Portuguesa para o Estudo da Obesidade de 1998 a 2000. Um especial destaque para a Associação Luso-Galaica de Endocrinologia, Diabetes e Metabolismo, da qual foi fundador e presidente e para o Mediterranean Group for the Study of Diabetes, do qual foi membro da direção de 1992 até 2000 e coordenador em Portugal do fórum Luso-espanhol. (ANEXO C-Revistas, Sociedades Científicas e Comissões)

Teve uma importante participação em júris de prémios científicos: vogal do Júri do Prémio Ernesto Roma (1982 e 1986), vogal do Júri do Prémio Eurico Pais (1987).[11] Foi presidente de Júris Nacionais, nomeadamente do Grau de Consultor da Carreira Médica Hospitalar e do Prémio/Bolsa Diabetes, atribuídos pelo INFARMED.

7. A vertente humana do Professor José Luís Medina

Um homem acessível, amigo do amigo, aberto às pessoas, com uma postura de dedicação e grande bondade para com os outros. Era exigente, de pensamento complexo e conhecido pelo seu sentido de humor e por adorar contar anedotas.

Sobretudo após a reforma, montou o cavalete e as telas e dedicou-se à pintura.

De igual modo, sempre apreciou a leitura, sobretudo os autores clássicos portugueses, gostava de música clássica e cinema.

Adorava fazer caminhadas e dar passeios em família. Era uma pessoa muito presente, que adorava ter a família reunida. Tinha as suas brincadeiras com os filhos e com as netas, que adorava. Cantavam músicas, contavam histórias e discutiam questões culturais. Tinha o hábito de partilhar, regularmente, pequenos excertos, palavras sábias ou conselhos por *e-mail* com os filhos.

Evidenciava uma grande paixão pelo Futebol Clube do Porto e gostava de praticar golf. O desporto que mais gostava de ver na televisão era o ciclismo.

ANEXO C. Revistas, Sociedades Científicas e Comissões.

Pertenceu aos Corpos Editoriais ou ao Conselho Científico das seguintes revistas médicas:
Arquivos de Medicina; Atheroma; Avances en Diabetologia - "Organ de expression de la Sociedad Española de Diabetes"; Boletim da Sociedade Portuguesa de Diabetologia; Boletim da Sociedade Portuguesa das Doenças Ósseas e Metabólicas; Cadernos de Endocrinologia do Notícias Médicas, nomeadamente como coordenador; Educação Médica; Endocrinologia, Metabolismo e Nutrição; Geriatria; Giornale italiano di Patologia Clínica; Jornal Clínico "Comportamento alimentar e nutrição"; Notícias Médicas (Médico Prático); Revista Portuguesa de Nutrição; Revista Portuguesa de Reumatologia e Patologia Osteoarticular; Revista de Alimentação Humana; Revista "A Razão"; Jornal do Diabético, nomeadamente como diretor; Revista Acta Médica Portuguesa;
Foi membro das seguintes Sociedades Científicas:
Sociedade Portuguesa de Medicina Interna; Sociedade Portuguesa de Endocrinologia; Sociedade Portuguesa de Diabetologia; Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo; Sociedade portuguesa para o Estudo da Obesidade; Sociedade Portuguesa de Endocrinologia Pediátrica; Sociedade Portuguesa de Andrologia (De 1984 até 1996 como relator do Conselho Fiscal); Sociedade Portuguesa de Pediatria; Sociedade Portuguesa de Medicina do Trabalho; Sociedade Portuguesa das Doenças Ósseas Metabólicas (SPODOM); Sociedade Portuguesa de Ciências da Nutrição e Alimentação; Sociedade das Ciências Médicas de Lisboa; Associação Luso-Galaica de Endocrinologia, Diabetes e Metabolismo; Sociedade Ibero-Americana de Osteologia e Metabolismo Mineral; American Diabetes Association; Diabetic Education Study Group (DESG - EASD); European Association for the Study of Diabetes (EASD); Endocrine Society (USA); Growth Hormone Research Society; International Diabetes Federation; Mediterranean Group for the Study of Diabetes;
Foi membro das seguintes Comissões:
Comissão Nacional de acompanhamento do Programa Nacional da Diabetes da Direção Geral da Saúde; Comissão Nacional para a normalização da Hormona do Crescimento do Ministério da Saúde, da qual foi presidente; Grupo de trabalho sobre indicações terapêuticas da Hormona do crescimento da Hormona do Crescimento do adulto; Comissão Consultiva do Serviço de Saúde e de Desenvolvimento humano da Fundação Calouste Gulbenkian; Comissão Científica do Observatório Nacional da Diabetes (Sociedade Portuguesa de Diabetologia); Comissão Conjunta entre o Programa Nacional da Diabetes), a Associação Protetora dos Diabéticos em Portugal e a Sociedade Portuguesa de Diabetologia, na apresentação do Programa de Atividades do Observatório Nacional da Diabetes, grupo parlamentar da Assembleia da República; Comissão Nacional de Farmácia e Terapêutica (subcomissão de terapêutica da Diabetes- terapêutica oral); Comissão Nacional de elaboração do Regulamento do Colégio da especialidade de Endocrinologia-Nutrição da Ordem dos Médicos; Comissão de Estudo dos antidiabéticos orais do INFARMED;

Gostava muito de viajar, tendo como viagens de referência o Japão, os EUA e a Austrália.

O Professor deixou uma marca fortemente positiva em todos com quem viveu. É recordado como alguém muito apaixonado por tudo quanto fazia.

Reflexão

O Professor José Luís Medina teve uma carreira vasta e completa em diversas dimensões.

Como Docente, conseguia conciliar uma enorme boa disposição, com exigência na qualidade da prática médica. Passava uma imagem de excelente clínico, lançando sempre pistas aos seus alunos para o interesse da investigação. Foi Professor Catedrático Jubilado da FMUP.

Ao nível da carreira clínica, é indubitavelmente uma das personalidades mais importantes da Endocrinologia Portuguesa. Pela sua enorme curiosidade, sempre esteve atento aos avanços científicos e procurou estar permanentemente atualizado sobre as melhores práticas médicas e a evidência mais recente. Como médico, era extremamente dedicado aos doentes e às suas preocupações, não só de uma perspetiva médica, como pessoal. Sempre acreditou que conhecendo melhor o contexto pessoal e familiar, social e ambiental, em que os doentes estão inseridos, estaria mais capacitado para os tratar. Possuía uma enorme capacidade de relacionamento e empatia com os doentes, com os seus pares e, ainda, com outros profissionais de saúde, nomeadamente enfermeiros, nutricionistas, psicólogos, farmacêuticos. Foi um grande dinamizador da Endocrinologia Portuguesa, transformando o Serviço numa escola de formação de especialistas e abrindo caminho para a sua formação alargada. Desta forma, teve um forte contributo para a criação de uma rede de Endocrinologia na zona Norte. No trabalho, é realçada a preocupação em conhecer e aprender com pessoas experientes, mas também a enorme capacidade de acolhimento dos mais novos. Sempre procurou transmitir ensinamentos, dicas e sugestões de boa prática clínica.

Desde sempre demonstrou um forte interesse pela investigação, tendo publicado mais de 200 trabalhos científicos. Foi membro do Conselho Editorial de várias revistas, não só nacionais, como também internacionais e Presidente das três principais sociedades portuguesas de referência na Endocrinologia: a Socie-

dade Portuguesa de Endocrinologia, Diabetes e Metabolismo, a Sociedade Portuguesa para o Estudo da Obesidade e a Sociedade Portuguesa de Diabetologia.

Conclusão

José Luís Medina Vieira é uma personalidade singular na Medicina Portuguesa, sendo uma referência na área da Endocrinologia e um exemplo para os especialistas da área. Edificou um importante legado na FMUP e em todas as áreas nas quais se envolveu. Deixou em todos a marca de um excelente profissional e de uma pessoa com excelente disposição e alegria de viver.

Contributorship Statement / Declaração de Contribuição:

Barbosa, MC: Pesquisa de literatura e escrita do texto.
Ferraz, AR; Carvalho, DC: Revisão crítica.
Ferraz, AR; Carvalho, DC; Ramos, LP: Revisão crítica e aprovação final.
Todos os autores aprovaram a versão final.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Medina JL. Curriculum Vitae. Porto: Faculdade de Medicina do Porto; 1987
2. Medina JL. Ascaris lumbricoides; Echinococcus granulosus; Fasciola hepatica). [Dissertação para Ato de Licenciatura apresentada à Faculdade de Medicina do Porto]. Porto: FMUP; 1988.
3. Faculdade de Medicina do Porto. Termos de posse e de aceitação de nomeação de pessoal docente e não docente (1914-1973) - Termo de posse de 1969. Porto: FMUP; 1969.
4. Faculdade de Medicina do Porto. Série Livros de cadastro de pessoal-Percurso Profissional na Universidade do Porto do professor José Luís Medina Vieira. Porto: FMUP; 1988.
5. Faculdade de Medicina do Porto. Termos de posse e de aceitação de nomeação de pessoal docente e não docente (1914-1973) - Termo de posse de 1972 Porto: FMUP; 1972.
6. Medina JL. Dissertação de Candidatura ao grau de Doutor apresentada à faculdade de medicina da universidade do Porto: Contribuição para o estudo da lesão do sistema nervoso autónomo em diabéticos
7. Faculdade de Medicina do Porto. Relatórios Curriculares de professores associados: Relatório das Atividades desenvolvidas no quinquénio 1992-1996. Porto: FMUP; 1997
8. Diário do Governo n.º 189/1972, 1º Suplemento, Série I de 1972-08-14. (Decreto-Lei nº301/72)
9. Sigarra.up.pt (Homepage da internet). FMUP, Notícias, Jubilação do Professor Doutor Luís Medina [consultado em 4/02/2023]. Disponível em: https://sigarra.up.pt/fmup/pt/noticias_geral.ver_noticia?p_nr=1783
10. Diário do Governo n.º 257/1973, Série I de 1973-11-03 (N° 2 do Art° n° 61 – Portaria 760/73)
11. Arquivo do Centro Hospitalar e Universitário do São João
12. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007; 19: 349–57.

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Revisão

Subclinical Thyroid Dysfunction and Cardiovascular Disease

Inês Mariana Lourenço[a,#], Joana Correia-Chaves[a,#], Ana Rita Leite[a,b], Marta Borges-Canha[a,c], Madalena Von-Hafe[a,c], Catarina Vale[a,d], Adelino Leite-Moreira[a,e], João Sérgio Neves[a,b,*]

[a] *Cardiovascular R&D Centre – UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal.*
[b] *Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, Porto, Portugal.*
[c] *Department of Pediatrics, Centro Hospitalar Universitário de São João, Porto, Portugal.*
[d] *Department of Internal Medicine, Centro Hospitalar Universitário de São João, Porto, Portugal.*
[e] *Department of Cardiothoracic Surgery, Centro Hospitalar Universitário São João, Porto, Portugal.*
[#] *Equally contributing authors*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2023-04-26
Accepted/Aceite: 2023-07-10
Publicado / Published: 2023-10-18

Keywords:
Cardiometabolic Risk Factors;
Cardiovascular Diseases;
Heart Disease Risk Factors;
Heart Failure;
Thyroid Diseases;
Thyroid Hormones.

Palavras-chave:
Doenças Tiroideias;
Doenças Cardiovasculares;
Fatores de Risco Cardiovasculares;
Hormonas Tiroideias;
Insuficiência Cardíaca;
Fatores de Risco Cardiometabólico.

A B S T R A C T

Thyroid hormones are intricately related to the cardiovascular system. Therefore, it is expected that thyroid dysfunction, including subclinical thyroid disorders, significantly impacts the cardiovascular system, contributing to both cardiovascular and all-cause mortality.
Subclinical hyperthyroidism, defined by low or undetectable levels of serum thyroid-stimulating hormone with free triiodothyronine and thyroxine concentrations within the reference range, has been linked to an increased risk of hypertension, atrial fibrillation, coronary artery disease, endothelial dysfunction, and thromboembolic events.
Subclinical hypothyroidism, defined as increased serum thyroid-stimulating hormone in the presence of normal circulating free triiodothyronine and thyroxine levels, is associated with increased prevalence of cardiovascular-associated risk factors, such as hypertension and obesity, as well as low levels of high-density lipoprotein. It also increases the risk for atherosclerosis and myocardial infarction.
The prognosis of heart failure is known to be adversely impacted by both subclinical thyroid dysfunctions. Subclinical hyperthyroidism appears to increase the risk of acute heart failure, possibly by incrementing the risk of arrhythmias, such as atrial fibrillation. In turn, subclinical hypothyroidism has been associated with the development of heart failure in patients with and without underlying heart disease.
Although treatment of these subclinical thyroid dysfunctions could be beneficial and alter the course of several cardiovascular diseases, its benefit on cardiovascular risk and mortality remains unclear. There is still no clear evidence to support an undeniable benefit of treatment of subclinical hypothyroidism or hyperthyroidism.

Disfunção Tiroideia Subclínica e Doença Cardiovascular

R E S U M O

As hormonas tiroideias encontram-se intrinsecamente relacionadas com o sistema cardiovascular, pelo que é expectável que as disfunções da função tiroideia, incluindo as disfunções subclínicas da tiroide, tenham um impacto significativo no sistema cardiovascular, contribuindo para a mortalidade de causa cardíaca e por todas as causas.
O hipertiroidismo subclínico, definido por concentrações séricas diminuídas ou indetetáveis de hormona estimuladora da tiroide e valores séricos normais das hormonas tiroideias, parece associar-se a um risco acrescido de hipertensão arterial, fibrilhação auricular, doença arterial coronária, disfunção endotelial e eventos tromboembólicos.

* Autor Correspondente / Corresponding Author.
E-Mail: joaosergioneves@gmail.com (João Sérgio Neves)
Alameda Hernâni Monteiro, 4200-319 Porto, Portugal

https://doi.org/10.26497/ar230029

O hipotiroidismo subclínico, definido por concentrações séricas aumentadas de hormona estimuladora da tiroide e valores séricos normais das hormonas tiroideias, está associado a um aumento da prevalência dos fatores de risco cardiovasculares, tais como hipertensão e obesidade, bem como níveis diminuídos de lipoproteína de alta densidade. O hipotiroidismo subclínico também se associa ao aumento do risco de aterosclerose e de enfarte agudo do miocárdio.
Além disso, o prognóstico de insuficiência cardíaca poderá ser prejudicado por ambas as disfunções subclínicas da tiroide. O hipertiroidismo subclínico parece aumentar o risco de insuficiência cardíaca aguda, possivelmente pelo aumento do risco de arritmias, tais como a fibrilhação auricular. Por sua vez, o hipotiroidismo subclínico tem sido associado ao desenvolvimento de insuficiência cardíaca em doentes com e sem doença cardíaca subjacente.
Embora o tratamento destas disfunções subclínicas da tiroide possa ser benéfico e alterar o curso de várias doenças cardiovasculares, o seu benefício sobre o risco cardiovascular e a mortalidade permanece pouco claro. Ainda não há evidência clara que sustente um benefício inegável do tratamento em doentes com hipotiroidismo ou hipertiroidismo subclínico.

Introduction

It is widely recognized that the thyroid function is intricately related with the cardiovascular system.[1,2] Likewise, thyroid dysfunction, including subclinical thyroid disorders, and cardiovascular diseases (CVDs) are highly correlated.[3–5]

Subclinical thyroid dysfunction comprises both subclinical hypothyroidism (SHypo) and subclinical hyperthyroidism (SHyper) and presents as altered serum levels of thyroid stimulating hormone (TSH), elevated or decreased, respectively, but levels of thyroxine (T4) and triiodothyronine (T3) within their respective reference ranges.[6]

Given the high prevalence and clinical relevance of both subclinical thyroid dysfunction and CVDs, we aim to highlight the pathophysiological and clinical links between both entities.[4]

SHypo is defined as increased serum TSH in the presence of normal circulating free T4 and T3 levels and comprises two categories regarding TSH levels: mild SHypo which presents with mildly increased TSH (above upper reference limit to 10.0 mIU/L) and severe SHypo with severely increased TSH (>10 mIU/L).[7] Usually, it is an asymptomatic condition. If present, symptoms are similar though less evident than those observed in overt hypothyroidism. It is a common disorder, with a prevalence ranging from 4% to 15% in the general population and up to 20% among women aged over 60 years, especially those with a positive thyroid autoimmunity and/or rich diet iodine intake.[8–11] Raposo *et al* estimated a prevalence of 2.7% of mild SHypo and 0.6% of severe SHypo in the Portuguese population, both being more common among women.[7]

Elevated TSH levels are believed to have the same aetiology as overt hypothyroidism, Hashimoto's thyroiditis being the most common cause. Another cause could be a slight decrease in thyroid function in the elderly which leads to slightly higher TSH levels that tend to increase with age, even in the absence of thyroid disease.[11,12]

SHyper can be defined as persistently low levels of serum TSH with free T3 and T4 concentrations within the reference range. SHyper comprises two categories according to its severity: grade 1 when low levels of serum TSH are detected (0.1 mIU/L to below the lower reference limit), and grade 2, when serum TSH is very low or undetectable (<0.1 mIU/L).[7] This condition is common in the general population and its frequency is variable, depending on sex, age, and iodine intake. It is particularly common in elderly patients, affecting 10%-15% in patients over 65 years of age.[8,13–15] Raposo *et al* estimated a prevalence of 0.8% of SHyper grade 1 and 0.6% grade 2 among Portuguese people.[7]

SHyper may be caused by endogenous or exogenous factors, such as multinodular goiter, thyroid adenomas or treatment with levothyroxine (LT4) in doses used to suppress TSH in differentiated thyroid cancer.[16,17] SHyper is often asymptomatic and, therefore, this diagnosis is usually made incidentally through the detection of alterations in screening exams.[8]

Methods

The search strategy used for this review article was to search PubMed with the terms "Thyroid Hormones", "Thyroid Diseases", "Subclinical Thyroid Disorders", "Cardiovascular Diseases", "Cardiovascular Risk Factors", "Heart Failure", "Cardiometabolic Risk Factors" and combinations of these terms. We selected original and review articles published in English.

Thyroid Hormones Physiology

The main thyroid hormones (THs) consist of T4 and T3 and are produced by the thyroid gland, which takes part in a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis.[13,18–20] The thyroid gland releases THs mostly as T4, which is de-iodinated peripherally to T3 via deiodinases type I and II or transformed irreversibly into inactive isomers such as reverse T3 and 3,3-diiodothyronine (T2) by deiodinase type III.[18,19,21]

THs regulate major basal metabolic pathways and almost every tissue in the body has thyroid hormone receptors (TRs). THs main effects at the genomic level are mediated by nuclear TRs, that are closely associated with chromatin and bind to THs with high affinity and specificity. The receptors consist of intracellular DNA binding proteins that bind to T3 with a higher affinity than T4, making T3 twenty times more potent than T4. These hormones are lipophilic and circulate in the body mostly bound to transporter proteins. After binding to the receptor, they form hormone-receptor complexes and bind to thyroid hormone response elements (TREs) in the regulatory regions of target genes, modulating essential functions in growth, development, and metabolism of several tissues. TREs are considered ligand-regulatable transcription factors as they bind to THs and DNA to regulate transcription.[18,19,21–23]

Thyroid Hormones and the Cardiovascular System

THs act on the heart through genomic and nongenomic effects mostly mediated by T3.[24,25] The effects of T3 in the heart appear through the action of TRs, specifically the alfa isoform (TRα), which is the main TR isoform present in this organ. THs lead to physiologic hypertrophy and have positive ionotropic, chronotropic and lusitropic effects.[14,24–27] At a vascular level, most effects of THs are mediated through non-genomic pathways.[28]

Genomic effects

Evidence suggests that T3 regulates the calcium concentration in cardiomyocytes through the upregulation of sarcoplasmic reticulum calcium-activated ATPase 2 (SERCA2a), which lowers the intracellular concentrations of Ca^{2+} by pumping this ion into the sarcoplasmic reticulum during diastole.[26,27] In turn, T3 promotes the downregulation of phospholamban, enhancing the velocity of myocardial relaxation.[24,29] Additionally, T3 affects multiple ion channels including Na^+/K^+ ATPase, Na^+/Ca^{2+} exchanger, and voltage-gated K^+ channels (Kv1.5, Kv4.2, Kv4.3).[29] It has been described that T3 promotes signalling pathways which alter gene expression leading to cardiac hypertrophy through the increase of adenosine triphosphatase (ATP), SERCA2a, upregulation of myosin heavy chain α gene (*MHC*α) and downregulation of *MHC* β gene expression.[27] The increase of atrial natriuretic peptide (ANP) and decrease of protein kinase C (PKC) both lead to physiologic cardiac hypertrophy as well. Additionally, β1 adrenergic receptor is positively regulated by T3 leading to its inotropic and chronotropic cardiac effects.[27,29]

Non-genomic effects

Thyroid hormones also act through nongenomic mechanisms, producing faster effects on cardiac inotropism and chronotropism. This is achieved through the promotion of acute phosphorylation of phospholamban, mediated by intracellular kinase pathways, leading to the attenuation of its inhibition of SERCA2a.[27]

Additionally, THs have important effects on the vascular system. T3 reduces peripheral vascular resistance through activation of phosphatidylinositol 3 kinase (PI3K)/ serine/threonine-protein kinase (AKT) signaling pathways inducing endothelium-derived nitric oxide (NO) synthase phosphorylation, therefore increasing NO production.[24,30,31]

T3 downregulates angiotensin II type 1 receptor mRNA expression at both transcriptional and posttranscriptional levels, further promoting vascular relaxation.[32] Evidence suggests that T3 contributes to angiogenesis and augments the density of small arterioles, including coronary arterioles.[24]

The cardiovascular system is sensitive to small and persistent alterations of THs concentrations, such as those present in subclinical thyroid dysfunction. It is therefore expected that these conditions would lead to significant changes in cardiovascular homeostasis.[14]

The Impact of Thyroid Hormones on Cardiovascular Risk Factors

Regulation of body weight

THs are important regulators of food intake, adiposity as well as lipid and glucose metabolism, and therefore have an impact in energy expenditure and body weight. There is a bidirectional relationship between THs and weight changes as both influence one another.[33]

Hypothyroidism and SHypo are associated with higher body mass index and obesity. SHypo is also associated with metabolic syndrome (MetS).[9,33] Moreover, SHypo seems to be an independent predictor of NASH and NASH-related advanced fibrosis among patients with non-alcoholic fatty liver disease (NAFLD).[34] On the other hand, in hyperthyroid patients, enhanced energy expenditure and weight loss is usually seen.[33]

Obesity impacts the hypothalamic-pituitary-thyroid axis and is associated with impaired thermogenesis and insulin tolerance.[33] The latter leads to hyperleptinemia which enhances TSH secretion. TSH promotes the differentiation of adipocytes and contributes to the maintenance of obesity. Obese patients have increased levels of inflammatory cytokines which lead to a reduction in iodide uptake and could lead to morphological alterations in the thyroid gland.[35]

Lipid metabolism

THs largely influence lipid metabolism by the regulation of cholesterol synthesis and degradation, through the activity of essential enzymes. THs act on the liver, mainly on TRβ-1, enhancing the expression of the sterol response element-binding protein 2 (Srebp-2) which in turn, increases the expression of LDL receptors (LDLRs) leading to increased hepatic cholesterol uptake.[8,18,36,37] Evidence suggests that THs decrease proprotein convertase subtilisin/kexin type 9 (PCSK9), which consists of a downregulator of the expression of LDLRs.[38,39] THs promote the activity of both lipoprotein lipase in adipose tissue and hepatic lipase activity in the liver.[40] It is therefore widely accepted that thyroid dysfunction can lead to impaired lipid metabolism.

Hypothyroidism characteristically presents with increased total and LDL cholesterol levels, and slightly decreased or within the normal range HDL levels. This is also evident in patients with SHypo, suggesting that this condition might be linked to dyslipidaemia/hypercholesterolemia. There is evidence suggesting SHypo may be linked to hypertriglyceridemia.[40] These changes increase the risk of developing atherosclerosis and coronary artery disease (CAD).[9,10,14] In contrast, hyperthyroidism leads to a catabolic state presenting with reduced plasma levels of cholesterol (Fig. 1).[37]

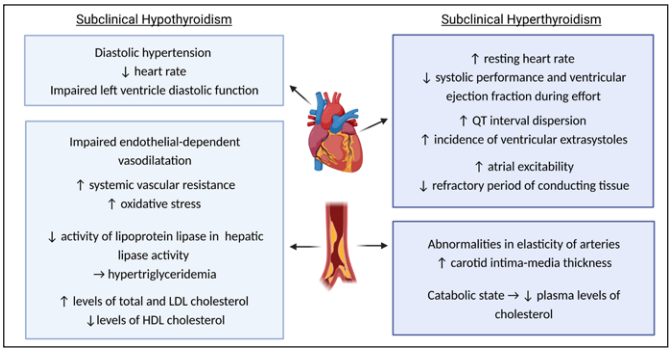


Figure 1. Effects in the heart and vessels of subclinical hypothyroidism and subclinical hyperthyroidism.

Regulation of glucose metabolism

THs are involved in the regulation of glucose metabolism by acting peripherally on a myriad of different organs modulating insulin secretion and glucose uptake. THs promote pancreatic β-cell growth and enhance insulin and glucagon secretion by pancreatic β-cells and α-cells, respectively.[43,44]

THs act on the pancreas, specifically T3, by stimulating β-cell development and acting as an anti-apoptotic factor for these cells, thus improving glucose metabolism on diabetic mice (Fig. 2).[41,43]

THs act peripherally in the gastrointestinal tract; T3 promotes

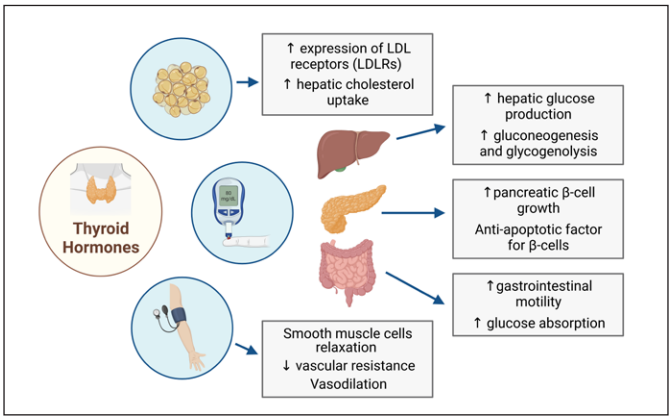


Figure 2. Effects of thyroid hormones on cardiovascular risk factors.

gastrointestinal motility, which increases glucose absorption leading to oxyhyperglycemia, by rapidly increasing blood glucose after oral glucose intake (Fig. 2).[42] In the liver, T3 enhances the expression of glucose transporter 2 (GLUT2) which favours the uptake of glucose by the hepatocytes, and potentiates both gluconeogenesis and glycogenolysis (Fig. 2).[41,44]

Although through different mechanisms, both hyperthyroidism and hypothyroidism are associated with increased risk of insulin resistance. In hypothyroidism, there is decreased glucose utilization by peripheral tissues. In hyperthyroidism there is predominantly enhancement of glucose production, absorption, and utilization.[45]

Hypothyroidism and SHypo are associated with insulin resistance and glucose intolerance. Diminished levels of THs potentiate gluconeogenesis, negatively impact glucose absorption and delay glucose uptake peripherally.[41,46] Treatment of hypothyroidism leading to a euthyroid state reportedly ameliorates insulin homeostasis. SHypo confers around 13% increased risk of developing type 2 diabetes mellitus (T2DM).[33]

Patients with T2DM seem to have a significantly increased risk of developing SHypo when compared with patients without diabetes.[47] Patients with T2DM and SHypo appear to have an increased risk of developing diabetic complications, such as, diabetic nephropathy, retinopathy, peripheral neuropathy and peripheral arterial disease.[42,47]

Although hyperthyroidism enhances glucose transporter type 4 (*GLUT4*) gene expression and glucose uptake in skeletal muscles, its potentiation of glucose absorption on the gastrointestinal tract, along with the enhancement of gluconeogenesis and glycogenolysis poses a great risk for developing T2DM later in life.[8,41,48]

Regulation of systemic blood pressure

THs are regulators of systemic blood pressure. This regulation is mediated by inotropic, chronotropic and lusitropic cardiac effects, as well as vascular effects which lead to reduction of systemic vascular resistance (Fig. 2).[13,49]

SHyper may result in abnormalities in elasticity of arteries, with increased carotid intima-media thickness but the mechanisms behind these alterations remain unclear (Fig. 1). It has been largely associated with increased blood pressure, predominantly systolic blood pressure.[13,49,50]

In turn, SHypo can lead to impaired endothelial-dependent vasodilatation, due to a decrease of production of NO, resulting in endothelial dysfunction and diastolic hypertension (Fig. 1).[51] Evidence suggests that the level of elevation of TSH correlates with the magnitude of these effects.[37] These patients also seem to have an attenuated vasodilatory response to acetylcholine and present with increased carotid artery intima-media thickness, thus increasing arterial stiffness.[51]

Regulation of coagulation and inflammation

Coagulation parameters seem to be impaired by THs disorders resulting in increased cardiovascular risk. Hypothyroidism leads to a state of hypocoagulability and hyperfibrinolysis culminating in an increased risk of bleeding. It is associated with an acquired von Willebrand syndrome type 1 and these patients frequently have lower levels of von Willebrand factor and coagulating factor VIII, as well as increased prothrombin time, activated partial thromboplastin time (aPTT), and clotting time when compared to control individuals.[52,53]

In contrast, SHypo and SHyper are associated with prothrombotic states.[53,54] SHypo seems to be associated with a prothrombotic effect, due to the increased levels of coagulation factor VII, plasminogen activator inhibitor-1 (PAI-1) and diminished global fibrinolytic activity seen in this thyroid dysfunction.[53] Likewise, SHyper favours hypercoagulability and diminishes fibrinolysis.[53,54]

Overt hypothyroidism reduces the effect of vitamin K antagonists (VKAs) while hyperthyroidism increases its effects due to modulation of VKAs' sensitivity.[55] Although SHyper does not seem to impact therapy with VKAs, SHypo may be a cause of international normalised ratio lability.[55,56]

Inflammation results in a decreased peripheral conversion of T4 to T3. Elevated C-reactive protein and serum homocysteine levels are considered risk factors for the development of atherosclerosis and have been reported in patients with overt hypothyroidism but not SHypo.[57]

Both hyperthyroidism and hypothyroidism lead to oxidative stress. In hyperthyroidism there is enhanced reactive oxygen species production whereas hypothyroidism is associated with diminished levels of antioxidants.[58]

Effects of Subclinical Hypothyroidism on Cardiovascular Function and Disease

Subclinical thyroid dysfunctions have been associated with an increased risk of all-cause mortality in both men and women.[75]

These conditions have been linked to cardiovascular risk factors, such as alterations in blood pressure, and enhanced risk for atherosclerosis.[59–61]

SHypo seems increase the risk of CVDs in those with higher plasma TSH levels, particularly above 10 mU/L and in adults younger than 65 years old.[8,11,14]

Potential mechanisms for the linkage of SHypo with CVDs include arterial stiffness, increased systemic vascular resistance, increased oxidative stress, an inflammatory state driven by TSH apoptosis-derived microparticles, cardiac dysfunction and diastolic hypertension.[16,30,62] SHypo also leads to lower heart rate (Fig. 1) and impairment of myocardial relaxation, diminishing cardiac preload.[14]

It is well established that SHypo increases the risk for atherosclerosis and myocardial infarction.[63,64] Due to the fact that these patients are more prone to develop hypertension, dyslipidaemia, endothelial dysfunction, and myocardial fibrosis, their risk of CAD events and subsequent death is augmented, especially in people under 65 years old.[14,65–67]

The evidence regarding the link between SHypo and stroke is inconsistent. While some studies found no association others

found a higher risk of stroke in SHypo patients younger than 65 years old and with higher TSH concentrations.[60]

Effects of Subclinical Hyperthyroidism on Cardiovascular Function and Disease

SHyper is frequently associated with an increased resting heart rate and left ventricular mass, often accompanied by impaired left ventricular relaxation and diastolic filling. It has been reported that it reduces systolic performance and ventricular ejection fraction during effort and consequently decreases exercise tolerance.[17,68] The cardiovascular risk in patients with SHyper may be significantly affected by their age and the presence of comorbidities.[15]

SHyper may be associated with a slight increase in QT interval dispersion, incidence of ventricular extrasystoles, elevated nocturnal arterial blood pressure, and heart rate variability (Fig. 1). It may also be related with a sympathovagal imbalance state, characterized by diminished cardiovascular vagal modulation with relative higher sympathetic activity and increased renin angiotensin-aldosterone axis activation. The assessment of heart rate variability and QT dispersion in patients with SHyper could represent a useful tool in the monitorization of cardiovascular risk and support the decision of whether to treat patients with this condition.[69,70] Enhancement of atrial excitability and shortening of the refractory period of the conducting tissue are likely contributors to the adverse arrhythmogenic effects.[17]

Persistent SHyper leads to altered cardiac morphology and function causing arrhythmias, namely atrial fibrillation (AF). Both SHypo and SHyper appear to increase the risk of AF as there seem to be a "U shaped" relationship between the risk of this arrythmia and TSH levels.[71]

The risk of AF seems to be two or three times higher in patients with SHyper than in subjects with normal levels of serum TSH, especially after the sixth decade of life. This risk augments with the lowering of TSH levels, especially for those below 0.10 mIU/L.[12,15,49,72] Moreover, in a study by Li *et al*, in patients who underwent radiofrequency catheter ablation for AF, those with SHyper were associated with a markedly higher prevalence of recurrence of AF, than those with SHypo. The latter had a similar recurrence rate of AF to those without TH dysfunction.[73] Reduced levels of TSH also seem to potentiate the risk of AF, leading to more than five-fold higher incidence of this disease.[74]

The relationship between SHyper and the incidence of stroke is yet to be enlightened although it is possible that this condition increases the risk of stroke due to its association with AF.[8]

Evidence suggests that SHyper causes increased risk of hypertension, CAD events and deaths and increased thrombogenicity.[75,76] SHyper is also associated with a augmented risk of major adverse cardiovascular events (MACE), especially in women, although when follow-up is longer than ten years, SHypo contributes to a higher risk of MACE than SHyper, according to Fang *et al*.[77]

Differentiated thyroid cancer (DTC) is relatively prevalent at a young age. Long-term TSH suppression therapy has been associated with increased CVDs and all-cause mortality and increased risk of AF, independently from known risk factors.[78,79] Therefore, the initial standard treatment of DTC does not include TSH suppression therapy for all patients anymore and only patients with biochemically or structurally incomplete disease are presently recommended to undergo moderate to total suppression, whilst the other stages are treated with mild to no suppression.[80]

Subclinical Thyroid Hormone Dysfunction and Heart Failure

Heart failure (HF) is a major public health issue and an important cause of morbimortality worldwide.[67] HF is a chronic and progressive disease characterized by structural or functional impairment of ventricular filling or blood ejection.[67,81] It is one of the most common causes of hospitalization in geriatric patients above 65 years old.[82]

As mentioned, THs can influence the expression of genes involved in calcium handling and contractile properties of cardiomyocytes.[67] They have influence on inotropic, chronotropic and lusitropic properties of the myocardium, cardiac growth, myocardial activity and vascular function.[67] Due to the myocardium's sensitiveness to THs, persistent subclinical thyroid dysfunction can lead to the development of HF, secondary to systolic and/or diastolic myocardial dysfunction.[9,83]

Both SHyper and SHypo are associated with adverse prognosis of HF and with more severe symptoms.[84]

Patients with SHypo, particularly those with TSH levels above 10 mIU/L, have a higher risk of developing HF, regardless of the presence of underlying heart disease.[67] Additionally, SHypo is thought to worsen the prognosis of those with previously diagnosed HF, increasing the risk of hospitalization and death. This risk is especially elevated in the geriatric population, which have a higher risk for CVDs.[62,82,84] Therefore, subclinical thyroid dysfunction may potentially be a useful and promising predictor of the long-term prognosis in these patients.[85]

SHyper may increase the risk of acute HF, possibly by increasing heart rhythm, but also due to its association with an increased risk of atrial arrhythmias, such as AF, which can cause acute decompensated HF.[81]

Previous studies have shown that administration of T3 has increased cardiac output and decreased peripheral vascular resistance in patients with SHypo.[9] Levothyroxine supplementation on SHypo may be beneficial, particularly in regard to the heart´s functioning; however, its beneficial role in cardiovascular risk or mortality remains to be clarified.[82]

Table 1. Clinical cardiovascular effects of subclinical hypothyroidism and hyperthyroidism.

Subclinical Hypothyroidism	Subclinical Hyperthyroidism
↑ LDL cholesterol	↑ risk of atrial fibrillation
↑ risk of atherosclerosis	Increased thrombogenicity
↑ risk of cardiovascular disease, namely myocardial infarction	Possible ↑ risk of stroke
↑ risk of myocardial fibrosis	↑ risk of hypertension
↑ risk of hypertension	↑ risk of major adverse cardiovascular events
↑ development of chronic HF	↑ risk of cardiovascular death
↑ risk for progression of chronic HF	↑ risk of acute and decompensated HF

Treatment of Subclinical Thyroid Disorders on Cardiovascular Disease

Subclinical hypothyroidism

There is still no clear evidence to support an undeniable benefit of replacement treatment with levothyroxine for reducing the

risk of CVDs in individuals with SHypo, especially in those with milder forms of this thyroid dysfunction (TSH levels below 10 mU/L) or older subjects (above 75 years of age).[9,10,40,59]

The retrospective observational analysis of the Whickham survey cohort was the first study that suggested the potential advantages of using levothyroxine as a treatment for SHypo, showing a significant reduction in all-cause mortality among subjects treated with levothyroxine.[86] Similar results were described by Anderson *et al*, although only among patients under 65 years old.[87] A broader cohort study found significantly lower events of ischemic heart disease and all-cause mortality in treated participants between 40 and 70 years old.[88]

In the opposite direction, several studies did not find significant benefits in the use of levothyroxine in subjects with SHypo. A cohort study with patients older than 18 years old found no differences in all-cause mortality, MACE or hospital events.[89] The randomized clinical trial TRUST included participants older than 65 years old but was underpowered to evaluate differences in cardiovascular events.[90]

Patients with SHypo may benefit from levothyroxine replacement treatment as it seems to improve the lipid profile, with a decrease in total and LDL cholesterol levels that, although modest, could be significant in terms of reduction of the incidence of CAD. Left ventricular function and markers of subclinical atherosclerosis and endothelial dysfunction also seem to improve, and early treatment of SHypo could prevent the progression to overt hypothyroidism.[10,91]

American Thyroid Association recommends the treatment with levothyroxine whenever TSH levels surpass 10 mIU/L and that it should be considered in patients with TSH levels above 4.5 mIU/L with elevated CVD risk.[92] Initial dose of levothyroxine should be lower for treating patients with SHypo and should be titrated slowly as need, maintaining close monitoring of the onset of cardiac symptoms.[93]

European Thyroid Association recommends levothyroxine treatment for patients younger than 65 years old with TSH levels above 10 mIU/L or with SHypo and have symptoms consistent with hypothyroidism.[94] Since it is possible to identify TSH levels transiently increased, it is suggested to repeat TSH, T4 and thyroid peroxidase antibodies ideally in a 1 to 3 month period after initial documentation of increased serum TSH and T4 within reference range.[94]

The Portuguese Society of Endocrinology, Diabetes and Metabolism and the Thyroid Study Group, recommend an individualized decision to treat SHypo for young adults with symptoms suggestive of hypothyroidism, goiter, thyroid peroxidase antibodies, marked elevation of TSH levels, dyslipidemia or CVD (except tachyarrhythmias).[95]

Due to the lack of evidence to support the guidelines for treatment of SHypo with HT, Bekkering *et al* suggested that asymptomatic patients with SHypo or with non-specific symptoms should not be treated.[96]

Therefore, the decision to treat SHypo should be based on clinical judgment, clinical practice, and expert opinion. It should consider specific and individualized evaluation, based on patient's age, degree of TSH elevation, symptoms, pre-existent cardiovascular risk, and other co-morbidities.[11,97] Treatment institution must be gradual, and closely monitored. Special attention must be taken when initiating levothyroxine treatment for SHypo in the elderly.[59]

Subclinical hyperthyroidism

International guidelines support treatment in patients aged above 65 years old presenting with TSH levels under 0.10 mU/L, in order to decrease the risk of cardiovascular events and progression to overt hyperthyroidism.[98] To this day, clinical trials regarding the treatment of SHyper are lacking. Therefore, the decision to treat SHyper should be based on patient age, symptoms related with hyperthyroidism, level of TSH suppression, and overall cardiovascular risk.[8,13]

Treatment of SHyper is the same as for hyperthyroidism and comprises thionamides, radioactive therapy and thyroid surgery. Cardioselective beta blockers, such as propranolol, atenolol or metoprolol, can be used to treat adrenergic symptoms. Due to the possible side effect of hypotension, blood pressure should be monitored in patients using beta blockers.[99]

The treatment of SHyper with reestablishment of normal serum TSH values, can reduce heart rate and left ventricular thickness. Moreover, treatment of SHyper may prevent the possible progression to complex arrythmias and to more advanced heart disease.[100]

Conclusion

Subclinical thyroid dysfunctions have a significant impact on the cardiovascular system contributing to cardiac and all-cause mortality.

Subclinical hypothyroidism has been linked to an increased prevalence of several cardiovascular-associated risk factors, such as hypertension and obesity, as well as low levels of high-density lipoprotein. There is evidence that elevated TSH concentrations related to this disorder are associated with increased risk for ischemic heart disease and HF.

Subclinical hyperthyroidism is associated with an increased risk of endothelial dysfunction, hypertension, atrial fibrillation, CAD events, thromboembolic events and acute HF.

Treatment of these dysfunctions could be beneficial, but its benefit in cardiovascular risk and mortality is still not clear. Therefore, more studies, ideally randomized clinical trials, should be performed to clarify the utility of treatment of subclinical thyroid dysfunction in CVDs.

Contributorship Statement / Declaração de Contribuição:

IML and JCC: Conceptualization, writing the initial draft and review. ARL, MBC, MHV, CV, ALM, JSN: Conceptualization and review. All authors approved the final version to be published.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Moolman JA. Thyroid hormone and the heart. Cardiovasc J S Afr. 2002;13:159–63.
2. Klein I, Danzi S. Thyroid Disease and the Heart. Curr Probl Cardiol. 2016;41:65–92.
3. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379:1142–54.
4. Manolis AA, Manolis TA, Melita H, Manolis AS. Subclinical thyroid dysfunction and cardiovascular consequences: An alarming wake-up call? Trends Cardiovasc Med. 2020;30:57–69.
5. Paschou SA, Bletsa E, Stampouloglou PK, Tsigkou V, Valatsou A, Stefanaki K, et al. Thyroid disorders and cardiovascular manifestations: an update. Endocrine. 2022;75:672–83.
6. Wiersinga WM. Guidance in Subclinical Hyperthyroidism and Subclinical Hypothyroidism: Are We Making Progress? Eur Thyroid J. 2015;4:143–8.
7. Raposo L, Martins S, Ferreira D, Guimarães JT, Santos AC. Metabolic Syndrome, Thyroid Function and Autoimmunity - The PORMETS Study. Endocr Metab Immune Disord - Drug Targets. 2019;19:75–83.
8. Delitala AP. Subclinical Hyperthyroidism and the Cardiovascular Disease. Horm Metab Res Horm Stoffwechselforschung Horm Metab. 2017;49:723–31.
9. Chrysant SG. The current debate over treatment of subclinical hypothyroidism to prevent cardiovascular complications. Int J Clin Pract. 2020;74:e13499.
10. Lioudaki E, Mavroeidi NG, Mikhailidis DP, Ganotakis ES. Subclinical hypothyroidism and vascular risk: an update. Horm Athens Greece. 2013;12:495–506.
11. Pasqualetti G, Tognini S, Polini A, Caraccio N, Monzani F. Is subclinical hypothyroidism a cardiovascular risk factor in the elderly? J Clin Endocrinol Metab. 2013;98:2256–66.
12. Barbesino G. Thyroid function changes in the elderly and their relationship to cardiovascular health: a mini-review. Gerontology. 2019;65:1–8. doi: 10.1159/000490911.
13. Palmeiro C, Davila MI, Bhat M, Frishman WH, Weiss IA. Subclinical hyperthyroidism and cardiovascular risk: recommendations for treatment. Cardiol Rev. 2013;21:300–8.
14. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. Clin Investig Arterioscler. 2014;26:296-309. doi: 10.1016/j.arteri.2014.07.003.
15. Biondi B. Endogenous subclinical hyperthyroidism: who, when and why to treat. Expert Rev Endocrinol Metab. 2011;6:785–92.
16. Biondi B, Fazio S, Palmieri EA, Tremalaterra R, Angellotti G, Bonè F, et al. Effetti dell'ipertiroidismo subclinico cronico da terapia con levotiroxina su morfologia e funzione cardiaca . Cardiol Rome Italy. 1999;44:443–9.
17. Biondi B, Palmieri EA, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: clinical features and treatment options. Eur J Endocrinol. 2005;152:1–9.
18. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev. 2001;81:1097–142.
19. Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Oct 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK500006/
20. Nilsson M, Fagman H. Development of the thyroid gland. Dev Camb Engl. 2017;144:2123–40.
21. Armstrong M, Asuka E, Fingeret A. Physiology, Thyroid Function. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Nov 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537039/
22. Paisdzior S, Schuelke M, Krude H. What is the Role of Thyroid Hormone Receptor Alpha 2 (TRα2) in Human Physiology? Exp Clin Endocrinol Diabetes. 2022;130:296-302. doi: 10.1055/a-1716-7980.
23. Mathew P, Gujral J, Rawla P. Hyperthyroidism. In: StatPearls [Internet]. Treasure Island : StatPearls Publishing; 2022 [cited 2022 Nov 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537053/
24. Dillmann WH. Biochemical basis of thyroid hormone action in the heart. Am J Med. 1990;88:626–30.
25. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:501–9.
26. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res. 2004;59:31–50.
27. Grais IM, Sowers JR. Thyroid and the heart. Am J Med. 2014;127:691–8.
28. Samuel S, Zhang K, Tang YD, Gerdes AM, Carrillo-Sepulveda MA. Triiodothyronine Potentiates Vasorelaxation via PKG/VASP Signaling in Vascular Smooth Muscle Cells. Cell Physiol Biochem. 2017;41:1894–904.
29. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res. 2004;59:31–50.
30. Owen PJD, Sabit R, Lazarus JH. Thyroid disease and vascular function. Thyroid Off J Am Thyroid Assoc. 2007;17:519–24.
31. Morello F, Perino A, Hirsch E. Phosphoinositide 3-kinase signalling in the vascular system. Cardiovasc Res. 2008;82:261–71.
32. Fukuyama K, Ichiki T, Takeda K, Tokunou T, Iino N, Masuda S, et al. Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertens Dallas Tex. 1979. 2003 ;41:598–603.
33. Kalra S, Aggarwal S, Khandelwal D. Thyroid Dysfunction and Dysmetabolic Syndrome: The Need for Enhanced Thyrovigilance Strategies. Int J Endocrinol. 2021;2021:9641846.
34. Kim D, Kim W, Joo SK, Bae JM, Kim JH, Ahmed A. Subclinical Hypothyroidism and Low-Normal Thyroid Function Are Associated With Nonalcoholic Steatohepatitis and Fibrosis. Clin Gastroenterol Hepatol. 2018;16:123-31.e1. doi: 10.1016/j.cgh.2017.08.014.
35. Yadav J, Jain N, Dayal D. Alterations of thyroid function in overweight and obese children: an update. Indian J Child Health. 2018;5:145–50.
36. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94:355–82.
37. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. Med Clin North Am. 2012;96:269–81.
38. Zhu X, Cheng S yann. New insights into regulation of lipid metabolism by thyroid hormone. Curr Opin Endocrinol Diabetes Obes. 2010;17:408–13.
39. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein-2 (SREBP-2). J Biol Chem. 2003;278:34114–8.
40. Sue LY, Leung AM. Levothyroxine for the Treatment of Subclinical Hypothyroidism and Cardiovascular Disease. Front Endocrinol. 2020;11:591588.
41. Eom YS, Wilson JR, Bernet VJ. Links between Thyroid Disorders and Glucose Homeostasis. Diabetes Metab J. 2022;46:239–56.
42. Nishi M. Diabetes mellitus and thyroid diseases. Diabetol Int. 2018;9:108–12.
43. Verga Falzacappa C, Mangialardo C, Madaro L, Ranieri D, Lupoi L, Stigliano A, et al. Thyroid Hormone T3 Counteracts STZ Induced Diabetes in Mouse. Agoulnik I, editor. PLoS One. 2011;6:e19839.
44. Gierach M, Gierach J, Junik R. Insulinoopornosc a choroby tarczycy. Endokrynol Pol. 2014;65:70–6.
45. Sinha RA, Singh BK, Yen PM. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. Trends Endocrinol Metab. 2014;25:538–45.
46. Joffe BI. Diabetes mellitus and hypothyroidism: Strange bedfellows or mutual companions? World J Diabetes. 2014;5:901.
47. Han C, He X, Xia X, Li Y, Shi X, Shan Z, et al. Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. Veves A, editor. PloS One. 2015;10:e0135233.
48. Klieverik LP, Janssen SF, Riel A van, Foppen E, Bisschop PH, Serlie MJ, et al. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. Proc Natl Acad Sci. 2009;106:5966–71.
49. Collet TH, Gussekloo J, Bauer DC, den Elzen WPJ, Cappola AR, Balmer P, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med. 2012;172:799-809. doi: 10.1001/archinternmed.2012.402
50. Giontella A, Lotta LA, Overton JD, Baras A, on behalf of Regeneron Genetics Center, Sartorio A, et al. Association of thyroid function with blood pressure and cardiovascular disease: a Mendelian randomization. J Pers Med. 2021;11:1306.
51. Owen PJD, Rajiv C, Vinereanu D, Mathew T, Fraser AG, Lazarus JH. Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. J Clin Endocrinol Metab. 2006;91:2126–32.
52. Xu Q, Wang Y, Shen X, Zhang Y, Fan Q, Zhang W. The effect of subclinical hypothyroidism on coagulation and fibrinolysis: a systematic review and meta-analysis. Front Endocrinol. 2022;13:861746.
53. Ordookhani A, Burman KD. Hemostasis in hypothyroidism and autoimmune thyroid disorders. Int J Endocrinol Metab. 2017;15:e42649.
54. Elbers LPB, Fliers E, Cannegieter SC. The influence of thyroid function on the coagulation system and its clinical consequences. J Thromb Haemost. 2018;16:634–45.
55. Squizzato A, Galli L, Van Zaane B, Romualdi E, Stuijver DJ, Dentali F,

et al. The effect of subclinical hypothyroidism on vitamin K antagonist treatment. Thromb Res. 2012 ;129:520–2.
56. Bucerius J, Naubereit A, Joe AY, Ezziddin S, Biermann K, Risse J, et al. Subclinical hyperthyroidism seems not to have a significant impact on systemic anticoagulation in patients with coumarin therapy. Thromb Haemost. 2008;100:803–9.
57. Parent S, Cujec B. Subclinical hypothyroidism and heart failure: chicken or egg? Can J Cardiol. 2018;34:11–2.
58. Mancini A, Di Segni C, Raimondo S, Olivieri G, Silvestrini A, Meucci E, et al. Thyroid Hormones, Oxidative Stress, and Inflammation. Mediators Inflamm. 2016;2016:1–12.
59. Delitala AP, Scuteri A, Maioli M, Mangatia P, Vilardi L, Erre GL. Subclinical hypothyroidism and cardiovascular risk factors. Minerva Med. 2019;110:530–45.
60. Chaker L, Baumgartner C, den Elzen WPJ, Ikram MA, Blum MR, Collet TH, et al. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis. J Clin Endocrinol Metab. 2015;100:2181–91.
61. Catli G, Abaci A, Büyükgebiz A, Bober E. Subclinical hypothyroidism in childhood and adolescense. J Pediatr Endocrinol Metab. 2014;27:1049-57. doi: 10.1515/jpem-2014-0089.
62. Bielecka-Dabrowa A, Godoy B, Suzuki T, Banach M, von Haehling S. Subclinical hypothyroidism and the development of heart failure: an overview of risk and effects on cardiac function. Clin Res Cardiol. 2019;108:225-33. doi: 10.1007/s00392-018-1340-1.
63. Erem C. Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. Clin Endocrinol. 2006;64:323–9.
64. N J, Francis J. Atrial fibrillation and hyperthyroidism. Indian Pacing Electrophysiol J. 2005;5:305–11.
65. Gong N, Gao C, Chen X, Fang Y, Tian L. Endothelial function in patients with subclinical hypothyroidism: a meta-analysis. Horm Metab Res. 2019;51(:691–702.
66. Rodondi N, den Elzen WPJ, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304:1365–74.
67. Francois J, Al-Sadawi M, Casillas J, Botti E, Soni L, Ponse D, et al. Hypothyroidism and heart failure: epidemiology, pathogenetic mechanisms & therapeutic rationale. Int J Clin Res Trials. 2020;5:146.
68. Duggal J, Singh S, Barsano CP, Arora R. Cardiovascular risk with subclinical hyperthyroidism and hypothyroidism: pathophysiology and management. J Cardiometab Syndr. 2007;2:198–206.
69. Kaminski G, Makowski K, Michalkiewicz D, Kowal J, Ruchala M, Szczepanek E, et al. The influence of subclinical hyperthyroidism on blood pressure, heart rate variability, and prevalence of arrhythmias. Thyroid. 2012;22:454-60. doi: 10.1089/thy.2010.0333.
70. Galetta F, Franzoni F, Fallahi P, Tocchini L, Graci F, Gaddeo C, et al. Changes in autonomic regulation and ventricular repolarization induced by subclinical hyperthyroidism. Biomed Pharmacother. 2010;64:546-9. doi: 10.1016/j.biopha.2009.10.001.
71. Huang M, Yang S, Ge G, Zhi H, Wang L. Effects of thyroid dysfunction and the thyroid-stimulating hormone levels on the risk of atrial fibrillation: a systematic review and dose-response meta-analysis from cohort studies. Endocr Pract. 2022;28:822–31.
72. Jabbar A, Pingitore A, Pearce SHS, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol. 2017;14:39–55.
73. Li RB, Yang XH, Zhang JD, Wang D, Cui XR, Bai L, et al. The association between subclinical thyroid dysfunction and recurrence of atrial fibrillation after catheter ablation. Front Cardiovasc Med. 2022;9:902411.
74. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J. 2001;142:838–42.
75. Berta E, Lengyel I, Halmi S, Zrínyi M, Erdei A, Harangi M, et al. hypertension in thyroid disorders. Front Endocrinol. 2019;10:482.
76. Osuna PM, Udovcic M, Sharma MD. Hyperthyroidism and the heart. Methodist DeBakey Cardiovasc J. 2017;13:60–3.
77. Fang H, Zhao R, Cui S, Wan W. Sex differences in major cardiovascular outcomes and fractures in patients with subclinical thyroid dysfunction: a systematic review and meta-analysis. Aging. 2022;14:8448–85.
78. Klein Hesselink EN, Klein Hesselink MS, De Bock GH, Gansevoort RT, Bakker SJL, Vredeveld EJ, et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. J Clin Oncol. 2013;31:4046–53.
79. Klein Hesselink EN, Lefrandt JD, Schuurmans EP, Burgerhof JGM, Groen B, Gansevoort RT, et al. Increased risk of atrial fibrillation after treatment for differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2015;100:4563–9.
80. Links TP, Van Der Boom T, Zandee WT, Lefrandt JD. Cardiovascular effects of overt and subclinical hyperthyroidism: focus on differentiated thyroid cancer. Endocr Connect. 2021;10:R43–51.
81. Vidili G, Delitala A, Manetti R. Subclinical hyperthyroidism: the cardiovascular point of view. Eur Rev Med Pharmacol Sci. 2021;25:3264–71.
82. Panday P, Arcia Franchini AP, Iskander B, Anwer F, Oliveri F, Kakargias F, et al. Subclinical hypothyroidism in geriatric population and its association with heart failure. Cureus. 2021;13:e14296.
83. Triggiani V, Angelo Giagulli V, De Pergola G, Licchelli B, Guastamacchia E, Iacoviello M. Mechanisms Explaining the Influence of Subclinical Hypothyroidism on the Onset and Progression of Chronic Heart Failure. Endocr Metab Immune Disord Drug Targets. 2016;16:2–7.
84. Nanchen D, Gussekloo J, Westendorp RGJ, Stott DJ, Jukema JW, Trompet S, et al. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. 2012;97:852–61.
85. Yang G, Wang Y, Ma A, Wang T. Subclinical thyroid dysfunction is associated with adverse prognosis in heart failure patients with reduced ejection fraction. BMC Cardiovasc Disord. 2019;19:83.
86. Razvi S, Weaver JU, Vanderpump MP, Pearce SHS. The Incidence of Ischemic Heart Disease and Mortality in People with Subclinical Hypothyroidism: Reanalysis of the Whickham Survey Cohort. J Clin Endocrinol Metab. 2010;95:1734–40.
87. Andersen MN, Olsen AM, Madsen JC, Faber J, Torp-Pedersen C, Gislason GH, et al. Levothyroxine substitution in patients with subclinical hypothyroidism and the risk of myocardial infarction and mortality. PLoS One. 2015;10:e0129793. doi: 10.1371/journal.pone.0129793.
88. Razvi S, Weaver JU, Butler TJ, Pearce SH. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. Arch Intern Med. 2012;172:811-7. doi: 10.1001/archinternmed.2012.1159.
89. Andersen MN, Olsen AMS, Madsen JC, Kristensen SL, Faber J, Torp-Pedersen C, et al. Long-Term Outcome in Levothyroxine Treated Patients With Subclinical Hypothyroidism and Concomitant Heart Disease. J Clin Endocrinol Metab. 2016;101:4170–7.
90. Ogunsakin A, Solomon SS, Dagogo-Jack S. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med. 2017;377:e20. doi: 10.1056/NEJMc1709989.
91. Abreu IM, Lau E, de Sousa Pinto B, Carvalho D. Subclinical hypothyroidism: to treat or not to treat, that is the question! A systematic review with meta-analysis on lipid profile. Endocr Connect. 2017;6:188–99.
92. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18:988–1028.
93. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014;24:1670–751.
94. Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of subclinical hypothyroidism. Eur Thyroid J. 2013;2:215–28.
95. Freitas C, Rodrigues F, Rocha G, Simões H, Miguel M, Azevedo T. Diagnosis, treatment and follow up of primary hypothyroidism in the adult. Position Statement of the Portuguese Society of Endocrinology, Diabetes and Metabolism (SPEDM) and the Thyroid Study Group (GET). Rev Port Endocrinol Diabetes Metab. Rev Port Endocrinol Diabetes Metab. 2019;14:167-79. doi:10.26497/na190056
96. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ. 2019;365:l2006. doi: 10.1136/bmj.l2006
97. The EMIL-Study, Ludwig U, Holzner D, Denzer C, Greinert A, Haenle MM, et al. Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: a cross-sectional study of a random population sample aged 18 to 65 years. BMC Endocr Disord. 2015;15:41.
98. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J. 2015;4:149–63.
99. Tsai K, Leung AM. Subclinical hyperthyroidism: a review of the clinical literature. Endocr Pract. 2021;27:254–60.
100. Sgarbi JA, Villaça FG, Garbeline B, Villar HE, Romaldini JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. J Clin Endocrinol Metab. 2003;88:1672–7.

SPEDM

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Guidelines

Republication of "2023 Update: Luso-Brazilian Evidence-Based Guideline for the Management of Antidiabetic Therapy in Type 2 Diabetes"

Marcello Casaccia Bertoluci [1,2,a], Wellington S. Silva Júnior [3,b], Fernando Valente [4,a], Levimar Rocha Araujo [5,a], Ruy Lyra [6,a], João Jácome de Castro [7,d,*], João Filipe Raposo [8,c], Paulo Augusto Carvalho Miranda [9,b], Cesar Luiz Boguszewski [10,b], Alexandre Hohl [11,b], Rui Duarte [12,c], João Eduardo Nunes Salles [13,a], José Silva-Nunes [8,c], Jorge Dores [14,15,d], Miguel Melo [16,c], João Roberto de Sá [4,17,a], João Sérgio Neves [18,19,d], Rodrigo Oliveira Moreira [20,21,22,b], Marcus Vinícius Bolívar Malachias [23,a], Rodrigo Nunes Lamounier [24,a], Domingos Augusto Malerbi [25,b], Luis Eduardo Calliari [13,a], Luis Miguel Cardoso [32,34,d], Maria Raquel Carvalho [26,d], Hélder José Ferreira [27,c], Rita Nortadas [12,c], Fábio Rogério Trujilho [28,33,b], Cristiane Bauermann Leitão [1,2,b], José Augusto Rodrigues Simões [29,c], Mónica Isabel Natal dos Reis [30,c], Pedro Melo [31,35,d], Mafalda Marcelino [7,d], and Davide Carvalho [36,d]

[a] *Sociedade Brasileira de Diabetes (SBD)*
[b] *Sociedade Brasileira de Endocrinologia e Metabologia (SBEM)*
[c] *Sociedade Portuguesa de Diabetologia (SPD)*
[d] *Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM)*

[1] *Faculdade de Medicina da Universidade Federal do Rio Grande do Sul, Brasil.*
[2] *Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre, Brasil.*
[3] *Disciplina de Endocrinologia, Departamento de Medicina I, Universidade Federal Maranhão, São Luís, Brasil.*
[4] *Faculdade de Medicina do ABC, Brasil.*
[5] *Faculdade de Ciências Médicas de Minas Gerais, Brasil.*
[6] *Universidade Federal de Pernambuco, Brasil.*
[7] *Serviço de Endocrinologia do Hospital Universitário das Forças Armadas, Lisboa, Portugal.*
[8] *NOVA Medical School, Universidade Nova de Lisboa, Portugal.*
[9] *Clínica de Endocrinologia e Metabologia da Santa Casa Belo Horizonte, Brasil.*
[10] *Divisão de Endocrinologia (SEMPR), Departamento de Clínica Médica, Universidade Federal do Paraná, Curitiba, Brasil.*
[11] *Departamento de Clínica Médica da Universidade Federal de Santa Catarina, Brasil.*
[12] *Associação Protectora dos Diabéticos de Portugal, Portugal.*
[13] *Faculdade de Ciências Médicas da Santa Casa de São Paulo, Brasil.*
[14] *Centro Hospitalar e Universitário de Santo António, Portugal.*
[15] *Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Portugal.*
[16] *Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitário de Coimbra, Faculdade de Medicina da Universidade de Coimbra, Portugal.*
[17] *Escola Paulista de Medicina, Universidade Federal de São Paulo, BR.*
[18] *Cardiovascular R&D Centre (UnIC@RISE), Faculdade de Medicina da Universidade do Porto, Portugal.*
[19] *Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, Portugal.*
[20] *Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE), Rio de Janeiro, Brasil.*
[21] *Faculdade de Medicina do Centro Universitário Presidente Antônio Carlos (UNIPAC/JF), Juiz de Fora, Brasil.*
[22] *Faculdade de Medicina do Centro Universitário de Valença (UNIFAA), Valença, Brasil.*
[23] *Faculdade de Ciências Médicas de Minas Gerais, Brasil.*
[24] *Departamento de Clínica Médica da Faculdade de Medicina da Universidade Federal de Minas Gerais, Brasil.*
[25] *Hospital Israelita Albert Einstein, São Paulo, Brasil.*
[26] *Hospital CUF, Tejo, Portugal.*
[27] *Clínica Grupo Sanfil Medicina, Coimbra, Portugal.*
[28] *Faculdade de Medicina da UniFTC, Salvador, Brasil.*
[29] *Faculdade de Ciências da Saúde da Universidade da Beira Interior, Portugal.*
[30] *Unidade Integrada de Diabetes Mellitus do Hospital de Vila Franca de Xira, Portugal.*
[31] *Serviço de Endocrinologia, Hospital Pedro Hispano, Matosinhos, Portugal.*
[32] *i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal.*
[33] *Centro de Diabetes e Endocrinologia da Bahia (CEDEBA), Salvador, Brasil.*
[34] *Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitário de Coimbra, Portugal.*
[35] *Unidade de Endocrinologia, Instituto CUF, Porto, Portugal.*
[36] *Faculdade de Medicina da Universidade do Porto, Portugal.*

[*] Autor Correspondente/Corresponding Author:
Correio eletrónico: jjcastro@sapo.pt (João Jácome de Castro)
Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM),
Rua Fernando Vicente Mendes, Nº 1B, 1º Dto., 1600-892 Lisboa, Portugal

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Republicado / Republished: 2023-10-18

Keywords:
Diabetes Mellitus, Type 2/drug therapy;
Diabetes Mellitus, Type 2/therapy;
Guidelines;
Hypoglycemic Agents;
Sodium-Glucose Transporter 2 Inhibitors.

A B S T R A C T

Background: The management of antidiabetic therapy in people with type 2 diabetes (T2D) has evolved beyond glycemic control. In this context, Brazil and Portugal defined a joint panel of four leading diabetes societies to update the guideline published in 2020.
Methods: The panelists searched MEDLINE (via PubMed) for the best evidence from clinical studies on treating T2D and its cardiorenal complications. The panel searched for evidence on antidiabetic therapy in people with T2D without cardiorenal disease and in patients with T2D and atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and diabetic kidney disease (DKD). The degree of recommendation and the level of evidence were determined using predefined criteria.
Results and Conclusions: All people with T2D need to have their cardiovascular (CV) risk status stratified and HbA1c, BMI, and eGFR assessed before defining therapy. An HbA1c target of less than 7% is adequate for most adults, and a more flexible target (up to 8%) should be considered in frail older people. Non-pharmacological approaches are recommended during all phases of treatment. In treatment naïve T2D individuals without cardiorenal complications, metformin is the agent of choice when HbA1c is 7.5% or below. WhenHbA1c is above 7.5% to 9%, starting with dual therapy is recommended, and triple therapy may be considered. When HbA1c is above 9%, starting with dual therapy is recommended, and triple therapy should be considered. Antidiabetic drugs with proven CV benefit (AD1) are recommended to reduce CV events if the patient is at high or very high CV risk, and antidiabetic agents with proven efficacy in weight reduction should be considered when obesity is present. If HbA1c remains above target, intensification is recommended with triple, quadruple therapy, or even insulin-based therapy. In people with T2D and established ASCVD, AD1 agents (SGLT2 inhibitors or GLP-1 RA with proven CV benefit) are initially recommended to reduce CV outcomes, and metformin or a second AD1 may be necessary to improve glycemic control if HbA1c is above the target. In T2D with HF, SGLT2 inhibitors are recommended to reduce HF hospitalizations and mortality and to improve HbA1c. Inpatients with DKD, SGLT2 inhibitors in combination with metformin are recommended when eGFR is above 30 mL/min/1.73 m². SGLT2 inhibitors can be continued until end-stage kidney disease.

Palavras-chave:
Diabetes Mellitus Tipo 1/tratamento farmacológico;
Diabetes Mellitus Tipo 1/tratamento; Directrizes;
Hipoglicemiantes;
Inibidores do Transportador 2 de Sódio-Glicose.

Republicação de "Atualização 2023: Recomendações Luso-Brasileiras Baseadas na Evidências para a Gestão da Terapêutica Antidiabética na Diabetes Tipo 2"

R E S U M O

Introdução: A gestão da terapêutica antidiabética em pessoas com diabetes tipo 2 (DM2) evoluiu para além do controlo glicémico. Neste contexto, o Brasil e Portugal definiram um painel conjunto de quatro sociedades líderes em diabetes para atualizar as diretrizes publicadas em 2020.
Métodos: Os autores recorreram à base de dados MEDLINE (via PubMed) para identificar a melhor evidência clínica sobre o tratamento da DM2 e suas complicações cardiorrenais. O painel procurou evidência sobre a terapêutica antidiabética em pessoas com DM2 sem doença cardiorenal e em doentes com DM2 e doença cardiovascular aterosclerótica (ASCVD), insuficiência cardíaca (IC) ou doença renal crónica (DRC). O grau de recomendação e o nível de evidência foram determinados usando critérios predefinidos.
Resultados e Conclusões: Em todas as pessoas com DM2, o risco cardiovascular (CV), a HbA1c, o IMC e a taxa de filtração glomerular (eGFR) devem ser considerados antes de definir a terapêutica antidiabética. Um alvo de HbA1c abaixo de 7% é adequado para a maioria dos adultos com diabetes, sendo um alvo mais flexível (até 8%) considerado para pessoas idosas frágeis. Abordagens não farmacológicas são recomendadas durante todas as fases de tratamento. Em pessoas com DM2 que não apresentam complicações cardiorrenais, a metformina é o agente de escolha quando a HbA1c é inferior a 7,5%. Para valores de HbA1c entre 7,5% e 9%, recomenda-se o início de terapêutica dupla, e pode ser considerada a terapêutica tripla. Quando a HbA1c é superior a 9%, recomenda-se o início da terapêutica dupla, e a terapêutica tripla deve ser considerada. São recomendados medicamentos antidiabéticos com benefício CV comprovado (AD1) para reduzir eventos CV se o doente apresentar alto ou muito alto risco CV, e agentes antidiabéticos com eficácia comprovada na redução do peso na presença de obesidade. Se a HbA1c continuar acima do alvo, é recomendada a intensificação com terapêutica tripla, quádrupla ou com terapêutica insulínica. Em pessoas com DM2 e ASCVD estabelecida, os agentes AD1 (inibidores SGLT2 ou agonistas de GLP-1 com benefício CV comprovado) são recomendados para reduzir os eventos CV, e a metformina ou um segundo AD1 podem ser necessários para melhorar o controlo glicémico se a HbA1c estiver acima do alvo. Na DM2 com IC, são recomendados inibidores SGLT2 para reduzir as hospitalizações e mortalidade por IC e para melhorar a HbA1c. Em doentes com DRC, são recomendados inibidores SGLT2 em combinação com metformina quando a eGFR estiver acima de 30 mL/min/1,73 m². Os inibidores de SGLT2 podem ser continuados até a fase terminal da doença renal.

Introduction

Treatment of type 2 diabetes mellitus (T2D) has evolved rapidly in recent years. New agents and strategies have amplified the scopus for managing T2D, and much new evidence has emerged. Therefore, the four leading Diabetes Societies from Brazil and Portugal (Sociedade Brasileira de Diabetes [SBD], Sociedade Brasileira de Endocrinologia e Metabologia [SBEM], Sociedade Portuguesa Diabetologia [SPD], and Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo [SPEDM]) joined to update the initial version of Portuguese-Brazilian guideline on the management of hyperglycemia in T2D, published in 2020[1]. The panel gathered the best evidence in the field, and a grade of recommendation was established through polls.

What is new in the 2023 UPDATE?

The 2023 UPDATE brings a paradigm shift from the previous guideline focused on the treatment of hyperglycemia. The new evidence-based recommendations guide the management of antidiabetic therapy, which involves aspects beyond glycemic control, such as achieving and maintaining a healthy weight and cardiorenal protection.

Non-pharmacological approaches were revised, and they now include recommendations related to sleep duration, sitting time, and the use of continuous glucose monitoring (CGM). There have been notable updates in the criteria used to select the most appropriate therapy. For this purpose, the 2023 UPDATE recommends stratifying cardiovascular (CV) risk and defining weight status, renal function, and glycated hemoglobin (HbA1c) level of all individuals with T2D. The panel included a new table with revised CV risk factors and new CV risk markers of subclinical disease or end-organ lesion, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and advanced microvascular complications (proliferative diabetic retinopathy, severe cardiac autonomic neuropathy, and advanced stages of renal disease).

Although pharmacological treatment still includes AD1 (antidiabetic agents with proven CV benefits) and AD (anti-hyperglycemic agents with proven CV safety), the 2023 UPDATE highlights agents with efficacy in weight management, i.e., glucagon-like peptide-1 receptor agonists (GLP-1 RA) and the new class of dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor co-agonists. Moreover, in individuals without clinical cardiorenal complications but with high CV risk, AD1 should be considered to primary cardiorenal prevention; if very high ASCVD risk, AD1 are recommended. If obesity is present, the agents with efficacy in weight management should be considered, and GLP-1 RA should be the choice if high/very high CV risk.

To avoid clinical inertia, the best strategy for naïve patients and treatment intensification in patients that have not achieved the HbA1c target were updated. Now, triple therapy may be considered if initial HbA1c > 7.5-9.0% and should be considered in asymptomatic adults with initial HbA1c > 9%. Furthermore, if insulin-based therapy (IBT) is indicated for a patient no longer in use of GLP-1 RA, a fixed-ratio co-formulation (FRC) insulin/GLP-1 RA should be considered over basal insulin or basal-bolus whenever available. If obesity is present, however, combination of basal insulin and GLP-1 RA titrated to the highest doses approved for weight loss should be considered. The periodicity of HbA1c evaluation was also updated, considering clinical aspects and cost-benefit issues.

In patients with established atherosclerotic cardiovascular disease (ASCVD), the 2023 UPDATE recommends SGLT2 inhibitors (SGLT2i) or GLP-1 RA as initial therapy. To intensify blood glucose control, metformin association or a combination of GLP-1 RA and SGLT2i may be considered. In patients with heart failure (HF), SGLT2i are now preferred independently of the ejection fraction, and intensification should be considered with metformin or GLP-1 RA. A warning for avoiding GLP-1 RA in patients with advanced HF with reduced ejection fraction was added due to recent evidence of increased risk of ventricular arrhythmias in this scenario.

The algorithm for management of patients with T2D and renal disease was restructured and estimated glomerular filtration rate (eGFR) and albuminuria are critical references for decisions. Although SGLT2i should not be initiated when eGFR is < 30 mL/min/1.73 m², they can be maintained until dialysis.

Methods

The main objective of this guideline was to support the decision-making process in clinical practice, considering the best evidence available. The panel was formed by 33 experts with extensive expertise in diabetes from both countries. Clinical topics requiring updated positions were ASCVD, HF, chronic kidney disease (CKD), and the management strategy for T2D in patients without vascular complications, focusing on controlling hyperglycemia and cardiorenal protection.

The panel compiled a narrative review by searching MEDLINE (via PubMed) for randomized clinical trials (RCTs), meta-analyses, and high-quality observational studies related to T2D. The best evidence available was reviewed, and when high-quality evidence was not available from the literature, the panel gave opinions on various clinical scenarios. These opinions were gathered and analyzed by an international voting system, allowing a consensus to be reached after multiple rounds of discussion.

A list of 45 statements was carefully created and scored according to the class of recommendation and level of evidence (Figs. 1 and 2).

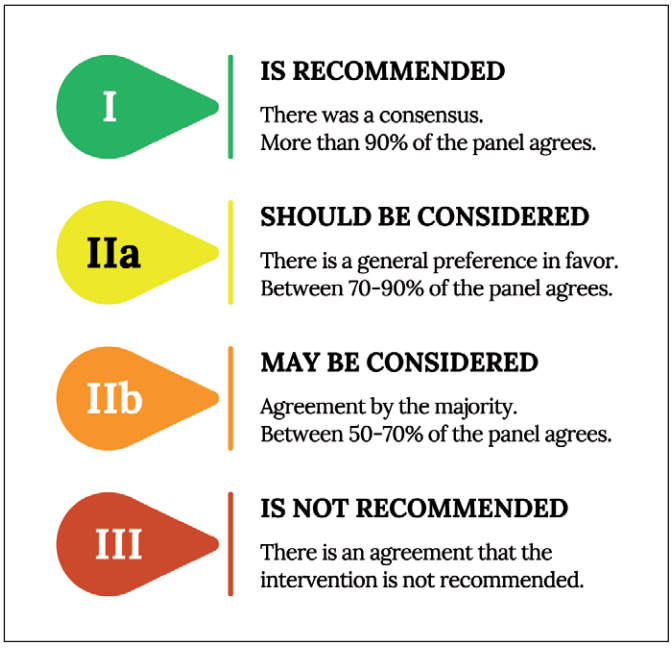


Figure 1. Class of recommendation.

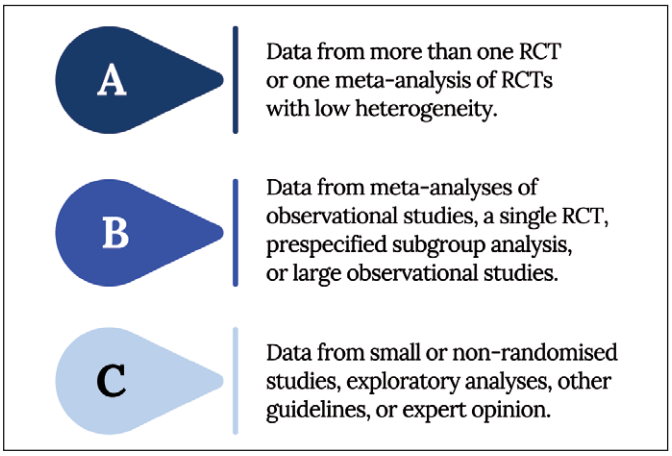


Figure 2. Level of evidence.

Recommendations

General Assessment

R1. It IS RECOMMENDED that all treatment naïve adults with T2D have their cardiovascular risk status stratified, the renal function assessed, and body mass index and HbA1c determined before defining the use of antidiabetic agents.

I | C

Summary of evidence:

- This panel considered assessing the CV risk essential before defining the most appropriate antidiabetic treatment (Figure 3). In general, the risk of long-term occurrence of CV events is twice as high in T2D compared to the general population of the same age[30]. The differences between individuals, however, are very heterogeneous according to age, the presence of risk factors, previous CV disease (CVD), previous CV events, and baseline renal function[1,2,9].
- The Emerging Risk Factors Collaboration group performed a meta-analysis of individual data from 102 prospective studies of patients with T2D without baseline cardiovascular disease[30]. Regressions were adjusted for age, sex, smoking, systolic blood pressure, and body mass index (BMI) to calculate vascular disease hazard ratios (HRs). The analysis included data from 698,782 people. Adjusted HRs with diabetes were: 2.00 (95% CI] 1.83 to 2.19) for coronary heart disease; 2.27 (95% CI 1.95 to 2.65) for ischemic stroke; 1.56 (95% CI 1.19 to 2.05) for hemorrhagic stroke; 1.84 (95% CI 1.59 to 2.13) for unclassified stroke and 1.73 (95% CI 1.51 to 1.98) for the combination of other vascular deaths. Overall, T2D conferred a twofold excess risk for a wide range of vascular diseases, independently from other risk factors.

Glycemic Targets

R2. In adults with T2D, an HbA1c target of less than 7% IS RECOMMENDED to reduce the incidence of microvascular complications.

I | A

Summary of evidence:

- Improved blood-glucose control decreases the progression of diabetic microvascular disease. The UKPDS 33 trial[31] showed that reducing HbA1c to a target of below 7% is associated with reduced microvascular complications. A total of 3,867 newly diagnosed patients with T2D were randomly assigned to intensive treatment (sulfonylurea or insulin-based therapy [IBT]) or conventional treatment (diet alone). The intensive group aimed to attain fasting plasma glucose (FPG) of less than 108 mg/dL vs. the best achievable FPG with diet alone in the conventional group. Three aggregate endpoints were considered: (1) any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction [MI], angina, HF, stroke, renal failure, any amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness, or cataract extraction); (2) diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death); and (3) all-cause mortality (ACM). After ten years, the median HbA1c was 7% (interquartile range 6.2 to 8.2%) in the intensive group vs. 7.9% (6.9 to 8.8%) in the conventional group. For any diabetes-related endpoint, the risk was 12% lower in the intensive group (95% CI 1 to 21, P = 0.029) than in the conventional group. The risk reduction in any diabetes-related composite endpoint was attributable to a 25% risk reduction (95% CI 7 to 40, P = 0.0099) in microvascular outcome events.
- The frequency and severity of diabetic microvascular complications were examined in the Kumamoto study[32], a small randomized clinical trial (RCT) of 110 individuals with T2D observed for eight years. The study was divided into primary and secondary arms according to the presence of retinopathy to evaluate if intensive glycemic control could decrease the frequency or severity of microvascular complications. Patients were assigned to multiple insulin injections (MIT), administering three or more daily insulin injection therapy or conventional insulin injection therapy (CIT), administering 1 or 2 daily intermediate-acting insulin injections. In both primary and secondary prevention cohorts, the worsening in retinopathy and nephropathy were significantly lower (P < 0.05) in the MIT group than in the CIT group.

R3. In most adults with T2D, an HbA1c target of less than 7% IS RECOMMENDED to reduce the long-term incidence of macrovascular complications.

I | B

Summary of evidence:

- After UKPDS was finished, the post-trial observational phase monitored 3,277 patients for five years, with no attempts to maintain their previously assigned therapies.[33] All patients were assessed through questionnaires, and seven prespecified aggregate clinical outcomes from the UKPDS were considered. Although between-group differences in HbA1c levels were lost after the first year, relative risk reductions persisted at ten years for any diabetes-related endpoint (9%, P = 0.04) and microvascular disease (24%, P = 0.001). A risk reduction for myocardial infarction (MI) (15%, P = 0.01) and all-cause mortality (ACM) (13%, P = 0.007) was observed. In the metformin group, significant risk reductions persisted for any diabetes-related endpoint (21%, P = 0.01), MI (33%, P = 0.005), and ACM (27%, P = 0.002). Despite an early loss of glycemic differences, a continued reduction in microvas-

RISK CLASS	AGE	RISK FACTORS	SUBCLINICAL DISEASE OR END-ORGAN LESION	CV EVENTS
			No or not known	No CV events
LOW / INTERMEDIATE	Men < 50 y [2] Women < 56 y [2]	No risk factors		
HIGH		One or two of the following: • Duration of diabetes > 10 y [3] [a] • Metabolic syndrome [4] [b] • Systemic hypertension [5] • Current smoking [6] [c] • High LDL-c [7] • Family history of premature coronary heart disease [8] [d]	Any of the following: • eGFR 30-59 mL/min/1.73 m^2 [7] • Albuminuria 30-300 mg/g with eGFR ≥ 45 mL/min/1.73 m^2 [9] • Non-proliferative diabetic retinopathy [10,11] • Early/definite CAN [12] [e] • CAC > 10 U Agatston [13] [f] • Carotid plaque (intima-media thickness > 1.5 mm), CCTA with a definite plaque, or any arterial stenosis < 50% [14,15] [g] • Ankle-brachial index < 0.9 [16] • Abdominal aortic aneurysm [17-21] [h] • NT-proBNP ≥ 125 pg/mL, BNP ≥ 35 mg/dL, or hs-TnT ≥ 99th percentile upper reference limit [22-28]	No CV events
VERY HIGH		• ≥ 3 risk factors • Familial hypercholesterolemia [7]	Any of the following: • Albuminuria > 300 mg/g of creatinine [9] • Albuminuria 30-300 mg/g with eGFR < 45 mL/min/1.73 m^2 [9] • eGFR < 30 mL/min/1.73 m^2 [9] • Proliferative diabetic retinopathy [10,11] • Severe CAN [29] [e] • Severe atherosclerotic disease (stenosis ≥ 50%) in any vascular territory [7]	Any CV event [7]: • Acute coronary syndrome • Stable angina • Myocardial infarction • Ischemic stroke • Transient ischemic attack • Any revascularization • Peripheral artery obstruction • Limb amputation

LEGEND:

BNP, B-type natriuretic peptide; CAC, coronary artery calcium score; CAN, cardiac autonomic neuropathy; CCTA, computed tomography coronary angiography; CV, cardiovascular; eGFR, estimated glomerular filtration rate; hs-TnT, high sensitivity troponin T; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a] Valid for patients in whom the onset of diabetes occurred after 18 years of age

[b] Metabolic syndrome consists of abdominal circumference > 90 cm for men and > 80 cm for women, plus at least 2 of the following: triglycerides > 150 mg/dL; high-density lipoprotein cholesterol (HDL-c) < 40 mg/dL in men and < 50 mg/dL in women; blood pressure ≥ 130/85 mmHg or treatment for hypertension; fasting blood glucose ≥ 100 mg/dL or type 2 diabetes

[c] Current smoking is defined when the last smoking episode occurred less than 1 year before the time of stratification

[d] Family history of premature coronary heart disease is defined as the presence of coronary events in 1st-degree relatives (father, mother, or siblings) when occurring before 55 years of age in men or before 65 years of age in women

[e] Early CAN: 1 of the 3 heart rate tests abnormal or 2 borderline; definite CAN: ≥ 2 of the heart rate tests abnormal; severe CAN: ≥ 2 of the heart rate tests abnormal and ≥ 1 of the blood pressure tests abnormal or both borderline

[f] When available, CAC scoring should be the preferred modality

[g] CCTA should not be performed routinely in truly asymptomatic patients

[h] Patients sufering from an abdominal aortic aneurysm are at elevated risk of cardiovascular morbidity and mortality, due to common risk factors and comorbidities associated with the aneurysm

Figure 3. CV risk assessment in adults with T2D.

cular risk and risk reductions for MI and ACM was observed during the ten years of post-trial follow-up.

- The UKPDS 88[34], a long-term observational follow-up from the original UKPDS study, examined the impact of early and delayed glucose-lowering therapy and the incidence of ACM and MI in T2D 20 years after randomization. The effect of HbA1c values over time was analyzed by weighting them according to their influence on following ACM and MI risks. HRs for a 1% higher HbA1c for ACM were 1.08 (95% CI 1.07 to 1.09), 1.18 (95% CI 1.15 to 1.21), and 1.36 (95% CI 1.30 to 1.42) at 5, 10, and 20 years, respectively for MI, was 1.13 (95% CI 1.11 to 1.15) at five years, increasing to 1.31 (95% CI 1.25 to 1.36) at 20 years. A 1% lower HbA1c from diagnosis generated an 18.8% (95% CI 21.1 to 16.0) ACM risk reduction 10-15 years later, whereas delaying this reduction until ten years after diagnosis showed a seven-fold lower 2.7% (95% CI -3.1 to -2.3) risk reduction. Early detection of diabetes and intensive glucose control from diagnosis is essential to decrease the long-term risk of glycemic complications.

R4. In frail older adults with T2D, a less strict HbA1c target, up to 8%, IS RECOMMENDED to minimize hypoglycemia without increasing mortality.

I | B

Summary of evidence:

- Glycemic targets must be individualized based on peoples' personal characteristics, needs, and preferences. In frail older adults with T2D, a less strict HbA1c target is recommended to minimize hypoglycemia. This panel highlights, however, that HbA1c should not exceed 8%, to avoid symptomatic hyperglycemia and increases in mortality in older adults with diabetes.
- An epidemiological study using the data from the NHANES III (1994-1998) of 7,333 adults over 65 years analyzed mortality and the relationship between HbA1c and the risk of ACM and cause-specific mortality.[35] Compared with those with diagnosed diabetes and an HbA1c < 6.5%, the HR for ACM was significantly greater for adults with diabetes with an HbA1c > 8%. HRs were 1.6 (95% CI 1.02 to 2.6) and 1.8 (95% CI 1.3 to 2.6) for HbA1c 8-8.9% and ≥ 9%, respectively (P for trend < 0.001).
- In a retrospective cohort study from the Kaiser Permanente Northern California database[36], including 71,092 patients with T2D aging more than 60 years, the relationships between baseline HbA1c and subsequent outcomes (nonfatal complications [acute metabolic, microvascular, and CV events] and mortality) were analyzed. The mean cohort age was 71.0 ± 7.4 years, and the mean HbA1c was 7 ± 1.2%. The risk of any nonfatal complication rose when HbA1c ≥ 6% (adjusted HR 1.09, 95% CI 1.02 to 1.16, for HbA1c 6-6.9% and 1.86, 95% CI 1.63 to 2.13, for HbA1c ≥ 11%). Mortality, however, had a U-shaped relationship with HbA1c. Compared with HbA1c < 6%, mortality risk was lower when HbA1c was between 6-9% (e.g., 0.83, 95% CI 0.76 to 0.90, for HbA1c 7-7.9%) and higher when HbA1c ≥ 11% (1.31, 95% CI 1.09 to 1.57). The risk of any endpoint (complication or death) became significantly higher at HbA1c ≥ 8%. Patterns generally were consistent across age groups (60-69, 70-79, and ≥ 80 years).
- To investigate the association between HbA1c variability over time and mortality in older people with T2D, a 5-year retrospective cohort was assessed using The Health Improvement Network database[37]. The cohort included 587,000 primary care practices in the UK with patients of either sex who were above 70 years and older with type 1 or type 2 diabetes. The primary outcome was time to ACM. The primary exposure variables were mean HbA1c and variability of HbA1c over time. The observation included a 4-year run-in period with a 5-year follow-up from 2007 to 2012. A total of 54,803 people were enrolled, of whom 17,680 (8,614 [30.7%] of 28,017 women and 9,066 [33.8%] of 26,786 men) died during the observation period. The data showed a J-shaped distribution for mortality risk in both sexes, with significant increases in HbA1c values greater than 8% and less than 6%. Excess mortality risk was not significant for men at HbA1c values of 8% to less than 8.5%. Mortality increased with increasing HbA1c variability in all models (overall and for both sexes). Both low and high levels of glycemic control were associated with an increased mortality risk. The degree of variability also seems to be an essential factor, suggesting that a stable glycemic level in the middle range is associated with lower risk, and glycemic variability over time in HbA1c is essential in understanding mortality risk in older people with diabetes.

R5. It IS RECOMMENDED to measure HbA1c once every 12 weeks in patients that have not achieved the HbA1c target, after changing therapy, or in unstable situations.

I | C

R6. It IS RECOMMENDED to measure HbA1c at least once every 24 weeks in patients meeting treatment goals.

I | C

Summary of evidence:

- Recommendations 5 and 6 were based on the expert opinion of more than 90% of this panel, based on the current best clinical practice of Brazilian and Portuguese board members, considering cost-effective issues.

Management of Antidiabetic Therapy in Adults Without Cardiorenal Disease

Figure 4 depicts the approach to managing antidiabetic therapy in adults with T2D and without cardiorenal disease.

R7. Non-pharmacological approaches, such as nutritional intervention focusing on weight control, physical exercise, decreasing sitting time, improving sleep duration, stopping smoking, and stress management, ARE RECOMMENDED during all phases of treatment in T2D to improve glycemic control.

I | B

Summary of evidence:

- Lifestyle measures should be recommended universally as the basis for diabetes treatment, as sustained remission of T2D is related to the degree of weight loss.
- Weight loss is associated with sustained remission of T2D. The DIRECT study[38] was an open-label, cluster-randomized,

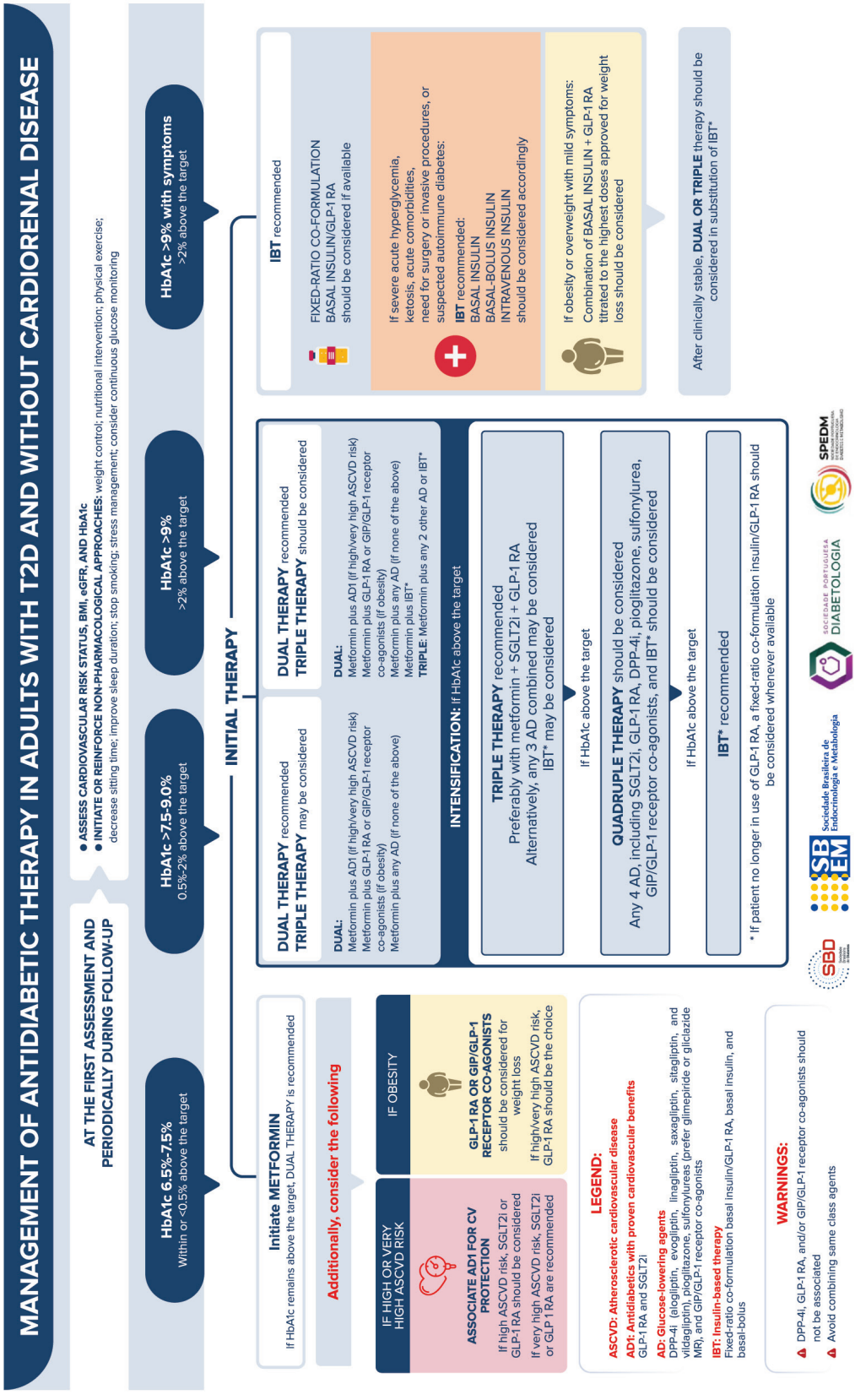


Figure 4. Management of antidiabetic therapy in adults with T2D and without cardiorenal disease.

controlled trial conducted at primary healthcare units in the United Kingdom (UK) that assessed remission of T2D during a direct care-led weight-management program. The study randomized overweight/obese patients recently diagnosed with T2D to an integrated structured weight management program (intervention) (n = 149) or the standard of care by UK guidelines (n = 149). The intervention included the withdrawal of antidiabetic drugs, total diet replacement (825–853 kcal/d formula diet for 12–20 weeks), and stepped food reintroduction (2–8 weeks), followed by structured support for weight-loss maintenance. The primary outcome was a weight loss of at least 15 kg and remission of T2D, defined as an HbA1c < 6.5% after withdrawal of antidiabetic agents at 12 and 24 months. At 24 months, 11% of patients in the intervention group and 2% of controls had achieved weight loss of at least 15 kg (odds ratio [OR] 7.49, 95% CI 2.05 to 7.32, P = 0.0023), and remission of diabetes was seen in 36% in the intervention group and 3% in the control group (OR 25.82, 95% CI 8.25 to 80.84, P < 0.0001). In a post hoc analysis of the whole study population, of those participants who maintained at least 10 kg weight loss (45 of 272 with data), 29 (64%) achieved remission; 36 (24%) of 149 participants in the intervention group maintained at least 10 kg weight loss.

- The association of sleep duration with CVD incidence and mortality in high-risk T2D populations was evaluated in a prospective study, which included 18,876 participants with T2D in the UK Biobank who were free of CVD and cancer at baseline.[39] During an average follow-up of 11-12 years, there were 2,570 incident cases of ASCVD and 598 CVD deaths. Compared with sleeping for seven hours daily, the multivariable-adjusted HRs of ≤ 5 and ≥ ten h/d were 1.26 (95% CI 1.08 to 1.48) and 1.41 (95% CI 1.16 to 1.70) for incident ASCVD, 1.22 (95% CI 0.99 to 1.50) and 1.16 (95% CI 0.88 to 1.52) for coronary artery disease, 1.70 (95% CI 1.23 to 2.35) and 2.08 (95% CI 1.44 to 3.01) for ischemic stroke, 1.02 (95% CI 0.72 to 1.44) and 1.45 (95% CI 1.01 to 2.10) for peripheral artery disease, and 1.42 (95% CI 1.02 to 1.97) and 1.85 (95% CI 1.30 to 2.64) for CVD mortality. Short and long sleep durations were independently associated with increased risks of CVD onset and death among people with T2D.
- A meta-analysis[40] examined the association of total daily sitting time with CVD and T2D, with and without adjustment for physical activity. Nine studies with 448,285 participants were included. A higher real daily sitting time was associated with an increased risk of CVD (HR 1.29, 95% CI 1.27 to 1.30, P < 0.001) and T2D (HR 1.13, 95% CI 1.04 to 1.22, P < 0.001). The increased risk for T2D was not affected after adjusting for physical activity (HR 1.11, 95% CI 1.01 to 1.19, P < 0.001). The increased risk was attenuated for CVD but significant (HR 1.14, 95% CI 1.04 to 1.23, P < 0.001). The authors concluded that higher levels of total daily sitting time are associated with an increased risk of CVD and T2D, independent of physical activity. Therefore, the total daily sitting reduction is recommended in public health guidelines.
- A meta-analysis[41] of 47 studies assessing sedentary behavior in adults, adjusted for physical activity, was performed on outcomes for CVD and diabetes, cancer, and ACM. Inactive times were quantified using self-report. Significant HRs were found with ACM (HR 1.24, 95% CI 1.09 to 1.41), CVD mortality (HR 1.17, 95% CI 1.10 to 1.25), CVD incidence (HR 1.14, 95% CI 1.00 to 1.72), cancer mortality (HR 1.17, 95% CI 1.10 to 1.24), cancer incidence (HR 1.13, 95% CI 1.05 to 1.21), and T2D incidence (HR 1.91, 95% CI 1.64 to 2.22). HRs associated with sedentary time and outcomes were more pronounced at lower physical activity levels than higher ones. There was marked heterogeneity in research designs and the assessment of sedentary time and physical activity. Prolonged sedentary time was independently associated with deleterious health outcomes regardless of physical activity.

R8. Continuous glucose monitoring SHOULD BE CONSIDERED to improve glycemic control in T2D after considering the cost-benefit ratio.	
IIa	B

Summary of evidence:

- In a meta-analysis[42] of 13 real-world observational trials (data from 2,415 participants) involving adults with T2D, the use of intermittently scanned continuous glucose monitoring (isCGM) was associated with a significant reduction in HbA1c. The fall in HbA1c occurred at 3–4 months (-0.45%, 95% CI -0.57% to -0.33%), continuing through 4.5–7.5 months (-0.59%, 95% CI -0.80% to -0.39%) and was sustained after that for at least 12 months. The sustained reduction in HbA1c indicates that it is a consequence of using the isCGM system rather than transient confounding factors around initiation. Furthermore, meta-regression analysis shows that the degree of change in HbA1c was predicted by the HbA1c at baseline, such that a more significant reduction in HbA1c was seen for users with a higher baseline HbA1c.
- In a multicentric RCT[43] to determine the effectiveness of CGM in adults with T2D (n = 175) treated with basal insulin (without prandial insulin) in primary care practices, CGM resulted in significantly better glycemic control at eight months as compared with blood glucose meter (BGM) monitoring. Mean HbA1c level decreased from 9.1% at baseline to 8% at eight months in the CGM group and from 9% to 8.4% in the BGM group (adjusted difference -0.4%, 95% CI -0.8% to -0.1%, P = 0.02). In addition, the mean percentage of CGM-measured time in the target glucose range of 70 to 180 mg/dL was 59% in the CGM group vs. 43% in the BGM group (adjusted difference 15%, 95% CI 8% to 23%, P < 0.001) and the mean percentage of time at greater than 250 mg/dL was 11% vs. 27%, respectively (adjusted difference -16%, 95% CI -21% to -11%, P < 0.001). The mean glucose values were 179 mg/dL in the CGM group vs. 206 mg/dL in the BGM group (adjusted difference -26 mg/dL, 95% CI -41 to -12, P < 0.001).
- The IMMEDIATE study[44] was a multisite, open-label, 16-week RCT to examine the efficacy and patient satisfaction of isCGM in non-insulin-treated adults with T2D. The participants (n = 116) were randomized 1:1 to receive a diabetes self-management education (DSME) plus isCGM (the isCGM + DSME group) or DSME plus blinded CGM (the DSME group). At 16 weeks of follow-up, the isCGM + DSME group had a significantly greater mean time in range (+9.9% [+2.4 h], P < 0.01), significantly less time above range (-8.1% [-1.9 h], P = 0.037), and a greater reduction in mean HbA1c (-0.3%, 95% CI -0.7% to 0%, P = 0.048) vs. the DSME group. The time below range was low and not significantly different between groups, and hypoglycemic events were few in both groups. Glucose monitoring satisfaction was higher among isCGM users (adjusted difference -0.5, 95% CI -0.7 to -0.3, P < 0.01).

R9. In treatment-naïve adults recently diagnosed with T2D, without CVD or CKD, at low or intermediate CV risk, in whom HbA1c is 6.5-7.5%, metformin IS RECOMMENDED to improve glycemic control, mitigate diabetes progression, and prevent diabetes-related outcomes.	
I	B

Summary of evidence:

- This panel concluded that, in T2D, metformin is highly efficacious in reducing hyperglycemia, well-tolerated, cheap, and safe, and can slow down the natural progression of T2D while reducing diabetes-related outcomes. However, the role of metformin in reducing CV outcomes is unclear.
- The UKPDS 34 study[45] investigated whether intensive blood-glucose control with metformin could reduce diabetes-related outcomes. In an RCT including 4,075 participants, a subgroup of 1,704 overweight people with newly diagnosed T2D was assigned to either conventional treatment with diet alone (n = 411), intensive control with metformin (n = 342), or intensive control with a sulfonylurea or IBT (n = 951). The median duration was 10.7 years. The primary outcome measures were any diabetes-related clinical endpoint, diabetes-related death, and ACM. The overall mean HbA1c at baseline was 7.2 ± 1.5%. Compared with the conventional group, patients in the metformin group had risk reductions of 32% (95% CI 13 to 47, P = 0.002) for any diabetes-related endpoint, 42% for diabetes-related death (95% CI 9 to 63, P = 0.017), and 36% for ACM (95% CI 9 to 55, P = 0.011). Among patients allocated to intensive glycemic control, metformin showed a more significant effect than chlorpropamide, glibenclamide (glyburide), or IBT for any diabetes-related endpoint (P = 0.0034), ACM (P = 0.021), and stroke (P = 0.032). Intensive glucose control with metformin decreased the risk of diabetes-related endpoints in overweight people with T2D. In addition, it was associated with less weight gain and fewer hypoglycemic attacks than IBT and sulfonylureas.
- Metformin can also mitigate the progression from prediabetes to T2D. The Diabetes Prevention Program (DPP)[46] was an RCT comparing intensive lifestyle intervention or metformin vs. placebo in a cohort of people with prediabetes who were selected at very high risk of developing T2D. After the trial, an observational phase, the DPP Outcome Study (DPPOS), which included 2,776 (88%) of the surviving DPP cohort, was analyzed by intention-to-treat based on the original DPP assignment. During DPPOS, the lifestyle group was offered lifestyle reinforcement semi-annually, and the metformin group received unmasked metformin. During a mean 15 years of follow-up, lifestyle intervention and metformin reduced diabetes incidence rates by 27% (P < 0.0001) and 18% (P = 0.001), respectively, vs. the placebo group. There was an apparent decline in group differences over time. The cumulative incidences of T2D were 55%, 56%, and 62%, respectively, and the prevalence at the study-end of microvascular outcome composite outcome (nephropathy, neuropathy, and retinopathy) was not significantly different among the treatment groups (11–13%). Lifestyle intervention or metformin significantly reduced diabetes development over 15 years. There were no overall differences in the combined microvascular outcome among treatment groups. However, those who did not progress to diabetes had a lower prevalence of microvascular complications than those who progressed.

R10. In adults with T2D at high or very high CV risk, an AD1 IS RECOMMENDED for reduction of CV events.	
I	B

Summary of evidence:

- This panel defined as AD1 the anti-hyperglycemic agents with proven CV benefits, i.e., SGLT2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA).
- SGLT2i favorably affects CV events and CV mortality in high-risk adults with T2D. A meta-analysis[47] of 6 randomized, placebo-controlled CV outcomes trials (CVOTs) with SGLT2i included data from 6 trials comprising 46,969 patients with T2D, 66.2% with ASCVD. Overall, SGLT2i reduced the risk of MACE by 10% (HR 0.90, 95% CI 0.85 to 0.95), with no significant heterogeneity of associations with outcome. The presence or absence of ASCVD did not modify the association with outcomes for MACE (P for interaction = 0.10). There was also no difference between the subgroups with baseline HbA1c above or below 8.5% (P for interaction = 0.09). SGLT2i also reduced CV mortality by 15% (HR 0.85, 95% CI 0.78 to 0.93, without differences between patients with or without previous ASCVD; P for interaction = 0.44). These data support recommendations to prioritize the use of SGLT2i in patients at high ASCVD risk.
- GLP-1 RA reduces MACE, CV mortality, and ACM in high-risk patients with T2D. In a meta-analysis[48] including data from 8 trials comprising 60,080 patients, GLP-1 RA reduced MACE by 14% (HR 0.86, 95% CI 0.80 to 0.93), with no significant heterogeneity between subgroups with or without established ASCVD (P for interaction = 0.18). Overall, GLP-1 RA reduced CV mortality by 13% (HR 0.87, 95% CI 0.80 to 0.94) and ACM by 12% (HR 0.88, 95% CI 0.82 to 0.94), with no increase in the risk of severe hypoglycemia, retinopathy, or pancreatic adverse effects. This data supports current recommendations to prioritize the use of GLP-1 RA in patients at high ASCVD risk.

R11. In adults with T2D and obesity, GLP-1 RA or GIP/GLP-1 receptor co-agonists SHOULD BE CONSIDERED for improving weight loss.	
IIa	A

Summary of evidence:

- The STEP 2 study[49] was a double-blind, double-dummy, randomized phase 3 clinical trial that assessed the efficacy and safety of the once-a-week subcutaneous GLP-1 RA semaglutide, in doses of 2.4 mg vs. 1.0 mg vs. placebo, for weight management in adults with T2D and overweight or obesity. The study enrolled adults with a BMI ≥ 27 kg/m² and HbA1c 7-10% who had been diagnosed with T2D for at least 180 days before screening. Patients were randomly allocated (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and HbA1c to SC injection of semaglutide 2.4 mg, semaglutide 1.0 mg, or visually matching placebo, once a week for 68 weeks, plus a lifestyle intervention. Co-primary endpoints were percentage change in body weight and achievement of weight reduction of at least 5% at 68 weeks for semaglutide 2.4 mg vs. placebo, assessed by intention to treat. A total of 1,210 were randomly assigned to semaglutide 2.4 mg (n = 404), sema-

glutide 1.0 mg (n = 403), or placebo (n = 403) and included in the intention-to-treat analysis. The estimated change in mean body weight from baseline to week 68 was -9.6% with semaglutide 2.4 mg vs. -3.4% with placebo. The estimated treatment difference (ETD) for semaglutide 2.4 mg vs. placebo was -6.2% (95% CI -7.3 to -5.2; P < 0.0001). At week 68, more patients on semaglutide 2.4 mg than on placebo achieved weight reductions of at least 5% (267 [68.8%] of 388 vs. 107 [28.5%] of 376; OR 4.88, 95% CI 3.58 to 6.64, P < 0.0001). In adults with overweight/obesity and T2D, semaglutide 2.4 mg once a week significantly decreased body weight compared with placebo.

- The SURPASS 1 study[50] was a 40-week, double-blind, randomized, placebo-controlled, phase 3 trial to assess efficacy, safety, and tolerability of GIP/GLP-1 receptor co-agonist tirzepatide monotherapy vs. placebo in adults with T2D inadequately controlled by diet and exercise alone. The primary endpoint was the mean change in HbA1c from baseline at 40 weeks. A total of 478 individuals were randomly assigned to tirzepatide 5 mg (n = 121 [25%]), 10 mg (n = 121 [25%]), 15 mg (n = 121 [25%]), or placebo (n = 115 [24%]). At 40 weeks, all tirzepatide doses were superior to placebo for changes from baseline in HbA1c, fasting serum glucose, body weight, and HbA1c targets of < 7% and < 5.7%. Mean HbA1c decreased from baseline by 1.87% with tirzepatide 5 mg, 1.89% with tirzepatide 10 mg, and 2.07% with tirzepatide 15 mg vs. +0.04% with placebo, resulting in estimated treatment differences vs. placebo of -1.91%, -1.93%, and -2.11%, respectively (all P < 0.0001). More participants on tirzepatide than on placebo met HbA1c targets of < 7% (87-92% vs. 20%) and ≤ 6.5% (81-86% vs. 10%), and 31-52% of patients on tirzepatide vs. 1% on placebo reached an HbA1c < 5.7%. Tirzepatide induced a dose-dependent body weight loss ranging from 7 to 9.5 kg. Tirzepatide showed important improvements in glycemic control and body weight without increased risk of hypoglycemia. The safety profile was consistent with GLP-1 RA, indicating a potential monotherapy use of tirzepatide for T2D treatment.

R12. In treatment-naïve asymptomatic adults with T2D, at low or intermediate CV risk, in whom HbA1c is above 7.5%, dual therapy, including metformin and a second AD1 or AD, IS RECOMMENDED to improve glycemic control.	
I	A

Summary of evidence:

Adding SGLT2i:

- Compared with placebo, SGLT2i reduced HbA1c levels when used as monotherapy (weighted mean difference [WMD] 0.79%, 95% CI 0.96% to 0.62%, I^2 71%) or add-on treatment (WMD 0.61%, 95% CI 0.69% to 0.53%, I^2 73%).[51]

Adding GLP-1 RA:

- The efficacy of adding liraglutide to metformin was compared with the addition of placebo or glimepiride to metformin in subjects previously treated with oral antidiabetic therapy. In a 26-week, double-blind, double-dummy, placebo, and active-controlled, parallel-group trial, 1,091 adults with T2D were randomly assigned to once-daily liraglutide (either 0.6, 1.2, or 1.8 mg/d injected SC), to placebo, or to glimepiride (4 mg once daily).[52] All treatments were in combination therapy with metformin (1 g twice daily). Baseline HbA1c was 7-11% if on previous monotherapy > 3 months or 7-10% if previous dual therapy > 3 months. HbA1c values were reduced in all liraglutide groups vs. the placebo group (P < 0.0001), with mean decreases of 1% for 1.8 and 1.2 mg liraglutide and glimepiride and 0.7% for 0.6 mg liraglutide vs. an increase of 0.1% for placebo. Liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with glimepiride, when both had background therapy with metformin.

Adding DPP-4i:

- Dual therapy with DPP-4i and metformin is efficacious and safe. A meta-analysis[53] assessing the long-term efficacy and safety of DPP-4i combined with metformin compared to metformin alone in patients with T2D included seven RCTs lasting at least 24 weeks. The decline in HbA1c was greater with dual therapy. The difference was -0.54% (95% CI -0.63 to -0.45), with no increase in hypoglycemia (HR 0.79, 95% CI 0.48 to 1.30).

Adding pioglitazone:

- The addition of pioglitazone (30 mg/d) to other antidiabetic agents (metformin or sulfonylureas) led to more significant reductions in HbA1c level by –1.16% (95% CI –1.41 to –0.90) compared with placebo.[54]

Adding sulfonylureas:

- The safety of sulfonylureas in relation to CV outcomes was demonstrated in the CAROLINA head-to-head RCT[55] (glimepiride vs. linagliptin) in the TOSCA.IT head-to-head trial[56] (glimepiride vs. pioglitazone), and in the ADVANCE trial[57] (gliclazide MR).
- In a meta-analysis[58] of RCTs, CV safety was also extended to glibenclamide (glyburide). This panel considered that sulfonylureas are safe in relation to CV risk. However, they are associated with an increased incidence of hypoglycemia. Therefore, prescriptions must be individualized for each patient.
- Among the sulfonylureas, gliclazide MR is associated with a lower risk of hypoglycemia. In the GUIDE trial[59], a head-to-head comparison of gliclazide MR and glimepiride (n = 845), hypoglycemia occurred less frequently with gliclazide MR than with glimepiride (3.7% vs. 8.9%, respectively; P = 0.003).

Adding GIP/GLP-1 receptor co-agonists:

- A systematic review and meta-analysis[60] evaluating the efficacy and safety of tirzepatide against placebo or active comparator in people with T2D included six RCT (data from 6,579 subjects; 4,410 in the tirzepatide group and 2,054 in the control group). Tirzepatide treatment reduced HbA1c, the primary endpoint (WMD -1.07%, 95% CI -1.44 to -0.56, I^2 98%). Secondary efficacy endpoints also improved with tirzepatide. Fasting serum glucose (WMD -21.50 mg/dL, 95% CI -34.44 to -8.56), body weight (WMD -7.99 kg, 95% CI -11.36 to -4.62, I^2 99%), blood pressure, and fasting lipid profiles, without increasing hypoglycemia, either as monotherapy or add-on therapy. Tirzepatide increased the risk of gastrointestinal adverse events (risk ratio 3.32, 95% IC 1.3 to 8.5, I^2 95%) as add-on therapy, but not in terms of pancreatitis or cholelithiasis. Furthermore, tirzepatide presented a dose-response effect (1 mg to 15 mg) on decreased HbA1c and body weight.

R13. In treatment-naïve asymptomatic adults with T2D, in whom HbA1c is 7.5% to 9%, triple therapy, including metformin and two AD1 or AD, MAY BE CONSIDERED to improve glycemic control.

IIb | A

Summary of evidence:

- This panel considered that, in general, triple therapy is effective and safe for improving glycemic control. In addition, most studies indicate superior HbA1c-lowering efficacy with triple than with dual therapy. Therefore, it is likely that patients with HbA1c closer to 9% are potential candidates for initial triple therapy.
- Considering the combination of metformin, SGLT2i and GLP-1 RA, the AWARD-10 trial[61] randomized 424 patients who were on SGLT2i and metformin to receive dulaglutide 1.5 mg (n = 142), dulaglutide 0.75 mg (n = 142), or placebo (n = 140). The primary objective was to test for superiority of dulaglutide vs. placebo regarding the change in HbA1c from baseline at 24 weeks. HbA1c was reduced further in patients receiving all three drugs (dulaglutide 1.5 mg: -1.34% ± 0.06 and dulaglutide 0.75 mg: -1.21% ± 0.06) than in those receiving two drugs (placebo plus metformin/SGLT2i: -0.54% ± 0.06, P < 0.0001). Triple therapy improved glycemic control significantly, with acceptable tolerability.
- The DURATION-8 study[62] was a 28-week, multicenter, double-blind, active-control trial of T2D patients with HbA1c 8–12% who were on metformin monotherapy. Patients (n = 695) were randomly assigned to receive exenatide plus dapagliflozin, exenatide plus placebo, or dapagliflozin plus placebo. The primary endpoint was a change in HbA1c from baseline to week 28. At 28 weeks, the change in HbA1c was -2% (95% CI -2.2 to -1.8) in the exenatide/dapagliflozin group, -1.6% (95% CI -1.8 to -1.4) in the exenatide group, and -1.4% (95% CI -1.6 to -1.2) in the dapagliflozin group. The combination of exenatide and dapagliflozin significantly reduced HbA1c from baseline to week 28 compared with exenatide alone (-0.4%, 95% CI -0.6 to -0.1, P = 0.003) or dapagliflozin alone (-0.6%, 95% CI -0.8 to -0.3, P < 0.001), and was well tolerated.
- The combination of empagliflozin and linagliptin was examined as second-line therapy in subjects with T2D inadequately controlled on metformin in a double-blind RCT[63]. Patients were randomized to empagliflozin plus linagliptin or each drug alone in different dosages as an add-on to metformin for 52 weeks. The primary endpoint was the change in HbA1c from baseline at week 24. At week 24, decreases in HbA1c from a baseline of 7.90–8.02% were superior with empagliflozin/linagliptin than with empagliflozin 25 mg or linagliptin 5 mg alone as add-ons to metformin. Overall, 61.8% attained HbA1c < 7% with the combination of empagliflozin 25 mg/linagliptin 5 mg, while only 32.6% did with empagliflozin 25 mg alone (OR 4.2, 95% CI 2.3 to 7.6, P < 0.001), and 36.1% with linagliptin 5 mg alone (OR 3.5, 95% CI 1.9 to 6.4, P < 0.001). Efficacy was maintained at week 52. The proportion of subjects with adverse events over 52 weeks was similar across treatment arms (68.6–73%), with no hypoglycemic events requiring assistance.
- The empagliflozin/linagliptin combination as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components and was well tolerated. In an open-label clinical trial[64], 106 patients recently diagnosed with T2D were randomized to metformin/pioglitazone/exenatide (triple therapy) and 115 to metformin, followed by sulfonylurea and glargine U100 (conventional treatment) with an HbA1c target of < 6.5% for two years. Patients receiving triple therapy had a more significant reduction in HbA1c level than those receiving conventional treatment (5.95% vs. 6.50%; P < 0.001). In addition, despite lower HbA1c, participants on triple therapy experienced a 7.5-fold lower rate of hypoglycemia than patients on conventional treatment. Triple therapy was also associated with weight loss vs. weight gain in those receiving conventional treatment (-1.2 kg vs. +4.1 kg, respectively; P < 0.01).
- A post hoc analysis[65] of three RCTs of sequential or concomitant add-on of dapagliflozin and saxagliptin to metformin compared the safety of triple therapy (dapagliflozin plus saxagliptin + metformin) vs. dual therapy (dapagliflozin or saxagliptin plus metformin). At 24 weeks, the incidence of any adverse and serious adverse events was similar between the triple and dual therapy groups and between the concomitant and sequential add-on groups. Urinary tract infections were more common in the sequential groups than concurrent groups; genital infections were reported only with the sequential add-on of dapagliflozin to saxagliptin plus metformin. Hypoglycemia occurred in < 2% of patients across all groups.
- A network meta-analysis[66] compared the efficacy of adding a third AD in patients with T2D not well controlled (HbA1c > 7%) by dual therapy with metformin and sulfonylurea. The meta-analysis included only RCTs of at least 24 weeks' duration. The primary outcomes were a change in HbA1c, weight change, and severe hypoglycemia frequency. A total of 18 trials involving 4,535 participants, with a mean duration of 31 weeks, were included. Compared with placebo, drug classes did not differ regarding the effect on HbA1c level, with reductions ranging from -0.70% (95% CI -1.33% to -0.08%) to -1.08% (95% CI -1.41% to -0.77%). Weight gain was seen with IBT (2.84 kg, 95% CI 1.76 to 3.90 kg) and with thiazolidinediones (4.25 kg, 95% CI 2.76 to 5.66 kg), while weight loss was seen with GLP-1 RA (-1.63 kilograms, 95% CI -2.71 to -0.60 kg). IBT caused twice more severe hypoglycemic episodes than non-insulin ADs. No agent was superior to any other in terms of HbA1c.

R14. In treatment-naïve, asymptomatic adults with T2D, in whom HbA1c > 9%, metformin plus IBT SHOULD BE CONSIDERED to improve glycemic control.

IIa | A

Summary of evidence:

- A meta-analysis[67] comparing CV and metabolic outcomes in insulin-based vs. non-insulin-based glucose-lowering therapy included 18 RCTs (data from 19,300 patients). In 16 trials, insulin had superior efficacy in achieving glycemic control (HR 0.20, 95% CI 0.28 to 0.11) and was associated with superior reductions in HbA1c. Baseline HbA1c among all included studies ranged from 7.4 to 9.7%. There was no significant between-group difference in ACM or CV events risk. However, the risk of hypoglycemia was higher among patients receiving insulin (relative risk 1.90, 95% CI 1.44 to 2.51). Non-insulin treatment was associated with more ad-

verse drug reactions (54.7% vs. 45.3%, P = 0.044).

- Compared with oral ADs, early intensive insulin therapy in patients with newly diagnosed T2D is associated with a favorable impact on recovery and maintenance of β-cell function, as well as prolonged glycemic remission. A multicenter RCT[68] compared the effects of transient intensive insulin therapy (continuous subcutaneous insulin infusion [CSII] or multiple daily injections [MDI]) vs. oral antidiabetic agents on β-cell function and diabetes remission. A total of 382 treatment-naïve patients with recently diagnosed T2D were randomized to receive insulin or oral hypoglycemic agents for rapid initial correction of hyperglycemia. The mean HbA1c at baseline was 9.5–9.8%. Treatment was stopped once normoglycemia had been achieved and remained stable for two weeks; patients were then followed on a diet and exercise alone. Intravenous glucose tolerance tests were performed, and glucose, insulin, and proinsulin levels were measured. The primary endpoint was the duration of glycemic remission and remission rate at one year. More patients achieved target glycemic control in the insulin groups than those treated with oral ADs. In addition, the 1-year remission rate was significantly higher in the insulin groups (51.1% and 44.9% vs. 26.7% with oral ADs; P = 0.0012). β-cell function, assessed by the homeostasis model assessment of β-cell function (HOMA-β) and acute insulin response, also improved significantly after intensive therapy. The increase in acute insulin response was sustained in the insulin groups but considerably declined in the oral ADs group at one year in all patients who achieved remission.

Summary of evidence:

R15. In treatment-naïve, asymptomatic adults with T2D, in whom HbA1c > 9%, triple therapy including metformin and two other AD1 or AD SHOULD BE CONSIDERED to improve glycemic control.	
IIa	A

- See the summary of evidence in recommendation 13.

R16. In adults with T2D, HbA1c > 9%, and signs or symptoms of hyperglycemia (polyuria, polydipsia, weight loss), insulin-based therapy IS RECOMMENDED to improve glycemic control.	
I	C

Summary of evidence:

- This panel recommended using insulin-based therapy (IBT) in T2D patients with symptoms of hyperglycemia. There is general agreement that IBT is necessary when signs or symptoms of insulin deficiency are present. This statement is based primarily on the pathophysiology of T2D, plausibility, and clinical experience.

R17. In adults with T2D, obesity, and HbA1c > 9%, without severe signs or symptoms of hyperglycemia, a combination of basal insulin and GLP-1 RA therapy SHOULD BE CONSIDERED to improve glycemic control.	
IIa	A

Summary of evidence:

- A meta-analysis of RCTs[69] assessed the efficacy and safety of short and long-acting GLP-1 RA, both used in combination with basal insulin, in adults with T2D. A total of 14 RCTs were included. Eight trials examined short-acting and six long-acting GLP-1 RA. Differences in HbA1c, fasting plasma glucose, body weight, and adverse events were compared between studies using short-or long-acting GLP-1 RA. Long-acting GLP-1 RA was more effective in reducing HbA1c (Δ -6 mmol/mol, 95% CI -10 to -2, P = 0.007), fasting plasma glucose (Δ -0.7 mmol/L, 95% CI -1.2 to -0.3, P = 0.007), and body weight (Δ -1.4 kg, 95% CI -2.2 to -0.6, P = 0.002) and raised the proportion of patients achieving an HbA1c target < 7% (P = 0.03) more than the short-acting ones. Furthermore, patients reporting symptomatic (P = 0.048) but not severe (P = 0.96) hypoglycemia were fewer with long- vs. short-acting GLP-1 RA added to insulin. In addition, a lower proportion of patients reported nausea (-52%, P < 0.0001) or vomiting (-36%, P = 0.0002) with long-acting GLP-1 RA. GLP-1 RA improved HbA1c, fasting plasma glucose, and body weight when added to basal insulin. Long-acting GLP-1 RA, however, was significantly more effective for glycemic and body weight control and displayed better gastrointestinal tolerability.

Intensification

R18. In adults with T2D and without cardiorenal complications, whose HbA1c remains above target despite dual therapy, triple therapy IS RECOMMENDED to improve glycemic control.	
I	A

Summary of evidence:

- See the summary of evidence in recommendation 13.

R19. In adults with T2D without cardiovascular or renal complications, whose HbA1c remains above target despite triple therapy, quadruple therapy IS RECOMMENDED to improve glycemic control.	
I	C

Summary of evidence:

- Quadruple therapy was evaluated in an open-label observational trial[70] in patients with uncontrolled T2D (HbA1c 7.5–12%) despite three oral ADs. The objective was to address the effectiveness and safety of adding empagliflozin or glargine U100 as a fourth agent in patients already on metformin, DPP-4i, and glimepiride. A total of 268 patients were included: 142 on empagliflozin (25 mg/d) and 126 on glargine U100. After 24 weeks, HbA1c reduced from baseline by 1.5 ± 1.2% (P < 0.001) in the empagliflozin group and by 1.1 ± 1.8% (P < 0.001) in the glargine U100 group. Moreover, HbA1c and FPG were significantly reduced (HbA1c, P=0.004; FPG, P=0.008, respectively) in the empagliflozin group vs. the glargine U100 group. In addition, hypoglycemic adverse events were significantly higher in the glargine U100 group vs. the empagliflozin group (P=0.001). Therefore, quadruple therapy with SGLT2i, metformin, DPP-4i, and sulfonylurea was effective and safe for treating T2D.

- An open-label, prospective, 52-week study [71] was conducted in T2D to compare the effectiveness and safety of adding empagliflozin 25 mg/d or dapagliflozin ten mg/d as part of a quadruple therapy regimen for patients already on metformin, glimepiride, and DPP-4i, and still inadequately controlled (HbA1c 7.5–12%). The primary outcome was a change in HbA1c. In total, 350 patients were enrolled to receive empagliflozin (n = 176) or dapagliflozin (n = 174). After 52 weeks, both groups had significant reductions in HbA1c. The decline, however, was more important in the empagliflozin group (P < 0.001). Safety profiles were similar in the two groups, demonstrating that quadruple therapy can be used effectively in patients with T2D.

R20. In adults with T2D whose HbA1c remains above target despite quadruple therapy, adding insulin-based therapy IS RECOMMENDED to improve glycemic control.	
I	C

Summary of evidence:

- In a 26-week open-label trial[72], patients receiving GLP-1 RA therapy (liraglutide once daily or exenatide twice daily) plus metformin alone or metformin plus pioglitazone and a sulfonylurea were randomly assigned to receive insulin degludec plus liraglutide once daily (n = 292) or to continue GLP-1 RA therapy and oral ADs at the pre-trial dose (n = 146). At 26 weeks, superior HbA1c reductions had been achieved with the insulin degludec/liraglutide combination (ETD -0.94%, P < 0.001).

R21. In asymptomatic adults with T2D requiring IBT, a fixed-ratio co-formulation insulin/GLP-1 RA SHOULD BE CONSIDERED over basal insulin or basal-bolus insulin, whenever available, to improve glucose control.	
IIa	B

Summary of evidence:

- A preplanned subgroup analysis of a meta-analysis[73] included 6 RCTs (n = 4,213) comparing fixed-ratio co-formulation (FRC) insulin/GLP-1 RA vs. up-titration of basal insulin on metabolic control in adults with T2D. All trials had at least 24 weeks' duration of intervention, and, for the most, the control group was on glargine U100 or degludec. The FRC therapy led to a mean HbA1c decrease significantly greater than basal insulin up-titration (WMD -0.50%, 95% CI -0.67 to -0.33%, P < 0.001, I^2 91%), more patients at HbA1c target (relative risk [RR] 1.48, 95% CI 1.23 to 1.77, P < 0.001, I^2 92.3%), similar hypoglycemic events (RR 0.87, 95% CI 0.72 to 1.04, P = 0.114, I^2 72.9%), and weight reduction (WMD -2.0, 95% CI -2.6 to -1.4, P < 0.001, I^2 86%).
- A RCT[74] assessed the efficacy and safety of initiating FRC insulin degludec/liraglutide vs. basal-bolus insulin in adults with uncontrolled T2D under basal insulin and metformin. All participants were randomized to FRC or glargine U100 plus insulin aspart up to 4 times daily. The FRC elicited HbA1c reductions comparable to basal-bolus (ETD 0.02%, 95% CI -0.16 to 0.12); non-inferiority confirmed (P < 0.0001). The number of severe or confirmed symptomatic hypoglycemia events was lower with co-formulation vs. basal-bolus (risk ratio 0.39, 95% CI 0.29 to 0.51), and body weight decreased with co-formulation and increased with basal-bolus (ETD 23.6 kg, 95% CI 24.2 to 22.9). Total daily insulin dose was lower with co-formulation (40 units) than basal-bolus (40 units vs. 84 units total [52 units basal], respectively; ETD -44.5 units, 95% CI 248.3 to 240.7, P < 0.0001). By week 26, approximately 90% of patients on basal-bolus reported taking at least three insulin injections per day vs. the once-daily single injection with FRC.
- A retrospective analysis of an extensive database[75] compared outcomes in adults with T2D under basal insulin therapy who were newly initiated on FRC insulin glargine U100/lixisenatide or basal-bolus insulin therapy. Cohorts were propensity score–matched in a 1:1 ratio on baseline characteristics (n = 2,140; 1,070 individuals in each group). The primary endpoint was persistence with therapy at 12 months. Secondary endpoints included treatment adherence, hypoglycemia, and HbA1c change at 12 months. Treatment persistence was higher for FRC vs. basal-bolus (HR 0.51, 95% CI 0.46 to 0.57, adjusted P < 0.001). In addition, adherence was higher (adjusted OR 4.00, 95% CI 3.25 to 4.91) and hypoglycemic events were lower (adjusted RR 0.61, 95% CI 0.45 to 0.84) for FRC vs. basal-bolus. HbA1c reduction from baseline, however, was slightly more significant for basal-bolus insulin therapy (0.65 vs. 0.84%, least squares mean [LSM] 0.58 vs. 0.73%, LSM difference 0.15%, 95% CI 0.04 to 0.34).

Management of Antidiabetic Therapy in Adults With T2d and Atherosclerotic Cardiovascular Disease (ASCVD)

Figure 5 depicts the approach to managing antidiabetic therapy in adults with T2D and ASCVD.

R22. In adults with T2D with clinical ASCVD, SGLT2i or GLP-1 RA (AD1) ARE RECOMMENDED to reduce cardiovascular events and CV mortality.	
I	A

Summary of evidence:

- SGLT2i favorably affects CV events and CV mortality in high-risk adults with T2D. A meta-analysis[47] included data from 6 CVOTs of SGLT2i, comprising 46,969 unique patients with T2D and 31,116 (66.2%) with ASCVD. The primary outcomes were MACE and each one of its components (MI, stroke, or CV death). Overall, SGLT2i reduced the risk of MACE by 10% (HR 0.90, 95% CI 0.85 to 0.95), with no significant heterogeneity of associations with outcome. The presence or absence of ASCVD did not modify the association with outcomes for MACE (P for interaction = 0.10). Specifically, in patients with ASCVD, the HR was 0.89 (95% CI 0.84 to 0.95). There was also no difference between the subgroups with baseline HbA1c below or above 8.5% (P for interaction = 0.09). SGLT2i also reduced CV mortality by 15% (HR 0.85, 95% CI 0.78 to 0.93), without differences between patients with or without previous ASCVD (P for interaction = 0.44). Specifically, in patients with ASCVD, the HR was 0.83 (95% CI 0.76 to 0.92).
- GLP-1 RA reduces MACE, CV mortality, and ACM in high-risk patients with T2D. In a meta-analysis[48] including eight

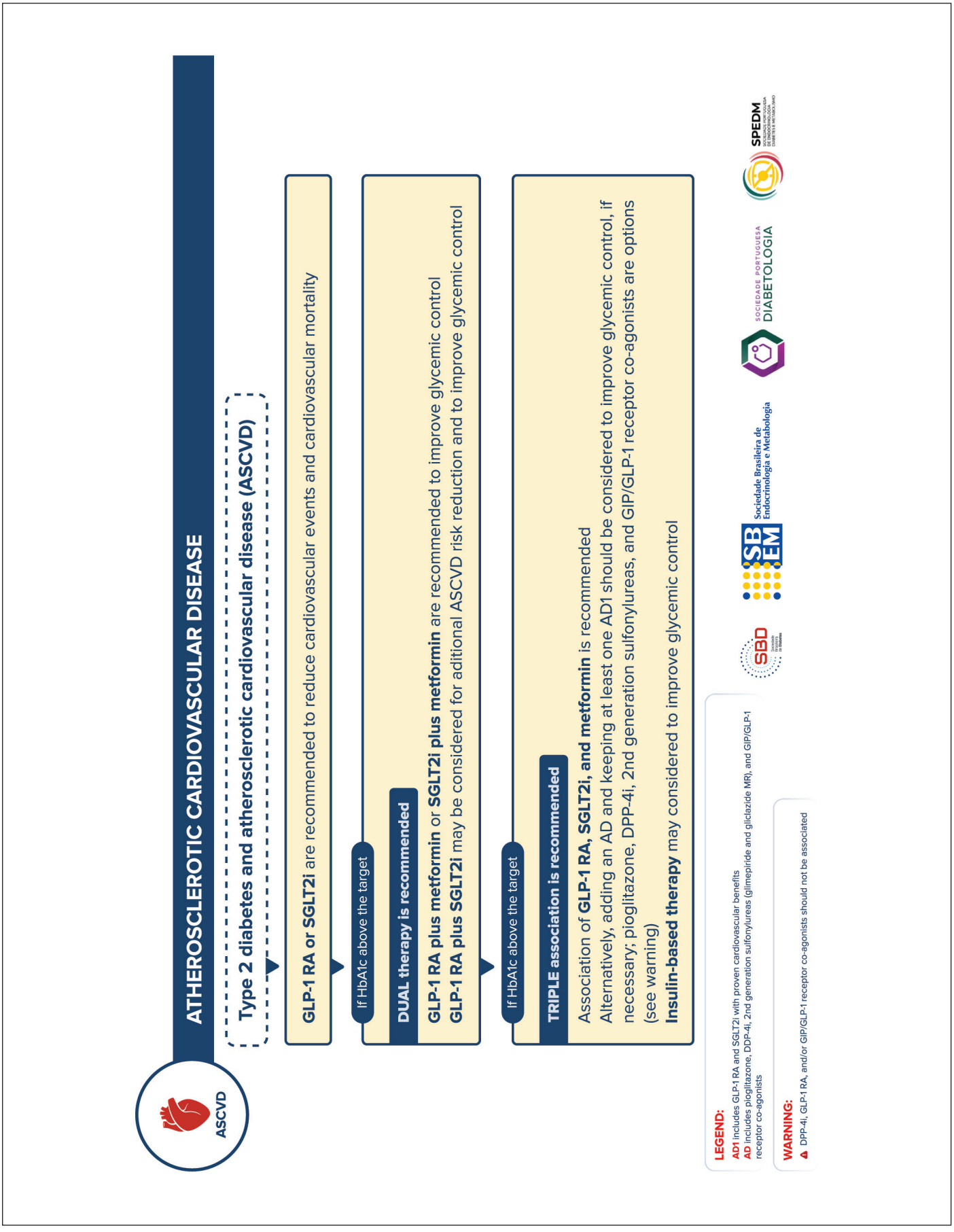


Figure 5. Management of antidiabetic therapy in adults with T2D and ASCVD.

trials, comprising data from 60,080 patients, GLP-1 RA reduced MACE by 14% (HR 0.86, 95% CI 0.80 to 0.93), with no significant heterogeneity between patients with or without ASCVD (P for interaction = 0.94) or HbA1c baseline values (P for interaction = 0.14). Specifically, in patients with ASCVD, the HR was 0.85 (95% CI 0.78 to 0.92). Overall, GLP-1 RA also reduced CV mortality by 13% (HR 0.87, 95% CI 0.80 to 0.94) and ACM by 12% (HR 0.88, 95% CI 0.82 to 0.94).

- In a meta-analysis[76] of 6 RCTs with SGLT2i (data from 51,743 participants), CV outcomes and mortality were stratified according to baseline metformin use, ranging from 21% to 82%. SGLT2i reduced the risk of MACE, with and without concomitant metformin use (HR 0.93, 95% CI 0.87 to 1.00 and HR 0.82, 95% CI 0.71 to 0.86, respectively; P for interaction = 0.14). Treatment with SGLT2i results in clear and consistent reductions in CV outcomes and mortality regardless of whether patients are receiving or not receiving metformin.
- Despite the lower risk of CV events in patients treated with canagliflozin[77] or injectable semaglutide[78] vs. placebo, it is essential to note that, in the CANVAS Program[77], patients treated with canagliflozin had a greater risk of amputation (HR 1.97, 95% CI 1.41 to 2.75), primarily at the level of the toe or metatarsal; in the SUSTAIN-6 trial[78], rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (HR 1.76, 95% CI 1.11 to 2.78, P = 0.02) in those who received injectable semaglutide. These adverse effects are new findings for which the mechanisms are unknown. Therefore, this panel recommended caution in using canagliflozin in patients at risk for amputation and injectable semaglutide in those with proliferative retinopathy.

R23. In adults with T2D and clinical ASCVD, who are in use of either SGLT2i or a GLP-1 RA, combining GLP-1 RA plus SGLT2i MAY BE CONSIDERED, as it is associated with fewer CV events and decreased all-cause mortality.

IIb | B

Summary of evidence:

- In a large, real-world observational study[79], 12,584 adults with T2D that received either SGLT2i or sulfonylureas to baseline GLP-1 RA were identified within 3 United States datasets. Subjects were 1:1 matched, using the propensity score, adjusting for baseline covariates. The composite CV endpoint included MI, stroke, and ACM. The adjusted pooled HR of SGLT2i initiators vs. sulfonylureas initiators was 0.76 (95% CI 0.59 to 0.98). This decrease in the primary outcome was driven by reductions in the risk of MI (HR 0.71, 95% CI 0.51 to 1.003) and ACM (HR 0.68, 95% CI 0.40 to 1.14) but not stroke (HR 1.05, 95% CI 0.62 to 1.79). In this cohort already on GLP-1 RA, the association with SGLT2i vs. sulfonylurea was associated with a more significant CV benefit.
- In an exploratory analysis of the AMPLITUDE-O trial[80], the effects of the GLP-1 RA efpeglenatide on MACE, expanded MACE, renal composite outcome, MACE, or death outcome, and hospitalizations for heart failure (hHF), as well as adverse events, appeared to be independent of concurrent SGLT2i use, as judged by point estimates in patients receiving compared with those not receiving baseline SGLT2i and lack of any formal interactions. These data support combined SGLT2i and GLP-1 RA therapy in T2D.
- To evaluate the effects of GLP-1 RA on CV outcomes in adults with T2D treated with or without SGLT2i, a study[81] included a post hoc analysis of the Harmony Outcomes trial, a CVOT of albiglutide by background SGLT2i use. In addition, a trial-level meta-analysis of the Harmony Outcomes trial and the AMPLITUDE-O trial (efpeglenatide) was performed, combining the treatment effect estimates according to SGLT2i use. The results evidenced that, in patients with T2D and CVD, GLP-1 RA reduced CV events independently of SGLT2i use (P for interaction = 0.7 for MACE in the post hoc analysis; the HRs for MACE in the meta-analysis were 0.78 [95% CI 0.49 to 1.24] with SGLT2i and 0.77 [95% CI 0.76 to 0.92] without SGLT2i, P for interaction = 0.95). These findings suggest that combining GLP-1 RA with SGLT2i may further reduce CV risk.

R24. In adults with T2D and clinical ASCVD, who either use SGLT2i or GLP-1 RA and HbA1c remains above the target, dual therapy with AD1 plus metformin IS RECOMMENDED to improve glycemic control.

I | A

Summary of evidence:

- This panel did not find studies that evaluate sequential therapy using metformin as an add-on baseline therapy with any AD1. Notwithstanding, there is evidence about using AD1 as an add-on baseline therapy with metformin. In a network meta-analysis[82], the change in HbA1c level in patients receiving metformin-based background therapy varied from -0.63% to -0.51% with SGLT2i and from -1.33% to -0.43% with GLP-1 RA.

R25. In adults with T2D and clinical ASCVD, who use SGLT2i or GLP-1 RA, and HbA1c is still above the target, dual therapy with 2 AD1 SHOULD BE CONSIDERED to improve glycemic control.

IIa | A

Summary of evidence:

- A systematic review and meta-analysis[83] of 7 RCTs (data from 1,913 patients, baseline HbA1c level 8-9.3%) compared the combination of GLP-1 RA plus SGLT2i vs. either agent alone to existing therapy. The combination therapy improved HbA1c (primary outcome) vs. GLP-1 RA (-0.61%, 95% CI -1.09 to -0.14) and SGLT2i (-0.85, 95% CI -1.19 to -0.52).

R26. In adults with T2D, clinical ASCVD and HbA1c above the target despite dual therapy, triple therapy with metformin and a combination of two AD1 (SGLT2i and GLP-1 RA) IS RECOMMENDED to improve glycemic control and further reduce cardiovascular events.

I | A

Summary of evidence:

- See the summaries of evidence for recommendations 23 and 25.

R27. In adults with T2D, ASCVD, and HbA1c above the target despite dual therapy, triple therapy including one AD (pioglitazone, second-generation sulfonylureas or DPP-4i) or IBT with at least one AD1 MAY BE CONSIDERED to improve glycemic control.

IIb | A

Summary of evidence:

- The efficacy and safety of DPP-4i and pioglitazone in improving hyperglycemia in patients with ASCVD are well established in the TECOS[84] (sitagliptin), SAVOR-TIMI 53[85] (saxagliptin), CARMELINA[86] (linagliptin), and PROactive[87] (pioglitazone) trials. In addition, the efficacy and safety of sulfonylureas in patients with ASCVD were confirmed in CAROLINA[55] (glimepiride) and TOSCA.IT[56] (glimepiride) and ADVANCE[57] (gliclazide MR), as well as in a meta-analysis of RCTs.
- A meta-analysis[88] and risk-benefit assessment of pioglitazone were conducted, including studies that compared pioglitazone with a control (antidiabetic agents without pioglitazone) in patients with either established CVD or high CV risk. The use of pioglitazone compared to a control group that did not use it resulted in a 14% and 23% significant reduction in odds of major adverse cardiac events (MACE: Mantel-Haenszel odds ratio [MH-OR] 0.86, 95% CI 0.75 to 0.98), and stroke (MH-OR 0.77, 95% CI 0.60 to 0.99), respectively. The number needed to treat (NNT) for the reduction in MACE and stroke was 80 and 151, respectively. Notwithstanding, pioglitazone significantly increased the odds of HF (MH-OR 1.47, 95% CI 1.26 to 1.71) and hHF (MH-OR 1.48, 95% CI 1.21 to 1.81). The number needed to harm (NNH) for HF and hHF were 34 and 44, respectively, making these findings clinically significant. The authors concluded that pioglitazone should only be reserved for treating high CV risk or established CVD.
- The CV safety profile and HF risk of vildagliptin were evaluated in a retrospective meta-analysis[89] of prospectively adjudicated CV events, including trials in high-risk patients with T2D. Patient-level data from 17,446 patients were pooled from 40 double-blind, randomized, controlled phase III and IV vildagliptin studies. The primary endpoint was the occurrence of MACE (MI, stroke, and CV death). Vildagliptin was not associated with an increased risk of adjudicated MACEs vs. comparators (Mantel-Haenszel risk ratio [MH-RR] 0.82, 95% CI 0.61 to 1.11). Moreover, there was no significant increased risk of HF events in vildagliptin-treated patients (MH-RR 1.08, 95% CI 0.68 to 1.70).

Management of Antidiabetic Therapy in Adults with T2d and Heart Failure (HF)

Figure 6 depicts the approach to managing antidiabetic therapy in adults with T2D and HF.

R28. In adults with T2D and HF, therapy with SGLT2i IS RECOMMENDED to reduce CV mortality and hHF and to improve glycemic control.

I | A

Summary of evidence:

- In a systematic review and meta-analysis[47] of 6 CVOTs of SGLT2i, including data from 46,969 patients with T2D, SGLT2i reduced the risk of CV death or hHF by 22% (HR 0.78, 95% CI 0.73 to 0.84), with a similar benefit in patients with and without HF history. In addition, SGLT2i reliably reduces the hospital admission rate for HF regardless of existing ASCVD or HF history.
- In a meta-analysis[90] of 5 RCTs including 21,947 participants with HF (with or without T2D), SGLT2i reduced the risk of composite CV death or hHF (HR 0.77, 95% CI 0.72 to 0.82), CV death (0.87, 95% CI 0.79 to 0.95), and ACM (0.92, 95% CI 0.86 to 0.99). These outcomes were consistent in trials of HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) and across all five trials.

R29. In adults with T2D and HF, whose HbA1c remains above target despite therapy with SGLT2i, dual therapy by adding metformin IS RECOMMENDED to improve glycemia control.

I | B

Summary of evidence:

- There are no RCTs evaluating the effects of metformin on glycemic control, specifically in patients with T2D and HF. Notwithstanding, observational evidence suggests that metformin is safe and associated with decreased mortality in patients with this profile.
- A 9-year prospective observational study[91] assessed the effect of starting metformin on the prognosis of patients with newly diagnosed HF and new-onset T2D. A total of 1,519 patients were enrolled; the mean age was 71 years, 53.8% were women, and 51.3% had preserved systolic function. Over a median follow-up of 57 months, 1,045 patients (68.8%) died, and 1,344 (88.5%) were hospitalized for decompensation of HF. There were no cases of lactic acidosis attributable to metformin use. Metformin was associated with decreased mortality (HR 0.85, 95% CI 0.82 to 0.88), driven by lower CV mortality (HR 0.78, 95% CI 0.74 to 0.82), as well as a lower hospitalization rate (HR 0.81, 95% CI 0.79 to 0.84).
- Metformin treatment in advanced HFrEF patients with T2D is associated with better outcomes by mechanisms beyond improving glycemic control. In a prospective observational study[92], propensity score-matched, including 847 stable patients with advanced HFrEF (67.7% New York Heart Association [NYHA] III/IV, left ventricular ejection fraction [LVEF] 23.6 ± 5.8%) followed for a median of 3.1 years, the subgroup of patients treated with metformin (22.9% of patients with T2D in the study) had better event-free survival even after adjustment for brain natriuretic peptide (BNP), BMI, and eGFR (HR 0.70, 95% CI 0.50 to 0.98, P = 0.035). No significant interaction was found between metformin therapy and NYHA functional class, LVEF, right ventricular dysfunction grade, BNP level, eGFR, renin-angiotensin-aldosterone system blockade, beta-blocker treatment, presence

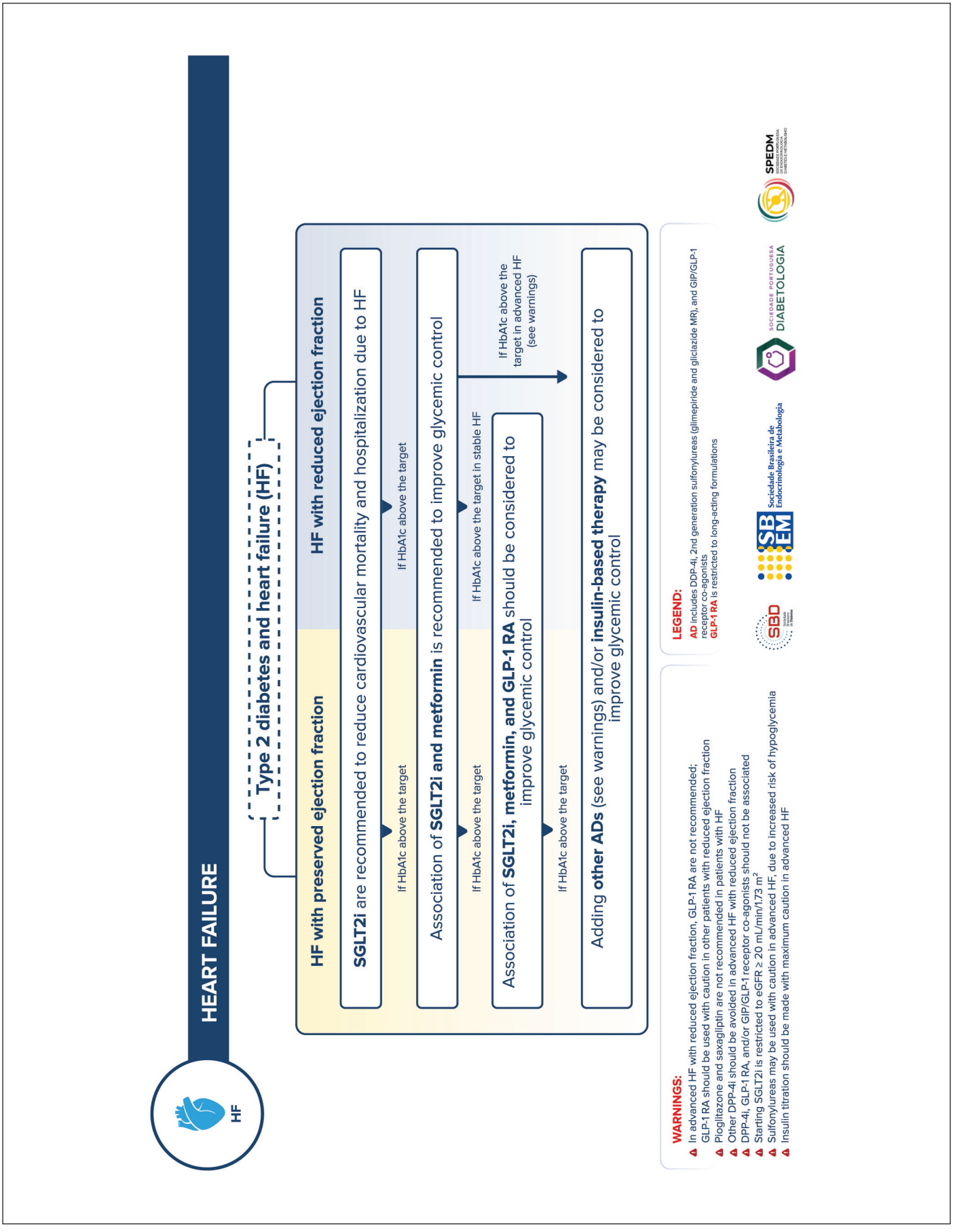


Figure 6. Management of antidiabetic therapy in adults with T2D and HF.

of implantable cardioverter/defibrillator, or cardiac resynchronization therapy (P for interaction ≥ 0.20).
- In an observational study[93] of 5,852 patients with HF, metformin prescription was independently associated with reduced risk of composite mortality/hHF at 12 months (HR 0.81, 95% CI 0.67 to 0.98, P = 0.03).

R30. In adults with T2D and heart failure with preserved ejection fraction (HFpEF) whose HbA1c remains above target despite dual therapy with metformin and SGLT2i, triple therapy by adding GLP-1 RA is safe and SHOULD BE CONSIDERED to improve glycemic control.

IIa | B

Summary of evidence:

- This panel did not find studies addressing the effect of GLP-1 RA on HF outcomes in T2D patients with HFpEF. Therefore, the following data refers to the impact of GLP-1 RA on HF-related outcomes in patients with T2D, with or without CVD.
- GLP-1 RA reduced the risk of hHF or CV death among patients without HF. In a meta-analysis[94] of 7 RCTs (data from 54,092 adults with T2D; 84% without HF, of whom 8,460 using GLP-1 RA), GLP-1 RA reduced the risk of hHF or CV death (HR 0.84, 95% CI 0.76 to 0.92) and ACM (HR 0.85, 95% CI 0.79 to 0.92).
- In a meta-analysis[95] of 7 CVOTs, including data from 56,004 adults with T2D, with or without established CVD, GLP-1 RA treatment reduced hospital admission for HF by 9% (0.91, 0.83 to 0.99; P = 0.028).
- To assess the impact of GLP-1 RA on HF or hHF in patients with T2D, a systematic review[96] included 21 RCTs (n = 18,270) and 4 observational studies (n = 111,029). In 20 RCTs, there was a lower incidence of HF with GLP-1 RA vs. control (OR 0.62, 95% CI 0.31 to 1.22). Three cohort studies evaluating GLP-1 RA vs. different comparators provided evidence that GLP-1 RA does not increase the incidence of HF. One RCT provided evidence that GLP-1 RA was not associated with hHF. The conclusion was that GLP-1 RA does not increase the risk of HF or hHF among people with T2D.

R31. In adults with T2D and HFpEF whose HbA1c remains above target despite dual therapy with metformin and SGLT2i, triple therapy by adding DPP-4i other than saxagliptin MAY BE CONSIDERED to improve glycemic control.

IIb | B

Summary of evidence:

- In a meta-analysis[97] of 4 CVOTs to assess the effects of DPP-4i on CV events (including studies with sitagliptin, alogliptin, saxagliptin, and linagliptin), the pooled analysis resulted in a neutral effect on MI, stroke, and the combination of MI plus stroke, CV death, and hHF. DPP-4i were neutral as far as all aspects of CV outcomes. Notably, in SAVOR-TIMI 53, saxagliptin increased the risk of hHF (see recommendation 36).
- The CV safety profile and HF risk of vildagliptin were evaluated in a retrospective meta-analysis[89] of prospectively adjudicated CV events, including trials in high-risk patients with T2D, such as those with congestive HF and moderate to severe renal impairment. Patient-level data from 17,446 patients were pooled from 40 double-blind, randomized, controlled phase III and IV vildagliptin studies. Assessments of the individual HF events (requiring hospitalization or new onset) were secondary endpoints. Confirmed HF events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients (RR 1.08, 95% CI 0.68 to 1.70).

R32. In adults with T2D, HFpEF, and HbA1c above target despite triple therapy (metformin, SGLT2i, and GLP-1 RA), adding IBT MAY BE CONSIDERED to improve glycemic control.

IIb | B

Summary of evidence:

- Although this panel did not find RCTs addressing the safety of insulin in patients with clinically established HF or at high risk of HF, there is an agreement that adding IBT may be considered a safe option to improve glycemic control whenever HbA1c target is not reached despite triple therapy, in patients with stable HF. This panel highlights, however, that close monitoring is advisable in patients with advanced HF.
- A sub-analysis of the ORIGIN trial[98] showed that glargine U100 has a neutral effect on both initial and recurrent hHF. The trial randomized 12,537 patients with prediabetes or diabetes at high CV risk to either glargine U100 or placebo. People with more severe HF (NYHA III/IV) were excluded. There were no differences between groups in hHF (HR 0.90, 95% CI 0.77 to 1.05) over the 2.5 years of follow-up.
- The ORIGINALE study[99] measured the post-trial effects of insulin glargine U100 for an additional 2.7 years. Of 12,537 randomized participants, post-trial data were analyzed for 4,718 allocated initially to insulin glargine U100 (2,351) vs. standard care (2,367). From randomization to the end of post-trial follow-up, no differences were found between groups in hHF (1,958 vs. 1,910 events; HR 1.03, CI 95% 0.97 to 1.10, P = 0.38).
- The DEVOTE trial[100] was a treat-to-target, double-blind CVOT in 7,637 adults with T2D and high CV risk, randomized to insulin degludec or glargine U100. The primary endpoint of this secondary analysis was time to the first hHF. Severe hypoglycemia was adjudicated. Overall, 372 (4.9%) patients experienced hHF (550 events). There was no significant difference in the risk of hHF between treatments (HR 0.88, 95% CI 0.72 to 1.08, P = 0.227). Prior HF was the strongest predictor of future hHF events (HR 4.89, 95% CI 3.9 to 6.4, P < 0.0001). In patients with T2D and high CV risk, there were no treatment differences in terms of hHF.

R33. In adults with T2D and stable HFrEF, in whom HbA1c is above target despite dual therapy, the association of GLP-1 RA MAY BE CONSIDERED to improve glycemic control.

IIb | B

Summary of evidence:

- A meta-analysis[94] of 7 RCTs included 54,092 patients with T2D (16% with HF history; n = 8,460). Among the subgroup of patients without HF, GLP-1 RA reduced the risk of hFH or CV death (HR 0.84, 95% CI 0.76 to 0.92) and ACM (HR

0.85, 95% CI 0.79 to 0.92). In addition, a reduction of ASCVD events was observed regardless of HF history. However, GLP-1 RA did not reduce the composite of hHF or CV death (HR 0.96, 95% CI 0.84 to 1.08) or ACM (HR 0.98, 95% CI 0.86 to 1.11) in the subgroup of patients with HF history.

R34. In advanced heart failure with reduced ejection fraction (HFrEF), GLP-1 RA is not recommended, due to possible increases in the risk of cardiac adverse events, including hHF and all-cause mortality.

III | B

Summary of evidence:

- In the FIGHT trial[101], which included 300 patients with advanced HFrEF (hospitalization in the last 14 days; 59% with T2D; median LVEF of 25%) followed for 180 days, treatment with liraglutide did not reduce the primary endpoint of a global rank score of time to death, time to re-hospitalization for HF, and time-averaged proportional change in NT-proBNP. In a post hoc analysis of the totality of events (first and recurring), there was a trend towards increased risk with liraglutide of total HF hospitalizations or ACM (96 vs. 143 events, incidence rate ratio [IRR] 1.41, 95% CI 0.98 to 2.04, P = 0.064) and total arrhythmias (21 vs. 39, IRR 1.76, 95% CI 0.92 to 3.37, P = 0.088). Actual prespecified events of interest were increased with liraglutide vs. placebo (196 vs. 295, IRR 1.43, 95% CI 1.06 to 1.92, P = 0.018). Total hHF or ACM risk with liraglutide was higher among NYHA III/IV (IRR 1.86, 95% CI 1.21 to 2.85) and patients with T2D.
- In the LIVE trial[102], which included 241 patients with stable HFrEF, liraglutide did not improve left ventricular systolic function. It was associated with increased heart rate and more cardiac severe adverse events (10% in patients treated with liraglutide vs. 3% in the placebo group, P = 0.04).
- In a posthoc analysis of the EXSCEL trial[103], exenatide significantly increased the risk of hHF in patients with an LVEF < 40% but not in those with LVEF ≥ 40%.
- A meta-analysis[104] of the FIGHT trial and the subgroup with LVEF < 40% in the EXSCEL trial showed that GLP-1 RA increased the risk of hHF in those with reduced ejection fraction (OR 1.49, 95% CI 1.05 to 2.10).

R35. In adults with T2D and HF, initiating sulfonylureas MAY BE CONSIDERED with care due to a possible increase in mortality risk and new hospitalization in patients with recent hospitalizations due to HF.

IIb | B

Summary of evidence:

- In an observational study[93] of 5,852 Medicare beneficiaries patients hospitalized for HF and not prescribed metformin or sulfonylurea before admission, sulfonylurea initiation within 90 days of discharge was associated with increased risk of mortality (HR 1.24, 95% CI 1.00 to 1.52, P = 0.045) and hHF (HR 1.22, 95% CI 1.00 to 1.48, P = 0.050) at 12 months, regardless of ejection fraction, as compared with patients not prescribed therapy.
- |An observational study[105] investigated if ACM was associated with sulfonylureas in patients with HF. Patients hospitalized for the first time due to HF, alive 30 days after discharge, on monotherapy with a specific type of sulfonylureas were followed for a mean of 744 days. There were 1097 patients on glimepiride; 1031 on glibenclamide (glyburide); 557 on glipizide; 251 on gliclazide; and 541 on tolbutamide. During the observation period, 2242 patients (64%) died. Compared to gliclazide, which was defined as the reference, the risk of death was similar among all types of sulfonylureas: glimepiride (HR 1.10, 95% CI 0.92 to 1.33), glibenclamide (HR 1.12, 95% CI 0.93 to 1.34), glipizide (HR 1.14, 95% CI 0.93 to 1.38), and tolbutamide (HR 1.04, 95% CI 0.85 to 1.26). Significant differences in mortality risk among sulfonylureas in patients with HF were unlikely.

R36. Saxagliptin and pioglitazone ARE NOT RECOMMENDED in patients with HF due to the increased risk of worsening HF.

III | B

Summary of evidence:

- In the SAVOR-TIMI 53 trial[85], T2D adults at risk of CV events (n = 16,492) were randomly assigned to receive saxagliptin or placebo and followed for a median of 2.1 years. The primary efficacy and safety endpoint was the classic MACE. There were more hHF in the saxagliptin group vs. the placebo group (3.5% vs. 2.8%; HR 1.27, 95% CI 1.07 to 1.51, P = 0.007). The NNH was 143, with HF occurring early in the first year of treatment. Patients with high NT-proBNP levels, CKD, or previous HF were at increased risk.
- A meta-analysis[88] and risk-benefit assessment of pioglitazone was conducted, including studies that compared pioglitazone with a control (antidiabetic agents without pioglitazone) in patients with either established CVD or having high CV risk. The use of pioglitazone compared to the control group resulted in a 14% and 23% significant reduction in odds of MACE (MH-OR 0.86, 95% CI 0.75 to 0.98) and stroke (MH-OR 0.77, 95% CI 0.60 to 0.99), respectively. The NNT for the reduction in MACE and stroke was 80 and 151, respectively. Notwithstanding, pioglitazone significantly increased the odds of HF (MH-OR 1.47, 95% CI 1.26 to 1.71) and hHF (MH-OR 1.48, 95% CI 1.21 to 1.81). The NNH for HF and hHF were 34 and 44, respectively, making these findings clinically significant. Therefore, the authors concluded that pioglitazone should be reserved for treating T2D with high CV risk or established CVD only in selected patients where other antidiabetics are precluded and not routinely.

Management of Antidiabetic Therapy in Adults with T2d and Kidney Disease (DKD)

Figure 7 depicts the approach to managing antidiabetic therapy in adults with T2D and DKD.

R37. In adults with T2D and eGFR ≥ 60 mL/min/1.73 m² plus albuminuria (≥ 200 mg/g) or eGFR 30–59 mL/min/1.73 m², dual therapy with SGLT2i plus metformin IS RECOMMENDED to attenuate long-term renal function loss, prevent end-stage renal disease, reduce mortality due to renal causes, and to improve glycemic control.

I | A

Summary of evidence:

- A systematic review and meta-analysis[106] of SGLT2i included

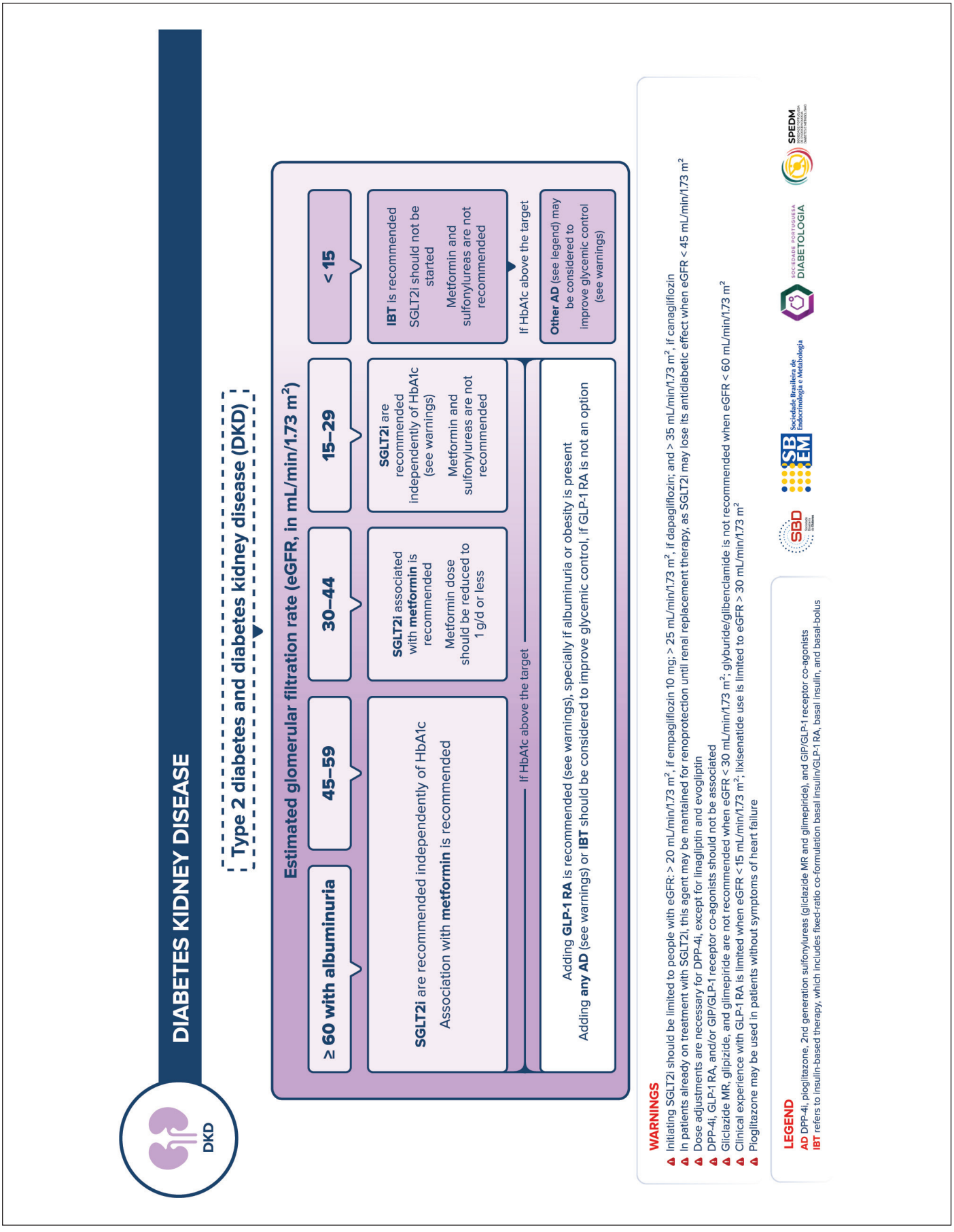


Figure 7. Management of antidiabetic therapy in adults with T2D and DKD.

13 trials, with at least six months of duration, involving 90,409 adults (82.7% with T2D). The primary efficacy outcome was kidney disease progression (sustained ≥ 50% decrease in eGFR from randomization, a sustained low eGFR, end-stage kidney disease [ESKD], or death from kidney failure). Mean baseline eGFR ranged from 37–85 mL/min/1.73 m². Compared with a placebo, allocation to an SGLT2i reduced the risk of kidney disease progression by 37% (RR 0.63, 95% CI 0.58 to 0.69), with similar RRs between patients with and without diabetes.

- A meta-analysis[107] of 27 studies (data from 7,363 adults with T2D and mild to moderate CKD treated with SGLT2i) demonstrate that, beyond HbA1c reduction (–0.29%, 95% CI –0.39 to –0.19), SGLT2i improve blood pressure, body weight, and albuminuria. Furthermore, SGLT2i attenuated the annual decline in eGFR slope (placebo-subtracted difference of 1.35 mL/min/1.73 m²/year, 95% CI 0.78 to 1.93) and reduced the risk of the composite renal outcome (HR 0.71, 95% CI 0.53 to 0.95). No other additional safety concerns when SGLT2i in individuals with CKD were observed.
- This panel considered that SGLT2i might be used along with metformin in patients with CKD (eGFR ≥ 30 mL/min/1.73 m²) to improve glycemic control. In the CREDENCE trial[108] (canagliflozin), 57.8% of the participants were on background therapy with metformin without interfering with renal benefits.
- A meta-analysis[76] of 6 RCTs of SGLT2i, enrolling 51,743 participants, reported kidney or mortality outcomes by baseline metformin use. Background metformin therapy varied from 21% in DAPA-HF to 82% in DECLARE-TIMI 58. The HRs for the composite effect of worsening kidney function, ESKD, or kidney death were 0.58 (95% CI 0.48 to 0.69) with metformin and 0.63 (95% CI 0.48 to 0.83) without metformin (P for interaction = 0.62).

R38. In adults with T2D and albuminuria 30-200 mg/g, SGLT2i IS RECOMMENDED to attenuate renal function loss, prevent ESRD, and reduce mortality due to renal causes.	
I	B

Summary of evidence:

- Subgroup analysis in a meta-analysis[109] of CV or kidney outcome trials of SGLT2i (data from 38,723 participants) reported effects on primary kidney outcomes (defined as substantial loss of kidney function, ESKD, or death due to kidney disease) in people with T2D according to the levels of albuminuria. The outcomes were stratified in subgroups according to baseline albuminuria categories: < 30 mg/g (RR 0.46, 95% CI 0.33 to 0.63, P = 0.0001); 30-300 mg/g (RR 0.69, 95% CI 0.47 to 1.00, P = 0.051), and > 300 mg/g (RR 0.52, 95% CI 0.38 to 0.69, P < 0.0001). Renoprotection was consistent across studies irrespective of baseline albuminuria (P for trend = 0.66).

R39. In adults with T2D and albuminuria, GLP-1 RA SHOULD BE CONSIDERED to attenuate the albuminuria progression and improve glycemic control.	
IIa	B

Summary of evidence:

- A systematic review and meta-analysis[110] compared the effect of GLP-1 RA and SGLT2i in kidney outcomes, including data from 8 trials (77,242 patients; 55.6% with GLP-1 RA and 44.4% with SGLT2i). GLP-1 RA reduced the risk of progression of kidney disease (HR 0.82, 95% CI 0.75 to 0.89, P < 0.001), which was exclusively dependent on albuminuria.

R40. Whenever HbA1c is above target despite dual therapy in T2D adults with eGFR ≥ 60 mL/min/1.73 m² plus albuminuria (≥ 200 mg/g) or with eGFR 30–59 mL/min/1.73 m², triple therapy with metformin, SGLT2i, and GLP-1 RA IS RECOMMENDED to reduce renal outcomes and to improve glycemic control.	
I	B

Summary of evidence:

- Sensitivity analysis of the REWIND trial[111] showed a reduced incidence of eGFR decline ≥ 40% and ≥ 50% (HR 0.70, 95% CI 0.57 to 0.85, P = 0.0004 and HR 0.56, 95% CI 0.41 to 0.76, P = 0.0002, respectively), thus supporting the hypothesis that dulaglutide may preserve kidney function. In this trial, 81% were on metformin, and 45% were on sulfonylurea.
- The AWARD-10[61], a 24-week phase 3b RCT, placebo-controlled, assessed the safety and efficacy of the addition of dulaglutide to the ongoing treatment regimen in patients whose T2D was inadequately controlled with SGLT2i, with or without metformin. A total of 424 patients were randomized to dulaglutide 1.5 mg (n = 142), dulaglutide 0.75 mg (n = 142), and placebo (n = 140). The reduction in HbA1c at 24 weeks was more significant in patients receiving dulaglutide vs. placebo (dulaglutide 1.5 mg: -1.34%, dulaglutide 0.75 mg: -1.21%, placebo: -0.54%; P < 0.0001 for both groups vs. placebo). Serious adverse events were reported for 5 (4%) participants in the dulaglutide 1.5 mg group, 3 (2%) in the dulaglutide 0.75 mg group, and 5 (4%) in the placebo group. Dulaglutide as an add-on treatment to SGLT2i, with or without metformin, resulted in significant and clinically relevant improvements in glycemic control, with acceptable tolerability consistent with dulaglutide's established safety profile.

R41. In adults with T2D, eGFR ≥ 60 mL/min/1.73 m² plus albuminuria (≥ 200 mg/g) or eGFR 30-59 mL/min/1.73 m² independently of albuminuria and HbA1c above target despite dual therapy, triple therapy with metformin, SGLT2i and an alternative AD (replacing GLP-1 RA) MAY BE CONSIDERED to improve glycemic control.	
IIb	A

Summary of evidence:

Adding DPP-4i:

- Linagliptin: The CARMELINA trial[86], a multicenter non-inferiority RCT, evaluated linagliptin vs. placebo in 6,979 adults with T2D and high CV and renal risks during a median follow-up of 2.2 years. Participants had either an eGFR between 45 and 75 mL/min/1.73 m² plus UACR > 200 mg/g or an eGFR between 15 and 45 mL/min/1.73 m² regardless of UACR. Around 40% of patients had dual therapy at baseline and received triple therapy. The mean eGFR was 54.6 mL/min/1.73 m², and most patients had eGFR between 30 and 60 mL/min/1.73 m². The primary outcome (MACE) was similar

in both groups (HR 1.02, 95% CI 0.89 to 1.17), indicating safety (P < 0.001), as was the renal outcomes (ESKD, death due to renal failure, or a sustained eGFR decline ≥ 40%; HR 1.04, 95% CI 0.89 to 1.22, P = 0.62). The rates of adverse events, serious adverse events, and adverse events leading to discontinuation were not different between linagliptin and placebo. Linagliptin is considered safe for renal failure.

- Sitagliptin: The safety of sitagliptin in adults with T2D and moderate to severe CKD (eGFR < 50 mL/min/1.73 m², including adults with ESKD on dialysis) was assessed in a 54-week, randomized, double-blind, parallel-group study[112]. Participants in the sitagliptin group (n = 65) and placebo group (n = 26) had baseline HbA1c between 6.5 and 10%. At 54 weeks, patients continuously treated with sitagliptin had a mean change from baseline in HbA1c of -0.7% (95% CI -0.9 to -0.4).
- The COMPOSIT-R trial[113] included 614 T2D adults with CKD (eGFR 60–90 mL/min/1.73 m²) and HbA1c of 7-9.5%, who were on metformin alone or metformin plus sulfonylurea. Participants were randomized to sitagliptin or dapagliflozin. The mean eGFR at baseline was 79.4 ± 11.3 mL/min/1.73 m². Around 30% of patients were on dual therapy. After 24 weeks, the change in HbA1c from baseline was more remarkable with sitagliptin (-0.51%, 95% CI -0.60 to -0.43) than dapagliflozin (-0.36%, 95% CI -0.45 to -0.27); the difference was -0.15% (95% CI -0.26 to -0.04) to sitagliptin vs. dapagliflozin (P = 0.006). Overall, adverse events were similar between groups. No serious adverse events or deaths were reported with triple therapy.

Adding pioglitazone:

- A meta-analysis[114] evaluated the efficacy and safety of thiazolidinediones, including pioglitazone and rosiglitazone, in treating T2D patients with renal impairment. Nineteen RCTs were included, covering 1,818 participants, with a mean age ranging from 43.4 to 71.1 years, mean baseline HbA1c of 6.9 to 9.2%, and mean follow-up of 24 weeks. Of the 19 RCTs, one trial (5.3%) enrolled patients who have undergone renal transplantation, five (26.3%) enrolled dialysis patients, and 13 (68.4%) included patients with mild to moderate renal impairment. Fourteen trials (73.7%) used pioglitazone as the intervention, four (21.1%) used rosiglitazone, and one (5.3%) used both. Thiazolidinediones were not associated with an increased risk of ACM (RR 0.40, 95% CI 0.08 to 2.01) and did not increase the risk of HF (RR 0.64, 95% CI 0.15 to 2.66, I^2 0%). Compared to the control, however, they significantly increased the risk of edema (RR 2.96, 95% CI 1.22 to 7.20).
- A small efficacy and tolerability trial[115] randomized 93 adults with T2D and CKD (eGFR < 60 mL/min/1.73 m² or albuminuria, of whom 30% were stage II, 32% were stage III, and 27% were stage IV) to pioglitazone 15 mg (standard-dose) or 7.5 mg (low-dose) for 24 weeks. The mean change in HbA1c did not differ between the standard-dose and low-dose groups (-1.1 ± 1.6 and -1.4 ± 1.5, P = 0.543, respectively). Standard-dose pioglitazone was associated with greater increases in body weight, fat mass, total body mass, total body water, and extracellular water compared to the low-dose regimen. Compared to patients in the low-dose group, those in the standard-dose group experienced significant, though modest, weight gain (3.5 ± 3.2 vs. 0.2 ± 4.4 kg; mean difference between groups 3.3 kg, 95% CI 1.3 to 5.2). No significant adverse effects (including hypoglycemia, congestive HF, and abnormal liver function) were identified. This study indicated that low-dose pioglitazone has similar efficacy while promoting less weight gain than standard-dose pioglitazone in patients with CKD.

Adding sulfonylureas:

- The safety of sulfonylureas was evaluated in the CAROLINA trial[55], a head-to-head, active-controlled, randomized trial that assessed the impact of linagliptin vs. glimepiride on CV outcomes in high-risk patients (many with CKD). The eGFR (mL/min/1.73 m²) was 30–59 in 19% and 15–29 in 0.4% of participants. The primary outcome was time to the first occurrence of a MACE event to establish the noninferiority of linagliptin vs. glimepiride. A primary outcome event occurred in 356 of 3,023 patients (11.8%) in the linagliptin group and 362 of 3,010 (12%) in the glimepiride group (HR 0.98, 95% CI 0.84 to 1.14; P < 0.001 for non-inferiority). Thus, linagliptin met the noninferiority criterion but not the superiority criterion (P = 0.76). The incidence of adverse events was similar in the linagliptin and glimepiride groups. Hypoglycemia, as expected, was increased in the glimepiride group: 10.6% in the linagliptin group and 37.7% in the glimepiride group (HR 0.23, 95% CI 0.21 to 0.26).

R42. In adults with T2D, eGFR ≥ 60 mL/min/1.73 m² plus albuminuria (≥ 200 mg/g) or eGFR 30-59 mL/min/1.73 m² independently of albuminuria and HbA1c above target despite triple therapy, quadruple therapy including metformin, SGLT2i, GLP-1 RA and a fourth AD or IBT MAY BE CONSIDERED to improve glycemic control.	
IIb	C

Summary of evidence:

- Although this panel did not find significant efficacy evidence for QUADRUPLE therapy in T2D patients with mild to moderate renal failure, it may be considered that this strategy is necessary to lower blood glucose in some patients. Furthermore, it is reasonably safe in stage 3 CKD (eGFR 30-60 mL/min/1.73 m²), when most agents can be used, provided that their dosages are adjusted when appropriate. Special attention is warranted with metformin, which should be replaced when the eGFR falls below 30 mL/min/1.73 m². Sulfonylureas also demand caution due to this population's increased risk of hypoglycemia.

R43. In adults with T2D, eGFR < 30 mL/min/1.73 m², and HbA1c mildly above target, either DPP-4i or GLP-1 RA (if eGFR 15–30 mL/min/1.73 m²) MAY BE CONSIDERED to improve glycemic control.	
IIb	B

Summary of evidence:

Adding DDP-4i:

- The DPP-4i class (sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and evogliptin) was also tested in small studies in T2D patients undergoing hemodialysis, and safety should be confirmed in larger studies.
- In a small trial[116], 64 patients with T2D were randomized to sitagliptin (in the reduced dosage of 25 mg/d) and 65 to glipizide 2.5 mg/d. There were 28 patients (43%) with eGFR

< 30 mL/min/1.73 m². After 54 weeks, the mean reduction in HbA1c level from baseline was 0.72% (95% CI 0.95% to 0.48%) in the sitagliptin group and 0.87% (95% CI 1.11% to 0.63%) in the glipizide group. The incidence of symptomatic hypoglycemia was 6.3% in the sitagliptin group vs. 10.8% in the glipizide group (difference 4.8%, 95% CI 15.7% to 5.6%). Severe hypoglycemia did not occur in the sitagliptin group vs. 7.7% in the glipizide group (difference 7.8%, 95% CI 17.1% to 1.9%). Sitagliptin monotherapy was effective and well tolerated in patients undergoing hemodialysis.

- In a multicenter RCT [117], adults with T2D, either drug-naive or not, who had inadequate glycemic control (HbA1c 6.5-10%) and an eGFR < 30 mL/min/1.73 m², were randomized to vildagliptin 50 mg/d (n = 83) or sitagliptin 25 mg/d (n = 65). After 24 weeks, the adjusted mean change in HbA1c was -0.54% from a baseline of 7.52% with vildagliptin and -0.56% from a baseline of 7.80% with sitagliptin (P = 0.874). Both agents were well tolerated, with overall similar safety profiles.
- In a small non-randomized safety trial[118], 16 patients with T2D undergoing hemodialysis received alogliptin 6.25 mg/d for two years. Baseline serum creatinine was 10.6 ± 1.0 mg/dL. Mean HbA1c dropped from 7.1 to 5.8% during the treatment. None of the patients exhibited significant adverse effects, such as hypoglycemia. However, one patient experienced a drug-related rash, and four withdrew from this study during treatment.
- The effects of monotherapy with linagliptin five mg/d in 21 adults with T2D undergoing hemodialysis was examined in a 6-month non-randomized trial[119]. Linagliptin was administered daily. Glycated albumin dropped from 21.3% ± 0.6% to 18% ± 0.6% over the 6-month treatment period, and body weight did not change. None of the patients experienced hypoglycemia.
- In a sub-analysis of the SAVOR-TIMI trial[120], adults with T2D at risk for CV events, randomized to saxagliptin or placebo, were stratified according to eGFR (mL/min/1.73 m²): > 50 (n = 13,916), 30-50 (n = 2,240), or < 30 (n = 336). After a median follow-up of 2 years, saxagliptin was like placebo for the primary outcome (MACE) and secondary composite outcomes, irrespective of renal function (all P for interactions ≥ 0.19). The relative risk of hHF with saxagliptin was similar (P for interaction = 0.43) in participants with eGFR > 50 (HR 1.23, 95% CI 0.99 to 1.55), eGFR 30-50 (HR 1.46, 95% CI 1.07 to 2.00), and eGFR < 30 (HR 0.94, 95% CI 0.52 to 1.71). In these CKD patients, the median HbA1c at one year was lower in saxagliptin-treated vs. placebo (7.1% vs. 7.7%, P = 0.002). At least one adverse event occurred in 152 (88%) saxagliptin-treated patients with renal impairment compared with 126 (77%) patients treated with placebo (P = 0.006), with no significant difference in severe adverse events.

Adding GLP-1 RA:

- Data for the use of GLP-1 RA in T2D with severe renal failure (< 30 mL/min/1.73 m²) are derived from subsets of more extensive trials that included a minimal number of patients, such as 2.5% in LEADER RENAL[121] (liraglutide), 2.5% in SUSTAIN-6[78] (injectable semaglutide), and 1% in REWIND RENAL[111] (dulaglutide). Thus, data on the safety of GLP-1 RA in this population is limited.

R44. In adults with T2D, eGFR < 30 mL/min/1.73 m², and HbA1c above target, IBT IS RECOMMENDED to improve glycemic control.	
I	B

Summary of evidence:

- Glargine U100 is safe and effective in T2D patients with severe renal failure, yielding rapid HbA1c reductions with a stable half-life and longer duration of action. In a small non-randomized study[122], 89 patients with T2D and CKD (mean eGFR 34.1 ± 11.5 mL/min/1.73 m²), who were poorly controlled or experienced frequent hypoglycemia on oral ADs or NPH insulin, were prescribed glargine U100 at bedtime. The dose started at 0.1 units/kg and was titrated to the target. At four months of follow-up, HbA1c had declined from 8.4% ± 1.6 to 7.7% ± 1.2 (P < 0.001). BMI was unaffected (P = 0.96). Mild symptomatic hypoglycemia was experienced by 12.5% of patients, and no other adverse events were reported.
- A small single-center retrospective observational study[123] evaluating adults with T2D and CKD using basal insulin for at least 24 weeks assessed the efficacy and safety of glargine U100 (n = 35) vs. degludec (n = 37). In advanced renal failure (stage 4 CKD), there was less hypoglycemia with degludec than glargine U100 (P = 0.009), indicating that degludec may be a safer option.

R45. In adults with T2D and eGFR < 30 mL/min/1.73 m², already on treatment with SGLT2i, it MAY BE CONSIDERED to continue the SGLT2i unless not tolerated or ESKD is initiated.	
IIb	C

Summary of evidence:

- In the EMPA-KIDNEY trial[124], patients with CKD (eGFR 20 to < 45 mL/min/1.73 m² or eGFR of 45-90 mL/min/1.73 m² and UACR ≥ 200 mg/g) were randomly assigned to receive empagliflozin ten mg/d or matching placebo (n = 6,609). The primary outcome was a composite of the progression of kidney disease. During a median of 2.0 years of follow-up, progression of kidney disease occurred in 13.1% in the empagliflozin group and 16.9% in the placebo group (HR 0.72, 95% CI 0.64 to 0.82, P < 0.001). Results were consistent across the subgroups defined according to eGFR ranges, including patients with eGFR < 30 mL/min/1.73 m².
- The KDIGO 2020 guideline[125] states that long-term benefits of SGLT2i regarding eGFR preservation are observed despite the initial decline and a reversible decrease after initiating SGLT2i. This is generally not an indication to discontinue therapy. In the CREDENCE trial[108], canagliflozin was continued among participants whose eGFR fell below 30 mL/min/1.73 m². Based on the CREDENCE protocol, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 mL/min/1.73 m² unless not tolerated or ESKD is initiated.

Conclusion

The management of antidiabetic therapy in people with T2D must consider aspects beyond glycemic control, requiring a more comprehensive approach, which should be patient-centered and consider the best evidence available. All individuals with T2D must have their CV risk status stratified, the renal function as-

sessed, and BMI and HbA1c determined before defining the use of antidiabetic agents. A personalized HbA1c target, usually < 7% for most adults with T2D, should be reassessed regularly, once every 12 weeks, in unstable situations, or at least once every 24 weeks, in patients meeting goals. Non-pharmacological approaches, such as nutritional intervention focusing on weight control, physical exercise, decreasing sitting time, improving sleep duration, stopping smoking, and stress management, are recommended during all phases of treatment, and the use of CGM should be considered, bearing in mind the cost-benefit ratio.

Metformin is the agent of choice in treatment-naïve adults recently diagnosed with T2D, without CVD or CKD, either in monotherapy or initial combination with AD1 or ADs, depending on the CV risk assessment, BMI, and HbA1c level. Notably, in adults with T2D at high or very high CV risk, AD1 is recommended for the reduction of CV events; if obesity is present, GLP-1 RA or GIP/GLP-1 receptor co-agonists (e.g., tirzepatide) should be considered, independently of HbA1c, for improving weight loss. In people whose HbA1c remains above target, dual, triple, and quadruple therapy, or IBT, should be considered to improve glycemic control. In asymptomatic adults with T2D requiring IBT, FRC insulin/GLP-1 RA should be considered (if available) over basal or basal-bolus insulin when available. Moreover, if HbA1c > 9% and severe signs or symptoms of hyperglycemia (polyuria, polydipsia, weight loss) are present, IBT must be the choice.

In adults with T2D with clinical ASCVD, AD1 is recommended to reduce CV events and CV mortality. Notwithstanding, if HbA1c remains above target, combining GLP-1 RA plus SGLT2i may be considered, followed by metformin, other ADs, or IBT to improve glycemic control. In adults with T2D and HF, therapy with SGLT2i is recommended to reduce CV mortality and hHF and to improve glycemic control, and if HbA1c remains above target despite treatment with SGLT2i, metformin is recommended, and other ADs or IBT may be considered, avoiding saxagliptin and pioglitazone. Furthermore, in advanced HFrEF, GLP-1 RA is not recommended due to the increased risk of serious cardiac adverse events, and initiating sulfonylureas is not recommended in adults with T2D and recent hHF due to the possible increased risk of mortality and new hospitalization.

In adults with T2D, DKD, and eGFR ≥ 30 mL/min/1.73 m², therapy with SGLT2i is recommended, significantly to improve renal outcomes; these cut-offs of eGFR may vary according to specific SGLT2i agent (20 mL/min/1.73 m², if empagliflozin 10 mg[124]; 25 mL/min/1.73 m², if dapagliflozin[126]; and 35 mL/min/1.73 m², if canagliflozin[108]). If HbA1c is above target, metformin is usually the second agent of choice, although GLP-1 RA should be considered if albuminuria is present to attenuate its progression and to improve glycemic control. Whenever HbA1c is above target despite dual therapy, triple therapy with metformin, SGLT2i, and GLP-1 RA is recommended to reduce renal outcomes and to improve glycemic control. Suppose eGFR < 30 mL/min/1.73 m², IBT is recommended, although either DPP-4i or GLP-1 RA (if eGFR 15–30 mL/min/1.73 m²) may be considered if HbA1c is mildly above target. In adults with T2D and eGFR < 30 mL/min/1.73 m², already on treatment with SGLT2i, it may be continued unless not tolerated or ESKD is initiated. These recommendations synthesize the best evidence for managing antidiabetic therapy in people with T2D.

Abbreviations

ACM: all-cause mortality
AD: antidiabetic drug
AD1: first-line antidiabetic drugs
ASCVD: atherosclerotic cardiovascular disease
BGM: blood glucose meter
BMI: body mass index
BNP: brain natriuretic peptide
CGM: continuous glucose monitoring
CI: confidence interval
CIT: conventional insulin injection therapy
CKD: chronic kidney disease
CSII: continuous subcutaneous insulin infusion
CV: cardiovascular
CVD: cardiovascular disease
CVOT: CV outcome trial
DKD: diabetes kidney disease
DPP-4i: dipeptidyl peptidase-4 inhibitors
DSME: diabetes self-management education
eGFR: estimated glomerular filtration rate
ESKD: end-stage kidney disease
ETD: Estimated treatment difference
FPG: fasting plasma glucose
FRC: fixed-ratio co-formulation
GIP: glucose-dependent insulinotropic polypeptide
GLP-1 RA: glucagon-like peptide-1 receptor agonists
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
HF: heart failure
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
hHF: hospitalization for heart failure
HOMA-β: homeostasis model assessment of β-cell function
HR: hazard ratios
IBT: insulin-based therapy
IRR: incidence rate ratio
isCGM: intermittently scanned continuous glucose monitoring
LSM: least squares mean
LVEF: left ventricular ejection fraction
MACE: major adverse cardiovascular events
MDI: multiple daily injections
MH-OR: Mantel-Haenszel odds ratio
MH-RR: Mantel-Haenszel risk ratio
MI: myocardial infarction
MIT: multiple insulin injections
NHANES: National Health and Nutrition Examination Survey
NNH: number needed to harm
NNT: number needed to treat
NYHA: New York Heart Association
OR: odds ratio
RCT: randomized clinical trial
RR: relative risk
SBD: Sociedade Brasileira de Diabetes
SBEM: Sociedade Brasileira de Endocrinologia e Metabologia
SC: subcutaneous
SGLT2i: sodium-glucose cotransporter-2 inhibitors
SPD: Sociedade Portuguesa de Diabetologia
SPEDM: Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo
T2D: type 2 diabetes mellitus
UACR: urine albumin-creatinine ratio

UK: United Kingdom
WMD: weighted mean difference

Acknowledgments/Agradecimentos

We thank Kariane Davidson for secretariat support during the study and Yuri Régis C. Moraes for designing the algorithms.

Note: This article was originally published as: Bertoluci MC, Silva Júnior WS, Valente F, Araujo LR, Lyra R, de Castro JJ, et al. 2023 UPDATE: Luso-Brazilian evidence-based guideline for the management of antidiabetic therapy in type 2 diabetes. Diabetol Metab Syndr. 2023;15:160. doi: 10.1186/s13098-023-01121-x.
Nota: Este artigo foi originalmente publicado como: Bertoluci MC, Silva Júnior WS, Valente F, Araujo LR, Lyra R, de Castro JJ, et al. 2023 UPDATE: Luso-Brazilian evidence-based guideline for the management of antidiabetic therapy in type 2 diabetes. Diabetol Metab Syndr. 2023;15:160. doi: 10.1186/s13098-023-01121-x.

Ethical Disclosures / Responsabilidades Éticas

Ethical approval: Not applicable.
Consent to participate: Not applicable.
Consent for publication: All authors approved for publication.
Availability of data and material: Not applicable.

Conflicts of Interest / Conflitos de Interesse

CL: No competing interests; **CLB:** No competing interests; **DACM:** No competing interests; **DC:** AstraZeneca, Bial, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Servier; **FRT:** Abbott, Aché, AstraZeneca, Boehringer Ingelheim, Eli Lilly do Brasil, Eurofarma, HAUX, Mantecorp, Merck, Novo Nordisk, Sanofi, Servier, Takeda; **FV:** Novo Nordisk, AstraZeneca, Boehringer-Lilly, Abbott; **HJF:** No competing interests; **JARS:** No competing interests; **JD:** Novo Nordisk, Lilly, LifeScan, Amgen, Abbott, AstraZeneca, Boehringer Ingelheim, Ascencia Diabetes Care, MSD; **JENS:** Abbott Nutrition, AstraZeneca, Bayer Boeringher-Ingelheim, Eli Lilly, Merck Serono, Novartis, Novo Nordisk, Servier, Takeda; **JFR:** No competing interests; **JJC:** Abbott Diagnostics, AstraZeneca, BIAL, Boehringer-Ingelheim, Lilly, Menarini Diagnostics, Menarini Pharma, Merck Serono, MSD, Novartis, Novo Nordisk, Recordatti, Sanofi, Takeda; **JRS:** No competing interests; **JSN:** Abbott, AstraZeneca, Bial, Boehringer Ingelheim, Eli Lilly & Company, Janssen Pharmaceuticals, Medinfar, Merck SA, MSD, Mundipharma, Novartis Pharmaceuticals, Novo Nordisk, Roche, Sanofi, Servier, Tecnimede; **JSN:** AstraZeneca, BIAL, Boehringer Ingelheim, Lilly, Medinfar, Merck, MSD, Novartis, Novo Nordisk, Sanofi; **LC:** No competing interests; **LEC:** Abbott, Medtronic, Novo Nordisk, Roche; **LRA:** No competing interests; **MCB:** AstraZeneca, Aché, Boehringer-Ingelheim, Bayer, Novo Nordisk, Lilly; **MINR:** No competing interests; **MM:** Abbott, AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Sanofi/Genzyme; **MM:** No competing interests; **MRC:** No competing interests; **MVBM:** Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Libbs, Lilly, Novartis, Novo Nordisk, Roche, Viatris; **PACM:** No competing interests; **PM:** AstraZeneca, Novo Nordisk; **RD:** No competing interests; **RLSF:** Aché, Boheringer, Lilly, Mantecorp, Bracepharma, Novo Nordisk, Merck Serono, Procter & Gamble; **AH:** Novo Nordisk; **RN:** No competing interests; **RNL:** No competing interests; **ROM:** AstraZeneca, Novo Nordisk, Servier, Merck, Eurofarma, Bayer; **WSSJ:** Abbott, AstraZeneca, Libbs, Mantecorp, Merck, Novo Nordisk, Servier, Torrent.

Declaração de Contribuição/ Contributorship Statement

MCB conceived the study, defined logistic strategies, described and voted the polls, reviewed literature, organized and wrote the main manuscript, and revised the final manuscript as well as the figures; **WSSJ** reviewed literature, wrote, revised, and managed the manuscript, designed figures, and voted in all polls; **FV** organized logistic used in the polls, reviewed the literature, revised the manuscript, and voted in all polls; **LRA, RLSF, JJC, JFR, PACM**, and **CLB** organized the working groups from each society and voted in all polls; **AH, RD, JENS**, and **JSN** organized the meeting at Lisbon to discuss the format of the initial part of the guideline and voted in all polls; **JD** and **MM** organized special presential meetings at Vila Moura-Portugal to promote discussions and voted in all polls; **JRS** contributed with suggestions and revision of the renal part of the manuscript; **JSN** contributed with suggestions, edit, and wrote the part of the manuscript regarding heart failure; **ROM** revised the manuscript and voted in all polls; **MVBN** contributed with suggestions and revised the section of the manuscript concerning the ischemic heart disease; **RNL, DACM, LC, LEC, MRC, HJF, RN, FRT, CBL, JARS, MINR, PM**, and **MM** voted in all polls and revised the manuscript; DC conceived the study, organized the Portugal group, contained the manuscript, wrote part of the manuscript related to renal disease, revised the manuscript, and voted in all polls.

Funding

Sociedade Brasileira de Diabetes supported publication costs.

References / Referências

1. Bertoluci MC, Salles JEN, Silva-Nunes J, Pedrosa HC, Moreira RO, da Silva Duarte RMC, et al. Portuguese-Brazilian evidence-based guideline on the management of hyperglycemia in type 2 diabetes mellitus. Diabetol Metab Syndr. 2020 May 24;12:45. Doi 10.1186/s13098-020-00551-1.
2. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006;368:29–36.
3. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med. 2011;171:404–10.
4. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113–32.
5. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20. doi: 10.1001/jama.2013.284427.
6. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation. 1996; 93:450–6.
7. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337. doi 10.1093/eurheartj/ehab484.
8. Li R, O'Sullivan MJ, Robinson J, Saford MM, Curb D, Johnson KC. Family history of myocardial infarction predicts incident coronary heart disease in postmenopausal women with diabetes: the Women's Health Initiative

Observational Study. Diabetes Metab Res Rev. 2009; 25:725–32.
9. Chronic Kidney Disease Prognosis Consortium; Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010 Jun 12;375(9731):2073-81. doi: 10.1016/S0140-6736(10)60674-5.
10. Gerstein HC, Ambrosius WT, Danis R, Ismail-Beigi F, Cushman W, Calles J, et al. Diabetic retinopathy, its progression, and incident cardiovascular events in the ACCORD trial. Diabetes Care. 2013; 36:1266–71.
11. Kramer CK, Rodrigues TC, Canani LH, Gross JL, Azevedo MJ. Diabetic retinopathy predicts all-cause mortality and cardiovascular events in type 1 and 2 diabetes: a meta-analysis of observational studies. Diabetes Care. 2011; 34:1238–44.
12. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010 Jul;33(7):1578-84. doi 10.2337/dc10-0125.
13. Kramer CK, Zinman B, Gross JL, Canani LH, Rodrigues TC, Azevedo MJ, et al. Coronary artery calcium score prediction of all-cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ. 2013 Mar 25;346:f1654. doi: 10.1136/bmj.f1654.
14. Akazawa S, Tojikubo M, Nakano Y, Nakamura S, Tamai H, Yonemoto K, et al. The usefulness of carotid plaque (sum and maximum of plaque thickness) in combination with intima-media thickness for detecting coronary artery disease in asymptomatic patients with diabetes. J Diabetes Investig. 2016;7:396–403.
15. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014 Feb;232(2):298-304. doi 10.1016/j.atherosclerosis.2013.09.025.
16. Li J, Luo Y, Xu Y, Yang J, Zheng L, Hasimu B, et al. Risk factors of peripheral arterial disease and relationship between low ankle—brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with type 2 diabetes. Circ J. 2007;71:377–81.
17. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. Br J Surg. 2002;89:714–30.
18. Glimaker H, Holmberg L, Elvin A, Nybacka O, Almgren B, Bjorck CG, et al. Natural history of patients with abdominal aortic aneurysm. Eur J Vasc Surg. 1991;5:125–30.
19. Semmens JB, Norman PE, Lawrence-Brown MM, Holman CD. Influence of gender on outcome from ruptured abdominal aortic aneurysm. Br J Surg. 2000;87:191–4.
20. Lederle FA, Johnson GR, Wilson SE, Aneurysm D. Management veterans affairs cooperative S. Abdominal aortic aneurysm in women. J Vasc Surg. 2001;34:122–6.
21. Bath MF, Gokani VJ, Sidlof DA, Jones LR, Choke E, Sayers RD, et al. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015;102:866–72.
22. Huelsmann M, Neuhold S, Strunk G, Moertl D, Berger R, Prager R, et al. NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. Eur Heart J. 2008 Sep;29(18):2259-64. doi: 10.1093/eurheartj/ehn334.
23. Malachias MVB, Jhund PS, Claggett BL, Wijkman MO, Bentley-Lewis R, Chaturvedi N, et al. NT-proBNP by itself predicts death and cardiovascular events in high-risk patients with type 2 diabetes mellitus. J Am Heart Assoc. 2020 Oct 20;9(19):e017462. doi: 10.1161/JAHA.120.017462.
24. Prausmüller S, Resl M, Arfsten H, Spinka G, Wurm R, Neuhold S, et al. Performance of the recommended ESC/EASD cardiovascular risk stratification model in comparison to SCORE and NT-proBNP as a single biomarker for risk prediction in type 2 diabetes mellitus. Cardiovasc Diabetol. 2021 Feb 2;20(1):34. doi: 10.1186/s12933-021-01221-w.
25. Pandey A, Vaduganathan M, Patel KV, Ayers C, Ballantyne CM, Kosiborod MN, et al. Biomarker-based risk prediction of incident heart failure in pre-diabetes and diabetes. JACC Heart Fail. 2021 Mar;9(3):215-223. doi: 10.1016/j.jchf.2020.10.013.
26. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021 Mar 1:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
27. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, et al. Heart failure: An underappreciated complication of diabetes. A Consensus Report of the American Diabetes Association. Diabetes Care. 2022 Jul 7;45(7):1670-1690. doi: 10.2337/dci22-0014.
28. Wijkman MO, Claggett BL, Malachias MVB, Vaduganathan M, Ballantyne CM, Kitzman DW, et al. Importance of NT-proBNP and conventional risk factors for prediction of death in older adults with and without diabetes mellitus - A report from the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Res Clin Pract. 2022 Dec;194:110164. doi: 10.1016/j.diabres.2022.110164.
29. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care. 2003 Jun;26(6):1895-901. doi: 10.2337/diacare.26.6.1895.
30. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010 Jun 26;375(9733):2215-22. doi: 10.1016/S0140-6736(10)60484-9.
31. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.
32. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000 Apr;23 Suppl 2:B21-9.
33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89. doi: 10.1056/NEJMoa0806470.
34. Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA1c Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88. Diabetes Care. 2021 Jul 7;44(10):2231–7. doi: 10.2337/dc20-2439.
35. Palta P, Huang ES, Kalyani RR, Golden SH, Yeh HC. Hemoglobin A1c and Mortality in Older Adults With and Without Diabetes: Results From the National Health and Nutrition Examination Surveys (1988-2011). Diabetes Care. 2017 Apr;40(4):453-460. doi: 10.2337/dci16-0042.
36. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care. 2011 Jun;34(6):1329-36. doi: 10.2337/dc10-2377.
37. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018 Jun;6(6):476-486. doi: 10.1016/S2213-8587(18)30048-2.
38. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019 May;7(5):344-355. doi: 10.1016/S2213-8587(19)30068-3.
39. Han H, Wang Y, Li T, Feng C, Kaliszewski C, Su Y, et al. Sleep duration and risks of incident cardiovascular disease and mortality among people with type 2 diabetes. Diabetes Care. 2023 Jan 1;46(1):101-110. doi: 10.2337/dc22-1127.
40. Bailey DP, Hewson DJ, Champion RB, Sayegh SM. Sitting time and risk of cardiovascular disease and diabetes: A systematic review and meta-analysis. Am J Prev Med. 2019 Sep;57(3):408-416. doi: 10.1016/j.amepre.2019.04.015.
41. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015 Jan 20;162(2):123-32. doi: 10.7326/M14-1651.
42. Evans M, Welsh Z, Seibold A. Reductions in HbA1c with flash glucose monitoring are sustained for up to 24 Months: A meta-analysis of 75 real-world observational studies. Diabetes Ther. 2022 Jun;13(6):1175-1185. doi: 10.1007/s13300-022-01253-9.
43. Martens T, Beck RW, Bailey R, Ruedy KJ, Calhoun P, Peters AL, et al. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: A randomized clinical trial. JAMA. 2021 June 8;325(22):2262-2272. doi: 10.1001/jama.2021.7444.
44. Aronson R, Brown RE, Chu L, Bajaj HS, Khandwala H, Abitbol A, et al. IMpact of flash glucose Monitoring in pEople with type 2 Diabetes Inadequately controlled with non-insulin Antihyperglycaemic ThErapy (IMMEDIATE): A randomized controlled trial. Diabetes Obes Metab. 2023 Apr;25(4):1024-1031. doi: 10.1111/dom.14949.
45. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective

Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.
46. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015 Nov;3(11):866-75. doi: 10.1016/S2213-8587(15)00291-0.
47. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 Inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. JAMA Cardiol. 2021 Feb 1;6(2):148-158. doi: 10.1001/jamacardio.2020.4511.
48. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021 Oct;9(10):653-662. doi: 10.1016/S2213-8587(21)00203-5.
49. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021 Mar 13;397(10278):971-984. doi: 10.1016/S0140-6736(21)00213-0.
50. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021 Jul 10;398(10295):143-155. doi: 10.1016/S0140-6736(21)01324-6.
51. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74. doi: 10.7326/0003-4819-159-4-201308200-00007.
52. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 Jan;32(1):84-90. doi: 10.2337/dc08-1355.
53. Liu X, Xiao Q, Zhang L, Yang Q, Liu X, Xu L, et al. The long-term efficacy and safety of DPP-IV inhibitors monotherapy and in combination with metformin in 18,980 patients with type-2 diabetes mellitus--a meta-analysis. Pharmacoepidemiol Drug Saf. 2014 Jul;23(7):687-98. doi: 10.1002/pds.3586.
54. Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004 Oct 25;164(19):2097-104. doi: 10.1001/archinte.164.19.2097.
55. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA Randomized Clinical Trial. JAMA. 2019 Sep 24;322(12):1155-1166. doi: 10.1001/jama.2019.13772.
56. Vaccaro O, Masulli M, Nicolucci A, Bonora E, Del Prato S, Maggioni AP, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol. 2017 Nov;5(11):887-897. doi: 10.1016/S2213-8587(17)30317-0.
57. ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72. doi: 10.1056/NEJMoa0802987.
58. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitão C, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. PLoS Med. 2016;13:e1001992 (eCollection 2016 Apr).
59. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest. 2004 Aug;34(8):535-42. doi: 10.1111/j.1365-2362.2004.01381.x.
60. Tang Y, Zhang L, Zeng Y, Wang X, Zhang M. Efficacy and safety of tirzepatide in patients with type 2 diabetes: A systematic review and meta-analysis. Front Pharmacol. 2022 Oct 28;13:1016639. doi: 10.3389/fphar.2022.1016639.
61. Ludvik B, Frías JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2018 May;6(5):370-381. doi: 10.1016/S2213-8587(18)30023-8.
62. Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2016 Dec;4(12):1004-1016. doi: 10.1016/S2213-8587(16)30267-4.
63. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015 Mar;38(3):384-93. doi: 10.2337/dc14-2364.
64. Abdul-Ghani MA, Puckett C, Triplitt C, Maggs D, Adams J, Cersosimo E, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab. 2015 Mar;17(3):268-75. doi: 10.1111/dom.12417.
65. Del Prato S, Rosenstock J, Garcia-Sanchez R, Iqbal N, Hansen L, Johnsson E, et al. Safety and tolerability of dapagliflozin, saxagliptin and metformin in combination: Post-hoc analysis of concomitant add-on versus sequential add-on to metformin and of triple versus dual therapy with metformin. Diabetes Obes Metab. 2018 Jun;20(6):1542-1546. doi: 10.1111/dom.13258.
66. Gross JL, Kramer CK, Leitão CB, Hawkins N, Viana LV, Schaan BD, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med. 2011 May 17;154(10):672-9. doi: 10.7326/0003-4819-154-10-201105170-00007.
67. Anyanwagu U, Mamza J, Donnelly R, Idris I. Comparison of cardiovascular and metabolic outcomes in people with type 2 diabetes on insulin versus non-insulin glucose-lowering therapies (GLTs): a systematic review and meta-analysis of clinical trials. Diabetes Res Clin Pract. 2016;121:69–85.
68. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet. 2008 May 24;371(9626):1753-60. doi: 10.1016/S0140-6736(08)60762-X.
69. Huthmacher JA, Meier JJ, Nauck MA. Efficacy and Safety of Short- and Long-Acting Glucagon-Like Peptide 1 Receptor Agonists on a Background of Basal Insulin in Type 2 Diabetes: A Meta-analysis. Diabetes Care. 2020 Sep;43(9):2303-2312. doi: 10.2337/dc20-0498. PMID: 32910778.
70. Ku EJ, Lee DH, Jeon HJ, Oh TK. Effectiveness and safety of empagliflozin-based quadruple therapy compared with insulin glargine-based therapy in patients with inadequately controlled type 2 diabetes: An observational study in clinical practice. Diabetes Obes Metab. 2019 Jan;21(1):173-177. doi: 10.1111/dom.13476.
71. Ku EJ, Lee DH, Jeon HJ, Oh TK. Empagliflozin versus dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin, glimepiride and dipeptidyl peptide 4 inhibitors: a 52-week prospective observational study. Diabetes Res Clin Pract. 2019;151:65–73.
72. Linjawi S, Bode BW, Chaykin LB, Courrèges JP, Handelsman Y, Lehmann LM, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial Diabetes Ther. 2017 Feb;8(1):101-114. doi: 10.1007/s13300-016-0218-3.
73. Maiorino MI, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Esposito K, et al. Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018 Sep;20(9):2309-2313. doi: 10.1111/dom.13343.
74. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in patients with type 2 diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial. Diabetes Care. 2018 May;41(5):1009-1016. doi: 10.2337/dc17-1114.
75. Pantalone KM, Heller C, Lajara R, Lew E, Li X, Dex T, et al. Initiation of iGlarLixi versus basal-bolus insulin in adults with type 2 diabetes advancing from basal insulin therapy: The SoliComplex real-world study. Diabetes Spectr. 2023;ds220064. doi: 10.2337/ds22-0064.
76. Neuen BL, Arnott C, Perkovic V, Figtree G, de Zeeuw D, Fulcher G, et al. Sodium-glucose co-transporter-2 inhibitors with and without metformin: A meta-analysis of cardiovascular, kidney and mortality outcomes. Diabetes Obes Metab. 2021 Feb;23(2):382-390. doi: 10.1111/dom.14226.
77. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu

N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925.
78. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in patients with type 2 diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844. doi: 10.1056/NEJMoa1607141.
79. Dave CV, Kim SC, Goldfine AB, Glynn RJ, Tong A, Patorno E. Risk of cardiovascular outcomes in patients with type 2 diabetes after addition of SGLT2 inhibitors versus sulfonylureas to baseline GLP-1RA therapy. Circulation. 2021 Feb 23;143(8):770-779. doi: 10.1161/CIRCULATIONAHA.120.047965.
80. Lam CSP, Ramasundarahettige C, Branch KRH, Sattar N, Rosenstock J, Pratley R, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. Circulation. 2022 Feb 22;145(8):565-574. doi: 10.1161/CIRCULATIONAHA.121.057934.
81. Neves JS, Borges-Canha M, Vasques-Nóvoa F, Green JB, Leiter LA, Granger CB, et al. GLP1 receptor agonist therapy with and without SGLT2 inhibitors in patients with type 2 diabetes. J Am Coll Cardiol—forthcoming 2023.
82. Tsapas A, Avgerinos I, Karagiannis T, Malandris K, Manolopoulos A, Andreadis P, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: A systematic review and network meta-analysis. Ann Intern Med. 2020 Aug 18;173(4):278-286. doi: 10.7326/M20-0864.
83. Tanner M. In type 2 diabetes, GLP-1 RA plus SGLT2 inhibitor vs. either drug alone reduces HbA1c and SBP and may reduce body weight. Ann Intern Med. 2020 Nov 17;173(10):JC52. doi: 10.7326/ACPJ202011170-052.
84. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42. doi: 10.1056/NEJMoa1501352.
85. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26. doi: 10.1056/NEJMoa1307684.
86. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019 Jan 1;321(1):69-79. doi: 10.1001/jama.2018.18269.
87. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89. doi: 10.1016/S0140-6736(05)67528-9.
88. Sinha B, Ghosal S. Assessing the need for pioglitazone in the treatment of patients with type 2 diabetes: a meta-analysis of its risks and benefits from prospective trials. Sci Rep. 2020 Sep 25;10(1):15781. doi: 10.1038/s41598-020-72967-8.
89. McInnes G, Evans M, Del Prato S, Stumvoll M, Schweizer A, Lukashevich V, et al. Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients. Diabetes Obes Metab. 2015 Nov;17(11):1085-92. doi: 10.1111/dom.12548.
90. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767. doi: 10.1016/S0140-6736(22)01429-5.
91. Romero SP, Andrey JL, Garcia-Egido A, Escobar MA, Perez V, Corzo R, et al. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community. Int J Cardiol. 2013 Jun 20;166(2):404-12. doi: 10.1016/j.ijcard.2011.10.141.
92. Benes J, Kotrc M, Kroupova K, Wohlfahrt P, Kovar J, Franekova J, et al. Metformin treatment is associated with improved outcome in patients with diabetes and advanced heart failure (HFrEF). Sci Rep. 2022 Jul 29;12(1):13038. doi: 10.1038/s41598-022-17327-4.
93. Khan MS, Solomon N, DeVore AD, Sharma A, Felker GM, Hernandez AF, et al. Clinical outcomes with metformin and sulfonylurea therapies among patients with heart failure and diabetes. JACC Heart Fail. 2022 Mar;10(3):198-210. doi: 10.1016/j.jchf.2021.11.001.
94. Ferreira JP, Saraiva F, Sharma A, Vasques-Nóvoa F, Angélico-Gonçalves A, Leite AR, et al. Glucagon-like peptide 1 receptor agonists in patients with type 2 diabetes with and without chronic heart failure: A meta-analysis of randomized placebo-controlled outcome trials. Diabetes Obes Metab. 2023 Feb 1. doi: 10.1111/dom.14997.
95. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785. doi: 10.1016/S2213-8587(19)30249-9.
96. Li L, Li S, Liu J, Deng K, Busse JW, Vandvik PO, et al. Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies. BMC Cardiovasc Disord. 2016 May 11;16:91. doi: 10.1186/s12872-016-0260-0.
97. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Diabetes Res Clin Pract. 2019 Apr;150:8-16. doi: 10.1016/j.diabres.2019.02.014.
98. Gerstein HC, Jung H, Rydén L, Diaz R, Gilbert RE, Yusuf S. Effect of basal insulin glargine on first and recurrent episodes of heart failure hospitalization: the ORIGIN trial (outcome reduction with initial glargine intervention). Circulation. 2018;137:88–90.
99. ORIGIN Trial Investigators. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). Diabetes Care. 2016;39:709–16.
100. Pratley RE, Husain M, Lingvay I, Pieber TR, Mark T, Saevereid HA, et al. Heart failure with insulin degludec versus glargine U100 in patients with type 2 diabetes at high risk of cardiovascular disease: DEVOTE 14. Cardiovasc Diabetol. 2019 Nov 15;18(1):156. doi: 10.1186/s12933-019-0960-8.
101. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: A randomized clinical trial. JAMA. 2016 Aug 2;316(5):500-8. doi: 10.1001/jama.2016.10260.
102. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017 Jan;19(1):69-77. doi: 10.1002/ejhf.657.
103. Fudim M, White J, Pagidipati NJ, Lokhnygina Y, Wainstein J, Murin J, et al. Effect of Once-Weekly Exenatide in Patients With Type 2 Diabetes Mellitus With and Without Heart Failure and Heart Failure-Related Outcomes: Insights From the EXSCEL Trial. Circulation. 2019 Nov 12;140(20):1613-1622. doi: 10.1161/CIRCULATIONAHA.119.041659.
104. Neves JS, Packer M, Ferreira JP. Increased risk of heart failure hospitalization with GLP-1 receptor agonists in patients with reduced ejection fraction: a meta-analysis of the EXSCEL and FIGHT trials. J Card Fail. 2023 Apr 5:S1071-9164(23)00110-0. doi: 10.1016/j.cardfail.2023.03.017.
105. Andersson C, Gislason GH, Jørgensen CH, Hansen PR, Vaag A, Sørensen R, et al. Comparable long-term mortality risk associated with individual sulfonylureas in diabetes patients with heart failure. Diabetes Res Clin Pract. 2011 Oct;94(1):119-25. doi: 10.1016/j.diabres.2011.07.011.
106. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801. doi: 10.1016/S0140-6736(22)02074-8.
107. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019 May;21(5):1237-1250. doi: 10.1111/dom.13648.
108. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744.
109. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854. doi: 10.1016/S2213-8587(19)30256-6.
110. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention

of major adverse cardiovascular and renal outcomes in type 2 Diabetes Mellitus. Circulation. 2019 Apr 23;139(17):2022-2031. doi: 10.1161/CIRCULATIONAHA.118.038868.
111. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):131-138. doi: 10.1016/S0140-6736(19)31150-X.
112. Chan JC, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab. 2008 Jul;10(7):545-55. doi: 10.1111/j.1463-1326.2008.00914.x.
113. Scott R, Morgan J, Zimmer Z, Lam RLH, O'Neill EA, Kaufman KD, et al. A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: The CompoSIT-R study. Diabetes Obes Metab. 2018 Dec;20(12):2876-2884. doi: 10.1111/dom.13473.
114. Wang W, Zhou X, Kwong JSW, Li L, Li Y, Sun X. Efficacy and safety of thiazolidinediones in diabetes patients with renal impairment: a systematic review and meta-analysis. Sci Rep. 2017 May 11;7(1):1717. doi: 10.1038/s41598-017-01965-0.
115. Satirapoj B, Watanakijthavonkul K, Supasyndh O. Safety and efficacy of low dose pioglitazone compared with standard dose pioglitazone in type 2 diabetes with chronic kidney disease: A randomized controlled trial. PLoS One. 2018 Oct 31;13(10):e0206722. doi: 10.1371/journal.pone.0206722.
116. Arjona Ferreira JC, Corry D, Mogensen CE, Sloan L, Xu L, Golm GT, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013 Apr;61(4):579-87. doi: 10.1053/j.ajkd.2012.11.043.
117. Kothny W, Lukashevich V, Foley JE, Rendell MS, Schweizer A. Comparison of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment: a randomised clinical trial. Diabetologia. 2015 Sep;58(9):2020-6. doi: 10.1007/s00125-015-3655-z.
118. Nakamura Y, Inagaki M, Shimizu T, Fujita K, Inoue M, Gotoh H, et al. Long-term effects of alogliptin benzoate in hemodialysis patients with diabetes: a 2-year study. Nephron Clin Pract. 2013;123(1-2):46-51. doi: 10.1159/000351678.
119. Nakamura Y, Tsuji M, Hasegawa H, Kimura K, Fujita K, Inoue M, et al. Anti-inflammatory effects of linagliptin in hemodialysis patients with diabetes. Hemodial Int. 2014 Apr;18(2):433-42. doi: 10.1111/hdi.12127.
120. Udell JA, Bhatt DL, Braunwald E, Cavender MA, Mosenzon O, Steg PG, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. Diabetes Care. 2015 Apr;38(4):696-705. doi: 10.2337/dc14-1850.
121. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med. 2017 Aug 31;377(9):839-848. doi: 10.1056/NEJMoa1616011.
122. Niafar M, Nakhjavani M, Esteghamati A, Ziaee A, Jahed SA, Azmandian J, et al. Efficacy and safety of insulin glargine in type 2 diabetic patients with renal failure. J Diabetes Metab. 2012;3:189. doi: 10.4172/2155-6156.1000189.
123. Chaudhuri SR, Majumder A, Sanyal D. 1045-P: Basal insulins in advanced renal failure: time for a paradigm shift. Diabetes. 2020 Jun;69(Suppl 1):1045–P. doi: 10.2337/db20-1045-P.
124. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023 Jan 12;388(2):117-127. doi: 10.1056/NEJMoa2204233.
125. de Boer IH, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney Int. 2020 Oct;98(4):839-848. doi: 10.1016/j.kint.2020.06.024.
126. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. doi: 10.1056/NEJMoa2024816.

SPEDM

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Instruções aos Autores

Língua

O título, resumo e palavras-chave, se aplicável, devem ser apresentados em inglês e português.

Os manuscritos submetidos à Revista devem ser claramente escritos em português (de Portugal) e / ou inglês de nível razoável.

Copyright

Todos os artigos nesta revista são de Acesso Aberto e atendem aos requisitos das agências de financiamento ou instituições académicas. Relativamente à utilização por terceiros a Rev Port Endocrinol Diabetes Metab rege-se pelos termos da licença Creative Commons 'Atribuição – Uso Não-Comercial – Proibição de Realização de Obras Derivadas (by-nc-nd)'.

É da responsabilidade do autor obter permissão para reproduzir ilustrações, tabelas, etc. de outras publicações.

Após a aceitação de um artigo, os autores serão convidados a preencher um "Publishing Agreement". Será enviado um *e-mail* ao autor correspondente, confirmando a recepção do manuscrito juntamente com um formulário de *Publishing Agreement* ou um *link* para a versão *online* desse contrato.

Auto-Arquivo

Os autores ficam autorizados a disponibilizar os seus artigos em repositórios das suas instituições de origem, desde que mencionem sempre onde foram publicados e de acordo com a licença Creative Commons.

Taxa de Processamento do Artigo

Não há taxa de processamento de artigo.

Conduta Ética e Direitos Humanos e Animais

Os autores devem assegurar que o estudo que submetem para publicação está em conformidade com os princípios éticos e legais, quer no decurso da investigação quer na publicação, nomeadamente com as recomendações da Declaração de Helsínquia revistas em 2013 da Associação Médica Mundial (http://www.wma.net/en/20activities/10ethics/10helsinki), do ICMJE (http://www.icmje.org) e do Committee on Publication Ethics (COPE) (http://publicationethics. org/resources/guidelines). Nos casos adequados, os autores devem demonstrar que a investigação foi aprovada pela comissão de ética das instituições envolvidas e que as recomendações foram seguidas. Esta informação deve constar no texto do artigo. Qualquer suspeita de má conduta será investigada e denunciada. Não se devem apresentar imagens, nomes, números de processos clínicos que permitam a identificação das pessoas em estudo. Os estudos que envolvam experiências em animais devem ser conduzidos em conformidade com as *guidelines* definidas no "Guide for the care and use of laboratory animals" dos National Institutes of Health. Todos os estudos em animais deverão igualmente obedecer às guidelines ARRIVE (*Animal Research: Reporting of In Vivo Experiments*). Os autores deverão ainda consultar a legislação vigente a nível nacional que regula este tipo de estudos (Decreto Lei nº 113/2013 de 7/08/2013). Deve ser claramente explicitado no manuscrito que as *guidelines* acima referidas foram seguidas.

Privacidade e Consentimento Informado

Estudos em doentes ou voluntários requerem aprovação da comissão de ética e consentimento informado, o que deve ser documentado no artigo.

Os autores são responsáveis por obter o consentimento informado relativamente a cada indivíduo presente em fotografias, vídeos, descrições detalhadas, mesmo após tentativa de ocultar a respectiva identidade. Nomes, iniciais ou outras formas de identificação devem ser removidos das fotografias ou outras imagens. Devem ser omitidos dados pessoais, como profissão ou residência, excepto quando sejam epidemiologicamente relevantes para o trabalho. Os autores devem assegurar que não apresentam dados que permitam identificação inequívoca ou, caso isso não seja possível, devem obter o consentimento informado dos intervenientes (ou, quando aplicável, o parente mais próximo).

Permissões

Todo material previamente publicado e protegido por direitos autorais, incluindo ilustrações, figuras e tabelas, deve ser acompanhado de permissão escrita para reprodução dos detentores dos direitos autorais.

Conflito de Interesse e Fontes de Financiamento

Devem ser referidas todas as fontes de financiamento ao estudo descrito e a sua influência na concepção do manuscrito ou na decisão de submissão para publicação. O rigor e a exactidão dos conteúdos, assim como as opiniões expressas são da exclusiva responsabilidade dos autores.

Os autores são obrigados a divulgar todas as relações financeiras e pessoais que possam enviesar o trabalho. Para prevenir ambiguidade, os autores têm que explicitamente mencionar se existe ou não conflitos de interesse. Todos os autores devem completar e submeter o modelo de Declaração de Conflitos de Interesse (ICMJE *Form for Disclosure of Potential Conflicts of Interest*), disponível em: http://www.icmje.org/conflictsof-interest. Essa informação será mantida confidencial durante a revisão do manuscrito pelos revisores e não influenciará a decisão editorial, mas será publicada se o artigo for aceite. Se não existirem conflitos, os autores devem mencionar esse facto

Resultados de Ensaios Clínicos

A Rev Port Endocrinol Diabetes Metab apoia iniciativas que contribuam para uma melhor divulgação de resultados ensaios clínicos. Estas incluem o registo prospectivo de ensaios clínicos em bases de dados públicas adequadas. De acordo com as recomendações do ICMJE, a Rev Port Endocrinol Diabetes Metab exige o registo de todos os ensaios clínicos cujos dados sejam incluídos em trabalhos submetidos para publicação nesta revista.

O ICMJE adopta a definição da Organização Mundial de Saúde de ensaio clínico, que é "qualquer estudo de investigação que prospectivamente atribua a participantes humanos, individualmente ou em grupo, uma ou mais intervenções relacionadas com a saúde, com o objectivo de avaliar os seus resultados relacionados com a saúde". Esta definição inclui ensaios das fases I a IV. O ICMJE define intervenções relacionadas com a saúde como "qualquer intervenção usada para modificar um resultado biomédico ou relacionado com a saúde" e resultados relacionados com a saúde como "qualquer medida biomédica ou relacionada com a saúde obtida em doentes ou participantes".

Registo de Ensaios Clínicos

O registo numa base de dados pública de ensaios clínicos é condição necessária para a publicação de dados de ensaios clínicos na Rev Port Endocrinol Diabetes Metab, de acordo com as recomendações do International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org). Os ensaios devem ser registados anteriormente ou no início do período de recrutamento de doentes. Um ensaio clínico é definido como qualquer estudo de investigação que prospectivamente atribua a participantes humanos, individualmente ou em grupo, uma ou mais intervenções relacionadas com a saúde, com o objectivo de avaliar os seus resultados relacionados com a saúde. As intervenções relacionadas com a saúde incluem qualquer intervenção usada para modificar um resultado biomédico ou relacionado com a saúde (por exemplo, fármacos, procedimentos cirúrgicos, dispositivos médicos, tratamentos comportamentais, intervenções nutricionais e alterações do processo de prestação de cuidados). Os resultados relacionados com a saúde incluem qualquer medida biomédica ou relacionada com a saúde obtida em doentes ou participantes, incluindo medidas farmacocinéticas e eventos adversos. Os estudos puramente observacionais (aqueles em que a atribuição de uma intervenção médica não é do critério do investigador) não exigem registo.

O número de registo do ensaio clínico (TRN) bem como a data desse registo devem ser referidos no final do resumo do artigo.

Disponibilização dos Dados

A Rev Port Endocrinol Diabetes Metab sugere fortemente que todos os conjuntos de dados nos quais se baseiam as conclusões de um artigo sejam disponibilizados para os leitores. Sugere-se assim aos autores que assegurem que os seus dados ficam disponíveis em repositórios públicos (sempre que estes estejam disponíveis e sejam adequados), que sejam apresentados no manuscrito principal ou em arquivos adicionais, sempre que possível em formato tratável (por exemplo, em folha de cálculo e não em pdf).

A Rev Port Endocrinol Diabetes Metab exige uma declaração de disponibilização dos dados, presente no final de cada manuscrito. Para ensaios de fármacos ou dispositivos médicos, a declaração deve referir, pelo menos, que os dados relevantes de cada doente, devidamente anonimizados, estão disponíveis mediante pedido justificado aos autores.

Sugerem-se formulações para a referida declaração:
"Disponibilização dos dados: os dados individuais dos doentes [e/ou] o conjunto completo de dados [e/ou] o anexo técnico [e/ou] as especificações da análise estatística, estão disponíveis em [/doi] [com acesso livre/com as restrições] [do autor correspondente em]. Os participantes deram o seu consentimento informado para disponibilização de dados [ou... não foi obtido consentimento dos participantes, mas os dados apresentados estão anonimizados e o risco de identificação é reduzido... ou não foi obtido consentimento dos participantes, mas os benefícios potenciais da disponibilização destes dados justificam os prejuízos potenciais, uma vez que ...]"

Se os dados não estiverem disponíveis, deve ser referido o seguinte: "Disponibilização dos dados: não estão disponíveis dados adicionais."

Esta opção não se aplica a ensaios clínicos de fármacos ou dispositivos médicos.

Pode ser solicitado aos autores que disponibilizem os dados brutos em que basearam o seu artigo durante o processo de revisão e até 10 anos após a publicação.

Submissão dos Trabalhos

A submissão de um manuscrito implica que o trabalho descrito não tenha sido publicado previamente (excepto na forma de um resumo ou como parte de uma palestra publicada ou de uma tese académica), e que não está sendo considerado para publicação em outra revista, que o manuscrito foi aprovado por todos os autores e, tácita ou explicitamente, pelas autoridades competentes onde o trabalho foi realizado e que, se for aceite para publicação, não será publicada em outro lugar na mesma forma, em inglês ou em qualquer outra língua, incluindo electronicamente.

Todos os manuscritos devem ser acompanhados por uma carta de apresentação. Deve ser dada garantia na carta de apresentação de que o manuscrito não está sob consideração simultânea por qualquer outra revista. Na carta de apresentação, os autores devem declarar seus potenciais conflitos de interesse e fornecer uma declaração sobre a autoria.

Para verificar a originalidade, o artigo pode ser verificado pelo serviço de detecção de originalidade.

As submissões que não estejam em conformidade com estas instruções podem ser devolvidas para reformulação e reenvio.

Submissão do Manuscrito

Submeta o seu manuscrito em: http://spedmjournal.com/

Contacto

Em caso de dúvidas durante a submissão, contacte:
scientific.landscape@gmail.com

Preparação do Manuscrito

Uso de programa de processamento de texto

É importante que o arquivo seja guardado no formato nativo do processador de texto usado. O texto deve estar no formato de coluna única. Mantenha o *layout* do texto o mais simples possível.

Para evitar erros desnecessários, aconselhamos o uso das funções "verificação ortográfica" e "verificação gramatical" do seu processador de texto.

Tipologia dos Artigos

A Rev Port Endocrinol Diabetes Metab aceita a seguinte tipologia:

a) Artigos originais reportando investigação clínica ou básica;
b) Artigos de revisão (incluindo sistemáticas revisões e meta-análises);
c) Estudos de Caso/Casos Clínicos;
d) Imagens em Endocrinologia;
e) Editoriais, que são escritos a convite do Editor-Chefe e consistem em comentários sobre artigos publicados na revista ou sobre temas de relevância particular;
f) Cartas ao Editor, que consistem em pareceres concisos sobre artigos recentemente;
g) Perspectivas

h) *Guidelines*.

Os autores devem indicar na carta de apresentação qual o tipo de manuscrito que está a ser submetido para publicação.

Na primeira página/ página de título:

I. Título

Título em português e inglês, conciso e descritivo, sem abreviaturas e não excedendo os 120 caracteres. O título pode incluir um complemento de título com um máximo de 40 caracteres (incluindo espaços).

II. Autores e afiliações

Na linha da autoria, liste o Nome de todos os Autores (primeiro e último nome) e respectiva afiliação (departamento, instituição, cidade, país).

III. Subsídio

Todos os subsídio(s) ou bolsa(s) que contribuíram para a realização do trabalho.

IV. Autor Correspondente

Indicar claramente quem vai lidar com a correspondência em todas as fases de arbitragem e publicação, também pós-publicação. Endereço postal e *e-mail* do Autor responsável pela correspondência relativa ao manuscrito.

V. Resumo e *Keywords*

Um resumo conciso e factual é requerido. Um resumo é frequentemente apresentado separadamente do artigo, por isso deve ser capaz de ficar sozinho.

Resumo escrito em português e inglês. Nenhuma informação que não conste no manuscrito pode ser mencionada no resumo. O resumo não pode remeter para o texto, não podendo conter citações nem referencias a figuras.

No fim do resumo devem ser incluídas um máximo de 5 *Keywords* em inglês utilizando a terminologia que consta no Medical Subject Headings (MeSH), http://www.nlm.nih.gov/mesh/MBrowser.html,

VI. Resumo Estruturado

Um resumo estruturado, com as etiquetas de secção apropriadas, deve fornecer o contexto e objectivo do estudo, procedimentos básicos (seleção dos sujeitos de estudo ou animais de laboratório, métodos observacionais e analíticos), principais resultados (significância estatística, se possível) e principais conclusões. Deve enfatizar aspectos novos e importantes do estudo ou das observações. Secções: Introdução, Métodos, Resultados e Conclusão.

VII. Os autores também incluirão nesta página de título, sob a designação "Considerações éticas" a declaração de "**Protecção de pessoas e animais"**, **Confidencialidade dos dados e consentimento informado e Conflitos de interesse.**

Prémios e Apresentações prévias

Devem ser referidos os prémios e apresentações do estudo, prévias à submissão do manuscrito

Texto

Artigos Originais

Os artigos originais devem incluir as seguintes secções: Introdução, Material e Métodos, Resultados, Discussão e Conclusão, Agradecimentos (se aplicável), Referências, Tabelas e Figuras.

Os artigos originais não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 60 referências. Um resumo estruturado com o máximo de 350 palavras.

Article structure

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced.

Article type	Abstract	Keywords	Main text structure	Max. words	Tables/figures	References
Original Article	Max. 350 words; structured (Introduction and Objectives, Methods, Results and Conclusion(s)) Portuguese and English	Up to 6 Portuguese and English	Introduction; Methods; Results; Discussion; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 60
Review Article	Max. 350 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 100
Systematic Review	Max. 350 words; structured Portuguese and English	Up to 6 Portuguese and English	PRISMA	4000	Total up to 6	Up to 100
Case Report	Max. 150 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; Case report; Discussion; Conclusion(s) (optional); References; and figure legends, if any	2000	Total up to 4	Up to 25
Images in Endocrinology	None	Up to 6 Portuguese and English	Unstructured	500	Total up to 4	Up to 5
Editorial	None	None	Unstructured	1500	Total up to 2	Up to 20
Letter to the Editor	None	Up to 6 Portuguese and English	Unstructured	600	Total up to 1	Up to 10
Current Perspectives	None	Up to 6 Portuguese and English	Unstructured	1200	Total up to 2	Up to 10

Methods already published should be indicated by a reference: only relevant modifications should be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusion

The main conclusion of the study may be presented in a short Conclusion section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Artigos de Revisão

Os artigos de revisão são artigos abrangentes que sintetizam ideias antigas e sugerem novas. Abrangem áreas amplas. Podem ser de ciência clínica, investigação ou básica. Embora geralmente por convite do Editor-Chefe, ocasionalmente aceitamos artigos de revisão não solicitados sobre assuntos importantes ou sobre avanços recentes. Antes de submeter uma revisão, pedimos que envie ao Editor-Chefe um breve esboço (não mais de 500 palavras) indicando a importância e novidade do assunto, e por que está qualificado para escrevê-lo. Um convite para submissão não garante aceitação.

Os artigos de revisão não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Um resumo não estruturado com o máximo de 350 palavras.

Revisões Sistemáticas e Meta-Análises

As revisões sistemáticas podem ou não utilizar métodos estatísticos (meta-análises) para analisar e resumir os resultados dos estudos incluídos.

As Revisões Sistemáticas podem ser apresentadas no formato Introdução, Métodos, Resultados, Discussão. O assunto deve ser claramente definido. O objectivo de uma revisão sistemática deve ser produzir uma conclusão baseada em evidências. Nos Métodos devem fornecer uma indicação clara da estratégia de pesquisa da literatura, extracção de dados, classificação das evidências e análise. Deve ser seguida a normativa PRISMA (http://www.prisma-statement.org/).

O texto não deverá exceder 4000 palavras, excluindo um resumo estruturado (máximo de 350 palavras). Não poderá incluir mais de 10 referências, e até 6 tabelas ou figuras**.**

Caso Clínico

O relato de Casos Clínicos deve incluir as seguintes seções: Introdução, Caso Clínico e Discussão.

O texto não poderá exceder 2000 palavras, e não poderá exceder as 25 referências bibliográficas. Deve incluir um resumo não estruturado, que não exceda 150 palavras.

Deve ser seguida a normativa CARE (http://www.care-statement.org/).

Editoriais

Os Editoriais são da responsabilidade do grupo editorial ou solicitados por convite do Editor-Chefe e constituirão comentários sobre tópicos actuais ou comentários sobre artigos publicados na revista. Não devem exceder as 1200 palavras, um máximo de 20 referências bibliográficas e podem conter uma tabela e uma figura. Não têm resumo.

Cartas ao Editor

As cartas ao Editor consistem em comentários críticos sobre um artigo publicado na revista ou uma nota curta sobre um determinado tópico ou caso clínico. Cartas ao Editor não devem exceder 600 palavras e 10 referências e pode conter uma figura ou tabela. Não têm resumo.

Imagens em Endocrinologia

Esta secção destina-se à publicação de imagens clínicas, radiológicas, histológicas e cirúrgicas relacionadas com casos de endocrinologia, diabetes ou metabolismo.

O título não deve ter mais de oito palavras. Os autores devem ser no máximo quatro. As imagens devem ser de alta qualidade e valor educativo. São permitidas até 4 figuras**.** As legendas devem ser breves e informativas. Setas ou outros símbolos devem ser incluídos conforme necessário para facilitar a compreensão das imagens. O texto não deve exceder 500 palavras, até cinco referências, e deve incluir uma breve história clínica e dados relevantes do exame físico, testes laboratoriais e progressão clínica, conforme apropriado. Não têm resumo.

Perspectiva

Este é o tipo de manuscrito é submetido a convite do Conselho Editorial. Pode abranger uma ampla diversidade de temas relacionados com endocrinologia, diabetes, metabolismo e saúde: problemas atuais ou emergentes, políticas de gestão e saúde, história da medicina, questões de sociedade e epidemiologia, entre outros. Um Autor que deseje propor um manuscrito nesta seção deverá enviar um resumo ao Editor-Chefe, incluindo o título e a lista de autores para avaliação. O texto não deve exceder 1200 palavras, até 10 referências, e até 2 tabelas ou 2 figuras. Não têm resumo.

Guidelines

Os guias de prática clínica não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Resumo até 350 palavras.

Referências

I.Citação no texto

Certifique-se de que todas as referências citadas no texto também estão presentes na lista de referências (e vice-versa). As referências devem ser listadas usando algarismos árabes pela ordem em que são citados no texto.

As referências a comunicações pessoais e dados não publicados devem ser feitas diretamente no texto e não devem ser numeradas. Citação de uma referência como "in press" implica que o item tenha sido aceite para publicação. Os nomes das revistas devem ser abreviados de acordo com o estilo da Medline.

As referências a artigos publicados em revistas devem incluir o nome do primeiro autor seguido dos nomes dos restantes autores, o título do artigo, o nome da revista e o ano de publicação, volume e páginas.

Certifique-se de que os dados fornecidos nas referências estão corretos. Ao copiar referências, tenha cuidado porque já podem conter erros.

A lista de referências deve ser adicionada como parte do texto, nunca como uma nota de rodapé. Códigos específicos do programa de gestão de referências não são permitidos.

II. Formato

Uma descrição detalhada dos formatos de diferentes tipos de referência pode ser consultada em ICMJE *Recommendations* (http://www.icmje.org/recommendations/). Liste todos os autores se houver seis ou menos. *Et al* deve ser adicionado se houver mais de seis autores. Título do artigo, nome da revista, ano, volume e páginas.

III. Estilo de referência

Texto: Indicar as referências no texto por número (s) em expoente. Os autores podem ser referidos, mas o número de referência deve ser sempre dado.
Lista: Ordene as referências na lista pela ordem em que aparecem no texto
Exemplos:
Referência de artigo:

1. Isidori AM, Sbardella E, Zatelli MC, Boschetti M, Vitale G, Colao A, et al. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2015;100:3231-44.

Referência de livro:

2.Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 Health Survey: standard & acute forms. Lincoln: Quality Metric Incorporated; 2000.

Referência de capítulo de livro:

3. Castellano Barca G, Hidalgo Vicario M, Ortega Molina M. Transtorno del comportamento alimentário. In: Castellano Barca G, Hidalgo Vicario M, Redondo Romero A, editores. Medicina de la adolescência – atención integral. 2ª ed. Madrid: Ergon; 2004. p.415-29.

Referências Web:

4. No mínimo, o URL completo deve ser dado e a data em que o documento foi consultado. Qualquer outra informação, se conhecida (nomes de autor, datas, referência a uma publicação de origem, etc.), também deve ser dada.

Notas de Rodapé

As notas de rodapé devem ser evitadas. Quando imprescindíveis, devem ser numerados consecutivamente e aparecer ao pé da página apropriada.

Agradecimentos (facultativo)

Devem vir após o texto, e antes das referências, tendo como objectivo agradecer a todos os que contribuíram para o estudo mas que não têm peso de autoria. Nesta secção é possível agradecer a todas as fontes de apoio, quer financeiro, quer tecnológico ou de consultadoria, assim como contribuições individuais.

Abreviaturas

Não use abreviaturas ou acrónimos no título e no resumo e limite o seu uso. Abreviaturas não consagradas devem ser definidas na primeira utilização, por extenso, logo seguido pela abreviatura entre parenteses. A menos que a sigla seja uma unidade padrão de medição. Uso excessivo e desnecessário de acrónimos e abreviaturas deve ser evitado.

Unidades de Medida

Devem ser utilizadas as unidades Sistema Internacional de Unidades. As medidas de comprimento, altura, peso e volume devem ser expressas em unidades do sistema métrico (metro, quilograma ou litro) ou seus múltiplos decimais. As temperaturas devem ser dadas em graus Celsius (ºC) e a pressão arterial em milímetros de mercúrio (mm Hg) ou a hemoglobina em g/dL. Todas as medições hematológicas ou bioquímicas serão referidas no sistema métrico de acordo com o Sistema Internacional de Unidades (SI).

Nomes de Medicamentos

Identifique com precisão todos os medicamentos e produtos pelo nome genérico. Não é recomendável a utilização de nomes comerciais de fármacos (marca registrada), mas quando a utilização for imperativa, o nome do produto deverá vir após o nome genérico, entre parênteses, em minúscula, seguido do símbolo que caracteriza marca registada, em sobrescrito (®).

Tabelas e Figuras

Tabelas/Figuras devem ser numerados na ordem em que são citadas no texto e assinaladas em numeração árabe e com identificação, Figura/Tabela.

Cada figura e tabela incluídas no trabalho têm de ser referidas no texto: Uma resposta imunitária anormal pode estar na origem dos sintomas da doença (Fig. 2). Esta associa-se a outras duas lesões (Tabela 1).

Figura: Quando referida no texto é abreviada para Fig., enquanto Tabela não é abreviada. Nas legendas ambas as palavras são escritas por extenso.

Cada tabela e figura deve ser acompanhada da respectiva legenda, sucinta e clara. As legendas devem ser auto-explicativas (sem necessidade de recorrer ao texto).

Em relação aos gráficos deve ser explícito se a informação inclui valores individuais, médias ou medianas, se há representação do desvio padrão e intervalos de confiança e o tamanho da amostra (n).

As fotografias deverão incluir identificadores (setas e asteriscos). Poderão ser publicadas fotografias a cores, desde que consideradas essenciais.

Cada tabela deve ser utilizada para mostrar resultados, apresentando listas de dados individuais ou sumariando os mesmos, não devendo no entanto constituir duplicação dos resultados descritos no texto. Devem ser acompanhadas de um título curto mas claro e elucidativo. As unidades de medida usadas devem ser indicadas (em parêntesis abaixo do nome que encabeça cada categoria de valores) e os números expressos devem ser reduzidos às casas decimais com significado clínico.

Para as notas explicativas nas tabelas devem ser utilizados os seguintes símbolos e sequência: *, †, ‡, §, ||, ¶, **, ††, ‡‡ .

Se fotografias de doentes forem usadas, estes não devem ser identificáveis ou as fotografias devem ser acompanhadas de autorização por escrito para usá-las.

As imagens a cores são reproduzidas gratuitamente.

Princípios gerais:

• Numere as ilustrações de acordo com a sua sequência no texto.

• Forneça as legendas das ilustrações separadamente.

• Dimensione as ilustrações próximas das dimensões desejadas da versão publicada.

• Envie cada ilustração em ficheiro separado.

A inclusão de figuras e/ou tabelas já publicadas, implica a autorização do detentor de *copyright* (autor ou editor).

A submissão deve ser feita separadamente do texto, conforme as instruções da plataforma.

Os ficheiros das figuras devem ser fornecidos em alta resolução, 800 dpi mínimo para gráficos e 300 dpi mínimo para fotografias.

A publicação de ilustrações a cores é gratuita.

Material gráfico deve ser entregue em um dos seguintes formatos:
JPEG (. Jpg)
Portable Document Format (. Pdf)
PowerPoint (.ppt)
TIFF (. Tif)
Excel

Permissão para publicação: No caso de publicação de tabelas de livros ou revistas os autores são responsáveis por obter permissão, junto dos autores dos trabalhos de onde forem reproduzidos, para a referida publicação, e terão de a apresentar na submissão.

Ficheiros Multimedia

Os ficheiros multimedia devem ser enviados em ficheiro separado com o manuscrito. O material multimedia deve seguir os padrões de qualidade de produção para publicação sem a necessidade de qualquer modificação ou edição. Os ficheiros aceitáveis são: formatos MPEG, AVI ou QuickTime.

Anexos/ Apêndices

Quando necessário, os anexos devem ser utilizados para apresentar inquéritos longos ou detalhados, descrições de extensos cálculos matemáticos e / ou listas de itens. Devem ser colocados depois da lista de referências, se necessário, com legendas. Anexos longos, tais como algoritmos, pesquisas e protocolos, serão publicados apenas *online*; o URL será fornecido no artigo impresso onde o anexo é citado.

Se houver mais de um apêndice, eles devem ser identificados como A, B, etc. As fórmulas e equações em apêndices devem ser numeradas separadamente: Eq. (A.1), Eq. (A.2), etc.; Em apêndice posterior, a Eq. (B.1) e assim por diante. Da mesma forma para tabelas e figuras: Tabela A.1; FIG. A.1, etc.

Estilo

Rev Port Endocrinol Diabetes Metab segue AMA Manual Style (10ª edição).

Última revisão **Janeiro 2022**