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Editorial

Endocrinologia e Obesidade, Perspetivas Atuais e Esperança no Futuro

Endocrinology and Obesity, Current Perspectives and Hope for the Future

Paula Freitas [a]

[a] *Editor-chefe da Revista da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo*

Foi divulgado o primeiro *White Paper* da European Society of Endocrinology em maio deste ano que abordou como os Endocrinologistas podem contribuir para uma Europa Mais Saudável. Foram identificadas quatro principais áreas de política: 1) Obesidade; 2) Doenças endócrinas raras; 3) Cancro e Endocrinologia; 4) Disruptores endócrinos.

A obesidade é uma epidemia à escala global com múltiplas comorbilidades associadas e tornou-se rapidamente o problema de saúde mais prevalente em todo o mundo, com estimativas de que mais da metade de todos os adultos europeus vivem com pré-obesidade ou obesidade. Estima-se que a prevalência global de obesidade tenha quase triplicado desde 1975, afetando 650 milhões de adultos em 2016, o que nos leva a pensar que nos últimos 50 anos as mudanças de estilo de vida em todo o mundo foram enormes. Sem menosprezar o papel dos genes que não mudam rapidamente em meio século, os múltiplos fatores do ambiente têm um papel muito mais relevante.

Em 2019 associou-se uma nova pandemia – a COVID-19 – e existe evidência robusta de que as pessoas com várias doenças endócrinas como a obesidade, diabetes, insuficiência suprarrenal e síndrome de Cushing têm um risco aumentado de uma infeção por COVID-19 mais grave e têm piores "*outcomes*" e menor sobrevivência comparativamente aos doentes sem estas condições.

Os autores do *White Paper* sublinham que a obesidade deve ser urgentemente tratada como doença endócrina crónica recidivante. Dado que a evidência científica aponta para que esta seja uma doença endócrina, requerem-se soluções endócrinas. A Sociedade Europeia de Endocrinologia considera que todos os países europeus devem urgentemente classificar a obesidade como doença. Portugal foi pioneiro, e desde 2004 que a obesidade é considerada uma doença no nosso país. Mas, apesar de ser considerada uma doença, muito pouco tem sido feito pelo nosso poder político para a abordagem da obesidade ser igual à de outras doenças como, por exemplo, a diabetes e a hipertensão arterial. Do meu ponto de vista, a Endocrinologia moderna tem de ser cada vez mais abrangente do ponto de vista coletivo e obviamente com subespecialização em determinadas áreas do ponto de vista individual, mas sem nunca perder de vista a abrangência da nossa especialidade.

Os distúrbios endócrinos estão entre as doenças mais prevalentes da sociedade. Os distúrbios do sistema endócrino causam doenças como diabetes, obesidade, doenças da tireoide, distúrbios do crescimento, hipertensão, osteoporose, infertilidade e disfunção sexual e uma série de outras doenças relacionadas com o sistema endócrino. O Prof. Doutor Uberto Pagotto da Universidade de Bolonha referiu: "Mais de três quartos da população irá precisar de um Endocrinologista em algum momento da sua vida", o que, na minha opinião, vem

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colocar um ponto final à discussão que há uns anos se travava sobre o futuro da Endocrinologia. De facto, os distúrbios endócrinos são das doenças com mais impacto na sociedade.

Outro dos pontos deste documento foi o cancro e Endocrinologia, sendo referido que o cancro endocrinológico é a segunda causa de morte e morbilidade na Europa, com mais de 3,7 milhões de novos casos e 1,9 milhões de mortes anualmente. Estima-se que 40% dos cidadãos europeus terão um cancro ao longo da sua vida. Mais uma vez, a interação entre Endocrinologia e cancro é complexa, mas a evidência científica sublinha a intricada natureza desta interação em termos de prevenção, tratamento e pós -tratamento. E a obesidade foi identificada como um fator de risco independente para muitos cancros com quase 40% de todos os cancros atribuídos à obesidade ou pré-obesidade. O impacto dos múltiplos fatores do ambiente, e nomeadamente, dos disruptores endócrinos que têm efeitos em diferentes hormonas, está associado à obesidade e ao cancro, mas também à redução da fertilidade e alterações do neurodesenvolvimento, entre outros. Estes disruptores endócrinos estão por toda a parte, desde detergentes, retardadores de incêndios, aditivos alimentares, brinquedos das crianças, protetores solares, têxteis, detergentes antibacterianos, cosméticos, plásticos, pesticidas, etc.

Este *White Paper* da European Society of Endocrinology coloca a obesidade no centro dos problemas a "atacar" para tornar os europeus mais saudáveis.

E o que se passa em Portugal?

No momento em que escrevo este Editorial acaba de ser publicado em diário da República, a resolução da Assembleia da Républica n.º 195/2021, em que recomenda ao Governo medidas de prevenção, tratamento e combate à obesidade.

Entre as vinte e três medidas enumeradas no documento, a Assembleia da República recomenda ao Governo que:

- Dê cumprimento efetivo às medidas previstas nos Programas de Saúde Prioritários da "Promoção da Alimentação Saudável" e da "Promoção da Atividade Física";
- Reforce a implementação da Estratégia do Combate à Obesidade com medidas preventivas, direcionadas às causas da obesidade nos cuidados primários;
- Inicie e desenvolva o tratamento do doente com obesidade na rede hospitalar pública;
- Implemente medidas para que novos fármacos atualmente utlizados e autorizados pelo INFARMED, no combate à obesidade, sejam comparticipados pelo SNS, criando um subgrupo farmacológico para tratamento da obesidade e procedendo à sua comparticipação.

O movimento "Recalibrar a Balança", que reúne os principais *stakeholders* na área da obesidade em Portugal – a Sociedade Portuguesa para o Estudo da Obesidade (SPEO), a Associação de Doentes Obesos e Ex-Obesos (ADEXO) e a que mais recentemente se juntou a Sociedade Portuguesa de Endocrinologia, Metabolismo e Diabetes (SPEDM) – é uma plataforma que reúne consensos sobre a necessidade de uma resposta holística e equitativa contra a obesidade, assente em cinco prioridades muito alinhadas com a estratégia apontada por este texto comum: recalibrar a abordagem da obesidade, recalibrar a formação médica, recalibrar o papel dos cuidados de saúde primários, recalibrar o tratamento da obesidade e recalibrar a perceção pública.

Também no dia 27 de Junho o Ministério da Saúde, a Direção-Geral da Saúde e a Secretaria Regional da Organização Mundial da Saúde para a Europa organizou um evento virtual como principal objetivo de refletir sobre os desafios e as oportunidades que o mundo digital coloca na luta contra a obesidade, ainda sob a presidência Portuguesa da União Europeia.

Atualmente a obesidade é já uma doença crónica, complexa, multifatorial, recidivante e muito prevalente. Se nada for feito, estamos a comprometer o futuro das gerações vindouras.

Oxalá as resoluções da Assembleia da República hoje publicadas que recomendam ao Governo medidas de prevenção, tratamento e combate à obesidade não caiam em saco roto.

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Artigo Original

Predisposição e Diagnóstico de Doença Celíaca numa População Pediátrica com Diabetes Mellitus Tipo 1 Diagnosticada em Idade Inferior a 6 Anos

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Palavras-chave:
Criança;
Diabetes Mellitus Tipo 1;
Doença Celíaca;
Predisposição Genética para Doença.

R E S U M O

Introdução: A diabetes *mellitus* tipo 1 é uma das doenças autoimunes que podem estar associadas à doença celíaca. A prevalência de doença celíaca nos doentes com diabetes *mellitus* tipo 1 é dez vezes superior em relação à população geral. Este estudo teve como objetivo caracterizar a predisposição e o diagnóstico de doença celíaca em crianças com diabetes *mellitus* tipo 1 diagnosticada em idade inferior a 6 anos.
Métodos: Foi realizado um estudo retrospetivo das crianças diagnosticadas com diabetes *mellitus* tipo 1 antes dos 6 anos, entre janeiro de 2009 e novembro de 2019, observadas na Consulta de Diabetologia Pediátrica do Serviço de Pediatria do Hospital de Braga, centro de referência para colocação de sistemas de perfusão contínua de insulina da região do Minho. Foram pesquisados os seguintes antigénios leucocitários humanos: DR3-DQ2, DR5-DQ7, DR7-DQ2 e DR4-DQ8. Foi assumida predisposição para doença celíaca no caso de positividade para DR3-DQ2 e/ou DR4-DQ8 e/ou DR7-DQ2 combinado com DR5-DQ7. Foram realizados doseamentos de imunoglobulina A e de anticorpo anti-transglutaminase ou anti-endomísio ou imunoglobulina G (no caso de défice de imunoglobulina A). Perante suspeita de doença celíaca foi realizada endoscopia digestiva alta com biópsia.
Resultados: Foi encontrada positividade de antigénios leucocitários humanos-DQ2/DQ8 em 71% (25/35) dos casos rastreados e em dois casos foi efetuado posteriormente o diagnóstico de doença celíaca (classificação: Marsh3b). No grupo com predisposição para doença celíaca verificou-se predomínio no sexo feminino (72%) mas sem associação estatística significativa; mediana de idades superior em relação ao grupo sem predisposição (47 *versus* 42 meses, $p>0,05$); 5 casos apresentavam antecedentes pessoais de tiroidite autoimune e 2 casos apresentavam antecedentes familiares de doença autoimune (tiroidite autoimune e doença celíaca).
Conclusão: A percentagem de antigénio leucocitário humano de risco encontrada é inferior à descrita na literatura. Dos doentes rastreados com antigénio leucocitário humano, 71% apresentavam predisposição genética, e 5,7% (2/35) foram diagnosticados com doença celíaca. Não ocorreu nenhum diagnóstico de doença celíaca no grupo antigénio leucocitário humano negativo.

Keywords:
Celiac Disease;
Child;
Diabetes Mellitus, Type 1;
Genetic Predisposition to Disease.

Predisposition and Diagnosis of Celiac Disease in a Paediatric Population with Type 1 Diabetes Diagnosed Under Six Years-Old

A B S T R A C T

Introduction: Type 1 diabetes is one of the autoimmune diseases associated with celiac disease. The prevalence of celiac disease in type 1 diabetes patients is ten times higher than in the general population. This study aimed to characterize the predisposition and diagnosis of celiac disease in children with type 1 diabetes diagnosed under 6 years of age.

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Methods: We conducted a retrospective study of children with type 1 diabetes diagnosed under 6 years, between January 2009 and November 2019. All children were observed at the Pediatric Department of the Hospital de Braga, a reference centre for continuous insulin infusion treatment throughout the Minho region. The following human leukocyte antigen were screened: DR3-DQ2, DR5-DQ7, DR7-DQ2 and DR4-DQ8. Predisposition to celiac disease was assumed in case of positivity for DR3-DQ2 and/or DR4-DQ8 and/or DR7-DQ2 combined with DR5-DQ7. Immunoglobulin A and anti-transglutaminase or anti-endomysium antibody or immunoglobulin G (in case of immunoglobulin A deficiency) assays were performed. Given the suspicion of celiac disease, upper digestive endoscopy with biopsy was performed.
Results: Positivity for human leukocyte antigen-DQ2/DQ8 was found in 71% (25/35) of the screened cases and two cases of celiac disease were later diagnosed (classification: Marsh3b). There was a female predominance (72%) in the cases with predisposition to celiac disease but without significant association. Median age was higher in the group with predisposition to celiac disease (47 months *versus* 42 months, $p> 0.05$). In this group, 5 cases had personal history of autoimmune thyroiditis and 2 cases had family history of autoimmune disease (autoimmune thyroiditis and celiac disease).
Conclusion: The percentage of risk human leukocyte antigen found is lower than that described in literature. Seventy one per cent of the patients screened for human leukocyte antigen had a genetic predisposition and 5,7% (2/35) were diagnosed with celiac disease. There was no celiac disease diagnosis in the human leukocyte antigen negative group.

Introdução

A diabetes *mellitus* tipo 1 (DM1) caracteriza-se por um défice de insulina causado pela destruição autoimune das células beta pancreáticas.[1] A DM1 é a patologia endócrina mais frequente na idade pediátrica,[2] representando 5%-10% de todos os casos de diabetes,[3] e demonstrando uma incidência crescente nas últimas décadas em crianças com idade inferior a 6 anos.[4]

A DM1 é uma das doenças autoimunes que podem estar associadas à doença celíaca (DC). A prevalência de DC nos doentes com DM1 é dez vezes superior em relação à população geral. Esta associação ainda não está totalmente esclarecida, no entanto existem estudos que mostram que as patologias têm início em fatores comuns.[5] O risco de desenvolver DC parece estar relacionado com o tempo de exposição ao glúten (fator ambiental), com a idade ao diagnóstico da DM1 (maior risco se idade inferior a 6 anos) e com fatores imunológicos - antigénios leucocitários humanos classe II (HLA).[6] A DM1 e a DC cursam com alterações em genes comuns, nomeadamente nos genes *DQ2* e *DQ8*.[2] Em 90% dos casos a DM1 é diagnosticada previamente à DC[2,5] e a maioria apresenta a forma silenciosa, pelo que apenas 10% apresentam as manifestações clínicas típicas de DC.[2,7]

Este estudo teve como objetivo avaliar a prevalência da DC em doentes com DM1 com predisposição para DC (DM1 e HLA positivo).

Métodos

Foi realizado um estudo retrospetivo das crianças com diagnóstico de DM1 com idade inferior a 6 anos, no período entre 1 de janeiro de 2009 e 30 de novembro de 2019, e observadas na Consulta de Diabetologia Pediátrica do Serviço de Pediatria do Hospital de Braga, um centro de referência para colocação de sistemas de perfusão contínua de insulina na região do Minho.

O rastreio de DC é realizado no nosso Hospital, pela pesquisa de IgA para o anticorpo anti-transglutaminase (se défice de IgA, é feito diagnóstico por IgG) tal como recomendado pela European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) - *Guidelines for diagnosing coeliac disease 2019*.[8]

Foram pesquisados por rotina os seguintes HLA: DR3-DQ2, DR5-DQ7, DR7-DQ2 e DR4-DQ8. Foi assumida a existência de predisposição para DC no caso de positividade para DR3-DQ2 e/ou DR4-DQ8 e/ou DR7-DQ2 combinado com DR5-DQ7. Os HLA foram pesquisados, por rotina, ao diagnóstico de DM1 desde janeiro de 2012, ou posteriormente quando oportuno em análises anuais. Previamente a janeiro de 2012, foi realizada pesquisa de HLA perante forte suspeição de DC. Foram realizados doseamentos de Imunoglobulina A (IgA) e de anticorpo anti-transglutaminase ou anti-endomísio ou imunoglobulina G (IgG) (no caso de défice de IgA). Perante a suspeita de DC foi realizada endoscopia digestiva alta com biópsia pela Unidade de Gastrenterologia, Hepatologia e Nutrição Pediátrica (centro de referência para a região do Minho).

O diagnóstico de DC segue as *Guidelines for diagnosing coeliac disease* da European Society Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) redigidas em 2019, e é feitos nos casos com positividade para o anticorpo anti-transglutaminase e/ou para anti-endomísio e que apresentam alterações histológicas nas biópsias de intestino delgado compatíveis com atrofia das vilosidades intestinais.

Dezoito doentes eram provenientes de outros hospitais, e dentro destes, 12 doentes não tinham realizado pesquisa HLA e 4 encontravam-se sem resultados disponíveis pelo que foram excluídos.

Os dados recolhidos foram obtidos através da consulta do processo clínico dos doentes que cumpriam os critérios de inclusão.

A análises dos dados foi realizada com recurso ao programa IBM SPSS versão 20.0® e foi atribuída significância estatística para o valor de $p<0,05$. Dado estarmos perante uma amostra de reduzidas dimensões, e que não segue uma distribuição de acordo com a normalidade, as variáveis foram descritas de acordo com as medidas de distribuição central (mediana), medidas de dispersão (mínimo e máximo) e analisadas com recursos a testes não paramétricos (teste de Fisher para variáveis nominais e teste de Mann-Whitney para variáveis contínuas).

Resultados

Durante este período de tempo foram diagnosticadas 51 crianças com DM1 com idade inferior a 6 anos. As 35 crianças que realizaram pesquisa HLA tinham idade compreendida entre os 10 meses e os 5 anos e 11 meses, com uma mediana de 4 anos (47 meses). Foi constatado predomínio no sexo feminino com um ratio de 1,9:1 (23/35 *versus* 12/35). A duração mediana do tempo de seguimento foi de 48 meses (mínimo 7 e máximo 121).

Foi encontrada positividade de antigénios leucocitários humanos-DQ2/DQ8 em 71% (n=25) dos casos rastreados (Tabela 1). Entre os casos com predisposição para DC, foi efetuado o diag-

Tabela 1. HLA DQ2 / DQ8 pesquisadas.

Positivos HLA DQ2 / DQ8	25 (71%)
Positivos HLA DQ2 / DQ8	**10 (29%)**
Aguardam resultados	4
Sem pesquisa	12

nóstico de DC em duas crianças (classificação: Marsh3b). O primeiro caso diz respeito a uma adolescente do sexo feminino, com hipoglicemias frequentes e perda ponderal, com diagnóstico de DM1 aos 6 anos e de DC aos 12 anos. O segundo caso é referente a uma criança do sexo masculino, assintomática, com diagnóstico de DM1 aos 2 anos e de DC aos 7 anos. Estes dois casos não apresentavam antecedentes pessoais ou familiares de patologia autoimune.

Nos casos com predisposição para DC verificou-se predomínio no sexo feminino (72%), mas sem associação estatística significativa (p>0,05). A mediana de idades foi superior no grupo com predisposição para DC mas também sem associação significativa, (p>0,05), 47 meses no grupo com predisposição para DC *versus* 42 meses no grupo sem predisposição para DC, com valor mínimo de 20 meses e máximo de 71 meses, para ambos os grupos. A duração mediana do tempo de seguimento dos doentes com predisposição para DC foi de 48 meses (mínimo 7 e máximo 121). Em relação ao grupo com predisposição para DC, 5 crianças apresentavam antecedentes pessoais de tiroidite autoimune e 2 crianças tinham antecedentes familiares de doença autoimune (tiroidite autoimune e DC).

Não ocorreu nenhum diagnóstico de DC no grupo HLA negativo.

Foram realizados doseamentos de imunoglobulina A (IgA), ou imunoglobulina G (IgG) no caso de défice IgA, para o anticorpo antitransglutaminase, à data de diagnóstico de DM1, e nos rastreios anuais ou oportunos. Em nenhum doente houve alteração destes doseamentos, exceto nos dois doentes com diagnóstico de DC com positividade para IgG do anticorpo anti-transglutaminase.

Discussão

Os haplótipos HLA DQ2 e DQ8 estão presentes em mais de 90% das crianças com DM1, enquanto a prevalência destes haplótipos na população geral é de 40%-50%.[9] A positividade do HLA-DQ8 confere um risco superior de DM1 enquanto a positividade do HLA-DQ2 é responsável por um risco acrescido de DC.[10] Neste estudo, a prevalência de HLA positivos foi de 71%, inferior à percentagem encontrada noutros estudos,[5] o que se pode atribuir ao reduzido tamanho da amostra e à ausência de representatividade da população em estudo, uma vez que só se incluíram crianças com diagnóstico de DM1 abaixo dos 6 anos de idade.

A associação entre DM1 e DC ainda não está completamente estabelecida.[11] Duas teorias tentam explicar a relação entre estas duas patologias. A primeira sugere que, sendo a DM1 consequência de uma desorganização autoimune em contexto de um ambiente geneticamente predisponente, esta alteração da função imune conduz a um mecanismo de mímica molecular cruzada, no qual a gliadina ou a transglutaminase tecidual ativam as células T, que por sua vez, fazem reação cruzada com vários auto-antigénios. A segunda teoria defende que a DC, estando associada à estimulação imunológica e ativação policlonal de células β, conduz a outros distúrbios imunológicos em indivíduos geneticamente predispostos.[1] Nas crianças com DM1, a prevalência da DC varia entre 1%-16%, sendo superior à prevalência da população geral pediátrica que varia entre 0,2%-5,5%.[1] A prevalência de DC na população pediátrica de Braga em 2006 era de 1:134, ou seja de 0,6%.[11] Nesta amostra, a prevalência de DC foi de 5,7%, estando de acordo com o descrito na literatura e sendo superior à prevalência de DC na população em geral.

As crianças com DM1 têm um risco aumentado de DC nos primeiros dez anos após o diagnóstico.[2]

A International Society for Pediatric and Adolescent Diabetes (ISPAD) recomenda a realização do rastreio de DC nos doentes com DM1 no momento do diagnóstico e após 2-5 anos. Uma avaliação mais frequente estará indicada na presença de sintomatologia suspeita ou no caso de existir um familiar de primeiro grau com DC.[12] Neste estudo constatamos a existência de 71% dos casos com predisposição genética para DC, dos quais 8% apresentavam DC. A percentagem de casos HLA negativos correspondeu a 29%.

A European Society Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) redigiu em 2019 as *Guidelines for diagnosing coeliac disease* onde se recomenda como teste de rastreio a combinação de anticorpos totais de IgA e anticorpos IgA anti-transglutaminase, sugerindo que esta combinação é mais precisa do que outras combinações. A abordagem sem biópsia para o diagnóstico de DC é segura em crianças com valores elevados de IgA-TGA (≥10 vezes o limite superior do normal) com testes apropriados e IgA anti-endomísio positivo numa segunda amostra de soro. As crianças com IgA-TGA positivo, mas com títulos mais baixos (inferior a 10 vezes em relação ao limite superior) devem realizar biópsias para diminuir o risco de diagnóstico falso positivo. A análise de HLA e a presença de sinais e/ou sintomas não são critérios para confirmar o diagnóstico sem realização de biópsia.[8]

Apontamos como principais limitações deste estudo, o facto de ser retrospetivo, o tamanho reduzido da amostra.

De acordo com as limitações apontadas, os resultados obtidos foram inferiores ao encontrado na literatura, uma vez que 71% dos doentes rastreados com HLA têm predisposição genética para DC e destes, 8% (n=2) têm o diagnóstico DC. Em relação à amostra total estudada, 5,7% tem doença celíaca (2/35).

O rastreio de DC deverá ser efetuado de forma regular e atenta nos doentes com suscetibilidade, assim como nos familiares de primeiro grau. Nos casos HLA negativos, onde a probabilidade de ter DC é inferior a 1%, a atitude poderá ser expectante, reduzindo ansiedade, custos e atitudes invasivas, e apenas ser efetuado rastreio se clínica sugestiva. No nosso caso, não ocorreu nenhum diagnóstico de DC no grupo HLA negativo.

Enfatizamos a necessidade de estudos adicionais com maior número de pacientes, a fim de compreender melhor a contribuição dos haplótipos DQ2 e DQ8 para autoimunidade na DM1.

Os autores salientam ainda que não existem estudos semelhantes publicados na população Portuguesa.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Artigo Original

A Long-term Cost-Effectiveness Analysis of Treatments for Type 2 Diabetes in Portugal: Once-Weekly Semaglutide 1 mg Versus Once-Daily Empagliflozin 25 mg

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INFORMAÇÃO SOBRE O ARTIGO

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A B S T R A C T

Introduction: Management of type 2 diabetes includes aiming to maintain glycemic control, reduce cardiovascular events, with a low risk of hypoglycemic events and avoidance of weight gain. The present analysis assessed the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg for the treatment of patients with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy from a healthcare payer perspective in Portugal.
Methods: Long-term clinical and economic outcomes with once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were projected using the IQVIA CORE Diabetes Model. Clinical inputs in terms of patient characteristics and the impact of treatments on risk factors were based on an indirect comparison conducted using patient-level data from four randomized controlled trials as, to date, there is no head-to-head clinical trial comparing the two interventions. In the modeling analysis, both treatments were added to metformin and continued until glycated hemoglobin exceeded a threshold of 7.5%, at which point patients switched therapy to basal insulin. Pharmacy and complication costs, expressed in 2019 Euros (EUR), and utilities were applied. Future outcomes were discounted at 4% per annum.
Results: Over simulated patient lifetimes, once-weekly semaglutide 1 mg was associated with increased life expectancy (12.80 *vs* 12.70 years) and quality-adjusted life expectancy (7.18 vs 6.98 quality-adjusted life years [QALYs]) compared with once-daily empagliflozin 25 mg. The benefits resulted from a reduced incidence and delayed onset of projected diabetes-related complications. Increased pharmacy costs with once-weekly semaglutide were partially offset by cost savings resulting from avoided diabetes-related complications, most notably cardiovascular disease and renal disease, with mean per patient cost savings of EUR 110 and EUR 88, respectively. This led to an overall cost increase of EUR 2 804 per patient with once-weekly semaglutide (EUR 24 845 *vs* EUR 22 041). Once-weekly semaglutide was associated with an incremental cost-effectiveness ratio of EUR 14 114 per QALY gained versus once-daily empagliflozin.
Conclusion: Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes in Portugal.

Palavras-chave:
Análise Custo-Benefício;
Diabetes Mellitus/tratamento farmacológico;
Hipoglicemiantes.

Análise Custo-Efetividade a Longo Prazo de Tratamentos para a Diabetes tipo 2 em Portugal: Semaglutido 1 mg Semanal Versus Empagliflozina 25 mg Diário

R E S U M O

Introdução: A gestão da diabetes tipo 2 inclui a manutenção do controlo glicémico reduzindo eventos cardiovasculares, com risco diminuído de hipoglicemias ou aumento do peso corporal. A presente análise avaliou a relação custo-efetividade a longo prazo de semaglutido 1 mg semanal *versus* empagliflozina 25 mg diário, na diabetes *mellitus* tipo 2 inadequadamente controlada com

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metformina, em monoterapia, na perspetiva do Serviço Nacional de Saúde (SNS) em Portugal.
Métodos:Os resultados clínicos e económicos do tratamento com semaglutido 1 mg semanal e empagliflozina 25 mg diário foram projetados utilizando o *IQVIA CORE Diabetes Model*. Pela ausência de ensaios clínicos comparativos diretos, as características dos doentes e o impacto dos tratamentos nos fatores de risco basearam-se numa comparação indireta utilizando dados individualizados dos participantes de quatro ensaios clínicos aleatorizados incluídos. Na análise modelada, os tratamentos adicionados à metformina foram mantidos até que a hemoglobina glicada ultrapassasse o limiar 7,5%, momento em que os doentes transitaram para insulina basal. Foram considerados custos das complicações e da medicação, em Euros (2019), e aplicadas as utilidades geradas através da qualidade de vida relacionada com saúde. Aos custos projetados aplicou-se um desconto 4% ao ano.
Resultados: O semaglutido 1 mg foi associado a um aumento da esperança de vida (12.80 *vs* 12.70 anos) e da esperança de vida ajustada pela qualidade de vida (7.18 *vs* 6.98 anos de vida ajustados pela qualidade de vida [QALYs]) comparativamente a empagliflozina 25 mg. Estes benefícios resultam da menor incidência e do atraso no aparecimento das complicações da diabetes. Os custos adicionais com a medicação associados a semaglutido foram parcialmente compensados pela redução dos custos das complicações evitadas, especialmente doença cardiovascular e renal, em média de 110 EUR e 88 EUR, respetivamente, por doente. Isto conduziu a um balanço final de 2 804 EUR por doente (EUR 24 845 vs EUR 22 041). O semaglutido foi associado a um rácio custo-efetividade incremental de 14 114 por QALY ganho *versus* empagliflozina.
Conclusão: Quando comparado com empagliflozina 25 mg diário, o semaglutido 1 mg semanal é um tratamento custo-efetivo no tratamento da diabetes tipo 2, conforme projeções a longo prazo, na perspetiva do SNS em Portugal.

Introduction

The International Diabetes Federation estimates that in 2019 the prevalence of diabetes in Portugal was 9.8%, with type 2 diabetes making-up 90% of cases.[1,2] The prevalence is expected to rise to 11.2% by 2030 and to 12% by 2045.[1] Diabetes results in significant mortality in Portugal, with an estimated 5 796 deaths attributable to diabetes annually.[1] The Portuguese National Diabetes Observatory (Observatório Nacional da Diabetes) last estimated the cost of diabetes in 2015, finding that the condition was associated with costs between EUR 1 300 and EUR 1 550 million, equating to 0.7 to 0.9% of gross domestic product and 8% to 10% of total healthcare expenditure.[2] The most significant costs of diabetes were as a result of hospitalization to treat diabetes-related complications.[2] Improving glycemic control, lowering blood pressure, and reducing body weight have been shown to reduce the risk of developing diabetes-related complications.[3-6] Therefore improvements in outcomes for patients and reduced costs for the National Health Service (NHS) in Portugal can be achieved by improving treatment. Choosing therapies that are both effective and cost-effective is increasingly important in order to deliver high quality healthcare within constrained resources, as healthcare budgets come under increasing pressure.

The European Association for the Study of Diabetes (EASD) has released guidelines that recommend the use of GLP-1 receptor agonists or SGLT-2 inhibitors with proven cardiovascular benefits for patients with or at high risk of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease as second-line therapies (following metformin).[7,8] These therapies are also recommended for patients with a need to minimize the risk of hypoglycemia and those with a need to minimize weight gain or promote weight loss. Once-weekly semaglutide and once-daily empagliflozin have both been shown to be associated with a cardiovascular benefit.[7,8] Data on the relative effectiveness and cost-effectiveness of once-weekly semaglutide and once-daily empagliflozin is important, as physicians may be required to make decisions between which of these treatment options to prescribe.

There is currently no head-to-head clinical trial that allows a direct comparison of once-weekly semaglutide 1 mg with once-daily empagliflozin 25 mg. However, a meta-analysis has been conducted using individual patient data to compare the efficacy of the two interventions for the treatment of patients with type 2 diabetes previously receiving metformin monotherapy.[9] The meta-analysis was conducted in line with guidance on the conduct of indirect comparisons from the NICE Decision Support Unit.[10] The use of individual patient data, rather than aggregated clinical trial data, allows potential prognostic factors and effect modifiers to be adjusted for at an individual patient level, resulting in a potentially better isolation of the effect of a single treatment on outcomes of interest than when aggregated (i.e. clinical trial) data are used. The analysis captured data from four randomized controlled trials: SUSTAIN 2 (once-weekly semaglutide versus sitagliptin), SUSTAIN 3 (once-weekly semaglutide versus once-weekly exenatide), SUSTAIN 8 (once-weekly semaglutide versus canagliflozin) and PIONEER 2 (once-daily oral semaglutide versus once-daily empagliflozin). The primary regression analysis included all four trials, which had durations of 52 or 56 weeks, with a complementary analysis conducted using only the 52-week trials (SUSTAIN 8 and PIONEER 2). Outcomes were assessed for change from baseline in HbA1c, body weight, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, lipid parameters, and estimated glomerular filtration rate.

The present analysis aimed to assess the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg for the treatment of patients with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy from a healthcare payer perspective in Portugal, based on the results from previously published meta-analysis using patient-level data.

Methods

Modeling approach and overview

To assess the cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg, an analysis was performed over patient lifetimes using version 9.0 of the IQVIA CORE Diabetes Model. The features and capabilities of the model have been previously published.[11] The model reflects the natural course of diabetes, with risk factors developing over time and patients at risk of experiencing diabetes-related complications. Model outputs include time to onset and cumulative incidence of complications, life expectancy, quality-adjusted life expectancy

(expressed in quality-adjusted life years [QALYs]), direct costs and, incremental cost-effectiveness ratios (ICERs). Long-term outcomes projected by the model have been validated against real-life data in 2004 and more recently in 2014.[12,13]

The present analysis conducted for Portugal was aligned with previously published cost-effectiveness analyses of once-weekly semaglutide and oral semaglutide in the UK setting.[14,15] Outcomes were projected over patient lifetimes in order to capture all differences in long-term complications (and their impact on costs and quality of life) and mortality with once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg, as recommended in the methodological guidelines for economic evaluation of health technologies in Portugal.[16] Projected cost and clinical outcomes were discounted at 4% annually, in line with modelling guidelines for Portugal.[16] Base case and sensitivity analyses were performed using a second-order Monte Carlo approach, with baseline cohort characteristics, treatment effects, costs of complications, utilities and transition probabilities relating to myocardial infarction, stroke, congestive heart failure and angina sampled in each model iteration. This aimed to capture the uncertainty around model inputs and their impact on the development of diabetes-related complications.

Clinical data

The analysis used baseline characteristics taken from the pooled data from the studies that informed the meta-analysis: SUSTAIN 2, SUSTAIN 3, SUSTAIN 8 and PIONEER 2. The mean (standard deviation [SD]) age of the cohort was 56 (10.3) years, with mean duration of diabetes of 7 (5.9) years, mean HbA1c of 8.2 (1.0) %, and mean BMI of 32.8 (6.7) kg/m^2. Alcohol and tobacco consumption data were not collected in the clinical trials and therefore were assumed to be the same as the general Portuguese population.[17,18] Treatment effects associated with initiation of once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were based on the outcomes calculated in the meta-regression based on individual patient data (Table 1).[9] Once-weekly semaglutide 1 mg was associated with significantly greater improvements in HbA1c, total cholesterol, LDL cholesterol, triglycerides and BMI compared with once-daily empagliflozin 25 mg, while once-daily empagliflozin 25 mg was associated with significantly greater improvements in diastolic blood pressure and HDL cholesterol.

Treatment effects from the meta-analysis were applied in the first year of the analysis, after which HbA1c was assumed to increase based on the UKPDS progression equation in both arms. This resulted in HbA1c increasing over time, with the difference between the treatment arms gradually diminished. When HbA1c exceeded 7.5% (a commonly used threshold for treatment intensification) patients discontinued once-weekly semaglutide 1 mg or once-daily empagliflozin 25 mg and initiated treatment with basal insulin (assumed to be biosimilar glargine [insulin Abasaglar]). Initiation of basal insulin was assumed to result in a reduction in HbA1c, with this calculated using the "Core" multivariate equations for an insulin-naïve population estimated by Willis *et al*.[19] Both once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were associated with reductions in BMI, and these were assumed to persist while patients received initial treatments. BMI was assumed to return to baseline when basal insulin was initiated (thereby abolishing the difference between the treatment arms). In both arms, changes in blood pressure and serum lipids were based on the natural progression algorithms built into the IQVIA CORE Diabetes Model, based on the UKPDS and Framingham data, respectively.

Costs

Costs captured all costs falling within the NHS budget, in line with modeling guidelines for Portugal.[16] Direct costs captured included pharmacy costs, costs associated with diabetes-related complications and patient management costs. All costs were expressed in 2019 Euros (EUR). Unit costs of diabetes medications were based on the pharmacy selling price (PSP) including value added tax (VAT) and captured the appropriate reimbursement levels. Once-weekly semaglutide is supplied with needles included in the pack and therefore do not need to be purchased separately, once-daily empagliflozin is delivered orally and therefore needles are not required, and basal insulin (following treatment switching) was associated with the use of one needle per day. It was assumed that patients receiving once-weekly semaglutide and

Table 1. Treatment effects associated with once-weekly semaglutide 1 mg and once-daily empagliflozin

Parameter	Mean (standard error)		Estimated treatment difference (Mean [95% confidence interval])	*p*-value
	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg		
HbA_{1c} (%)	−1.44 (0.03)	−0.83 (0.05)	−0.61 (−0.72 to −0.49)	<0.0001
HbA_{1c} (mmol/mol)	−15.7 (0.3)	−9.1 (0.5)	−6.7 (−7.9 to −5.4)	<0.0001
Systolic blood pressure (mmHg)	−4.11 (0.36)	−4.48 (0.56)	0.37 (−0.95 to 1.68)	0.5842
Diastolic blood pressure (mmHg)	−1.27 (0.23)	−2.39 (0.37)	1.12 (0.27 to 1.97)	0.0103
Total cholesterol (mg/dL)	−6.15 (0.90)	4.14 (1.39)	−10.28 (−13.56 to −7.01)	<0.0001
HDL cholesterol (mg/dL)	1.53 (0.22)	2.63 (0.34)	−1.10 (−1.89 to −0.30)	0.0073
LDL cholesterol (mg/dL)	−2.48 (0.77)	4.18 (1.19)	−6.66 (−9.44 to −3.87)	<0.0001
Triglycerides (mg/dL)	−31.16 (3.36)	−15.13 (5.17)	−16.03 (−28.17 to −3.90)	0.0097
BMI (kg/m^2)	−1.92 (0.06)	−1.32 (0.09)	−0.60 (−0.81 to −0.39)	<0.0001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	0.15 (0.23)	−0.06 (0.37)	0.21 (−0.65 to 1.07)	0.6304

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

once-daily empagliflozin did not use any self-monitoring of blood glucose (SMBG) testing due to the low rates of hypoglycemic events, but that patients receiving basal insulin used one SMBG test per day. Annual costs of treatment were calculated from an NHS perspective with once-weekly semaglutide 1 mg, once-daily empagliflozin 25 mg, and basal insulin (assumed to be 40 IU daily based on the defined daily dose).[20] Costs of complications and patient management were taken from NHS tariffs where possible, in line with guidance for Portugal, with peer-reviewed publications and expert advice used to fill data gaps.[16]

Utilities

The analysis captured the impact of diabetes-related complications on quality of life by applying disutilities in the year of the event and in subsequent years. Utilities associated with each diabetes-related complication were taken from a 2014 review by Beaudet et al, with hypoglycemia disutilities coming from Evans *et al* 2013 (published after the literature searches by Beaudet *et al* had been completed).[21,22] Beaudet et al preferentially chose utilities elicited using the EQ-5D, which is aligned with guidance on economic evaluation in the Portuguese setting.[16]

Sensitivity analysis

The projection of outcomes over patient lifetimes using a health-economic model is associated with uncertainty, and therefore a series of sensitivity analyses with alternative model inputs were performed to assess the robustness of the model results. The base case analysis used a 50-year time horizon, and the impact of shortening the time horizon of the analysis was examined by running analyses over 20- and 10-year time horizons. Annual discount rates of 4% were applied to future clinical and cost outcomes in the base case, and a sensitivity analysis was conducted with 0% discount rates applied. The base case analysis applied all treatment effects irrespective of statistical significance, and a sensitivity analysis was prepared with only the statistically significant differences between the treatments applied.

In the base case analysis, a disutility per BMI unit above 25 kg/m^2 of −0.0061 was applied, as used in previous analyses conducted by the National Institute for Health and Care Excellence.[23] In a sensitivity analysis an alternative value of −0.01 per BMI unit above 25 kg/m^2 was used, with this larger disutility gives greater impact to weight changes compared with the conservative disutility used in the base case analysis.[24] The base case analysis applied hypoglycemic event disutilities based on Evans *et al*, and a sensitivity analysis examined the impact of applying alternative disutilities for severe and non-severe hypoglycemic events as reported by Currie *et al*.[25]

The UKPDS 64 risk equations were used to predict the incidence of first cardiovascular events in the base case analysis, with the UKPDS 82 risk equations incorporated into the IQVIA CORE Diabetes model in 2014 applied in a sensitivity analysis. Whilst a validation study of the revised model has been published, the model owners suggest that the update is used in a sensitivity analysis, with the previous version used in the base case.[13]

HbA1c increased based on the UKPDS progression equation for the duration of the analysis in both arms of the base case analysis, and an alternative modeling approach was explored, with HbA1c increasing by 0.14% per year in both arms of the analysis while patients received once-weekly semaglutide 1 mg or once-daily empagliflozin 25 mg, based on the metformin arm of the ADOPT study.[26] When patients initiated basal insulin, HbA1c followed the UKPDS equation, as in the base case. In the base case analysis, BMI returned to baseline when treatment switching to basal insulin occurred, and an alternative was explored with BMI returning to baseline followed by a further increase based on the Willis *et al* equations.[19]

In order to maintain simplicity and transparency only one treatment switch was included in the base case analysis, and a sensitivity analysis was conducted with a second switch to basal bolus insulin when HbA1c exceeded 7.5% for the second time. A reduction in HbA1c and an increase in BMI were applied, based on the Willis *et al*. equations for insulin experienced patients.[19]

In the base case analysis, insulin Abasaglar (the most commonly used biosimilar insulin glargine analogue) was used as the basal insulin, and a sensitivity analysis was performed with the cost of insulin NPH applied. The base case analysis was performed using a second-order Monte Carlo approach, with sampling around inputs to capture both first and second order uncertainty. A sensitivity analysis was performed using a first-order Monte Carlo approach, with no sampling around baseline characteristics, treatment effects, costs of complications utilities or transition probabilities.

Results

Base case analysis

Long-term projections found that once-weekly semaglutide was associated with improved discounted life expectancy by 0.10 years and improved discounted quality-adjusted life expectancy of 0.20 QALYs per patient compared with once-daily empagliflozin 25 mg over patient lifetimes (Table 2). The greater reductions in HbA1c and BMI identified in the indirect comparison with once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg drove a reduced cumulative incidence and delayed time to onset of diabetes-related complications. This led to improved duration and quality of life with once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg. Furthermore, the improved glycemic control with once-weekly

Table 2. Long-term cost-effectiveness outcomes in the base case analysis

Outcomes	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference
Discounted life expectancy (years)	12.80 (12.65 to 12.96)	12.70 (12.55 to 12.86)	0.10 (0.09 to 0.12)
Discounted quality-adjusted life expectancy (QALYs)	7.18 (7.10 to 7.27)	6.98 (6.90 to 7.07)	0.20 (0.19 to 0.21)
Discounted direct costs (EUR)	24 845 (24 556 to 25 134)	22 041 (21 747 to 22 334)	2,804 (2,695 to 2,914)
ICER	EUR 14 114 per QALY gained		

Values are means (95% confidence intervals). EUR, euros; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

semaglutide 1 mg led to delayed switching to insulin compared with once-daily empagliflozin 25 mg. This resulted in a delay of the weight gain and hypoglycemic events associated with insulin therapy, driving further improvements in life expectancy and quality-adjusted life expectancy.

Projections suggest that once-weekly semaglutide 1 mg was associated with mean costs of EUR 24 845 compared with EUR 22 041 with once-daily empagliflozin 25 mg over patient lifetimes (Fig. 1). The higher acquisition cost of once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg and the increased duration of treatment due to improved glycemic control drove this increase in costs. However, once-weekly semaglutide 1 mg was associated with cost savings due to avoided diabetes-related complications, and this partially offset the increased treatment costs. Cost savings were identified in all categories of complications modelled but the most significant contributions were as a result of avoided cardiovascular disease and renal disease, with mean per patient cost savings of EUR 110 and EUR 88, respectively.

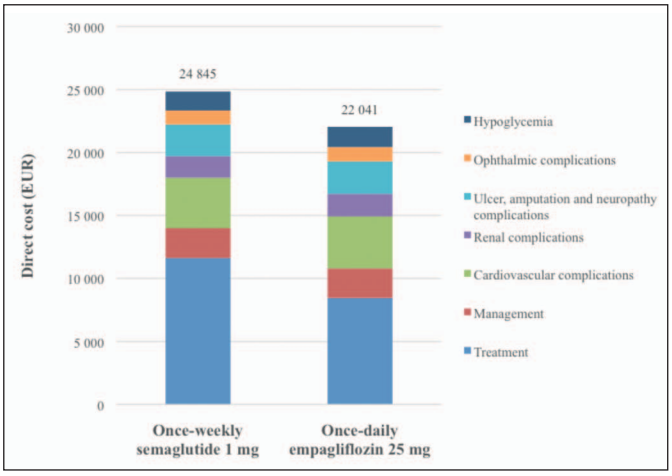

Figure 1. Direct costs over patient lifetimes

EUR, euros; QALY, quality-adjusted life year. Treatment costs captured the costs of diabetes medications and consumables; management costs included the costs of concomitant non-diabetes medications and screening; costs of cardiovascular complications included the costs of myocardial infarction, angina, congestive heart failure, stroke and peripheral vascular disease; costs of renal complications included the costs of dialysis and transplant, costs of ulcer, amputation and neuropathy complications included the costs of ulcer, gangrene, amputation, prosthesis, and neuropathy; costs of ophthalmic complications captured the costs of laser treatment, cataract surgery and blindness; costs of hypoglycemia included the costs of severe and non-severe hypoglycemic events.

Combination of cost and clinical outcomes to assess cost-effectiveness found that once once-weekly semaglutide 1 mg was associated with an ICER of EUR 14 114 per QALY gained versus once-daily empagliflozin 25 mg over patient lifetimes. This ICER falls below the willingness to pay threshold of EUR 30 000 per QALY gained where an intervention is considered cost-effective, with this threshold used as a benchmark when comparing with other health technologies.[16] In 90.6% of model iterations once-weekly semaglutide 1 mg was associated with improved outcomes and increased costs compared with once-daily empagliflozin 25 mg, and in a further 2.6% of model iterations once-weekly semaglutide 1 mg was associated with improved outcomes and cost savings (Fig. 2). At a willingness to pay threshold of EUR 30 000 per QALY gained there was a 77.6% probability that once-weekly semaglutide 1 mg was considered cost-effective (Fig. 3).

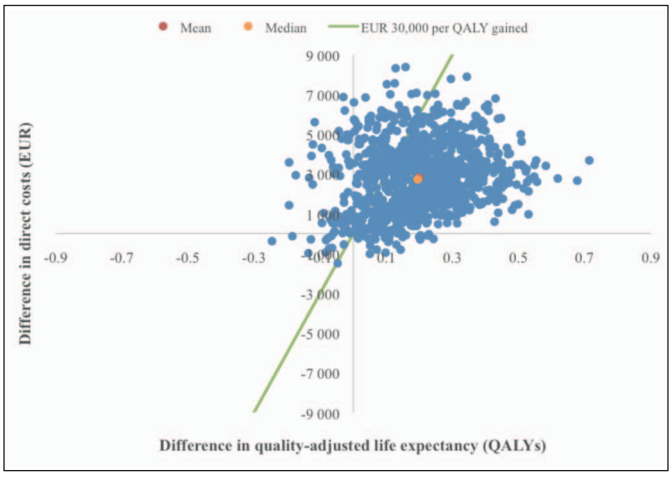

Figure 2. Cost-effectiveness scatterplot

EUR, euros; QALY, quality-adjusted life year.

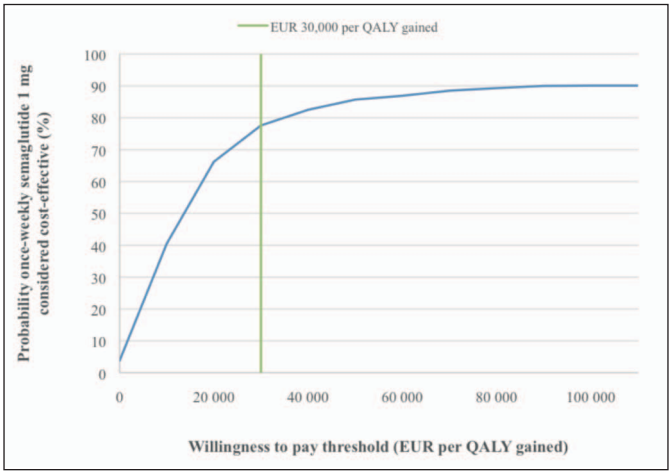

Figure 2. Cost-effectiveness acceptability curve

EUR, euros; QALY, quality-adjusted life year.

Sensitivity analysis results

Application of alternative model inputs and assumptions in sensitivity analyses did not change the conclusions of the analysis, with all calculated ICERs remaining below a willingness to pay threshold of EUR 30 000 per QALY gained (Table 3). Evaluating outcomes over shorter time horizons led to higher ICERs for once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg as the long-term benefits of once-weekly semaglutide 1 mg in terms of avoiding diabetes-related complications were not fully captured. When discount rates of 0% were applied, once-weekly semaglutide 1 mg was found to be more cost-effective than in the base case analysis, further reflecting the long-term benefits. When only treatment effects that were significantly different between the treatment arms applied, results remained similar to the base case.

When the impact of weight loss on quality of life was increased, the ICER was reduced compared with the base case analysis, as the greater reduction in BMI with once-weekly semaglutide 1 mg had a greater impact. In the analysis with the impact of hypoglycemic events on quality of life reduced, quality-adjusted life expectancy increased in both treatment arms, with a small reduction in the clinical benefits associated with once-weekly semaglutide 1 mg as the increased frequency of hypoglycemia in the

Table 3. Sensitivity analysis results

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (EUR)			ICER (EUR per QALY gained)
	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference	
Base case	7.18	6.98	0.20	24 845	22 041	2 804	14 114
20-year time horizon	6.36	6.18	0.19	19 632	16 873	2 760	14 821
10-year time horizon	4.55	4.40	0.15	12 737	9 863	2 874	19 046
Statistically significant different treatment effects only	11.19	10.90	0.29	44 344	41 239	3 106	10 683
0% discount rates	7.18	6.98	0.20	24 845	22 041	2 804	13 937
Alternative BMI disutility	6.80	6.59	0.21	24 845	22 041	2 804	13 580
Alternative hypoglycemia disutilities	7.64	7.47	0.17	24 845	22 041	2 804	16 429
UKPDS 82 risk equations applied	7.45	7.26	0.19	25 936	23 095	2 841	15 338
Linear annual HbA1c increase while patients receive initial therapies	7.71	7.24	0.47	26 468	21 500	4 969	10 631
BMI returned to baseline and then a further increase on treatment switching	7.13	6.93	0.20	24 830	22 034	2 796	13 755
Second treatment switch to basal-bolus insulin when HbA1c exceeded 7.5% during basal insulin treatment	6.24	5.95	0.28	36 499	34 606	1 893	6 664
Insulin NPH used as basal insulin	7.18	6.98	0.20	23 348	20 452	2 896	14 575
First-order Monte Carlo simulation	7.43	7.21	0.23	25 078	22 559	2 519	11 101

BMI, body mass index; EUR, euros; HbA1c, glycated hemoglobin; ICER, incremental cost-effectiveness ratio; NPH; Neutral Protamine Hagedorn; QALY, quality-adjusted life-year; UKPDS, United Kingdom Prospective Diabetes Study.

once-daily empagliflozin 25 mg arm (due to earlier switching to basal insulin) had a smaller impact on quality of life.

Use of alternative risk equations to estimate the incidence of cardiovascular events resulted in greater quality-adjusted life expectancy and costs in both arms. However, differences between the arms remained similar to the base case analysis, as did the ICER. When it was assumed that HbA1c increased by 0.14% in both arms (rather than using the UKPDS progression equation), differences in HbA1c were maintained for longer than in the base case, resulting in a greater improvement in quality-adjusted life expectancy with once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg. This resulted in a lower ICER than in the base case analysis. When it was assumed that BMI increased to above baseline levels on treatment switching, quality-adjusted life expectancy was reduced in both arms, but incremental outcomes and the calculated ICERs showed only small changes. When a second treatment switch to basal-bolus insulin was included in the modelling analysis, quality-adjusted life expectancy was reduced and costs increased in both arms. As well as delaying initiation of basal insulin, once-weekly semaglutide 1 mg also delayed switching to basal-bolus insulin, and this resulted in greater clinical benefits, a smaller increase in costs, and a lower ICER than in the base case. Use of a less costly basal insulin formulation (NPH) had only a small impact on cost outcomes, with the ICER remaining similar to the base case analysis. Similarly, projected outcomes remained comparable to the base case analysis when sampling of patient characteristics and treatment effects was turned off.

Discussion

Greater improvements in HbA1c and BMI with once-weekly semaglutide 1 mg *versus* once-daily empagliflozin 25 mg as described in a previously published meta-analysis were projected to result in reduced cumulative incidence and delayed time to onset of diabetes-related complications, increased life expectancy, and increased quality-adjusted life expectancy over patient lifetimes. Increased costs of treatment with once-weekly semaglutide 1 mg were partially offset by reduced costs of diabetes related complications. The projected ICER of EUR 14 114 per QALY falls below the willingness to pay threshold of EUR 30 000 per QALY gained where an intervention is considered cost-effective, with this threshold used as a benchmark when comparing with other health technologies in Portugal.[16] Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy in Portugal.

The present analysis was based on clinical data from a meta-analysis, and the strengths and weaknesses of this data source must be considered to provide context. The meta-regression was conducted using individual patient data, allowing for a better isolation of the effect of a treatment on each outcome of interest than when trial-level data are used. Additionally, the analysis was able to capture a wider range of outcomes (such as lipid parameters) than is possible based on published trial-level data, giving a more accurate reflection of the differences in risk factors for diabetes-related complications. There was limited heterogeneity between the included clinical trials, with all having a similar design and inclusion/exclusion criteria. However, there were some differences in trial designs, such as blinding and the study duration ranging from 52 to 56 weeks. To assess the importance of study duration on outcomes the authors conducted an analysis using only the 52-week trials, and this confirmed that study duration did not significantly impact the results. One potential downside of the approach is that no common comparator was included as an anchor. Unanchored indirect comparisons assume that all potential prognostic factors and effect modifiers are identified, and this is difficult to confirm for this (or any other) meta-analysis. It should also be

noted that data from randomized controlled trials were used to assess the cost-effectiveness of interventions in the real world, and therefore there is an implicit assumption that efficacy is similar in randomized controlled trials and routine clinical practice.

A previously published network meta-analysis (NMA) has compared the efficacy of once-weekly semaglutide 0.5 mg and 1 mg with SGLT-2 inhibitors, including once-daily empagliflozin 25 mg using trial-level data.[27] The clinical trials included showed some overlap with the analysis based on patient-level data, capturing SUSTAIN 2, SUSTAIN 7, and EMPA-REG MET. This NMA found that the estimated treatment difference in change from baseline in HbA1c for once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg was −0.80% (95% confidence interval [CI] −1.04 to −0.58%). The estimated treatment difference in change from baseline in weight was −2.05 kg (95% CI −2.94 to −1.15 kg), and the estimated treatment difference in change from baseline in systolic blood pressure: −2.47 mmHg (95% CI −5.79 to 0.83 mmHg). These results are similar to those calculated in the meta-regression based on individual patient data, with both showing significantly greater reductions in HbA1c and weight. Due to the similarities between the results, conducting a scenario analysis using the NMA data was not considered necessary.

The present analysis is the first to assess the cost-effectiveness of once-weekly semaglutide in Portugal, and therefore provides new information for healthcare payers. To date, only one published analysis has compared once-weekly semaglutide with once-daily empagliflozin.[28] This was based on the NMA conducted using trial-level data, and assessed cost-effectiveness from a healthcare payer perspective in Spain.[27,28] The analysis projected that once-weekly semaglutide 0.5 mg and 1 mg were associated with incremental cost-effectiveness ratios of EUR 3 090 and EUR 625 per QALY gained, respectively, versus once-daily empagliflozin 25 mg. These results concur with the present analysis, suggesting that once-weekly semaglutide is likely to be cost-effective versus once-daily empagliflozin.

The present analysis aimed to reflect clinical practice, with glycemic control declining over time and subsequent use of insulin therapy, and a consequent reduction in HbA1c accompanied by an increase in BMI and risk of hypoglycemia. This approach is also in line with previously published cost-effectiveness analyses, both in the peer-reviewed literature and in the NICE multiple technology appraisal of SGLT-2 inhibitors.[14,15,29] Using a clinically realistic approach aimed to ensure that the present analysis can be useful to healthcare decision makers. However, the present analysis captured only one treatment pathway, with switching from GLP-1 receptor agonists or SGLT-2 inhibitors to basal insulin. In clinical practice, alternative treatment pathways may be used, such as addition of an SGLT-2 inhibitor to a GLP-1 receptor agonist, addition of a GLP-1 receptor agonist to an SGLT-2 inhibitor, or continuation of previous therapies alongside basal insulin. There is currently a lack of clinical data to allow modelling of more these complex treatment pathways, and this is an area for future study.

Both once-weekly semaglutide and once-daily empagliflozin have been shown to reduce the risk of major adverse cardiovascular events compared with standard care in the SUSTAIN 6 and EMPA-REG OUTCOME trials, respectively.[30,31] However, data from these cardiovascular outcomes trials (CVOTs) were not incorporated in the present analysis. To date, no risk equations for projecting long-term outcomes in people with type 2 diabetes that include data from CVOTs have been published. Such an approach is challenging, as CVOTs generally enroll participants at high risk of experiencing cardiovascular events, and it is currently unknown whether these benefits would also be observed in lower risk populations. Furthermore, diabetes medications impact conventional cardiovascular risk factors, and the separation of the impact of these changes from the impact associated with the treatments themselves is difficult. Early analyses suggest that capturing cardiovascular risk can have an important impact on the results of long-term analyses, and therefore including this in revised risk equations represents a key goal for modelling analyses in the future.[32]

The present analysis projected outcomes over patient lifetimes based on short-term data, and this is associated with inherent uncertainty, particularly around how risk factors change over time and how well risk equations based on historic data predict outcomes for modern patients. However, projection of long-term outcomes remains the best available option to inform decision making in the absence of long-term clinical trial data, and is recommended in health-economic guidelines. The impact of uncertainty on the present analysis has been mitigated as far as possible by using a model that has been extensively published and validated and by conducting extensive sensitivity analyses.[12,13]

Conclusion

Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy in Portugal, based on a willingness to pay threshold of EUR 30 000 per QALY gained.

Responsabilidades Éticas

Conflitos de Interesse: Davide Carvalho recebeu honorários de consultoria e como palestrante e foi membro dos conselhos consultivos da AstraZeneca, Bial, Boehringer Ingelheim, Lilly, Merck Serono, MSD, Novartis, Novo Nordisk, Sanofi e Servier. Catarina Costa é funcionária da Novo Nordisk, Lda. Nino Hallén e James Baker-Knight são funcionários da Novo Nordisk A/S. Barnaby Hunt recebeu honorários de consultoria da Novo Nordisk A/S.
Fontes de Financiamento: Este estudo foi financiado pela Novo Nordisk A/S.
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 pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: Davide Carvalho has received honoraria for speaking and consulting and has served as a member of advisory boards for AstraZeneca, Bial, Boehringer Ingelheim, Lilly, Merck Serono, MSD, Novartis, Novo Nordisk, Sanofi and Servier. Catarina Costa is an employee of Novo Nordisk, Lda. Nino Hallén and James Baker-Knight are employees of Novo Nordisk A/S. Barnaby

Hunt is an employee of Ossian Health Economics and Communications, which received consulting fees from Novo Nordisk A/S.

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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 were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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Artigo Original

Type 2 Diabetes Remission One Year After Bariatric Surgery: A Comparison Between Sleeve Gastrectomy and Gastric Bypass

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INFORMAÇÃO SOBRE O ARTIGO

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Bariatric Surgery;
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A B S T R A C T

Introduction: Laparoscopic Roux-en-Y gastric bypass (LRYGB) is considered the gold standard metabolic surgery. Type 2 diabetes (T2D) remission successfully achieved after laparoscopic sleeve gastrectomy (LSG) suggested that this procedure is not only a restrictive one, but it also has beneficial metabolic effects. The aim of this study was to compare the rate of T2D remission between patients submitted to LRYGB and LSG 1 year after surgery and to evaluate possible predictors of T2D remission.
Methods: A retrospective study including 112 patients with T2D submitted to bariatric surgery in Hospital de Braga from January 2011 to December 2016 was performed. Anthropometric and metabolic parameters were recorded before and 12 months after surgery. T2D remission was defined as glycated hemoglobin (A1c) < 6% and fasting plasma glucose (FPG) < 100 mg/dL without diabetes pharmacological treatment (DPT) at the 1-year post-surgery evaluation. The data was analyzed using the IBM SPSS® software version 25.0 and statistical significance was set at p <0.05.
Results:Twelve months after surgery, there was a reduction in mean body mass index (BMI) (-13.40±4.7 for LSG and -13.55±5.3 for LRYGB, p=0.878), mean FPG and DPT frequencies. Patients submitted to LRYGB presented a greater decrease in plasma fasting insulin and A1c (-0.85 ± 0.9 for LSG and -1.50 ± 1.6 for LRYGB, p=0.039). Patients submitted to LSG presented T2D remission rates similar to those of patients that underwent LRYGB (40% after LSG and 38.6% after LRYGB, p=0.893). Baseline A1c and age at the time of the surgery were predictors of T2D remission.
Conclusion: Younger patients with better T2D control and optimized preoperative glycemic control have better chances to attain T2D remission, independently of the type of surgery.

Palavras-chave:
Cirurgia Bariátrica;
Diabetes Mellitus, Tipo 2/cirurgia;
Gastrectomia;
Bypass Gástrico.

Remissão de Diabetes Tipo 2 Um Ano Após Cirurgia Bariátrica: Uma Comparação entre Gastrectomia Vertical Calibrada e Bypass Gástrico

R E S U M O

Introdução: *Bypass* gástrico em Y-de-Roux (*bypass*) é considerado o *gold-standard* da cirurgia metabólica. O sucesso na remissão da diabetes tipo 2 (DM2) após gastrectomia vertical calibrada (*sleeve*) sugeriu que esta cirurgia não é apenas restritiva, mas também tem efeitos metabólicos benéficos. O objectivo deste estudo foi comparar a eficácia do *bypass* e do *sleeve* na remissão da DM2 um ano após cirurgia e determinar possíveis factores preditores de remissão da DM2.
Métodos: Estudo retrospectivo com 112 doentes com DM2 submetidos a cirurgia bariátrica no Hospital de Braga, de Janeiro de 2011 a Dezembro de 2016. Colheram-se parâmetros antropométricos e metabólicos antes e 12 meses após a cirurgia. A remissão da DM2 foi definida por hemoglobina glicosilada (A1c) < 6% e glicose plasmática em jejum (GJ) < 100 mg/dL sem tratamento para a diabetes (TPD) na reavaliação 1 ano após cirurgia. Os dados foram analisados através do *software* IBM SPSS® versão 25.0 e estabeleceu-se significância estatística para p <0,05.

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Resultados: Doze meses depois da cirurgia, verificou-se redução do índice de massa corporal (IMC) (-13,40±4,7 após *sleeve* e -13,55±5,3 após *bypass*, *p*=0,878), GJ e número de doentes sob TPD. Doentes submetidos a *bypass* apresentaram uma maior redução na insulina plasmática em jejum e A1c (-0,85 ± 0,9 após *sleeve* e -1,50 ± 1,6 após *bypass*, *p*=0,039). Doentes submetidos a *sleeve* apresentaram taxas de remissão da DM2 semelhantes às dos doentes submetidos a *bypass* (40% após *sleeve* e 38.6% após *bypass*, *p*=0,893). A A1c inicial e a idade no momento da cirurgia foram preditores de remissão da DM2.

Conclusão: Doentes mais jovens, com DM2 melhor controlada e controlo glicémico pré-operatório optimizado têm maior probabilidade de alcançar remissão de DM2, independentemente do tipo de cirurgia.

Introduction

According to the World Health Organization (WHO), obesity, defined as a BMI ≥30 kg/m^2, is the first pandemic of the 21st century and an often-neglected public health problem. In 2016, more than 1.9 billion adults were overweight and, of these, over 650 million were obese.[1]

Type 2 diabetes (T2D) is one of the many comorbidities associated to obesity, with an incidence that quadrupled in the past three decades, accounting for 90% of all the cases of diabetes in the world. T2D is the ninth major cause of death worldwide and its chronic complications, mainly cardiovascular, are the leading cause of morbidity and mortality in these patients.[2]

Bariatric surgery is a surgical treatment for patients with obesity with a BMI > 40 kg/m^2 or a BMI > 35-40 kg/m^2 with at least one obesity-related comorbidity.[3] Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are the two most popular procedures performed worldwide.[3] LRYGB consists in the creation of a small stomach pouch that is anastomosed to the jejunum through a Roux-en-Y alimentary limb and this anatomical reconfiguration is responsible for malabsorption and consequent weight loss. It also induces neurohormonal alterations with significant positive metabolic effects.[4] Besides LSG's mainly restrictive effects that lead to weight loss, recent data shows that it also induces metabolic improvements.[5] The resulting hormonal changes increase insulin secretion and insulin sensitivity and improve overall glycemic control,[4,6,7] thus, both surgeries seem to be able to improve metabolic control in patients with T2D.[8] Metabolic surgery should be recommended as a treatment option for T2D in patients with BMI ≥ 35 and may be considered for patients with BMI between 30 and 34.9 kg/m^2 who do not achieve durable weight loss and improvement in T2D with nonsurgical treatment.[9] Interestingly, gut hormones follow a distinct profile after a gastric restrictive surgery compared with the one observed with intestinal bypass.[6] Therefore T2D remission rate after LSG has been considered inferior to LRYGB.[4,8,10-12] A systematic review and meta-analysis from 1990 to 2006 reported T2D remission rates from 56.7% to 95.1%, depending on the type of surgery.[10] Some further studies aimed to verify T2D remission rates 1 year after LSG and LRYGB, accordingly to American Diabetes Association (ADA) criteria, and found rates of 50%-66.7% and 74%-87.5%, respectively.[4,13] Recent articles that also used the ADA remission criteria reported remission rates of 35.3% after LSG and 37.1% to 52.5% after LRYGB.[12,14,15] Nevertheless, some authors detected no statistical differences between LSG and LRYGB T2D remission rates and the hypothesis whether LSG might have the same efficacy as LRYGB in inducing T2D remission has been raised.[5,11,13,16-18] Besides the type of surgery, other factors have been suggested as predictors of T2D remission: BMI < 30 kg/m^2, inferior BMI reduction, older age, longer T2D duration, higher preoperative fasting plasma glucose (FPG), higher baseline glycated hemoglobin (A1c), higher baseline waist circumference, higher visceral fat area and preoperative use of insulin are associated to lower T2D remission rates after metabolic surgery.[11-13,18-20] On the contrary, other studies showed that preoperative BMI, age, gender, duration of T2D and BMI variation did not predict T2D remission.[19,20-25]

The aim of this study was to compare T2D remission rates 1 year after LRYGB and LSG. The secondary goal was to evaluate predictive factors of T2D remission after bariatric surgery.

Material and Methods

A retrospective review of our institution's bariatric surgery database and electronic medical record system for patients who underwent bariatric surgery was performed. From January/2011 to December/2016, 112 patients with obesity and T2D underwent bariatric surgery in the Surgery Department of our institution, a tertiary and academic hospital, with a Bariatric Surgery Center. To be eligible for surgery, patients must had met the criteria of European guidelines for obesity surgical treatment: body mass index (BMI) ≥ 40 kg/m^2 or BMI 35–40 kg/m^2 with co-morbidities in which surgically induced weight loss is expected to improve the disorder. To be considered for surgery, patients should have failed to lose weight or to maintain long-term weight loss, despite appropriate surgical and/or non-surgical comprehensive medical care.[26]

Our center has experience in LRYGB and LSG and both surgeries were performed through laparoscopy and following a standard surgical protocol. In LRYGB, the gastric fond is mobilized and the horizontal section line is set at the third gastric vessel of the small curvature. An 11 mm orogastric calibration probe is introduced, constructing the gastric reservoir until the angle of His. The gastro-jejunal anastomosis is set at the first proximal 90 cm. The food duct resulting from the jejuno-jejunal anastomosis has 120 cm. During LSG the surgeon uses an 11 mm orogastric calibration probe to determine the gastric section line, then sectioned with an endoscopic stapler (Endo GIA), resulting in a 100 mL volume stomach, with preservation of the pyloric function.

Prior to hospital discharge, patients received a dietary plan, starting with a high protein, low-fat and soft diet, then gradually progressing to a common meal. Follow-up appointments occurred with nutritionist that evaluated anthropometry and food plan compliance, and with bariatric surgeons, who assessed clinical and biochemical status of the patients at 1 year after surgery. Blood was collected by venipuncture between 8 a.m. and 11 a.m. after an overnight fast. Biochemical parameters were measured using routine techniques. The presence or absence of glucose-lowering medication was collected based upon physician registries.

T2D was defined as FPG ≥126 mg/dL in at least two measurements, A1c ≥6.5% or prescription of any diabetes pharmacological treatment (DPT).[9] To define T2D remission, a modified version of the ADA criteria was used, considering T2D complete remission if A1c < 6% and FPG < 100 mg/dL and the absence of glucose-lowering drugs at the 1-year post-surgery evaluation.[27] Patients included had at least one evaluation of FPG or A1c when T2D remission determination was not possible. The variables test-

ed for predictors of remission were chosen through an exploratory analysis of the differences between T2D remitters and non-remitters. A1c was the selected variable to evaluate T2D control. BMI reduction was calculated through the difference between BMI at 1 year and baseline BMI. There were no patients lost to follow-up.

The collected data was analyzed using the software IBM SPSS® version 25.0 and statistical significance was set at p <0.05. For continuous quantitative variables, the existence of normal distribution was tested through histogram observation and kurtosis and skewness analysis. To describe variables, we used central tendency measures (mean and median) and dispersion measures (standard-deviation and percentiles 25-75) for quantitative variables and absolute numbers and percentages for qualitative variables. To compare continuous variables with normal and non-normal distribution between groups, a T-test for independent variables and a Mann Whitney test were used, respectively. A pairwise T-test and the Wilcoxon test were used, respectively to compare continuous variables with normal and non-normal distribution within groups. To analyze differences between and within groups of categorical variables, the Chi-Square test/Fisher's exact test and McNemar's test test were used, respectively. In the logistic regression model, to assess predictors of T2D remission, a stepwise regression with a backward elimination approach was performed.

This study has been approved by the ethical committee of Hospital de Braga (Ref.ª 91/2019).

Results

Of the 112 patients included in the study, 63 (56.25%) were submitted to LSG and 49 (43.75%) underwent the LRYGB procedure. Two of the patients submitted to LRYGB had previously undergone LSG at 4 and 5 years ago. All patients completed 1 year of follow-up. Table 1 exhibits the patients' characteristics prior to surgery. Patients submitted to LSG had a shorter median T2D duration than patients submitted to LRYGB, higher frequency of treatment with lifestyle measures, as well as a lower prevalence of DPT, both oral antidiabetics (OAD) and insulin therapy (IT). Regarding biochemical parameters, patients submitted to LSG presented baseline lower levels of FPG, FPI and A1c than patients submitted to LRYGB.

Table 1. Characteristics of the population prior to surgery

	LSG (n=63)	LRYGB (n=49)	*p*
Female (n;%)	47; 74.6	39; 79.6	0.535
Age (n;m±SD years)	63; 47.63 ± 11.7	49; 50.29 ± 10.0	0.207
T2D duration (n;md(P25-P75) years)	59; 3.00 (2.0 - 4.0)	49; 5.00 (2.0 - 7.5)	0.018
BMI (n;m±SD kg/m²)	62; 45.51 ± 7.6	49; 43.74 ± 5.8	0.179
FPG (n;m±SD mg/dL)	63; 130.27 ± 38.5	49; 153.45 ± 56.1	0.015
FPI (n;md(P25-P75) uUI/mL)	63; 13.70 (10.1-23.5)	41; 18.50 (11.4-35.5)	0.040
A1c (n;m±SD %)	56; 6.77 ± 1.09	46; 7.43 ± 1.5	0.013
No DPT (n;%)	10; 15.9	2; 4.1	0.045
With DPT (n;%)	53; 84.1	47; 95.9	0.045
Under OAD (n;%)	53; 84.1	47; 95.9	0.045
Under IT (n;%)	3; 4.8	12; 24.5	0.005

LSG=laparoscopic sleeve gastrectomy; LRYGB=laparoscopic Roux-en-Y gastric bypass; T2D=type 2 diabetes; BMI=body mass index; FPG=fasting plasma glucose; FPI=fasting plasma insulin; A1c=glycated hemoglobin; DPT=diabetes pharmacological treatment; OAD=oral antidiabetics; IT=insulin therapy

At 1-year postoperative evaluation, both groups (LSG versus LRYGB) presented statistically significant improvements on BMI (-13.40±4.7 *vs* -13.55±5.3), FPG (-29.69±31.8 *vs* -47.23±53.0), fasting plasma insulin (FPI) (-8.74 (-15.6– (-3.4)) *vs* -18.70 (-30.7– (-10.8))), A1c (-0.85±0.9 *vs* -1.50±1.6), as well as a reduction in the prevalence of DPT (83.6% to 44.3% *vs* 95.8 to 47.9%) (Table 2).

Table 2. Comparison of Body Mass Index, Fasting Plasma Glucose, Fasting Plasma Insulin, glycated hemoglobin and prevalence of Diabetes pharmacological treatment at 0 and 12 months after Laparoscopic Vertical Sleeve Gastrectomy and Laparoscopic Roux-en-Y Gastric Bypass

	LSG		
Variables	**0 months**	**12 months**	***p***
BMI (n;m±SD kg/m²)	59; 45.09 ± 6.8	59; 31.70 ± 5.7	<0.001
FPG (n;m±SD mg/dL)	42; 125.05 ± 34.7	42; 95.36 ± 20.5	<0.001
FPI (n;md(P25-P75) uUI/mL)	39; 14.60 (9.8 – 23.4)	39; 5.12 (4.0 – 8.9)	<0.001
A1c (n;m±SD %)	37; 6.73 ± 1.1	37; 5.88 ± 1.1	<0.001
DPT (n;%)	51; 83.6	27; 44.3	<0.001
	LRYGB		
Variables	**0 months**	**12 months**	***p***
BMI (n;m±SD kg/m²)	47; 43.85 ± 5.9	47; 30.30 ± 3.7	<0.001
FPG (n;m±SD mg/dL)	40; 154.15 ± 52.7	40; 106.93 ± 36.9	<0.001
FPI (n;md(P25-P75) uUI/mL)	27; 24.30 (15.5 – 39.4)	27; 3.72 (2.8 – 8.7)	<0.001
A1c (n;m±SD %)	35; 7.42 ± 1.6	35; 5.92 ± 1.2	<0.001
DPT (n;%)	46; 95.8	23; 47.9	<0.001

LSG=laparoscopic sleeve gastrectomy; LRYGB=laparoscopic Roux-en-Y gastric bypass; BMI=body mass index; FPG=fasting plasma glucose; FPI=fasting plasma insulin; A1c=glycated hemoglobin; DPT=diabetes pharmacological treatment

Nevertheless, patients submitted to LRYGB presented greater reductions in mean FPI and mean A1c comparing with patients submitted to LSG (Table 3).

Table 3. Comparison of Body Mass Index, Fasting Plasma Glucose, Fasting Plasma Insulin, glycated hemoglobin, prevalence of Diabetes pharmacological treatment and Diabetes remission 12 months after Laparoscopic Vertical Sleeve Gastrectomy and Laparoscopic Roux-en-Y Gastric Bypass.

Variables	**12 months after LSG**	**12 months after LRYGB**	***p***
BMI (n;m±SD kg/m²)	59; - 13.40 ± 4.7	47; -13.55 ± 5.3	0.878
FPG (n;m±SD mg/dL)	42; -29.69 ± 31.8	40; -47.23 ± 53.0	0.076
FPI (n;md(P25-P75) uUI/mL)	39; -8.74 (-15.6 – (-3.4))	27; -18.70 (-30.7 – (-10.8))	0.001
A1c (n;m±SD %)	37; -0.85 ± 0.9	35; -1.50 ± 1.6	0.039
DPT (n;%)	27; 44.3	23; 47.9	0.704
Diabetes remission (n;%)	20; 40.0	17; 38.6	0.893

LSG=laparoscopic sleeve gastrectomy; LRYGB=laparoscopic Roux-en-Y gastric bypass; BMI=body mass index; FPG=fasting plasma glucose; FPI=fasting plasma insulin; A1c=glycated hemoglobin; DPT=diabetes pharmacological treatment

Patients submitted to LSG presented similar T2D remission rates to those of patients that underwent LRYGB (40.0% for LSG and 38.6 for LRYGB, *p*=0.893), and there were no differences in the number of patients under DPT at 12 months (44.3% for LSG and 47.9% for LRYGB, *p*=0.704) (Table 3).

Regarding differences between patients that presented or failed to achieve T2D remission at the 1-year postoperative evaluation, the first group was younger, presented lower baseline mean FPG and A1c and had a lower baseline prevalence of DPT and IT. Moreover, after surgery they presented a higher BMI reduction compared to patients that did not achieve T2D remission criteria (Table 4).

Table 4. Type 2 Diabetes remitters and non-remitters' characteristics

Variables	Remitters	Non-remitters	*p*
LSG proportion (n;%)	20; 54.1	30; 52.6	0.893
Female (n;%)	31; 41.9	43; 58.1	0.334
Age (n;m±SD years)	37; 44.59 ± 10.4	57; 52.21 ± 10.7	0.001
T2D duration (n;md(P25-P75) years)	37; 3.00 (1.5 – 5.0)	55; 4.00 (2.0 – 6.0)	0.076
BMI (n;m±SD kg/m²)	37; 44.55 ± 5.9	57; 44.40 ± 7.0	0.913
FPG (n;m±SD mg/dL)	37; 121.54 ± 28.9	57; 156.67 ± 56.1	<0.001
FPI (n;md(P25-P75) uUI/mL)	37; 17.60 (11.8 – 31.5)	49; 13.20 (9.9 – 25.1)	0.220
A1c (n;m±SD %)	36; 6.47 ± 1.1	50; 7.69 ± 1.4	<0.001
DPT (n;%)	29; 34.1	56; 65.9	0.002
IT (n;%)	0; 0	14; 100	0.002
BMI variation (n;m±SD Kg/m²)	37; -15.18 ± 5.0	55; -12.25 ± 4.8	0.006
Diabetes remission (n;%)	20; 40.0	17; 38.6	0.893

LSG=laparoscopic sleeve gastrectomy; T2D=type 2 diabetes; BMI=body mass index; FPG=fasting plasma glucose; FPI=fasting plasma insulin; A1c=glycated hemoglobin; DPT=diabetes pharmacological treatment; IT=insulin therapy

Logistic regression identified baseline A1c and age as predictors of T2D remission (OR=0.386 (95% CI: 0.223-0.668) and OR=0.938 (95% CI: 0.893-0.985), respectively) (Table 5).

Table 5. Predictors of type 2 diabetes remission

Variables	OR	95% CI	*p*
A1c (%)	0.386	0.223 – 0.668	0.001
Age (years)	0.938	0.893 - 0.985	0.011

Logistic regression. Included covariable: BMI variation. OR = odds ratio; 95% CI = 95% confidence interval; A1c=glycated hemoglobin; BMI=body mass index

Discussion

While previously thought to be a restrictive surgery, LSG has also effects in several gut hormones that ultimately promote insulin sensitivity and improve glucose homeostasis.[4,5,7] In fact, in this study patients submitted to both surgeries presented similar frequencies of T2D remission at the 1-year postoperative evaluation. The first studies that compared LSG and LRYGB efficacy in T2D treatment showed that remission occurred later in time and in a lesser magnitude in patients submitted to LSG.[4,6-8,10-13] Authors hypothesized that the procedures differed in the magnitude of hormonal alterations responsible for T2D remission.[6] The Oseberg study, a single-center, triple-blind, randomized controlled trial defined T2D remission as A1c ≤6.0% without the use of DPT at 1 year after surgery and concluded that remission rates were higher after LRYGB than after LSG.[28] On the contrary, a systematic review and meta-analysis from 2007 to 2012 revealed no statistically significant differences in T2D remission between LRYGB and LSG (76% and 68% at 1 year, respectively).[16] Recent studies applying ADA's T2D remission criteria demonstrated that LSG is as effective as LRYGB,5,7,11,13,16-18 with remission rates at 1 year of 37% in patients submitted to LSG and 42% in patients submitted to LRYGB.19 It is important to note that the use of these standardized criteria reduced the remission rates in both procedures.[20] The present study showed that patients submitted to LRYGB and LSG achieved 38.6% and 40.0% T2D remission, respectively, with no significant differences in the rate of T2D remission or in the number of patients under DPT at 12 months. Nevertheless, we must take into account that the baseline characteristics of these patients were different between the group submitted to LSG and LRYGB, as this last presented a higher frequency of patients under DPT and a superior IT prevalence. There were no differences in the reduction of BMI and FPG in both groups, although a significantly greater reduction in FPI and A1c levels was observed in patients submitted to LRYGB. In accordance with our results, SM-BOSS study showed that both procedures allowed significant weight loss at 1 year, without statistical differences.[29] Kashyap *et al*. showed no differences in weight loss between LRYGB and LSG at 4 weeks post-surgery, but FPG and FPI were further reduced with LRYGB. Moreover, it was evidenced that LRYGB was responsible for a greater decrease in insulin resistance, C-peptide level and insulin secretion and an increase in GLP-1 responsiveness to meal.[11] The STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) study showed that LRYGB was responsible for a greater reduction in BMI, FPG, A1c and DPT compared to LSG. In fact, 28% of patients still needed DPT after LSG, whereas none of the patients was using glucose-lowering drugs 1 year after LRYGB.[17,21] These differences suggest that LRYGB could be superior in improving glycemic control comparing to LSG, and this might be explained by the pattern of hormonal response that seems to be slightly different from the one elicited by LSG. After LRYGB there seems to be a reduced secretion of amylin, cholecystokinin and lower responsiveness to PP, associated to an increase in bile acids. There is also a reduction in ghrelin and an elevation in GLP-1 and PYY.[7,21,30] Moreover, the length of the gastro-intestinal tract bypass has weight loss-independent effects in glycemic control.[31] It has been hypothesized that the rapid metabolic improvement that occurs after LRYGB is one of the key factors affecting T2D remission and latter, the recurrence rates. On the other hand, LSG is responsible for diminishing ghrelin, elevating GLP-1 and PYY and improving responsiveness to glucagon and PP. The lack of interference with amylin and cholecystokinin and the absence of a gastro-intestinal tract bypass may explain the lower remission rates previously reported in patients submitted to LSG.[4,21]

Several predictive factors for T2D remission have been described in literature, such as baseline BMI, age, gender, initial FPG, baseline A1c, BMI postoperative reduction, T2D duration, preoperative treatment with insulin, C-peptide level, type of surgery, baseline waist circumference and visceral fat area.[5,7,10,12,15,19,20,25,32] Higher T2D re-

mission rates have been documented in patients with better glycemic control and younger age, irrespectively of initial BMI and type of surgery.[8,15,19,22,25] Recent studies aimed to verify the efficacy of both procedures in diabetic patients with BMI <35 kg/m² and Panunzi *et al* and Xiao Du *et al* concluded that T2D remission rates were similar in patients with BMI <35 kg/m² and BMI ≥35 kg/m².[22,23] Ramirez et al demonstrated similar improvement in glycemic control 1 year after metabolic surgery, despite different baseline BMI, reinforcing that initial BMI is not a predictor of T2D remission.[19,20,24] The majority of studies have suggested that the type of surgery and gender do not influence T2D remission.[7,19-22,25] Several authors reported that a shorter duration of T2D may independently predict higher T2D remission rates and lower risk of relapse.[7,12,15,20,21,32-34] In a previous study,[7] a strong correlation between BMI reduction and insulin sensitivity improvement was found, with no statistically significant differences between LRYGB and LSG. Although the metabolic alterations responsible for the improvement of glycemic control remain uncertain, the weight reduction and the consequent increase in insulin sensitivity emerge as potential mechanisms.[5,7,19] Whether this effect is exclusively dependent of weight loss is still controversial.[19] On the other hand, some studies reported no influence of BMI variation in T2D remission, in accordance with our study results.[19]

In this study patients that presented T2D remission were younger, had lower A1c, lower FPG, lower prevalence of DPT or IT and experienced a superior BMI reduction at the 1-year postoperative evaluation, compared to patients that failed to achieve T2D remission. Baseline A1c and age emerged as predictors of T2D remission in the logistic regression model. Our results are in accordance with other that evidenced that baseline A1c and age correlate negatively with T2D remission.[8,15,22] There were no differences in mean age between patients submitted to LSG and LRYGB, which may explain the similar T2D remission rates. On the other hand, the fact that patients submitted to LSG had lower baseline A1c might have favored their T2D remission rates.

LSG might be an option to treat patients with obesity and T2D, although LRYGB could cause a greater improvement in glycemic control. Nevertheless, LSG is a simpler technic with lower morbidity and efficacy in weight loss and control of comorbidities such as T2D. It also has other advantages like accessibility to gastrointestinal tract, absence of anastomosis, minimal nutritional deficiencies and better food tolerance and quality of life.[6,38]

Independently of the type of surgery, we conclude that younger patients with better glycemic control will have greater odds of achieving T2D remission. Thus, it is fundamental to optimize preoperative A1c in order to aim for the best results. Regarding age, younger patients may have better odds of having T2D remission, so future studies should focus on what is the best age to have surgery aiming to achieve T2D remission, while minimizing adverse effects from the surgeries.

This study has some limitations that deserve comment. First, it was a retrospective study with an associated bias not susceptible to rule out. Second, the sample size was small, thus it is possible that the power was insufficient to detect differences in some outcomes. Third, there were some missing variables at 0 and/or 12 months. Finally, there were differences in the initial characteristics of the patients submitted to LRYGB versus LSG that could have affected the 1-year post surgery outcomes.

Conclusion

In this study, 1 year after bariatric surgery, patients submitted to LSG and LRYGB presented similar rates of T2D remission. Patients submitted to LSG also presented mean BMI and FPG reductions similar to patients submitted to LRYGB. In our regression model, age and baseline A1c were found to be predictive of T2D remission. Thus, younger patients with better T2D control and optimized preoperative A1c have better chances to attain T2D remission, independently of the type of surgery.

Future studies are necessary to evaluate the duration of T2D remission after metabolic surgery and to explore differences in long-term remission between both surgeries.

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 pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.
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Ethical Disclosures

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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 were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.
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Artigo Original

Relationship Between Weight Loss and Insulin Resistance After an Obesity Medical Treatment Program

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INFORMAÇÃO SOBRE O ARTIGO

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A B S T R A C T

Introduction: It is known the interdependent relationship between obesity and insulin resistance. Studies point to a correlation between weight loss and insulin resistance reduction. The aim of this study was to verify weight loss and to evaluate its correlation with insulin resistance in patients followed in our project named "TObe", in which patients with obesity lose weight through an intensive medical intervention organized by Endocrinology and Nutrition.
Methods: Retrospective, observational and analytical study of 54 non-diabetic obese patients, with twelve months of follow-up in the "TObe" project. Data was collected from clinical appointments, and the nutritional status was evaluated through Body Mass Index (BMI) and insulin resistance through HOMA-IR index. Statistical analysis was performed with SPSSvs22, with a significance level of 0.05.
Results: Forty five (83.3%) patients were female and mean age was 43.13±14.59 years. Median BMI at the first appointment was 38.65 (P25: 36.71; P75: 42.68) kg/m^2 and median HOMA-IR was 3.14 (P25: 2.19; P75: 4.90). At twelve months, mean BMI decreased to 37.45±5.75 kg/m^2 (p<0.001). HOMA-IR variated to a median of 2.36 (P25: 1.78; P75: 4.22) (p=0.131; n=22). There was a correlation between BMI and HOMA-IR at baseline (r=0.350; p=0.010), at 12 months (r=0.525; p=0.002) and between BMI and HOMA-IR variations throughout the 12 months (r=0.320; p=0.050). Although waist circumference and weight also correlated with HOMA-IR, BMI had the strongest association. Fasting serum insulin (FSI) had a strong and positive correlation with HOMA-IR at baseline and 12 months.
Conclusion: The implementation of the project "TObe" resulted in significant weight loss over 12 months. The relationship between BMI and HOMA-IR was confirmed, as well as the correlation between weight loss and insulin resistance reduction, which was stronger for lower BMI. BMI was the anthropometric parameter with strongest association with HOMA-IR. FSI was the only analytical parameter with correlation with HOMA-IR.

Palavras-chave:
Obesidade/tratamento;
Perda de Peso;
Resistência à Insulina.

Relação Entre Perda de Peso e Resistência à Insulina Após Programa de Tratamento Médico da Obesidade

R E S U M O

Introdução: É conhecida da literatura a relação interdependente entre obesidade e resistência à insulina. Vários estudos apontam para uma correlação entre perda de peso e diminuição de resistência à insulina. O objectivo deste trabalho foi verificar a perda de peso e a sua correlação com a insulinoresistência em doentes seguidos no nosso projeto "TObe", no qual doentes com obesidade perdem peso através de uma intervenção médica intensiva organizada por Endocrinologia e Nutrição.
Métodos: Estudo retrospectivo, observacional e analítico de 54 doentes obesos, não diabéticos, com seguimento de 12 meses no projeto "TObe". Os dados das consultas foram recolhidos, avaliado

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o estado nutricional através do Índice de Massa Corporal (IMC) e a resistência à insulina através do Índice HOMA-IR. A análise estatística foi realizada com o programa SPSSvs22, com nível de significância de 0,05.

Resultados: Dos 54 doentes incluídos, 45 (83,3%) eram do sexo feminino e a média de idades foi 43,13±14,59 anos. A mediana do IMC inicial foi de 38,65 (P25: 36,71; P75: 42,68) kg/m^2 e a mediana do HOMA-IR de 3,14 (P25: 2,19; P75: 4,90). Aos 12 meses verificou-se uma redução do IMC para 37,45±5,75 kg/m^2 (p<0,001). Houve variação do HOMA-IR para 2,36 (P25: 1,78; P75: 4,22) (p=0,131; n=22). Encontrou-se uma correlação entre o IMC e o HOMA-IR inicial (r=0,350; p=0,010), aos 12 meses (r=0,525; p=0,002) e entre a variação do IMC e HOMA-IR ao longo dos 12 meses (r=0,320; p=0,050). Apesar do perímetro abdominal e peso também se correlacionarem com o HOMA-IR, o IMC demonstrou associação mais forte. Verificou-se uma correlação forte e positiva entre a insulina sérica em jejum (ISJ) e o HOMA-IR no início do projecto e aos 12 meses.

Conclusão: A implementação do projeto "TObe" resultou em perda ponderal significativa aos 12 meses. Confirmou-se a relação entre o IMC e o HOMA-IR e a existência de correlação entre perda de peso e diminuição de resistência à insulina, sendo esta mais forte para IMC menor. O IMC foi o parâmetro antropométrico com associação mais forte com o HOMA-IR. A ISJ foi o único parâmetro analítico com correlação com o HOMA-IR.

Introduction

Nowadays obesity affects more than one third of the world's population, representing a serious public health threat.[1]

It results from a chronic imbalance between energy intake and energy expenditure leading to adipose tissue accumulation. Although the pathophysiological mechanism is not well understood, adipose tissue has a central role in metabolic syndrome. It is an endocrine organ that under a stressor secretes adipocytokines responsible for a state of chronic and low grade inflammation that has systemic adverse effects. This is also called meta-inflammation and leads to chronic diseases such as type 2 diabetes, hypertension, hypercholesterolemia, atherosclerosis, non-alcoholic steatohepatitis, obstructive sleep apnea, asthma and cancer.[1-6] For instance, various studies reinforce that the presence of inflammatory markers in obese patients is the link to insulin resistance and a risk factor for type 2 diabetes.[3-6] Nevertheless, there are other well documented theories besides inflammation, such as mitochondrial dysfunction, hyperinsulinemia and lipotoxicity.[3,7] Insulin resistance results in impaired glucose uptake by insulin sensitive cells in the presence of hyperinsulinemia, compromises the inhibition of hepatic glucose synthesis and the inhibition of lipolysis. It starts many years before the beginning of type 2 diabetes and its incidence in the elderly ranges from 35% to 50%.[3,8,9]

Understanding the obesity-induced insulin resistance could potentially identify therapeutic targets for several metabolic diseases.[2] In this context, an anti-inflammatory treatment for type 2 diabetes has been studied.[5] Another example is seen with the cell energy surplus theory, which states that the excess of ATP leads to insulin resistance and so reducing its production or increasing its utilization would improve insulin sensitivity. It is supported by the fact that many insulin-sensitizing drugs inhibit ATP production, and weight loss, exercise or calorie restriction reduce ATP in insulin sensitive cells.[3]

Currently, medical treatment for obesity involves lifestyle intervention concerning nutrition, eating behavior and physical activity. Eventually pharmacological treatment may be used to ameliorate compliance and weight loss.[10,11] Insulin-sensitizing drugs, namely metformin, may be used when insulin resistance is present, although weight loss is the most effective strategy to prevent type 2 diabetes.[12] Patients with pre-diabetes should engage a behavioral lifestyle intervention to achieve and maintain 7% loss of initial body weight.[13]

According to studies, a moderate weight loss of around 5% is enough to improve insulin sensitivity, which improves further as the weight loss continues.[6 7,14-18]

Lifestyle intervention may be responsible for 4%-15% weight loss and the amount of patients achieving more than 5% loss of total body weight varies from 33% to 55%.[19]

The goal of this study was to determine: the effectiveness of an intensive medical treatment program for patients with obesity, in terms of weight loss and insulin sensitivity improvement; the correlation between weight loss and insulin resistance.

Material and Methods

Study design and Patients

A retrospective study with non-diabetic patients with obesity referred by general physicians to our center, a tertiary and academic hospital, between January 2016 and July 2017, was performed. These patients were submitted to an intensive medical treatment program for obesity called "TObe Project – medical Treatment of Obesity".

This project involved a multidisciplinary team of Endocrinologists and Nutritionists that elaborated a follow up plan for one year. Endocrinology appointments were performed at 0, 2, 6 and 12 months. Nutrition appointments took place 2 weeks and 1 month after the first Endocrinology appointment and scheduled thereafter so that there were 2 appointments between each one of the Endocrinology evaluations. The purpose of the first Endocrinology appointment was to collect the clinical data with emphasis in obesity history, risk factors and comorbidities, to perform physical exam to characterize obesity and search for endocrinopathy features, to assess body composition through bioelectrical impedance analysis (InBody®), to request blood and urine analysis to exclude endocrine secondary causes of obesity and to evaluate risk factors and comorbidities such as diabetes or dyslipidemia. Each patient received a manual that contained information about the disease, its management and tables which could be filled with treatment adherence and its results. In the first appointment, the patient was encouraged to start a nutritional and physical activity plan. In Nutrition's first appointment it was again evaluated body composition through bioelectrical impedance analysis (Tanita®), collected nutritional history with the most frequently consumed foods in a day recall method, established the weight goal and provided a personalized dietary plan based in calorie restriction. Weight monitoring and dietary plan revision were the goals of further Nutrition appointments. The 2 months Endocrinology re-

evaluation was an opportunity to see the results of the blood and urinary tests and monitor weight loss. Medical treatment could be started if a comorbidity was diagnosed or not well controlled. The diagnosis of an endocrinopathy was an exclusion criteria for entering the project. Patients without a secondary cause for obesity engaged nutritional and physical activity modifications, following a calorie restricted nutritional plan and practicing 150 minutes of aerobic exercise per week. Patients were clinically reassessed at 6 months and if weight loss was inferior to 5%, pharmacological and/or surgical treatment were considered. Patients that initiated pharmacotherapy or were referred to bariatric surgery were excluded from this study. At 12 months, the patients were clinically and biochemically reevaluated.

Data collection

Waist circumference, weight, fasting serum glucose (FSG), fasting serum insulin (FSI) and glycated hemoglobin (HbA1c) were collected at baseline and at 12 months of the program. We evaluated nutritional status through body mass index (BMI) (weight (kg)/height^2 (m)) and insulin resistance with HOMA-IR index (FSG (mg/dL) x FSI (mU/mL)/405). HbA1c was determined by high-performance liquid chromatography method.

Statistical analysis

The collected data was analyzed using the software IBM SPSS® version 22.0 and statistical significance was set at p <0.05. For continuous quantitative variables, the existence of normal distribution was tested through histogram observation and kurtosis and skewness analysis. To describe variables, we used central tendency measures (mean for normal distribution variables and median for asymmetric variables) and respective dispersion measures (standard-deviation and percentiles 25-75) for quantitative variables and absolute numbers and percentages for qualitative variables. A pairwise T-test and the Wilcoxon test were used, respectively to compare continuous variables with normal and non-normal distribution within groups. The correlation between variables was determined by the Spearman's correlation method.

Ethical considerations

The study was conducted in accordance with the amended Declaration of Helsinki 2013 and informed consent was collected from all the participants. It was approved by the ethical committee of Hospital de Braga on 15th July 2019 (Refª 132_2019).

Results

The study included 54 patients with obesity without diabetes that followed twelve months of our intensive medical intervention. Fourty five (83.3%) were female and 9 (16.7%) male, with a mean age of 43.13 ± 14.59 years and a mean height of 1.60 ± 0.09 meters. Table 1 displays the characteristics of the population at baseline and at twelve months.

At twelve months of the nutritional and physical activity optimization, a significant reduction of waist circumference, weight, BMI and HbA1c was verified (Table 1).

The patients lost a median of 6.35 (P25: 1.63; P75: 12.88) kg, which corresponded to a median of 6.05% (P25: 0.368; P75: 13.45) of initial weight; 58.1% lost more than 5% of initial body weight; BMI decreased a median of 2.48 (P25: 1.13; P75: 5.83) kg/m^2.

A positive correlation between BMI and HOMA-IR at the beginning of the intervention (rho (54) 0.350; p=0.010) and at twelve months (rho (22) 0.525; p=0.002) was verified. HOMA-IR variation was positively correlated with BMI reduction over one year (rho (22) 0.320; p=0.050).

There was also a correlation between waist circumference and HOMA-IR, which was positive at baseline (rho (54) 0.383; p=0.004), between weight and HOMA-IR, also positive at the beginning of the study (rho (54) 0.491; p<0.001) and between FSI and HOMA-IR, positive at baseline and 12 months (rho (50) 0.402; p=0.004 and rho (22) 0.957; p<0.001, respectively) (Table 2).

Discussion

The medical treatment program for patients with obesity ("TObe" project) allowed a clinically significant weight loss of 6.05% (0.368 - 13.45) of initial weight, with 58.1% of patients losing more than 5% of initial weight at twelve months. Although a trend for reduction in FSG, FSI and HOMA-IR was noted, it was not statistically significant. According to previous knowledge, a reduction in the insulin resistance index was expected along with weight reduction.[6,7,14-16] This fact may be related to the small dimension of this population, but also to the high inter-individual variation of HOMA-IR. Patients with an insulin resistant phenotype would still have a high HOMA-IR even after significant

Table 1. Characteristics of the patients at baseline and at twelve months of intensive medical treatment of obesity.

	Baseline	Twelve months	*p*
Waist circumference (md(P25-P75) cm; n/m±SD cm; n)	120.50 (113.00 - 129.25); 54	109.59 ± 13.41; 50	<0.001
Weight (md(P25-P75) kg; n)	100.90 (92.10 - 110.90); 54	95.95 (87.34 – 106.60); 54	<0.001
BMI (md(P25-P75) kg/m^2; n/m±SD kg/m^2; n)	38.65 (36.71 - 42.68); 54	37.45 ± 5.75; 54	<0.001
FSG (m±SD mg/dL; n/md(P25-P75) mg/dL; n)	90.56 ± 8.37; 54	88.50 (85.75 – 95.50); 42	0.594
HbA1c (m±SD %; n)	5.30 ± 0.34; 52	5.08 ± 0.31; 38	<0.001
FSI (md(P25-P75) uUI/mL; n)	12.55 (9.09 - 21.75); 50	9.67 (8.11 – 17.35); 25	0.276
HOMA-IR (md(P25-P75); n)	3.14 (2.19 - 4.90); 54	2.36 (1.78 – 4.22); 22	0.131

BMI=body mass index; FSG=fasting serum glucose; HbA1c=glycated hemoglobin; FSI= fasting serum insulin; m=mean; SD=standard deviation; md=median; P25=25th percentile; P75=75th percentile; n=number of patients

Table 2. Correlation between HOMA-IR and other evaluated variables at baseline and 12 months of intensive medical treatment of obesity.

	r	*p*
BMI at baseline (n=54)	0.350	0.010
BMI at 12 months (n=22)	0.525	0.002
BMI variation (n=22)	0.320	0.050
Waist circumference at baseline (n=54)	0.383	0.004
Waist circumference at 12 months (n=20)	0.274	0.243
Weight at baseline (n=54)	0.491	<0.001
Weight at 12 months (n=22)	0.317	0.151
FSG at baseline (n=54)	-0.025	0.855
FSG at 12 months (n=20)	0.327	0.159
HbA1c at baseline (n=52)	-0.040	0.779
HbA1c at 12 months (n=17)	-0.056	0.831
FSI at baseline (n=50)	0.402	0.004
FSI at 12 months (n=22)	0.957	<0.001

BMI=body mass index; FSG=fasting serum glucose; HbA1c=glycated hemoglobin; FSI= fasting serum insulin

weight loss and would benefit from more intensive interventions in order to lose more weight. On the other hand, in a subset of patients it is possible to find important HOMA-IR reductions with minor weight losses.[20,21]

Nevertheless, this study confirmed the correlation between BMI and HOMA-IR, which was positive at baseline, meaning that patients with higher BMI were more insulin resistant. This fact was studied by Abbasi et al21 and others.9,17 HOMA-IR variation correlated positively with BMI reduction along the twelve months. Furthermore, the correlation between HOMA-IR and BMI was stronger at twelve months, when patients had lower BMI, which, to the best of our knowledge, was not described in any other published work until now. Patients with higher BMI should be advised to engage more vigorous lifestyle interventions. After one year, patients with lower BMI had more potential for improvements in insulin sensitivity than patients with higher BMI. For this reason, reinforcing lifestyle measures for further weight loss in patients with already important BMI reduction could lead to an even better improvement in insulin sensitivity status.

This study also revealed significant reductions in waist circumference and weight at one year of "TObe" project and both were associated with HOMA-IR at baseline. Once more, there were no statistically significant correlations at twelve months probably because of population size and missing data.

Despite the fact that BMI, waist circumference and weight correlated positively with HOMA-IR, BMI had the strongest association. These findings corroborate previous study results and reinforce the importance of anthropometric evaluation of patients with obesity through BMI, which is easily executable in clinical practice and correlates well with insulin sensitivity status and the risk of type 2 diabetes and other metabolic diseases.[6,9,16,17,21,22]

The positive and strong correlation detected between FSI and HOMA-IR both at the beginning and at the end of the study is in accordance to the literature,[23] namely to Vogeser *et al*.[20] that concluded that FSI may be a simpler biochemical marker and equally useful as HOMA-IR determination in the monitoring and guidance of lifestyle interventions for patients with obesity. The authors added that dosing FSG alone has no interest to evaluate insulin resistance, which is in accordance with our results. Several studies concluded that both FSI and HOMA-IR were associated with progression to type 2 diabetes.[24-26] Although there was a statistically significant reduction of HbA1c, there was no correlation between HbA1c and HOMA-IR. This result is not in accordance with the literature: a German study concluded that HbA1c may be a simple biochemical indicator for predicting insulin resistance in healthy and young (less than 50 years) German individuals.[27] Other studies report that HbA1c and FSG reflect insulin resistance and predict type 2 diabetes risk in a nonlinear form, whilst FSI and HOMA-IR have a linear correlation with type 2 diabetes.[2]8 This difference may explain why the association of HbA1c with insulin resistance was not detected in the present study, besides the small sample size. Moreover, Saravia *et al*[29] showed that FSI has a stronger association with insulin resistance, metabolic syndrome and its complications than HbA1c, although these results were obtained in a male population.

It is important to emphasize the limitations of this study: small dimension of the population; selection bias, with patients from one specific geographic area of our country, referred only by general physicians to our hospital; no control group; a mainly female population; missing some variables in the twelve month evaluation; no other method apart from the patient report to evaluate the adherence to food plan and physical activity advised in the "TObe" program; no categorization of patients concerning insulin resistance phenotype.

Conclusion

The medical treatment program for patients with obesity was effective, with 58.1% of patients losing more than 5% of initial body weight at twelve months and a median of 6.05% (0.368 - 13.45) of weight loss.

Patients with higher initial BMI were more insulin resistant and the correlation between BMI and HOMA-IR continued positive at the twelve months and stronger when patients had lower

BMI. Patients with higher BMI should engage intensive dietary modifications and physical activity in order to lose weight and improve HOMA-IR. Reinforcing lifestyle interventions for further weight loss in patients with already important BMI reduction could lead to an even better improvement in insulin sensitivity.

Although waist circumference and weight were also correlated with insulin resistance, BMI was the anthropometric parameter with the strongest association with HOMA-IR, which makes it the most reliable measurement to evaluate insulin sensitivity status and the risk of type 2 diabetes and other metabolic diseases in this population.

FSI strongly correlated with HOMA-IR, corroborating the hypothesis that it can be a simpler biochemical marker and equally useful as HOMA-IR determination in the monitoring and guidance of lifestyle interventions for patients with obesity.

Further multicentre studies are necessary to evaluate the degree of improvement in insulin sensitivity status according to the lifestyle modification-induced weight loss, adjusting the results by age and gender.

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 pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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Ethical Disclosures

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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).
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Artigo Original

Plant-based Diets in Type 2 Diabetes Management: Perception of Healthcare Professionals

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A B S T R A C T

Introduction: Nutrition therapy plays a central role in diabetes management and growing evidence supports the use of plant-based diets for both preventing and treating type 2 diabetes. The aim of this study was to (1) to assess the level of knowledge among healthcare professionals regarding the therapeutic use of plant-based diets in diabetes management and (2) identify the barriers hindering the recommendation of this eating pattern to diabetic patients.
Methods: A nationwide online questionnaire was applied to 254 healthcare professionals, mainly endocrinologists, general practitioners, and nutritionists. The questionnaire evaluated (1) level of knowledge on the subject, (2) dietary recommendation practices, and (3) perceived barriers to the recommendation of plant-based diets to patients.
Results: Fifty-two percent of participants had never heard of the use of plant-based diets in the management of type 2 diabetes and 53% scored ≤2, on a scale of 1 to 5, their own knowledge about plant-based diets. Only 15.4% recommended plant-based diets to their diabetic patients. Healthcare professionals who had knowledge on the use of plant-based diets in diabetes management were 2.5 times more likely to recommend this eating pattern to their diabetic patients. The main barriers identified were lack of support to patients (35.4%), lack of scientific evidence (27.4%), and nonacceptance (23.6%)/ noncompliance (24.1%) by the patients.
Conclusion: Knowledge about plant-based nutrition is suboptimal and incorrect or outdated notions on this subject are still prevalent. Future educational interventions targeting healthcare professionals could effectively reduce morbimortality of type 2 diabetes and the associated costs.

Dieta Vegetariana no Tratamento da Diabetes Mellitus Tipo 2: Perspetiva dos Profissionais de Saúde

R E S U M O

Introdução: A nutrição tem um papel central no tratamento da diabetes e existe cada vez maior volume de evidência a comprovar o papel das dietas vegetarianas no tratamento e prevenção da diabetes *mellitus* tipo 2. Este estudo teve como objetivos (1) avaliar o nível de conhecimento entre profissionais de saúde relativamente ao papel terapêutico das dietas vegetarianas e (2) identificar barreiras e promotores da recomendação deste padrão alimentar às pessoas com diabetes.
Métodos: Foi aplicado um questionário *online* a nível nacional a 254 profissionais de saúde, nomeadamente Endocrinologistas, médicos de Medicina Geral e Familiar, e Nutricionistas. O questionário avaliou (1) o nível de conhecimento sobre o tema, (2) as práticas de recomendação alimentar, e (3) as barreiras percecionadas na recomendação deste padrão alimentar aos doentes.
Resultados: Cinquenta e dois por cento dos participantes não tinha ouvido falar do uso das dietas

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vegetarianas no tratamento da diabetes *mellitus* tipo 2, e 53% pontuou ≤2, numa escala de 1 a 5, o seu próprio conhecimento sobre as dietas vegetariana. Os participantes que tinham conhecimento sobre o uso das dietas vegetarianas no tratamento da diabetes tinham uma probabilidade 2,5 vezes superior de recomendar este padrão alimentar aos seus doentes. As principais barreiras identificadas foram a falta de apoio aos doentes (35,4%), a falta de evidência científica (27,4%), e a não-aceitação (23,6%) /não cumprimento (24,1%) da dieta pelos doentes.

Conclusão: O nível de conhecimento sobre as dietas vegetarianas é subótimo e noções erradas ou desatualizadas sobre este tema são prevalentes. Futuras intervenções educacionais dirigidas aos profissionais de saúde podem ser eficazes na redução da morbimortalidade da diabetes *mellitus* tipo 2 e custos associados.

Introduction

Diabetes is a serious, chronic disease and it is currently considered to be a global epidemic. It is a major cause of blindness, kidney failure, myocardial infarction, stroke, lower limb amputation and premature death.[1]

According to the International Diabetes Federation, in 2017, the prevalence of type 2 diabetes (T2D) in Europe among adults was 9.1%, and the prevalence of impaired glucose tolerance was 5.6%. By 2045 these numbers are expected to increase to 10.8% and 6.6%, respectively.[2] Importantly, Portugal is the country with the highest non-adjusted prevalence of diabetes in Europe, and in 2017 the prevalence among the adult population was 14.9%.2 According to the OECD (Organisation for Economic Co-operation and Development) report, the treatment of diabetes and its complications represented 10% of the health expenditure in Portugal in 2017, which is equivalent to 1% of the nation's GDP.[3] It is therefore imperative to design and implement cost-effective measures that help reduce diabetes-associated morbidity and mortality in Portugal.

It is now well-established that nutrition therapy has a central role in diabetes management. Nutrition therapy can reduce glycated hemoglobin by 1.0% to 2.0%, a glucose-lowering effect equivalent to that of metformin.[4,5] According to the American Diabetes Association (ADA) guidelines, an individualized medical nutrition therapy program is recommended for all people with T2D. Recommended eating patterns in these guidelines include the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), and plant-based diets.[6] In addition, in the 2020 Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes it is stated that "All patients should strive to attain and maintain an optimal weight through a primarily plant-based meal plan".[7]

In fact, there is growing evidence supporting the use of plant-based diets for both preventing and treating T2D.[8,9] Plant-based diets are typically defined as eating patterns that promote plant foods such as grains, legumes, vegetables, fruits, and nuts, and avoid or exclude animal products, such as meat, fish, and dairy. Whole-food plant-based diets, in addition, avoid processed, artificial foods and added fats or sugars.[10] Plant-based diets can be further classified according to the amount and type of animal products they include (see Table 1). Interestingly, both the Mediterranean diet[11,12] and the Dietary Approaches to Stop Hypertension (DASH)[13] are frequently described in the literature as plant-based diets.

Table 1. Types of plant-based diets

Vegan	Excludes any food of animal origin.
Ovo-lacto vegetarian	Excludes meat and seafood; includes eggs and dairy.
Pesco vegetarian	Excludes meat; includes seafood, eggs and dairy.
Semi vegetarian	Vegetarian diet with occasional consumption of foods of animal origin. Also known as "flexitarian" diet.

Several studies have shown that diabetic patients adhering to a plant-based diet will likely decrease their anti-diabetic medication requirements, including both insulin units and oral drugs.[14-17] According to the meta-analysis conducted by Yokoyama *et al*, plant-based diets are assotiated with greater improvement in glycemic control than diets tradicionally recommended to diabetic patients (such as the diet described in the ADA 2003 guidelines).[18] Additionally, plant-based diets are associated with a reduced risk of cardiovascular disease (CVD),[18,19] which is the number one cause of death in the diabetic population. Some studies have also proven plant-based diets to be beneficial for both preventing and treating diabetic microvascular complications, particularly diabetic neuropathy[20] and nephropathy.[21-25] Benefits regarding diabetic retinopathy are yet to be proven.

It is worth of noting that even though plant-based diets are associated with significant weight loss, which is by itself protective against diabetes, the health benefits of plant-based diets are best explained by several independent mechanisms.[4,10] Other proposed mechanisms include increased insulin sensitivity, improved gastrointestinal hormone response, lower oxidative stress, endothelial disfunction and inflammation.[17,26-28] Some recent studies have also hypothesized that changes in the gut microbiome induced by the diet may play a role.[4,28-30]

Unfortunately, despite the body of evidence supporting the several health benefits of plant-based diets, these are often perceived to be too extreme, difficult, and unacceptable.[31,32] Health care providers frequently assume their patients will be unwilling to adopt such diets.[31,33] Contrary to this, several studies have reported high levels of adherence and acceptability[31,32,34,35] among patients. For instance, the 74-week randomized controlled trial (RCT) conducted by Bernard *et al*, revealed that a low-fat vegan diet can be equally acceptable as the 2003 ADA guidelines diet. The authors have proposed that not limiting portion sizes and not counting calories or carbohydrates, in addition to experiencing new foods and flavors, are some of the factors that explain the reported high acceptability.[32]

It is therefore crucial to identify the barriers faced by healthcare professionals (HCP) in recommending plant-based diets to their patients and to develop effective strategies to overcome these same barriers.[36]

The aim of this study was to (1) assess the level of knowledge among HCP regarding the therapeutic use of plant-based diets in diabetes management and (2) identify the barriers hindering the recommendation of this eating pattern to diabetic patients.

Material and Methods

This study was approved by the Ethics Committees of (1) Centro Hospitalar Universitário de São João/Faculty of Medicine, Universidade do Porto; (2) Regional Health Administration of

Lisbon and Tagus Valley; and (3) North Regional Health Administration.

An online questionnaire was sent to HCP nationwide, targeting endocrinologists, general practitioners, and nutritionists. The questionnaire was available between October 2018 and February 2019. HCP who did not have regular contact with diabetic patients were excluded. The final sample included 254 participants.

The questionnaire used were carefully designed by our team, having in mind the aim of the study, and using the questionnaire developed by Lee et al31 as a reference point. It consisted of eight close-ended items, designed to evaluate: (1) demographic variables, (2) level of knowledge on the subject, (3) dietary recommendation practices, and (4) barriers to the recommendation of plant-based diets to patients.

Absolute and relative frequency counts (n, %) were used to describe categorical variables. All analyses were conducted using *IBM SPSS Statistics 24*, with significance set at alpha = 0.05.

Results

The HCP sample is described on Table 2. Regarding personal diet, 83.1% of health professionals followed an omnivore diet. Those who reported their diet to be "lactose free" or "gluten free", for example, were reclassified as omnivores since these diets do not exclude nor avoid animal products.

Table 2. Characteristics of the healthcare professional sample (n=254)

Characteristic	Healthcare Professional Sample (number, %)
Profession	
Endocrinologist	75 (29.5%)
General Practitioner	147 (57.9%)
Nutritionist	22 (8.7%)
Other	10 (3.9%)
Working area (n=218)	
North	56 (25.7%)
Centre	18 (8.3%)
Lisbon and Tagus Valley	142 (65.1%)
Azores and Madeira	2 (0.9%)
Personal diet	
Vegan	3 (1.2%)
Ovo-lacto vegetarian	1 (0.4%)
Pesco-vegetarian	9 (3.5%)
Semi-vegetarian	22 (8.7%)
Omnivore[1]	219 (86.2%)

[1] Of these 8 participants reported adhering to the Mediterranean diet (on the open answer space). Note: Absolut frequencies may not add up to 254 due to missing responses.

A little over half of the participants (52.8%) had not heard of the use of plant-based diets as part of the treatment of diabetes. Of those who did, the most frequently cited source of information were scientific articles (Table 3).

On a scale of 1 to 5 (1 representing the lowest level of knowledge/skills and 5 the highest), 53% of participants scored ≤2 their own knowledge about plant-based diets and its benefits on diabetic patients; and 61% scored ≤2 their skills of advising on and planning a healthy plant-based diet appropriate for diabetic patients (Fig. 1).

Regarding participants' beliefs about the benefits of plant-based diets in diabetic patients, specifically improvement in glycemic profile and glycated hemoglobin levels, discontinuation of oral antidiabetic agents, BMI, body weight and waist circumference reduction, and total cholesterol and LDL cholesterol reduction, 57%-67% said they "agree" or "strongly agree", 18%-35% said they "do not agree nor disagree" and 6%-12% said they "disagree" or "strongly disagree" that plant-based diets do exert these effects (Fig. 2).

Regarding guidelines' dietary recommendations, 57.1% of participants were not aware that both the ADA and the Canadian Diabetes Association (CDA) guidelines currently recommend plant-based diets as an appropriate and desirable option for diabetic patients.

In terms of dietary advice practices, 15.4% of participants rec-

Table 3. Healthcare professional questionnaire results

Question/Answers	Results (number, %)
Have you ever heard of the use of plant-based diets as part of the treatment of diabetes?	
Yes	119 (47.2%)
No	133 (52.8%)
IF YES (n=116), where did you get that information?	
Guidelines	28 (24.1%)
Scientific articles	64 (55.2%)
Lectures/Seminars	37 (31.9%)
Other healthcare professionals	30 (25.9%)
Other	9 (3.5%)
Did you know that the current American Diabetes Association and Canadian Diabetes Association guidelines recommend plant-based diets as an appropriate and desirable option for diabetic patients?	
Yes (Aware of the recommendations of one or both associations)	106 (42.1%)
No	146 (57.9%)
Do you recommend plant-based diets to your diabetic patients?	
Yes	39 (15.4%)
No, I recommend other eating patterns	196 (77.2%)
No, I don't do any recommendation regarding diet	19 (7.5%)
IF YES (n=53), what kind of plant-based diet do you usually recommend?	
Vegan	4 (7.5%)
Ovo-lacto vegetarian	12 (22.6%)
Pesco-vegetarian	22 (41.5%)
Semi-vegetarian	34 (64.2%)
IF YES (n=60), how frequently do you do it?	
Frequently	24 (40.0%)
Occasionally	30 (50.0%)
Rarely	6 (10%)
IF NOT (n=207), why?	
There is not enough scientific evidence about this subject	55 (26.6%)
Adequate guidelines do not exist	39 (18.8%)
Patients cannot carry out this diet	51 (24.2%)
Patients do not accept this diet	50 (24.2%)
Meal planning in this diet is too difficult for the patients	43 (20.8%)
There is not enough support to the patients to help them follow this diet	72 (34.8%)
Other	59 (23.2%)

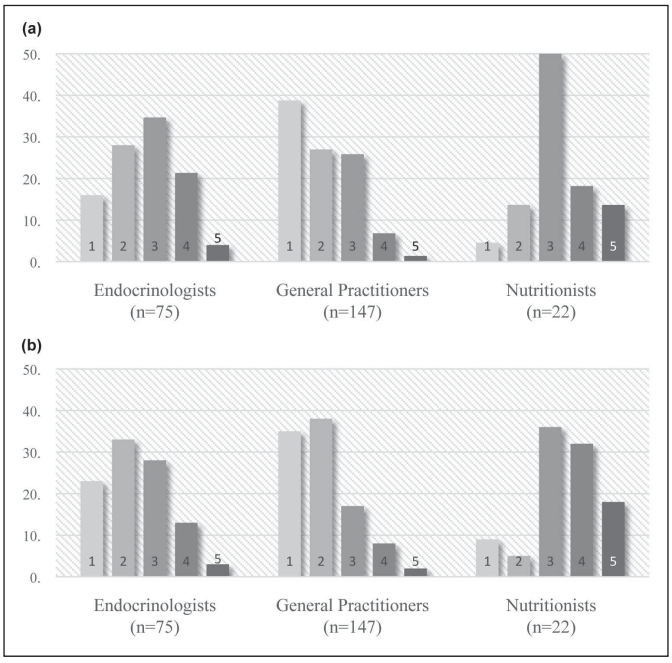

Figure 1. Healthcare professional self-reported level of (a) knowledge regarding the effects of plant-based diets on diabetic patients, and (b) skills of advising on and planning a healthy plant-based diet appropriate for diabetic patients, on a scale of 1 to 5 (1 representing the lowest level of knowledge/skills and 5 the highest).

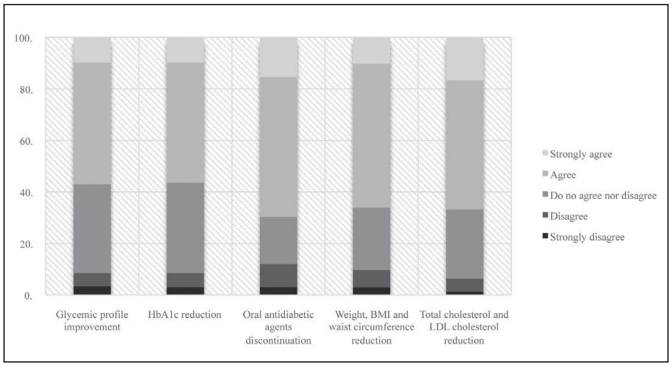

Figure 2. Healthcare professional beliefs regarding the effects of plant-based diets on several cardiometabolic endpoints

ommended plant-based diets to their diabetic patients. Of these, only 7.3% (4/53) recommended vegan diets. Less strict regimens, such as the semi-vegetarian or pesco-vegetarian were found to be more frequently recommended. Of the remaining 84.7%, 77.2% recommend other dietary patterns and 7.5% did not make dietary recommendations at all (Table 3).

Comparing areas of specialization, both endocrinologists and nutritionists reported significantly higher levels of awareness about plant-based diets (70%-74%). Interestingly, despite the lower level of awareness (31%), general practitioners reported levels of recommendation similar to those of other areas of specialization (Table 4).

HCP who had heard of the use of plant-based diets in diabetes management or those who were aware of ADA/CDA guidelines were 2.5 times more likely to recommend plant-based diets to their patients. However, rates of recommendation in this group were still low (22-24%) (Table 5).

No significant association was found between HCP personal

Table 4. Knowledge and dietary advice given by healthcare professionals according to area of specialization.

Knowledge and dietary advice given by healthcare professionals	Area of specialization			p [1]
	Endocrinologists (n=75)	Nutritionists (n=22)	General Practitioners (n=147)	
Have heard of using plant-based diets as part of the treatment of diabetes	69.7%	73.9%	30.6%	< 0.01
Are aware ADA and/or CDA guidelines recommend plant-based diets to diabetic patients	63.2%	47.8%	29.9%	< 0.01
Recommend plant based--diets to their diabetic patients	15.7%	9.5%	18.7%	0.72

[1] Refers to Fisher's exact test.

Table 5. Dietary advice given by healthcare professionals according to knowledge

Knowledge		Recommend plant-based diets to diabetic patients	p [1]
Have heard of using plant-based diets as part of the treatment of diabetes	Yes (n=119) No (n=133)	22% 9%	0.02
Are aware ADA and/or CDA guidelines recommend plant-based diets to diabetic patients	Yes (n=106) No (n=146)	24% 10%	< 0.01

[1] Refers to Fisher's exact test.

Table 6. Knowledge and dietary advice given by healthcare professionals according to personal diet.

Knowledge and dietary advice given by healthcare professionals	Personal diet		p [1]
	Omnivore (n=212)	Plant-based diet (n=42)	
Have heard of using plant-based diets as part of the treatment of diabetes	70%	31%	0.69
Are aware ADA and/or CDA guidelines recommend plant-based diets to diabetic patients	63%	30%	0.77
Recommend plant based-diets to diabetic patients	15%	17%	0.75

[1] Refers to Fisher's exact test.

diet and knowledge about the therapeutic use of plant-based diets in diabetic patients or its recommendation (Table 6).

Among those who did not recommend plant-based diets, the most commonly cited barriers were lack of support to patients (35.4%), lack of scientific evidence (27.4%), and nonacceptance (23.6%)/ noncompliance (24.1%) by the patients.

Questionnaire results are described in detail on Tables 3-6 and Fig.s 1-2.

Discussion

The main finding in our study was that having knowledge on the benefits of plant-based diets for diabetic patients significantly increases the likelihood of recommending this dietary pattern. This solidifies the importance of investing in medical student's nutrition curricula.[37]

An unexpected result was the similar recommendation rate reported by general practitioners, despite lower levels of knowledge compared to endocrinologists and nutritionists. This might be explained by the large focus general practitioners tend to give to preventive medicine, which often involves allocating more time and resources to promoting lifestyle changes among patients. Another possible explanation is that general practitioners recommend plant-based diets to diabetic patients for other health benefits other than improved glycemic control. It is possible that they do so with the goal of lowering the risk of cardiovascular disease, which is the number one cause of death among diabetic patients.

The barrier most frequently cited by HCP was lack of support to patients. Unfortunately, this is a major problem in most countries. Promoting diet changes is time-consuming and this is an impeditive barrier even for the most motivated physicians.[4,37] However, some tools do exist to help physicians educate their patients about plant-based diets. There are plenty of already existing resources that can be referred to patients, these include meal-planning guides and websites that list vegetarian restaurants. For example, in 2016 the Portuguese Directorate-General of Health (DGS) elaborated a guide for adopting a healthy vegetarian diet that is available online for anyone wishing to expand their knowledge on this diet.[38] Alternatively, patients can be referred to a nutritionist with experience in plant-based nutrition.[36,39]

Other prevalent barriers were non-adherence and non-compliance by patients, despite the evidence consistently reporting otherwise. Several studies have shown that a large portion of patients is in fact willing to adopt a more plant-based diet.[31,32,34,35] Hence, presumed unwillingness should not be used as a reason for not addressing plant-based nutrition.

Presumed non-compliance should also not be used as a deterrent. In 2015, Moore *et al* randomized 63 overweight and obese adults to five different diets: vegan, vegetarian, pesco-vegetarian, semi-vegetarian and omnivore. At six months, non-adherent vegan/vegetarian participants lost significantly more weight than non-adherent omnivore participants and had a significantly greater decrease in cholesterol intake than nonadherent pesco-vegetarian/semi-vegetarian or omnivore participants. Importantly, no differences were found in dietary adherence among the five dietary patterns. The authors therefore concluded that, even among non-adherent patients, recommending vegan or vegetarian diets may have a greater impact on health outcomes than recommending more moderate dietary patterns that include meat.[34]

Finally, 26.6% of healthcare professionals cited "not enough scientific evidence about this subject" as a barrier. This statement is categorically wrong and reflects how many physicians hold outdated beliefs about nutrition. Investment in healthcare professional's education is warranted. By doing so, more physicians will be propelled to implement this cost-effective, efficient strategy in their daily practice.[37]

Curiously, on open-ended questions, eight participants cited following a Mediterranean diet, and three participants mentioned recommending this eating patter to their patients. Similarly to plant-based diets, there are numerous published papers showing the beneficial effect of the Mediterranean eating pattern (MEP) on both diabetes-related and cardiovascular outcomes. For example, in the *PREDIMED* study, a multi-center randomized controlled trial including 7447 participants, after 4.8 years of follow-up, participants in the Mediterranean diet group had a hazard ratio of 0.69 of having cardiovascular events, compared to those in the control diet group.40 Admittedly, the MEP has not a consensual definition. However, according to both the ADA and the Portuguese Directorate-General, the Mediterranean eating pattern (MEP) is, in fact, plant-based (abundant in fruits, vegetables, cereals, beans, nuts and seeds), and red meat and eggs are consumed in small amounts and with low frequency.[11] Importantly, low meat consumption is one of the main proposed mechanisms for the health benefits of the MEP. Not stressing the importance of actively avoiding both processed and unprocessed meat might dampen the benefits obtained with the diet.

A similar study to ours was conducted in 2015 by Lee *et al*, in Canada, but because of the small sample size (n=25 HCP) strong conclusions could not be drawn. In this study, despite 72% of HCP reporting knowledge in the use of plant-based diets in diabetes management, only 32% recommended this dietary pattern to their patients. The most commonly cited barriers were plant-based diets not being realistic/being too difficult, low perceived acceptance by patients, and lack of clear clinical practice guidelines and diet-specific educational support.[31] These findings are in accordance with ours. The higher rates of knowledge and recommendation among Canadian HCP were expected since the vegan and vegetarian dietary patterns have been included in the CDA guidelines since 2013.

Importantly, the adoption of vegetarian diets is increasing worldwide, in fact, the prevalence of vegetarianism in Portugal has increased four-fold from 0.3% in 2007 to 1.2% in 2017.41 Nevertheless, many individuals may be getting information about plan-based diets from sources that are not trustworthy and may therefore be at risk of following an unhealthy vegetarian diet, which includes added sugars or refined grains, for example.[42,43] Therefore, both physician and medical student education on plant-based nutrition is warranted. To minimize the risk of nutrient deficiencies and maximize glycemic control it is essential for physicians to understand the principles of a well-balanced, healthy plant-based diet, which focus on whole foods, and steers away from added fats and sugars. Specifically, education should focus both on the theorical principles of plant-based nutrition, but also on the practical aspects of giving dietary advice, i.e., easy substitutes for animal source foods. Only then will HCP be able to provide dietary advice to motivated patients. In addition, it would be very helpful if hospitals could provide balanced and flavorful plant-based meals to hospitalized patients. This is not common practice in Portugal, yet it could be a possible way to familiarize both patients and physicians with plant-based diets. It is worth noting that in our study 92.5% participants reported recommending some dietary pattern (15.4% plant-based diets and 77.2% other dietary patterns), implying high rates of motivation to give dietary advice to patients, despite the mentioned barriers.

As most guidelines are in agreement that patients should follow the diet that they feel they can adhere to,[5,6,42,44] dietary advice should focus on motivating patients to reduce or exclude deleterious animal products and promote the consumption of protective foods, such a whole grains andvegetables,[36,37,42] while ensuring and adequate intake of both micro- and macronutrients.

Remarkably, despite somewhat high levels of awareness of guideline recommendations, only a fraction of HCP put these to practice. For example, among knowledgeable endocrinologists (63.2%), only one in four do recommend plant-based diets to patients. Future research should further investigate how to address barriers hindering faced by HCP when recommending plant-based diets and shape practical and effective strategies to motivate patients to adhere and maintain long-term adherence to plant-based diets.

One important limitation of this study is the convenience sampling method used. It can result in selection bias and thus limit the

generalization of the results. In fact, voluntary participants may be more knowledgeable about plant-based nutrition and thus the sample would be less representative of the population in study. Another limitation is the cross-sectional design of the study, which allows for associations to be drawn but not causation. The main strength of this study is having participants from different backgrounds. This was achieved by recruiting HCP from different areas of specialization and different localizations across the country.

Conclusion

The level of knowledge is suboptimal and incorrect or outdated notions on this subject are still prevalent among Portuguese HCP. Future educational interventions targeting HCP could effectively reduce the morbimortality of T2D and associated costs. Importantly, education of HCP on plant-based nutrition should cover both strict and flexible plant-based diets, such as the vegan diet on the one hand, or the DASH and Mediterranean diets on the other hand.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.
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Artigo Original

Gestational Diabetes: How Heavy is Obesity?

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A B S T R A C T

Introduction: Both obesity and gestational diabetes (GD) are independent risk factors for several pregnancy complications and neonatal adverse outcomes. With a growing incidence of metabolic syndrome, there is an increasing number of pregnant women with GD and obesity simultaneously. The objective of this study was to compare obstetric and perinatal outcomes between two groups of pregnant women with GD – Group 1 (G1) with normal body mass index (BMI) – 18.5-24.9 kg/m^2 – and Group 2 (G2) with obesity – BMI ≥30 kg/m^2.
Methods: It was a retrospective, comparative study between both groups (G1, n=284; G2, n=235). Inclusion criteria were: unifetal pregnancies with GD with surveillance in our institution between 2012-2018, excluding incomplete files. From this group we selected women with normal BMI and with obesity. The analysed parameters were demographic data, first-degree diabetes family history, previous GD and previous fetal macrosomia, gestational age at diagnosis of diabetes, weight gain during pregnancy, maternal, fetal and neonatal complications, metabolic control and therapy required, delivery and reclassification test. In the statistical analyses (p<0.05 as level of significance) we used the Chi-Square, Fisher, Kolmogorov-Smirnov and T-test.
Results: G2 had more 1st degree diabetes family history, previous GD and previous fetal macrosomia (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0.05). In G2 diagnosis of GD was earlier (p<0.05), excessive weight gain was higher (36% *vs* 13%, p<0.05), metabolic control was harder to achieve, needing pharmacological treatment in 53% *vs* 24% in G1, p<0.05. Chronic hypertension was more common in G2, but without statistical significance regarding preeclampsia. Gestational age at delivery was similar but G2 had more cesarean (37% *vs* 23%, p<0.05). G1 was associated with low birth weight (10% *vs* 5%, p<0.05), while G2 offspring had more macrosomia (8% *vs* 1%, p<0.05), neonatal hypoglycemia and respiratory distress syndrome, but admission to neonatal care unit was similar between groups. No differences were found in post-partum reclassification oral glucose tolerance test (OGTT).
Discussion and Conclusion: This study corroborates the burden of obesity as an additional risk factor in pregnant women with GD as it increases the risk of complications, fetal macrosomia and neonatal morbidities, with impaired metabolic control. Closer surveillance of these pregnancies should be reinforced, so that we can prevent maternal and neonatal adverse outcomes.

Palavras-chave:
Complicações na Gravidez;
Diabetes Gestacional;
Obesidade.

Diabetes Gestacional: Qual o Peso da Obesidade?

R E S U M O

Introdução: Tanto a obesidade como a diabetes gestacional (DG) são fatores de risco independentes para várias complicações da gravidez e desfechos neonatais adversos. Com o aumento da incidência de síndrome metabólica, o número de grávidas que apresentam simultaneamente DG e obesidade é crescente. O objetivo deste estudo foi comparar os resultados obstétricos e perinatais entre dois grupos de grávidas com DG – grupo 1 (G1) com índice de massa corporal (IMC) normal (18,5-24,9 kg/m^2) e grupo 2 (G2) com obesidade (IMC ≥ 30 kg/m^2).

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Métodos: Tratou-se de um estudo retrospetivo e comparativo entre os dois grupos (G1, n=284; G2, n=235). Foram critérios de inclusão gestações unifetais, com vigilância na instituição entre 2012-2018, excluindo-se processos incompletos. As variáveis estudadas foram: dados demográficos, antecedentes de diabetes em familiares de primeiro grau, DG prévia, macrossomia fetal anterior, idade gestacional no diagnóstico de diabetes, aumento ponderal durante a gravidez, complicações maternas, fetais e neonatais, controlo metabólico e terapêutica instituída, dados do parto e prova de tolerância à glicose oral (PTGO) de reclassificação.
Na análise estatística comparativa (p<0,05 como nível de significância) utilizaram-se os testes qui-quadrado, Fisher, Kolmogorov-Smirnov e Teste-t.
Resultados: No G2 verificou-se maior incidência de antecedentes familiares de diabetes, antecedentes de DG e macrossomia anterior (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0,05). No G2 verificou-se uma tendência de diagnóstico mais precoce da DG (p<0,05), o aumento ponderal excessivo foi superior (36% *vs* 13%, p<0,05) e o controlo metabólico mais difícil de atingir, com maior necessidade de instituição terapêutica farmacológica (53% *vs* 24% no G1, p<0,05). A hipertensão crónica foi mais comum no G2, sem diferenças estatisticamente significativas no desenvolvimento de pré-eclâmpsia.
A idade gestacional no parto foi semelhante entre grupos, mas o G2 apresentou maiores taxas de cesariana (37% *vs* 23%, p<0,05).
O IMC normal associou-se com maior frequência a baixo peso ao nascimento (10% *vs* 5%, p<0,05), enquanto a obesidade se associou a macrossomia (8% *vs* 1%, p<0,05). O G2 apresentou uma taxa superior de hipoglicemia neonatal e síndrome de dificuldade respiratória, sem diferenças na necessidade de internamento em unidade de cuidados neonatais. A prova de reclassificação revelou-se maioritariamente normal nos dois grupos, sem diferenças significativas.
Discussão e Conclusão: Este estudo corrobora a importância da obesidade como fator de risco acrescido nas grávidas com DG, tanto para complicações da gravidez como para maior dificuldade no controlo metabólico, maior risco de macrossomia fetal e de algumas complicações neonatais. Assim, reforça-se a necessidade de uma vigilância hospitalar adequada destas grávidas para prevenir desfechos neonatais adversos.

Introduction

Both obesity and gestational diabetes (GD) are independent risk factors for several pregnancy complications and neonatal adverse outcomes,[1-4] and their prevalence are increasing worldwide.[1]

The incidence of GD in obese women is higher than in the general obstetric population and the risk of GD increases with maternal BMI.[1]

Pregnancy, itself, is a condition of decreased insulin sensitivity and increased insulin response in women with normal glucose tolerance,[5] but in obese women there is an increase in insulin resistance by a mechanism that may involve higher plasma levels of triglycerides and non-esterified fatty acids and lower plasma levels of adiponectin, that predispose to GD.[1] Since they have subclinical decreased insulin sensitivity and β-cell dysfunction, the metabolic stress of pregnancy predisposes them to the manifestation of GD.[5]

Several studies reported that obese women with GD had a higher incidence of cesarean section, induced labor, gestational hypertension, preeclampsia, macrosomia, large for gestational age (LGA) newborns and maternal morbidity.[2-7] In one study the rate of preterm delivery was also increased in this group.[4] Not only obesity increases the risks associated with GD, but also the existence of an excessive gestational weight gain appears to enhance them.[2]

On the other hand, obesity without GD revealed to be an isolated risk factor for macrosomia, caesarean delivery, labor induction, low APGAR score and admission to neonatal intensive care unit and GD seemed to increase these risks.[4]

In contrast, the study of Hildén K *et al* (2019) revealed no interaction effect between GD and BMI for severe perinatal outcomes such as malformations, perinatal mortality, stillbirth, prematurity, low APGAR score, fetal distress or Erb's palsy.[8]

The HAPO study showed that maternal obesity was independently associated with fetal hyperinsulinemia[9] and other studies revealed that the long-term sequelae related to an abnormal in utero metabolic environment are also increased in these children.[5]

Even though obesity has a significant impact on the complications associated with GD, these complications can be minored, at least in part, by optimized glycemic control during pregnancy.[1,6]

In one study, GD was diagnosed earlier in overweight and obese women and the median fasting glucose values were superior in that groups.[3] Glucose intolerance associated with GD usually resolves postpartum, however, obese women with GD have twice the risk of subsequent type 2 diabetes compared with non-obese.[1]

In obese, proper diet and counselling prior to gestation and higher medical intervention during pregnancy are required to prevent macrosomia and LGA and to reduce maternal complications.[3]

The objective of this retrospective comparative study was to understand the impact of obesity in our population of pregnant women with GD. For that purpose, we compared obstetric and perinatal outcomes, as well as differences in the post-partum OGTT between two groups of pregnant women with GD – Group 1 (G1) with normal BMI and Group 2 (G2) with obesity.

Methods

Retrospective, comparative study between two groups (G1, n=284; G2, n=235). Inclusion criteria were: unifetal pregnancies with GD with surveillance in our institution between 2012 and 2018 (N=874), who have delivered in our hospital (62 excluded), obtaining a sample of 812 pregnancies. Diagnosis of GD was made by a fasting plasma glucose value ≥92 mg/dL on the first, second or third trimester or by glucose values ≥180 mg/dL or ≥153 mg/dL 1 hours and 2 hours after 75 g OGTT between 24 and 28 weeks of gestation.

From the main group we then selected pregnant women with normal BMI (G1) – n=284 and with obesity (G2) – n=235.The analyzed parameters were demographic data (age, country of origin), family and obstetric history, gestational age at diagnosis of diabetes, weight gain during pregnancy, maternal, fetal and neonatal complications, metabolic control (with HbA1c in 3rd trimester) and therapy required, mode of delivery, birth weight and results of reclassification OGTT.

Weight gain during pregnancy was classified according to Insti-

tute of Medicine 2009 recommendation[10]:

- Prepregnancy underweight (BMI <18.5 kg/m²) – recommended weight gain of 12.5-18 kg
- Prepregnancy normal weight (BMI 18.5-24.9 kg/m²) – recommended weight gain of 11.5-16 kg
- Prepregnancy overweight (BMI 25-29.9 kg/m²) – recommended weight gain of 7-11.5 kg
- Prepregnancy obese (BMI ≥30 kg/m²) – recommended weight gain of 5-9 kg

Polyhydramnios was defined as an amniotic fluid index ≥25 cm or when the deepest pocket was ≥8 cm, according to Fetal Medicine Barcelona.[11]

Hypertension in pregnancy, as defined by American College of Obstetrics and Gynecologists (ACOG),[12] was considered when women had systolic blood pressure ≥140 mg/dL and/or diastolic blood pressure ≥90 mmHg in two measures 4 hours apart; preeclampsia was defined as hypertension in pregnancy or systolic blood pressure ≥160 mg/dL or diastolic blood pressure ≥110 mmHg in two measures minutes apart and one of the following:

- 300 mg or more of proteinuria per 24 hour urine collection (or this amount extrapolated from a timed collection), protein/creatinine ratio of 0.3 mg/g or more or dipstick reading of 2+ (used only if other quantitative methods not available);
- Thrombocytopenia: Platelet count less than 100000/μL;
- Renal insufficiency: Serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease;
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal;
- Severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses;
- Pulmonary edema;
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.

The reclassification test was classified into four categories, according to WHO[13]: diabetes mellitus if the fasting value ≥126 mg/dL or the 2 hour value on a 75g OGTT ≥200 mg/dL, impaired fasting glucose if the fasting value is 110-125, impaired glucose tolerance if the 2 hour value is 140-199 mg/dL, normal if the first value is <110 mg/dL and the 2h value is <140 mg/dL. Fenton and Portuguese curves were used to access birth weight. Fetus were classified as large for gestational age (LGA - birth weight ≥90th centile), small for gestational age (SGA - birth weight ≤10th centile) and appropriate for gestational age (AGA - birth weight <90th and >10th centile)[14,15]. Macrosomia was defined as newborn weight ≥4000 g.

To evaluate metabolic control we used the HbA1c cut-off of 5.7%, as it is diagnostic of prediabetes according to ADA[16] and considering HbA1c values tend to be lower in pregnant compared with nonpregnant women.[17]

In the statistical analyses (p<0.05 as level of significance) we used the Chi-Square test or the Fisher exact test to examine association between two categorical variables, Kolmogorov-Smirnov test of normality, and T-test to compare the numerical variables..

The study was conducted in accordance with the amended Declaration of Helsinki as revised in 2013 and approved by the local institutional ethics committee – *"Comissão de Ética para a Saúde do HBA"* – on the 6th of November of 2020 (approval number 3399/2020).

Results

The mean maternal age was similar between groups (G1 33±5.7 y.o. *vs* G2 33±5.5 y.o.).

Obese women (G2) had more first-degree diabetes family history, previous GD and previous fetal macrosomia (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0.05).

In G2, diagnosis of GD was earlier (G1 21.8±8w *vs* G2 19.3±8.4w, p<0.05) – 44% in 1st trimester *vs* 29% in G1, 48% in 2nd trimester *vs* 57% in G1 and 8% in 3rd trimester *vs* 14% in G1, and excessive weight gain was higher (36% *vs* 13%, p<0.05), as we can see in Fig. 1.

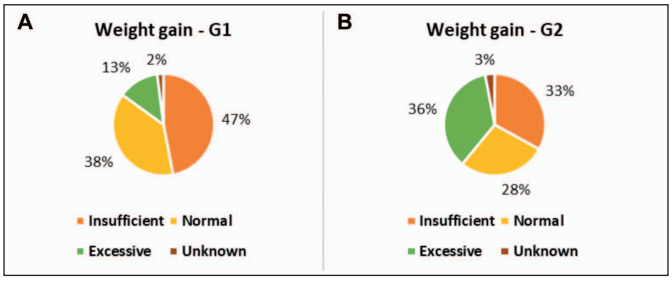

Figure 1. Weight gain in G1 (A) and G2 (B)

In obese pregnant women with GD, metabolic control was harder to achieve (Table 1). Although the mean HbA1c didn't show a significant difference between groups, G2 had higher rates of women with HbA1c≥5.7% in 3rd trimester. G2 had also a higher need for pharmacological treatment (53% *vs* 24% in G1) and combined therapy (metformin plus insulin), and those medications were started earlier, p<0.05.

Table 1. Differences in metabolic control and maternal-fetal complications

	G1	G2	*p* value
3rd Trimester HbA1c ≥5.7%	12.3%	25%	p<0.001
Mean HbA1c	5.2 ± 0.4%	5.5 ± 1.1%	NS
Need pharmacological treatment	24%	53%	p<0.001
Medication starting week	29 ± 6.7 w	26 ± 7.6 w	p<0.05
Needing insulin	8%	21.2%	p<0.001
Needing metformin	17.6%	46.4%	p<0.001
Insulin + metformin	2%	14.4%	p<0.001
Average daily dose of insulin	20 ± 25 U	26 ± 18 U	NS
Average daily dose of metformin	1254 ± 584 mg	1243 ± 599 mg	NS
Chronic hypertension	2.8%	21.3%	p<0.001
Gestational hypertension	2.8%	6%	NS
Preeclampsia	1%	3.4%	NS
Polyhydramnios	2.5%	1.7%	NS

Chronic hypertension was more common in G2, but no statistically significant differences in gestational hypertension or preeclampsia were found.

We found that gestational age at delivery was similar but G2 had higher cesarean rate, as well as higher rates of programmed delivery (induced labor or elective cesarean) and more macrosomia (all p<0.001). The average birth weight was higher in G2, while G1 was associated with higher rates of low birth weight newborns. Also, with both curves used we found higher rates of large for gestational age (LGA) newborns in G2 and of small for gestational age (SGA) newborns in G1 (p<0.05). While low birth weight was significantly associated with insufficient weight gain in normal BMI

mothers (p<0.01), the inverse was not verified in the obese group, where there were no statistical differences in weight gain in mothers with macrosomic newborns. The delivery and birth weight data are summarized in Table 2.

Table 2. Differences in delivery and birth weight between groups

	G1	G2	*p* value
Spontaneous labor	46%	26%	p<0.001
Inducted labor/elective cesarean	54%	74%	p<0.001
Gestational age at delivery	39 ± 1.2 w	39 ± 1.2 w	NS
Prematurity	4.9%	4.3%	NS
Vaginal delivery	77%	63%	p<0.001
Cesarean	23%	37%	p<0.001
Average birth weight	3 125 ± 468 g	3 329 ± 502 g	p<0.001
<2 500 g	10%	4.7%	p<0.05
≥4 000 g	1.4%	7.7%	p<0.001
Appropriate for gestational age			
Portuguese curves	80%	76%	p<0.001
Fenton curves	82%	84%	p<0.001
Large for gestational age			
Portuguese curves	5%	19%	p<0.001
Fenton curves	1%	8%	p<0.001
Small for gestational age			
Portuguese curves	15%	5%	p<0.001
Fenton curves	17%	8%	p<0.001
APGAR score <7 at 5th min	1%	1.7%	NS

APGAR scores were similar between groups. Regarding neonatal complications, G2 had more neonatal hypoglycemia and respiratory distress syndrome (p<0.05), but the rate of admissions to neonatal care unit was not significantly different between groups, despite it was slightly higher in G2 (9% *vs* 5.7%) (Table 3). The

Table 3. Neonatal morbidity

	G1	G2	*p* value
Admission to neonatal unit	5.7%	9%	NS
Neonatal hypoglycemia	0.4%	2.7%	p<0.05
Hyperbilirubinemia	5.8%	6.8%	NS
Respiratory distress syndrome	0.4%	3.6%	p<0.05
Neonatal sepsis	1.1%	3.6%	NS
Birth trauma	0.4%	0.5%	NS
Hypoxic encephalopathy	0%	0.5%	NS
Birth malformation	2%	0.5%	NS

main reasons of admission to neonatal care in G1 neonates were prematurity, neonatal sepsis and low birth weight, while in G2 the main reasons were neonatal sepsis, respiratory distress syndrome and hypoglycemia (Fig. 2).

There were no fetal or neonatal deaths in both groups and only one early pregnancy loss at 7 weeks of gestation occurred in G2.

No differences were found in reclassification OGTT, as shown in Table 4.

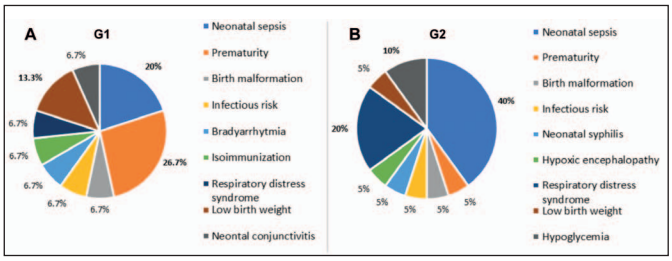

Figure 2. Main reasons for admission to neonatal care unit in G1 (A) and G2 (B)

Table 4. Post-partum reclassification with OGTT

	G1	G2	*p* value
Normal	76%	71%	NS
Impaired fasting glucose	0.7%	1.7%	NS
Impaired glucose tolerance	4.9%	6.3%	NS
Diabetes	0.4%	0%	NS
Lost to follow-up	18%	21%	-

Discussion and Conclusion

The results of this study corroborate the importance of obesity as an additional risk factor in pregnant women with GD.

We identified that obese women had more 1st degree diabetes history, previous GD and previous fetal macrosomia and the diagnosis of GD was earlier, which is in line with previous studies[3] and probably results from the fact that in obese women there is a status of insulin resistance.

In our study excessive weight gain was higher in obese women, which is in line with previous studies.[3] This reinforces the need of recognition by the women of the potential risks that overweight have in their pregnancies and in their own health and the need for a more intensive intervention in this group of women, with a multidisciplinary approach with the obstetrician, the nutritionist and the endocrinologist.

As expected, metabolic control was harder to achieve in obese women, as shown by the values of HbA1c in 3rd trimester and the higher need for pharmacological treatment and combined therapy with insulin plus metformin.

Chronic hypertension was more common in obese women, but no differences in gestational hypertension and preeclampsia, which contraries previous studies that showed a higher risk of preeclampsia in these women.[2-5,18] This can be justified by the current practice in our institution - screening of preeclampsia risk in 1st trimester applied to all pregnant women and starting low dose aspirin when indicated, to prevent early onset preeclampsia. Another hypothesis is that the increased metformin therapy in group 2 has protected those women from developing preeclampsia, as suggested by recent experimental studies in which metformin administration in early pregnancy decreased the rate of preeclampsia by a reduction in the production of antiangiogenic factors and improvement of endothelial dysfunction, probably through an effect on mitochondria.[19]

Gestational age at delivery was similar between groups but obese women had more cesarean and higher rates of induced labor, corroborating previous literature.[2,3,5]

As expected from previous studies,[2-4] obese women had more macrosomic newborns, with higher rates of LGA newborns in both weight classification curves we used.

Obesity was associated with neonatal hypoglycemia, in accordance with the HAPO study that revealed that maternal obesity was independently associated with fetal hyperinsulinemia.[9] In our study

respiratory distress syndrome was also more common in obesity group, but rates of admission to neonatal care unit were not statistically different between groups, despite it was slightly higher in G2. This contrasts with a previous study that showed that obesity without GD was a risk factor for treatment at neonatal unit and GD seemed to increase that risk in all BMI categories.[4]

Our study corroborates that of Hildén K *et al* (2019) that revealed no interaction effect between GD and obesity for newborn malformations, perinatal mortality, stillbirth, prematurity or birth trauma.[8]

It is known that obese women with a history of GD have twice the risk of subsequent type 2 diabetes compared with non-obese women.[1] Despite that, no differences were found in reclassification OGTT at 6-8 weeks post-partum between groups in our study. However, we must be aware that probably only a long-term follow-up would correctly identify those who will develop type 2 diabetes later in life, namely the ones with an unhealthy lifestyle and abnormal (higher) BMI.

With this study we can conclude that there is a need of a closer surveillance of these diabetic obese pregnant women, so that we can prevent maternal and neonatal adverse outcomes. Efforts should be made to reduce overweight and obesity prior to conception and to reduce excessive weight gain in obese women with GD.

The main limitation of this study is the fact that it was conducted in a single hospital, with a relatively small sample. However, this might end up being beneficial as a result of more standardized interventions by the reduced number of obstetricians involved in the surveillance of these pregnancies. The small sample size could be supplanted with the use of national data. Although, in that case, the outcomes would not be so comparable since surveillance and interventions in different institutions are not standardized.

Another limitation to our study is the fact that it did not include the overweight women with gestational diabetes. Although obesity is a disease with a continuous development spectrum, that includes the overweight, the authors considered that women with slight excess weight are not comparable to obese women in terms of cardiovascular risk. For that reason, since the number of overweight women is higher than the obese women group, the authors considered that it's inclusion in the study would skew the results. However, this study may lead to the development of a new prospective study to assess the impact of overweight in pregnancies complicated with GD.

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 pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.
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Artigo Original

Hipotiroidismo Congénito: A Experiência de uma Unidade de Endocrinologia Pediátrica

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Rastreio Neonatal;
Recém-Nascido;
Tiroxina.

R E S U M O

Introdução: O hipotiroidismo congénito é a doença endócrina congénita mais frequente. O diagnóstico e tratamento tardios resultam em atraso mental e alterações neurológicas irreversíveis.
O objetivo foi caracterizar os doentes com hipotiroidismo congénito e avaliar os outcomes clínicos e de reavaliação diagnóstica.
Métodos: Estudo retrospetivo e observacional, utilizando dados obtidos pela análise dos processos clínicos dos doentes, atualmente em seguimento, na unidade de endocrinologia pediátrica de um hospital terciário não considerado centro de referência.
Resultados: Foram incluídos 22 doentes com idade mediana de 7,5 anos (mínimo 4 meses; máximo 17 anos) sendo 12 do sexo feminino. A mediana do valor de TSH ao diagnóstico foi 201,5 mU/mL (mínimo 13,4; máximo 934) e da idade de início de tratamento foi 12,5 dias (mínimo 7; máximo 285). Apenas um doente não foi identificado no rastreio neonatal. A ecografia revelou disgenesia tiroideia em 70% (n=14) e só um doente realizou cintigrafia tiroideia. O sinal mais frequente ao diagnóstico foi a icterícia prolongada. Apresentavam anomalias congénitas associadas 27,3% (n=6) e história familiar de patologia tiroideia 18,2% (n=4). Após reavaliação diagnóstica aos 3 anos de idade, dois doentes foram reclassificados como hipotiroidismo congénito transitório. Nenhum doente apresentou alterações do crescimento estaturo-ponderal. Dez doentes realizaram avaliação formal do desenvolvimento psicomotor, dos quais 5 apresentavam alterações. Não se verificou associação entre: presença de sinais/sintomas ao diagnóstico com o valor de TSH inicial (p=0,694) nem com os achados ecográficos (p=0,285) e entre o valor inicial de TSH e os achados ecográficos (p=0,706). A presença de alterações do desenvolvimento psicomotor não mostrou ter associação com a idade de início de tratamento (p= 0,740) nem com o valor de TSH inicial (p=0,140)
Conclusão: Nesta coorte de doentes os dados são, na maioria, concordantes com os da literatura. Foi possível atingir o objetivo do desenvolvimento estaturo ponderal adequado. Contrariamente ao descrito noutros estudos, as alterações psicomotoras não pareceram ser relacionadas com atraso no início da terapêutica. Identificaram ainda a necessidade duma maior uniformização no seguimento.

Keywords:
Child;
Congenital Hypothyroidism/diagnosis;
Congenital Hypothyroidism/drug therapy;
Infant, Newborn;
Neonatal Screening;
Thyroxine.

Congenital Hypothyroidism: The Experience of a Pediatric Endocrinology Unit

A B S T R A C T

Introduction: Congenital hypothyroidism is the most common congenital endocrine disease. Late diagnosis and treatment results in mental retardation and irreversible neurological damage.
The objective was to characterize patients with congenital hypothyroidism and evaluate clinical outcomes and diagnostic reassessment.

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Methods: Retrospective and observational study, using data of the clinical processes of patients, currently under follow-up at the pediatric endocrinology unit of a tertiary hospital not considered a reference center.

Results: Twenty-two patients with a median age of 7.5 years (minimum 4 months; maximum 17 years) were included. Twelve patients (54.5%) were female. The median TSH measurement at diagnosis was 201.5 mU/mL (minimum 13.4; maximum 934) and the age at the start of treatment was 12.5 days (minimum 7; maximum 285). Only one patient was not identified in the neonatal screening. Ultrasound revealed thyroid dysgenesis in 70% (n=14) and only one patient performed thyroid scintigraphy. Prolonged jaundice was the most frequent sign at diagnosis. Of the total, 27.3 % (n=6) have associated congenital abnormalities and 18.2% (n=4) have family history of thyroid disease. After a diagnostic reassessment at 3 years old, two patients were reclassified as transient congenital hypothyroidism. None of the patient had growth disorders. Ten patients underwent a formal assessment of psychomotor development, and of these, five patients had abnormalities. No association was found between: the presence of signs/symptoms at diagnosis and the initial TSH value (p=0.694) neither with ultrasound findings (p=0.285) and between the initial TSH value and findings on thyroid ultrasound (p=0.706). The presence of abnormalities in psychomotor development did not show any association with the age at which treatment was started (p=0.740) nor with the initial TSH value (p=0.140).

Conclusion: In this cohort of patients, the data are mostly consistent with those in the literature. It was possible to achieve the goal of adequate growth. Contrary to that described in other studies, psychomotor changes did not seem to be related to delayed initiation of therapy. They also identified the need for greater uniformity in follow-up.

Introdução

O hipotiroidismo congénito (HC) é a doença endócrina congénita mais frequente[1] e caracteriza-se por uma diminuição da atividade biológica das hormonas tiroideias diagnosticada ao nascimento.[2] A prevalência estimada, em todo o mundo, é de 1:2000-4000 recém-nascidos (RN).[3-6] Em 2018, em Portugal, a incidência encontrada foi de 1:2481 recém-nascidos.[4]

Além de outras funções, as hormonas tiroideias desempenham um papel fundamental no desenvolvimento e maturação do sistema nervoso central desde estadios precoces, pelo que o seu défice pode acarretar consequências severas no desenvolvimento intelectual das crianças.[1,2] A maioria dos RN afetados não apresentam qualquer sintomatologia ao nascimento,[3] tornando-se por isso fundamental realizar um rastreio nos primeiros dias de vida que permita o diagnóstico e tratamento precoces, de forma a prevenir danos neurológicos e morbimortalidade associada.[5,6] Em Portugal, a inclusão do rastreio do HC no Programa Nacional de Diagnóstico Precoce ocorreu em 1981.[4]

O HC pode ser classificado como primário ou central (secundário ou terciário), permanente ou transitório.[6,7] O HC primário permanente é causado por uma disfunção primária da glândula tiróide e pode ser classificado em duas categorias: anomalias do desenvolvimento e da migração embrionária da glândula tiróide (disgenesia) ou defeitos no processo de síntese hormonal (dishormonogénese).[1,3,7] As disgenesias tiroideias (agenesia, ectopia ou hipoplasia) representam cerca de 85%-90% dos casos, sendo a maioria causada por ectopia (60%-65%) e agenesia (35%-40%).[2,5] A dishormonogénese é responsável por cerca de 10%-15% dos casos de HC primário permanente,[1,7] e resulta de defeitos enzimáticos hereditários que afetam direta ou indiretamente a disponibilidade intracelular de iodo, assim como a sua organificação, eventos cruciais no processo de síntese de hormonas tiroideias.[1] Na sua maioria, são de transmissão autossómica recessiva e cursam habitualmente com aumento do volume da glândula.[3,7] O HC central é causado pela falta do estímulo hipotálamo-hipofisário sobre a glândula tiroide por defeitos na produção de TSH (*thyroid-stimulating hormone* ou tireotropina), devido a disfunção hipotalâmica ou hipofisária,[3] e afeta cerca de 1:10000- 20000 RN's.[1] Nestes casos, a glândula tiroide apresenta-se com morfologia normal.[5] O défice isolado de TSH é uma causa rara de HC.[8] Habitualmente, está associado a défice de outras hormonas hipofisárias, tais como hormona do crescimento, prolactina, ACTH (ou corticotrofina), gonadotrofinas e/ou vasopressina (pan-hipopituitarismo).[5,8]

Nos casos de anomalia do desenvolvimento da glândula, o HC é sempre permanente. As formas com glândula eutópica e de normal morfologia são muitas vezes causas de HC transitório.[5] Este representa cerca de 40% dos casos, resolve durante os primeiros anos de vida[7] e está habitualmente relacionado com fatores extrínsecos à glândula tiróide, tais como fatores iatrogénicos (sobrecarga de iodo ou utilização materna de fármacos anti-tiroideus), ambientais (défice de iodo) ou autoimunes.[3,5,9]

O HC central transitório ocorre frequentemente nos RN prematuros, por imaturidade do eixo hipotálamo-hipófise-tiróide,[1,8] e excecionalmente também pode ocorrer em RN filhos de mãe com hipertiroidismo por doença de Graves.[8]

Em Portugal, o rastreio neonatal do HC é estabelecido através do doseamento da TSH numa amostra de sangue capilar colhida por picada no calcanhar, em papel de filtro (cartão de Guthrie), entre o terceiro e sexto dia de vida do RN.[1,4] Esta estratégia baseada no doseamento da TSH é sensível para a deteção de HC primário, incluindo casos ligeiros em que a TSH é elevada e os níveis de T4 total se mantêm normais. Contudo, não deteta casos de hipotiroidismo central, em que a TSH não está, por definição, aumentada face aos baixos níveis de T4 total, nem deteta casos com elevação tardia da TSH.[9]

No HC o dano cerebral depende diretamente do tempo decorrido desde a instalação do hipotiroidismo e o início de terapêutica adequada.[2] Assim, após confirmação do diagnóstico de HC, o RN deve iniciar de imediato terapêutica com levotiroxina oral.[1]

A deteção precoce do HC através do Programa Nacional de Diagnóstico Precoce permite evitar o atraso mental observado nas crianças com diagnóstico tardio.[2] É, ainda, imprescindível um seguimento estreito dos doentes com HC, tanto clínico como analítico.

O presente estudo tem como objetivo caracterizar os doentes com HC e avaliar os resultados clínicos à data atual e de reavaliação diagnóstica.

Material e Métodos

Foi realizado um estudo observacional e retrospetivo, utilizando dados obtidos pela análise dos processos clínicos de todos os doentes com HC, seguidos na unidade de endocrinologia pediátrica de um hospital terciário, não considerado centro de referência para esta patologia.

Os doentes atualmente com idade superior a 18 anos foram excluídos por o seu seguimento ser, à data do estudo, realizado por uma unidade de adultos.

Foram avaliadas variáveis demográficas (idade, sexo, idade gestacional, peso ao nascimento, idade de diagnóstico, idade de início de tratamento), achados imagiológicos (ecografia e/ou cintigrafia tiroideia) e analíticos (doseamento inicial de TSH), história familiar de patologia tiroideia, anomalias congénitas associadas, avaliação de desenvolvimento psicomotor e crescimento estaturo-ponderal e reavaliação diagnóstica aos 3 anos de idade.

Análise estatística

As variáveis quantitativas foram expressas como valores medianos e de intervalo (mínimo; máximo) e as variáveis qualitativas como valores absolutos e percentagem. Para a análise dos dados, foi utilizado o programa informático *Statistical Package for the Social Sciences* - SPSS versão 20.0(R), através de testes não-paramétricos, dada a distribuição não normal da amostra. O nível de significância estatística adotado foi o de $p< 0,05$.

Resultados

Desde 1993 foram seguidos nesta unidade um total de 40 doentes. Foram incluídos no estudo 22 doentes, com uma idade mediana de 7,5 anos (mínimo 4 meses; máximo 17 anos), sendo a maioria do sexo feminino (n=12; 54,5%). A mediana da idade gestacional foi de 38 semanas (mínimo 26; máximo 41) e do peso ao nascimento foi de 2990 g (mínimo 650 g; máximo 3860 g).

A Fig. 1 mostra a distribuição do número de diagnósticos por ano.

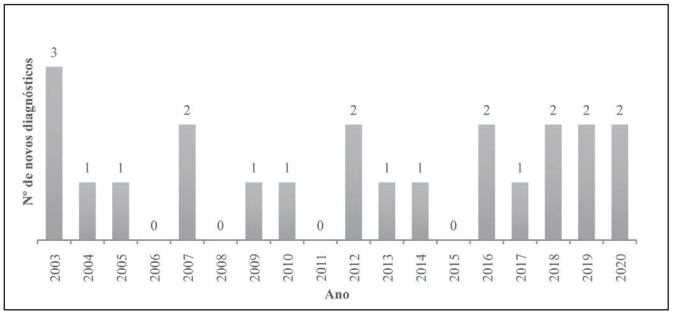

Figura 1. Distribuição do número de novos diagnósticos por ano.

Dezassete doentes foram inicialmente seguidos noutras unidades. Apenas um doente não foi identificado através do rastreio inserido no Programa Nacional de Diagnóstico Precoce (diagnóstico aos 43 dias de vida).

A mediana do valor de TSH ao diagnóstico foi de 201,5 mU/mL (mínimo 13,4; máximo 934) e a mediana da idade de início do tratamento foi de 12,5 dias (mínimo 7; máximo 285). Ao diagnóstico, nove (40,9%) doentes apresentavam algum sinal/sintoma, sendo a icterícia prolongada o mais frequente (n=9), seguido da hipotonia (n=2) e hipoglicemia (n=1). Não se verificou associação entre a presença de sinais/sintomas no momento do diagnóstico com o valor de TSH inicial (p=0,694). Ao diagnóstico, 20 (91%) doentes realizaram ecografia tiroideia e apenas um (4,5%) doente realizou cintigrafia tiroideia. Na ecografia tiroideia, 7 (35%) doentes apresentavam agenesia, cinco (25%) ectopia e dois (10%) achados compatíveis com hipoplasia tiroideia. Em 5 casos (25%) a ecografia não mostrou alterações e num doente (5%) foi inconclusiva. Nos casos de glândula tiroide ectópica (n=5), a localização sublingual foi a mais frequente (n=4). Não foi encontrada associação entre os achados ecográficos e o valor de TSH inicial (p=0,561) nem com a presença de sinais/sintomas ao diagnóstico (p=0,285). Foi encontrada história familiar de patologia tiroideia em quatro (18,2%) doentes. Seis doentes (27,3%) apresentavam anomalias congénitas sendo a pielectasia a mais frequente (n=2).

A Tabela 1 resume as variáveis demográficas e de caracterização dos doentes.

Após a reavaliação diagnóstica aos 3 anos de idade, 2 doentes foram reclassificados como HC transitório.

Nenhum doente apresentou alterações no crescimento estaturo-ponderal. Dez doentes (45,4%) realizaram avaliação formal do desenvolvimento psicomotor, sendo que em 5 foram identificadas alterações: 2 doentes apresentavam nível cognitivo global ligeiramente inferior à média, 1 doente com nível muito inferior, 1 doente com ligeiro atraso na área da locomoção e 1 doente com atraso da linguagem. A presença de alterações do desenvolvimento psicomotor não mostrou estar relacionada com a idade de início de tratamento (p=0,740) nem com o valor de TSH inicial (p=0,140).

Discussão

Considerando a incidência de HC encontrada no último relatório do Programa Nacional de Diagnóstico Precoce[4] (1:2481) e o número de nascimentos por ano no hospital de realização do estudo (3172 RN em 2019), verifica-se que o número de diagnósticos por ano posiciona-se dentro do expectável e encontra-se estável ao longo dos últimos anos, conforme se pode verificar na Fig. 1. A predominância do sexo feminino na amostra está também de acordo com os dados nacionais e internacionais.[4,5] Relativamente ao doente não identificado pelo rastreio inserido no Programa Nacional de Diagnóstico Precoce, tratava-se de um RN prematuro de 26 semanas de idade gestacional e com extremo baixo peso ao nascer (650 g), ou seja, com características frequentemente associadas a elevações tardias da TSH, o que num programa de rastreio baseado no doseamento de TSH, pode conduzir a um resultado falso negativo.[1,8,9] Com isto, reforça-se a importância dos clínicos manterem um elevado grau de suspeição para avaliar a existência de hipotiroidismo em qualquer RN ou lactente com sinais ou sintomas sugestivos ou com outra patologia de risco, independentemente do resultado do rastreio neonatal.

No que respeita à idade de início do tratamento com levotiroxina, a mediana encontrada está de acordo com as *guidelines* internacionais, que recomendam que o tratamento deverá ser iniciado tão precocemente quanto possível, e preferencialmente nas primeiras duas semanas de vida.[6] O doente com início mais tardio do tratamento, corresponde a um doente inicialmente seguido numa outra unidade de endocrinologia e que foi interpretado como um caso de hipotiroidismo subclínico. Nestes casos, segundo os consensos internacionais, quando os doentes apresentam níveis de T4 livre normais, é lícito não iniciar tratamento imediato e manter vigilância clínica e analítica.[3,6,9]

Tal como descrito na literatura, a maioria dos doentes apresentava-se assintomático ao diagnóstico.[3,8,10] Nos doentes sintomáticos, o sinal/sintoma mais frequente foi a icterícia prolongada, como descrito por Ünüvar *et al*.[11] Tal como no presente estudo, não foram encontradas descrições na literatura de associação do valor de TSH ao diagnóstico com a presença de sinais/sintomas.

Segundo as *guidelines* europeias,[6] ao diagnóstico deverá ser realizado um exame imagiológico da glândula tiroide, que poderá ser a ecografia e/ou a cintigrafia tiroideia. Como demonstrado pelos resultados apresentados na nossa amostra, a ecografia tiroideia

Tabela 1. Variáveis demográficas e de caracterização dos doentes

Total	**n= 22**	
Idade (mediana, mín.; máx.)	7,5 anos	4 meses; 17 anos
Sexo		
Feminino (n; %)	12	54,5
Masculino (n; %)	10	45,5
Idade gestacional (semanas; mediana, mín.; máx.)	38	26; 41
Peso ao nascimento (gramas; mediana, mín.; máx.)	2990	650; 3860
TSH ao diagnóstico (mU/mL; mediana, mín.; máx.)	201,5	13,4; 934
Sinais/sintomas ao diagnóstico (n; %)	9	40,9
Icterícia prolongada (n)	9	
Hipotonia (n)	2	
Hipoglicemia (n)	1	
Idade de início de tratamento (dias; mediana, mín.; máx.)	12,5	7; 285
História familiar de patologia tiroideia (n; %)	4	18,2
Mãe com agenesia parcial (n	1	
Mãe com doença de Graves (n)	1	
Avó paterna com bócio (n)	1	
Mãe com tiroidectomia por adenoma e avó com carcinoma tiroideu (n)	1	
Anomalias associadas (n; %)	6	27,3
Pielectasia (n)	2	
Atrésia esofágica (n)	1	
Surdez neurossensorial (n)	1	
Hipospádias (n)	1	
Diplegia espástica (n)	1	

foi o exame de imagem de primeira linha. Apenas dois doentes não realizaram ecografia tiroideia ao diagnóstico, sendo que em ambos o seguimento inicial foi feito por outras unidades. Contudo um destes doentes realizou cintigrafia tiroidea no momento do diagnóstico, que revelou ausência de captação de iodo. Na nossa unidade, a cintigrafia tiroideia é um exame de segunda linha, devido à exposição à radiação, custos elevados e frequente indisponibilidade dos radiofármacos. A cintigrafia tiroideia, atualmente, raramente é realizada ao diagnóstico, estando reservada para o momento de reavaliação diagnóstica após os 3 anos de idade, quando a ecografia não permite o diagnóstico definitivo. Relativamente aos achados ecográficos, a disgenesia tiroideia foi o achado mais frequente (em 70% dos casos), em concordância com o descrito por outros trabalhos.[5,12-15] Vários estudos apontam que os doentes com HC permanente apresentam valores mais elevados de TSH ao diagnóstico, comparativamente aos doentes com HC transitório.[15-18] Na nossa amostra esta associação não se verificou dado que não foram encontradas diferenças significativas dos valores medianos de TSH inicial com os diferentes achados ecográficos. Ünüvar *et al*[11] relataram a ausência de diferenças significativas na sintomatologia entre doentes com HC permanente e com HC transitório, tal como na nossa amostra em que não foi encontrada associação entre os achados ecográficos e a presença de sinais/sintomas ao diagnóstico.

Cerca de 10% dos RN com HC apresentavam outras anomalias congénitas nomeadamente cardíacas, genitourinárias, gastrointestinais ou esqueléticas, sendo as anomalias cardíacas as mais frequentes. O estrabismo e a surdez neurossensorial são alterações comuns nestes doentes, pelo que o seu rastreio deve ser realizado precocemente.[1,2,3,5,9] No presente estudo, a proporção de doentes com outras anomalias congénitas foi ligeiramente superior, contudo outros estudos já relataram uma incidência mais elevada e semelhante ao encontrado na nossa amostra.[19,20] Nesta amostra, contrariamente ao descrito na literatura, as anomalias do aparelho geniturinário foram as mais frequentes.

Independentemente de se tratar de um HC permanente ou transitório, o tratamento com levotiroxina deverá manter-se sem interrupções durante os primeiros 3 anos de vida, por forma a garantir que os níveis séricos hormonais se mantêm normais até ao completo desenvolvimento cerebral.[9] A agenesia ou a ectopia tiroideia garantem que estamos perante um caso de HC permanente.[1] Contudo, nos doentes com glândula tiroide eutópica (com ou sem bócio) ou nos doentes sem etiologia evidente após a avaliação imagiológica inicial, deverá ser realizada uma reavaliação diagnóstica aos 3 anos de idade por forma a excluir-se um HC transitório, com consequente possibilidade de suspensão do tratamento.[1,5,6] Tendo em conta os achados ecográficos iniciais, seis doentes apresentaram indicação para reavaliação diagnóstica. Em dois doentes esta reavaliação não foi realizada por ainda não terem atingido a idade indicada. Nos restantes quatro doentes, dois foram reclassificados como tendo um HC transitório e um doente ficou com o diagnóstico definitivo de HC permanente por agenesia tiroideia. O outro doente ainda não foi submetido a reavaliação apesar de atualmente já ter 4 anos de idade, em parte devido às contingências causadas pela pandemia COVID-19. Dos dois doentes que não realizaram ecografia tiroideia ao diagnóstico, um apresenta um HC permanente dados os achados da cintigrafia tiroideia e o outro ainda tem menos de 3 anos de idade. Assim, na amostra de 18 doentes, após reavaliação diagnóstica, encontramos 16 (88,9%) doentes com HC permanente e dois (11,1%) doentes com HC transitório. Estas proporções são bastante diferentes comparativamente ao descrito por outros estudos, que apontam para 40%-54% de casos de HC transitório.[5,7,21,22] Contudo, à data da realização do estudo, os nossos dados apresentam um importante viés que se deve ao facto de quatro doentes ainda não terem diagnóstico definitivo (dois RN pré-termo com muito baixo peso ou extremo baixo peso ao nascimento, um RN de termo com baixo peso ao nascer e um RN de termo com síndrome de dificuldade respiratória com necessidade de internamento em cuidados intensivos) existindo uma forte possibilidade de estarmos perante casos de HC transitório.

Todos os doentes apresentaram um crescimento estatural e ponderal adequado à idade o que é concordante com a literatura, que indica que doentes com HC diagnosticados precocemente através do rastreio neonatal, sob tratamento adequado e seguimento regular apresentam padrões de crescimento normais e atingem uma estatura final adequada.[1,6,23]

Apesar do HC ser a causa mais comum para atraso mental, o tratamento atempado e rigoroso permite um desenvolvimento neurológico normal.[1,23,24] O coeficiente de inteligência (QI) dos doentes tratados de forma precoce e adequada é normal e semelhante ao QI de crianças sem HC. Em alguns casos pode ser detetada uma disfunção cerebral mínima, como alterações do comportamento, alterações da linguagem ou da motricidade fina, com pouca ou nenhuma interferência na vida diária. Habitualmente estas situações estão relacionadas com uma idade de início de tratamento superior aos 15-21 dias de vida, dose sub-óptima de levotiroxina (por tratamento inadequado ou pouca adesão ao tratamento), gravidade do hipotiroidismo inicial e níveis de T4 livre desadequados durante o seguimento.[2,6,9,10] As guidelines europeias recomendam que o desenvolvimento psicomotor e a progressão escolar sejam monitorizadas e registadas em todas as crianças com HC. Nas crianças com formas graves da doença (agenesia tiroideia, concentrações muito baixas de T4 livre ao diagnóstico ou concentrações muito altas de TSH ao diagnóstico), com controlo endócrino sub-óptimo, especialmente durante o primeiro ano, ou provenientes de famílias economicamente desfavorecidas, deve ser prestada maior atenção a atrasos do desenvolvimento e dificuldades de aprendizagem.[6] Na nossa amostra, 10 doentes realizaram avaliação formal do desenvolvimento. Dos restantes doze doentes, seis ainda apresentam idade inferior a 3 anos, mas verificamos que existem seis doentes que apesar de terem indicação ainda não realizaram a avaliação formal do desenvolvimento, o que poderá implicar um atraso no diagnóstico de alterações do desenvolvimento e consequente atraso na implementação de estratégias de melhoria/correção das mesmas. Relativamente aos cinco doentes com alterações do desenvolvimento, todos iniciaram levotiroxina nos primeiros 16 dias de vida, sendo que o doente com alterações mais graves (atraso cognitivo global muito inferior à média) foi o que iniciou tratamento mais precocemente, aos 9 dias de vida. Contrariamente ao descrito na literatura não foi verificada relação entre a presença de alterações do desenvolvimento com a idade de início de tratamento nem com o valor de TSH ao diagnóstico. Contudo, outros estudos publicados relatam achados semelhantes aos encontrados na nossa amostra.[24-26]

Identificamos como viés e limitações deste estudo, a sua natureza retrospetiva que limita e prejudica os dados obtidos, o pequeno tamanho da amostra e o facto do seguimento de alguns doentes ter sido inicialmente realizado por outras unidades. Atendendo a que a nossa unidade não é centro de referência para esta patologia, o número de novos diagnósticos pode estar subestimado, dado que alguns doentes da nossa área de influência podem estar a ser seguidos por outras unidades. Os resultados obtidos corroboram, na sua maioria, as descrições da literatura o que evidencia o acertado diagnóstico, tratamento e seguimento prestado a estes doentes. Este estudo permitiu ainda identificar algumas falhas no seguimento dos doentes o que conduziu à atualização do protocolo de atuação da unidade, segundo as diretrizes internacionais mais recentes.

Em conclusão, a deteção do HC através do Programa Nacional de Diagnóstico Precoce revela-se de fundamental importância para o diagnóstico precoce e atempado destes doentes, permitindo evitar os danos neurológicos e morbimortalidade associada a diagnósticos tardios. Pela possibilidade de erros ou resultados falsos negativos no rastreio, os clínicos devem manter um elevado grau de suspeição, independentemente do resultado do rastreio neonatal. Enfatizamos com este estudo, a importância do tratamento precoce e seguimento estreito dos doentes de forma a prevenir as sequelas da doença, e com o objetivo de alcançar padrões de crescimento e neurodesenvolvimento semelhantes a crianças saudáveis.

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 pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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Artigo Revisão

Síndrome de Turner: Implicações na Idade Adulta

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Síndrome de Turner.

R E S U M O

A síndrome de Turner é a alteração cromossómica mais comum em mulheres, causada pela ausência total ou parcial do cromossoma X. Caracteriza-se por baixa estatura, disgenesia gonádica e envolvimento multissistémico, condicionando um aumento da morbilidade, mortalidade e redução significativa da qualidade de vida. Considera-se, assim, fundamental uma abordagem integrada e multidisciplinar destas mulheres na idade adulta. Este artigo procura descrever as principais implicações da síndrome de Turner na idade adulta bem como rever as mais recentes recomendações para o seu seguimento médico.

Keywords:
Adult;
Comorbidity;
Turner Syndrome.

Turner's Syndrome: Implications for Adult Life

A B S T R A C T

Turner syndrome is the most common chromosomal abnormalities in women, due to total or partial loss of the X chromosome. It is characterized by short stature, gonadal dysgenesis and systemic involvement, that leads to an increase in morbidity and mortality and a decrease in quality of life. Therefore, a multidisciplinary approach to these women in adulthood is mandatory. This article aims to describe the main implications of Turner syndrome and provide recommendations for its management in adult life.

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Introdução

A síndrome de Turner constitui uma das alterações cromossómicas mais comuns, causada pela ausência total ou parcial do cromossoma X, com ou sem mosaicismo, em indivíduos fenotipicamente femininos. Associa-se a um envolvimento sistémico com múltiplos achados clínicos que, classicamente, incluem baixa estatura, disgenesia gonádica e linfedema congénito.[1]

Tem uma incidência anual de 1/2500 a 1/3000 nascimentos do sexo feminino[2] e estima-se que afete aproximadamente 3% dos fetos femininos, mas a elevada ocorrência de abortos espontâneos faz com que apenas 1% destes fetos sobreviva até ao termo da gravidez.[3] O principal foco dos cuidados de saúde vai desde o diagnóstico pré-natal ou após o nascimento até à idade pediátrica e adolescência. No entanto, atualmente, tornou-se mais evidente que, na idade adulta, as mulheres com ST estão mais suscetíveis a alguns distúrbios como patologia cardiovascular, endócrina, renal, ortopédica, gastrintestinal, oftalmológica, entre outras, que parecem levar a um significativo aumento da morbilidade, da mortalidade e a uma diminuição da qualidade de vida.[4]

Neste contexto, considera-se fundamental a vigilância multidisciplinar das mulheres adultas com ST. Neste artigo procura-se fazer uma revisão das principais implicações associadas à ST na idade adulta segundo as mais recentes recomendações para o seguimento médico.

Genética

A ST, citogeneticamente, pode ser caracterizada por: monossomia do cromossoma X, presença de um cromossoma X anormal ou mosaicismo com outra linha celular e 45 X. A monossomia X é o cariótipo mais comum, que resulta de um anormal emparelhamento dos cromossomas sexuais durante a meiose materna e paterna ou por perda cromossómica durante a gametogénese. Na maioria dos casos o cromossoma X tem origem materna, no entanto, não parecem existir fenómenos de *imprinting*, já que o fenótipo não varia consoante o cromossoma X seja de origem materna ou paterna.[5] As anomalias estruturais do cromossoma X resultam em quebras no cromossoma X com o subsequente rearranjo de sequências do cromossoma.[3] O mosaicismo resulta da não disjunção cromatídea nas primeiras divisões do zigoto, resultando em 2 ou mais clones celulares.

Apesar de nem sempre se verificar uma relação genótipo-fenótipo, existem algumas particularidades associadas a subgrupos de diferentes cariótipos. Assim, o cariótipo 45 X está associado a um fenótipo mais grave e, mais frequentemente, a linfedema. Recentemente, tem vindo a aumentar a frequência de mulheres com mosaicismo 45 X/46 XX que têm um fenótipo mais fruste, das quais 40% apresentam puberdade e menarca espontâneas, apesar de ser comum a evolução para falência ovárica precoce. O cromossoma X em anel está associado a distúrbios neuropsiquiátricos com escassas anomalias estruturais congénitas. O isocromossoma Xq é a anomalia estrutural mais comum e está associada a doenças autoimunes, otites de repetição e diminuição da acuidade auditiva.[1] A presença de material genético do cromossoma SRY (45 X/46 XY) aumenta o risco de desenvolvimento de gonadoblastoma, um tumor raro que surge quase exclusivamente em gonadas disgenésicas na presença de mosaicismo Y. Por este motivo recomenda-se a pesquisa de material genético Y por técnicas de DNA ou FISH (*fluoresence in situ hybridization*) em todos os casos de ST associados à existência de fragmentos cromossómicos de origem desconhecida ou a sinais de virilização.

Manifestações Clínicas e Diagnóstico

Na ST existe um amplo quadro clínico que pode ir desde fenótipos graves com baixa estatura severa, disgenesia gonádica, linfedema, cardiopatia e dismorfia facial até a fenótipos mais ligeiros, com pequena redução da estatura ou falência ovárica prematura.[1,3] Também as manifestações clínicas variam com a idade.

A Tabela 1 ilustra as principais características clínicas associadas à ST e a sua prevalência aproximada.

Tabela 1. Manifestações clínicas mais comuns nas mulheres com síndrome de Turner e a sua prevalência estimada

Manifestação clínica	Frequência
Atraso no crescimento	95%-100%
Endocrinopatias	
Excesso de peso e obesidade	15%-50%
Intolerância à glicose	10%
Diabetes *mellitus* tipo 2	15%-30%
Dislipidemia	50%
Tiroidite com hipotiroidismo	70%
Patologia Cardiovascular	
Malformações cardiovasculares	25%-50%
Válvula aórtica bicúspide	14%-34%
Coartação da aorta	7%-14%
Aneurisma/dilatação da aorta	3%-42%
Hipertensão arterial	40%
Patologia Ortopédica e Osteoarticular	
Diminuição da densidade mineral óssea	50%-80%
Escoliose	20%-30%
Cubitus Valgus	50%
Micrognatia	60%
Patologia gastrintestinal e hepática	
Elevação das enzimas hepáticas	20%-80%
Doença Celíaca	8%
Doença Inflamatória Intestinal	0,15%-3%
Patologia Renal	
Duplicação total ou parcial do sistema pielocalicial	15%
Rim em ferradura	10%
Patologia Dermatológica	
Nevos melanocíticos	50%
Linfedema das mãos e pés	25%
Patologia Oftalmológica	
Erros de refração	40%
Estrabismo	30%
Ptose	10%
Patologia Otorrinolaringológica	
Hipoacusia	65%
Otites médias agudas	60%
Deformidades do ouvido externo	15%

Adaptado de Claus H, *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1–G70.[6]

No período pré-natal, os achados ecográficos fetais como: higroma cístico, hidropsia fetal, edema subcutâneo, encurtamento do fémur, aumento da translucência da nuca e malformações cardíacas e renais, devem levantar a suspeita de ST. Nos recém-nascidos, as características mais frequentemente associadas à ST são: edema das mãos e dos pés, baixa implantação das orelhas e cabelo, hipoplasia da mandíbula, cardiopatia congénita do coração esquerdo. O diagnóstico na infância surge frequentemente a partir

do estudo de baixa estatura e outras características como cubitus valgus, displasia ungueal, nevos pigmentados, encurtamento do 4º metacarpo, palato em ogiva e história de otite média crónica.[6] Já na adolescência, o atraso pubertário ou amenorreia primária não esclarecida são as principais características associadas à ST. Por fim, em alguns casos, o diagnóstico é realizado já em idade adulta, maioritariamente, na sequência da investigação de situações de infertilidade.[7,8]

Em todos os indivíduos do sexo feminino que apresentem achados típicos da doença deve realizar-se o cariótipo, como método de diagnóstico da ST. Pode ser feito em qualquer idade, sendo os picos do diagnóstico a idade fetal, lactentes, pré-puberdade (8 e 12 anos) e durante a adolescência tardia/jovem adulta.[9] No período pré-natal a confirmação por cariótipo pode ser realizada por biópsia das vilosidades coriónicas ou através da amniocentese. No período pós-natal, o cariótipo, geralmente de sangue periférico, identifica pelo menos 10% dos mosaicismos com limite de confiança de 95%. Metáfases adicionais podem ser realizadas por técnica de FISH em casos de forte suspeita de mosaicismo não detetado. Quando o cariótipo de sangue é normal e mantém-se a forte suspeita clínica de ST, um segundo tecido, habitualmente a pele, pode ser examinado.[10]

Transição da Adolescência para a Idade Adulta

O acompanhamento médico tem sido focado, sobretudo, no diagnóstico precoce e no seguimento em idade pediátrica, com especial atenção à estatura e à indução pubertária.[11] No entanto, nas últimas décadas, começou a ser notório que mulheres com ST são mais suscetíveis a alguns distúrbios que começam ou progridem na vida adulta, tais como: osteopenia/osteoporose, hipotiroidismo, diabetes mellitus (DM), dislipidemia, patologia cardíaca e nefro-urológica não congénita. A morbilidade e mortalidade é, significativamente, mais alta nestas mulheres, com uma esperança média de vida reduzida em cerca de 13 anos, à custa, maioritariamente, de doença cardiovascular e complicações da diabetes.[12,13]

Idealmente o processo de transição dos cuidados médicos deve ser realizado por um período de gestão partilhada entre o pediatra, o endocrinologista e outros médicos especialistas responsáveis pelo seguimento na idade adulta de modo a garantir uma transição bem-sucedida da vigilância médica.[6,8]

Vigilância na Idade Adulta e Comorbilidades Associadas

Durante a transição para a idade adulta as mulheres com ST devem ser submetidas a uma avaliação clínica detalhada, tendo em consideração não só as condições específicas associadas à ST, como também o rastreio de outras patologias com prevalência aumentada. Todas as patologias previamente identificadas e acompanhadas durante a idade pediátrica devem manter seguimento individualizado e especializado na idade adulta. A vigilância médica anual deve incluir exame físico detalhado com avaliação do peso e perímetro abdominal, tensão arterial, auscultação cardiopulmonar, exame físico à tiroide, exame mamário e exame ginecológico. A avaliação analítica deve ser realizada anualmente, devendo incluir hemograma com fórmula leucocitária, glicose plasmática e HbA1c, função renal, enzimas hepáticas, perfil lipídico, função tiroideia (TSH e T4 livre) e doseamento de vitamina D. A Tabela 2 esquematiza as recomendações para o seguimento das mulheres com ST.

Tabela 2. Recomendações para o seguimento das mulheres com ST ao diagnóstico e na idade adulta

	Ao diagnóstico	Seguimento na idade adulta
Avaliação Médica: História clínica Exame físico (peso, altura, perímetro abdominal, tensão arterial, auscultação cardiopulmonar, exame físico à tiroide, exame mamário e exame ginecológico, avaliação dermatológica)	I	Anual
Avaliação analítica: Hemograma com fórmula leucocitária Glicose plasmática e HbA1C Função renal (ureia e creatinina) Perfil lipídico (colesterol total, colesterol HDL, colesterol LDL e triglicéridos) Enzimologia hepática (aminotransferases, GGT e fosfatase alcalina) Função tiroideia (TSH e T4 Livre) Doseamento de 25-hidroxivitamina D	I	Anual
Avaliação Cardiovascular: Eletrocardiograma Ecocardiograma transtorácico Ressonância magnética cardíaca e dos grandes vasos	I	A cada 5 anos e antes do planeamento de gravidez
Densitometria óssea		A cada 5 anos
Rastreio doença celíaca		Se sintomas sugestivos
Ecografia renal	I	Sempre que justificável
Avaliação oftalmológica	I	Sempre que justificável
Audiometria	I	A cada 3-5 anos
Intervenção psicológica		Sempre que justificável

Adaptado de Claus H, *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1–G70.6; Collet-Solberg PF, *et al*. Endocrine diseases, perspectives and care in Turner syndrome. Arq Bras Endocrinol Metab. 2012;55-8.[20]

As principais alterações da síndrome que devem ser avaliadas e orientadas são:

1. Patologia endócrina e metabólica

O excesso de peso e a obesidade são características comuns na ST. A terapêutica hormonal durante a infância e adolescência pode mitigar algumas destas alterações.[14,15] Dado o risco aumentado de complicações cardiovasculares torna-se fundamental o controlo do peso e a adoção de estilos de vida saudáveis desde a infância. Neste sentido, recomenda-se o aconselhamento nutricional e o incentivo à prática regular de exercício físico individualizado.[6]

A homeostasia da glicose está alterada por vários mecanismos que incluem a disfunção da célula β, o aumento da resistência periférica à insulina e a hiperinsulinemia.[16,17] O risco de DM tipo 1 e tipo 2 está aumentado dez e quatro vezes, respetivamente, em qualquer idade.[18,19] A terapêutica da baixa estatura com doses supra-fisiológicas de somatropina (hormona do crescimento) não parece aumentar este desequilíbrio metabólico. Recomenda-se, assim, a avaliação anual da HbA1c e glicose plasmática a partir dos 10 anos de idade. Se confirmado o diagnóstico de DM deve-se pesquisar a presença de auto-anticorpos associados à DM tipo 1. Os autoanticorpos mais reconhecidos são: anti-ilheus de Langerhans (ICA), anti-insulina (IAA), anti-tirosina fosfatase (IA2),

anti-GAD (GADA) e os Acs anti-ZnT86.

Anomalias no perfil lipídico com aumento do colesterol LDL e triglicéridos e diminuição do colesterol HDL também são mais comuns nestas mulheres. A etiologia parece ser multifatorial sendo apontadas como principais causas a alteração da composição corporal, a insulinorresistência e a terapêutica com estrogénios.[20] Cerca de 50% das doentes, aos 21 anos, apresentam dislipidemia,[21] o que vai contribuir para o aumento do risco de complicações cardiovasculares. A partir dos 18 anos de idade, deve fazer-se avaliação regular do perfil lipídico quando existir pelo menos um fator de risco cardiovascular. O tratamento da dislipidemia segue as recomendações para a população em geral.[6]

Cerca de 70% das mulheres com ST apresenta hipotiroidismo primário e habitualmente de causa autoimune.[4] A tiroidite de Hashimoto é a mais frequente, no entanto a incidência de hipertiroidismo por doença de Graves também parece estar aumentada.[22,23] Mulheres com isocromossoma (46 XI(Xq)) têm uma prevalência particularmente aumentada de patologia autoimune da tiróide.3 É comum a manifestação da doença ser em idade precoce, estando a sua prevalência aumentada com o avançar da idade. A pesquisa de anticorpos anti tiroideus é habitualmente recomendada na altura do diagnóstico da disfunção tiroideia e a vigilância da função tiroideia deve ser pelo menos anual.[6]

Outras doenças auto-imunes endocrinológicas enquadradas na síndrome poliglandular autoimune tipo 2 são raras, apesar de terem prevalência aumentada na ST.

2. Patologia cardiovascular

A patologia cardiovascular representa uma das principais causas de morbimortalidade na ST, com uma incidência maior nas mulheres com cariótipo 45X, comparativamente aos mosaicismos ou outras anomalias estruturais do cromossoma X. As malformações cardíacas congénitas ocorrem em 23%-50% das mulheres, sendo as cavidades cardíacas esquerdas mais frequentemente envolvidas, com uma prevalência estimada de 15%-30% com válvula aórtica bicúspide e 7%-18% com coartação da aorta.[24] Por outro lado, a arteriopatia generalizada é comum, sendo um fator de risco independente para a dilatação da aorta torácica. A dissecção aórtica tem uma prevalência estimada em cerca de 40 casos por 100 000 habitantes/ano, sendo cerca de sete vezes superior à da população em geral.[25]

Mais recentemente também outros distúrbios cardiovasculares como hipertensão arterial, doença cardíaca isquémica e doença cerebrovascular se revelaram como fatores major para a redução da esperança média de vida nestas mulheres. A hipertensão arterial parece surgir numa idade precoce, podendo atingir até 40% das mulheres na idade adulta. Na maioria das vezes é idiopática, no entanto, a prevalência aumentada de alterações renais também pode contribuir para este aumento. A prevalência aumentada da doença cardíaca isquémica e doença cerebrovascular pode estar simplesmente relacionada com a hipertensão arterial ou a presença de outros fatores de risco cardiovasculares.[26]

O rastreio de distúrbios cardiovasculares deve ser iniciado desde o diagnóstico com avaliação da tensão arterial nos 4 membros, eletrocardiograma, ecocardiograma transtorácico (ETT) e ressonância magnética cardíaca (RMC) e dos grandes vasos. Posteriormente, a vigilância deve ser mantida com exame físico anual e ETT ou RMC a cada 5 anos e sempre antes de planeamento de gravidez.[6]

3. Patologia ortopédica e osteoarticular

Alterações músculo-esqueléticas são muito frequentes nas mulheres com ST e muitas delas estão associadas ao fenótipo, tais como: pescoço curto por hipoplasia das vertebras cervicais, razão segmento superior/inferior aumentada, palato em ogiva, alterações da ossificação dentária e micrognatia, *cubitus valgus* ou deformidade de Madelung (desvio externo e dorsal do rádio, com subluxação do cúbito distal).[27] Cerca de 20% a 30% das mulheres com ST tem escoliose. A sua etiologia é multifatorial e o risco aumenta com a idade e com a estatura.

Existe um risco acrescido de fraturas, mesmo com densidade mineral óssea normal.[28] Este facto parece estar relacionado com uma deficiência seletiva do osso cortical, independentemente do hipogonadismo. De ressalvar ainda que nas mulheres com deficiente ou ausência de terapêutica estrogénica podem ocorrer alterações do osso trabecular e risco de fraturas vertebrais, sobretudo após os 45 anos.[29] Assim, recomenda-se a realização de densitometria óssea após o início da terapêutica de substituição hormonal.

A diminuição do aporte de cálcio, bem como a deficiência de vitamina D também podem contribuir para o aumento do risco de fraturas ósseas pelo que se recomenda a dieta com alimentos ricos em cálcio e o doseamento da 25-hidroxivitamina D anualmente, com a sua reposição adequada em situações de deficiência.

4. Patologia gastrintestinal e hepática

A prevalência da doença inflamatória intestinal (DII) está aumentada nas mulheres com ST (0,15%-3%),[30] particularmente na presença do cariótipo Xq. Os sintomas tendem a aparecer na juventude e habitualmente são mais exuberantes comparativamente à população em geral. Recomenda-se que na presença de dor abdominal, diarreia, hemorragia intestinal e/ou perda de peso involuntária se faça a avaliação para DII6.

A doença celíaca tem também uma prevalência aumentada e habitualmente com sintomas logo na idade pediátrica. Neste sentido, é aconselhável o rastreio com doseamento dos anticorpos anti transglutaminase a partir dos 2-3 anos de idade e posteriormente a cada 2 anos, durante a infância e adolescência. Na idade adulta o rastreio deve ser realizado sempre que haja sintomas sugestivos.[31]

Um dos achados mais comuns na ST é a elevação assintomática das enzimas hepáticas, com uma prevalência variável entre 20% a 80%, por mecanismos ainda não completamente esclarecidos.[3] A terapêutica com estrogénios, por via oral ou transdérmica, tem demostrado uma melhoria e por vezes até normalização das enzimas hepáticas. Em casos de elevação importante das enzimas de padrão colestático (GGT e fosfatase alcalina) deve ser avaliada a etiologia. A terapêutica com ácido ursodesoxicólico deve ser considerada.[32,33]

5. Patologia renal

A patologia renal está presente em cerca de 24%-42% das mulheres. As alterações mais frequentes são: rim em ferradura, duplicação total ou parcial do sistema pielocalicial e malformações uretrais. A maioria destas alterações não acarreta significativa morbimortalidade, no entanto, podem resultar em infeções urinárias de repetição, hidronefrose ou hipertensão arterial de origem renovascular. As mulheres com ST devem ainda ser alertadas para a prevenção da infeção urinária.[34,35] É importante a realização de ecografia renal aquando do diagnóstico de ST e manter a vigilância sempre que justificável.

6. Patologia dermatológica

As alterações dermatológicas são muito frequentes na ST. A presença de nevos melanocíticos ocorre em cerca de 50% das mulheres, apesar de ser controverso o aumento de risco de melanoma. Também são achados frequentes a psoríase, alopecia areata e o vitiligo.[27]

O linfedema das mãos e pés é característico nas recém-nascidas. Habitualmente desaparece de forma espontânea nos primeiros 6 meses de vida. Por vezes, há recorrência na adolescência ou após início da terapêutica com estrogénios.[36]

7. Patologia oftalmológica

Na ST os erros de refração estão presentes em cerca de 40%, com aumento da incidência da miopia e hipermetropia, comparativamente à população em geral. O estrabismo é também uma das alterações oftalmológicas mais comuns, atingindo cerca de um terço das mulheres.[37] Outros distúrbios incluem: ptose palpebral e ambliopia. A avaliação por Oftalmologia torna-se assim essencial, desde o diagnóstico e ao longo da vida, visando o rastreio e a correção precoce.[6]

8. Patologia otorrinolaringológica

As malformações craniofaciais condicionam uma incidência elevada de otites médias agudas de repetição. As alterações da audição estão presentes em cerca de 2/3 das mulheres com ST, maioritariamente nas com ausência do braço curto do cromossoma X ou cromossoma X isolado.[38] A avaliação otorrinolaringológica é crucial no sentido do tratamento precoce dos défices auditivos, de modo a evitar o aumento do risco de isolamento social, depressão e até demência. Recomenda-se a avaliação por audiometria a cada 3-5 anos, a partir do diagnóstico. Em caso de otite média a antibioterapia e a colocação de tubos de ventilação transtimpânicos, devem ser instituídas, quando indicado.[38,39]

9. Função gonadal, fertilidade, técnicas de reprodução medicamente assistidas e gravidez

O hipogonadismo hipergonadotrófico e a amenorreia primária ou secundária pela disgenesia gonádica são características comuns na ST. Aproximadamente um terço das mulheres apresenta telarca espontânea e apenas 6% apresenta ciclos menstruais regulares. Assim, na grande maioria das mulheres com ST, recomenda-se a terapêutica hormonal de substituição (THS) para indução da puberdade, desenvolvimento dos caracteres sexuais secundários, normalização do crescimento uterino e alcance do pico de massa óssea.[6] Atualmente, recomenda-se iniciar THS, com estrogénios, aos 11-12 anos, na ausência de desenvolvimento pubertário e níveis aumentados de gonadotrofinas. As formulações transdérmicas devem ser preferidas, devendo-se iniciar com doses baixas de estrogénio (3-7 µg/dia) com incremento progressivo da dose a cada 6 meses, durante um período de 2-3 anos até à dose de 25-100 µg/dia. Se escolhida a formulação oral recomenda-se iniciar estradiol 0,25 mg/dia com aumento progressivo até à dose 2-4 mg/dia. A associação do progestativo deve ocorrer ao fim de dois anos de terapêutica estrogénica ou após hemorragia de privação. Deve preferir-se o uso de progesterona micronizada ou medroxiprogesterona por estarem associadas a baixo risco de neoplasia da mama, apesar de, nestas mulheres o risco de cancro da mama ser baixo e a THS não parecer aumentar este risco. As doses recomendadas são 100-200 mg/dia de progesterona micronizada ou 5-10 mg/dia de medroxiprogesterona do 20º ao 30º dia do ciclo menstrual. Esta abordagem sequencial combinada está associada à presença de hemorragia de privação e é preferida pelas mulheres mais jovens, enquanto que as formulações contínuas combinadas evitam a hemorragia uterina sendo preferível, habitualmente, por mulheres mais velhas.40 Os contracetivos orais combinados são considerados também uma opção nestas mulheres, na idade adulta, dado o seu uso prático e efeito anti contracetivo. Deve preferir-se o uso de progestativos de segunda (levonorgestrel) ou terceira geração (gestodeno e desogestrel) pelos seus efeitos anti androgénicos, associado a etinilestradiol em doses ≥ 0,03 mg. A combinação valerato de estradiol e dienogest também pode ser usada nestas mulheres. No entanto, não se recomenda o uso de contracetivos orais combinados em mulheres com: baixa densidade mineral óssea, antecedentes de enxaqueca, HTA e elevado risco tromboembólico. A escolha da THS deve ser individualizada, tendo em conta não só a preferência da mulher, como também eventuais patologias associadas.

A THS deve ser mantida enquanto os benefícios superarem os riscos, habitualmente, até à idade da menopausa. Após a idade da menopausa a eventualidade de manter a terapêutica estrogénica de substituição deve seguir as mesmas recomendações das restantes mulheres pós-menopáusicas.[6]

A disgenesia gonádica primária ou a falência ovárica precoce condicionam infertilidade. Apenas em 4%-8% das mulheres com ST ocorre gravidez espontânea, com taxas de aborto espontâneo na ordem dos 40% e risco elevado de malformações congénitas (34%). É por isso recomendável informar estas mulheres que a probabilidade de conceção espontânea diminui rapidamente com a idade. Em idade jovem poderá ser aconselhada a criopreservação de ovócitos após hiperestimulação ovárica como uma possível opção de preservação da fertilidade.[41]

Em caso de infertilidade, a gravidez poderá ser possível através da doação de oócitos e fertilização in vitro, com implementação após preparação do endométrio com esquemas baseados em estrogénios. Contudo, também nestes casos a taxa de aborto espontâneo parece ser elevada, variando de 16% a 80% das gravidezes. A terapêutica de substituição hormonal inadequada, úteros estruturalmente anormais e a presença de mecanismos autoimunes e/ou diminuição da recetividade do endométrio devido ao hipoestrogenismo a longo prazo, parecem estar na génese para o aumento da taxa de abortos espontâneos nas mulheres com ST.[42]

Também a gravidez nas mulheres com ST acarreta um maior risco de complicações obstétricas, nomeadamente distúrbios hipertensivos e pré-eclâmpsia. O risco de progressão para dissecção da aorta está aumentado na gravidez, embora pareça ser devido ao aumento da carga hemodinâmica e não ao aumento dos estrogénios circulantes.[3] Os partos por cesarianas são também mais frequentes, com taxas que rondam os 31% a 85% em gestações únicas.[43]

10. Malignidade

O risco relativo de neoplasias, no geral, não parece estar aumentado na ST44, contudo, o risco de cancro do cólon é 5 vezes superior. A associação da ST com o cancro do cólon ainda não é clara. O facto das mulheres com ST terem um aumento significativo da prevalência de doença inflamatória intestinal pode justificar o aumento do risco de malignidade. Também a deficiência prolongada de estrogénios parece desempenhar um papel importante na patogénese do cancro do colón.

A presença do mosaicismo com presença de material do cromossoma Y (SRY+) acarreta um risco aumentado de 7%-10% de gonadoblastoma. Nos gonadoblastomas 60% sofrem transformação maligna, dos quais 50% desenvolvem disgerminomas e 10% outros tumores das células germinativas. Nestas situações, a gonadectomia profilática em idade pubertária é recomendada.[45]

11. Desenvolvimento psicossocial e comportamento

As portadoras de ST têm inteligência normal com desenvolvimento motor e cognitivo adequados. No entanto são mais comuns as dificuldades na memória não-verbal, funções executivas

e concentração. A existência do cromossoma X em anel aumenta o risco de atraso cognitivo.[1] Em idade jovem é mais frequente o isolamento social associado à imaturidade e ansiedade generalizada.

Estas mulheres têm, habitualmente, atividades profissionais abaixo do esperado para o seu nível educacional, assumindo especial dificuldade em tarefas que exigem resposta rápida e multifacetada. Contudo, muitas delas atingem o ensino superior e têm carreiras profissionais consideradas de sucesso.[46,47]

As recomendações sugerem avaliação neuropsicológica periódica e apoio psicológico individualizado de modo a facilitar o processo de desenvolvimento de planos de autoestima e estratégias de integração na sociedade.[48]

Conclusão

A ST tem uma prevalência de cerca 25 a 50 por 100 000 mulheres.[6] Estas mulheres têm um aumento de risco significativo de várias patologias que muitas vezes começam na infância e progridem na vida adulta requerendo um acompanhamento regular e especializado. Após o *terminus* da puberdade e do crescimento, o seguimento deve ser mantido por uma equipa multidisciplinar no sentido de assegurar a vigilância de todas as condições clínicas associadas a esta síndrome.

Dada a diversidade de patologia endócrina da ST ao longo da vida, o médico endocrinologista é fundamental e indispensável nessa equipa multidisciplinar. O endocrinologista deve conhecer os diferentes aspetos inerentes a esta síndrome, centrando nele a ação dos cuidados, permitindo uma abordagem holística a longo prazo e assim, promover um aumento significativo da qualidade e esperança média de vida destas mulheres.

Responsabilidades Éticas

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Caso Clínico

Síndrome Poliglandular Autoimune Tipo 2: Uma Apresentação Invulgar de uma Doença Rara

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INFORMAÇÃO SOBRE O ARTIGO

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R E S U M O

A síndrome poliglandular autoimune (SPGA) é uma doença caraterizada pela associação de pelo menos duas doenças endócrinas do foro autoimune. A síndrome de Schmidt, consiste numa insuficiência suprarrenal primária associada a tiroidite autoimune.
Descreve-se o caso de uma doente com antecedentes pessoais de hipotiroidismo autoimune, que recorreu ao hospital por prostração, dor abdominal difusa e choque de etiologia pouco clara.
Admitida no Serviço de Medicina Intensiva, pela suspeita de insuficiência suprarrenal, iniciou terapêutica com corticoterapia. Após melhoria clínica e laboratorial, a doente foi transferida para enfermaria com a hipótese diagnóstica de SPGA tipo II.
Neste caso pretende-se destacar a dificuldade inerente ao diagnóstico, a sua gravidade na apresentação e a necessidade de intervenção precoce. Realça-se a importância do diagnóstico de doenças raras e com apresentação atípica.

Keywords:
Polyendocrinopathies, Autoimmune/diagnosis

Type 2 Polyglandular Autoimmune Syndrome: An Unusual Presentation of a Rare disease

A B S T R A C T

Autoimmune polyglandular syndrome (SPGA) is a disease characterized by the association of at least two autoimmune endocrine diseases. Schmidt's syndrome is a primary adrenal insufficiency associated with autoimmune thyroiditis.
We describe the case of a patient with a personal history of autoimmune hypothyroidism, who went to the hospital with prostration, diffuse abdominal pain and shock of unclear etiology.
Admitted to the Department of Intensive Care Medicine, due to the suspicion of adrenal insufficiency, she began therapy with corticosteroids. After clinical and laboratory improvement, the patient was transferred to the ward with the possible diagnosis of type II SPGA.
In this case it is intended to highlight the difficulty inherent in the diagnosis, its severity in presentation and the need for early intervention. The importance of diagnosing rare diseases with atypical presentation is emphasized.

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Introdução

As síndromes poliglandulares autoimunes (SPGA) são um grupo heterogéneo de doenças raras e poligénicas. São caracterizadas pela associação de pelo menos duas patologias autoimunes e que afetam pelo menos uma glândula endócrina.[1]

Neufeld e Blizzard em 1980 classificaram pela primeira vez as SPGA em dois grandes grupos, hoje divididos em quatro.[2]

A SPGA tipo II é a entidade do grupo com maior prevalência, de 2 para 100 000 habitantes, com predomínio em mulheres adultas de 3 para 1, pela maior prevalência de tiroidite autoimune neste género. A sua apresentação clínica é bastante heterogénea, com disfunção suprarrenal primária associada a pelo menos uma das seguintes patologias autoimunes, tiroidite autoimune (síndrome Schmidt), e/ou diabetes *mellitus* (DM) tipo I autoimune (síndrome de Carpenter).[3-6]

Apenas em 10% dos casos se verifica a presença síncrona das 3 patologias. Habitualmente a cronologia está bem definida, com o diagnóstico inicial de DM1, seguido da doença de Addison e da tiroidite autoimune.[5]

A sua fisiopatologia parece basear-se numa desregulação autoimune contra as glândulas endócrinas. Foram propostos mecanismos que apontam para a perda de seleção negativa de autoimunidade, a supressão da apoptose periférica e função das células T CD4+ CD25+ e a presença de um *trigger* externo com mimetização antigénica capaz de desencadear uma resposta imune com lesão progressiva de órgão.[5]

Tem índole genética e incidência familiar, estando descritos casos de transmissão autossómica dominante, de penetrância variável.[1]

Associa-se a antigénios que conferem maior risco para DM tipo 1, doença de Addison e doença celíaca, (HLA-DR3, DR4, A1 e B8) e a polimorfismos do gene *MIC-A* (codifica uma proteína maturadora dos linfócitos T), *PTPN22* (selecção/apoptose de células T) e CTLA-4 (ligando de CD28, inibe a activação e proliferação de linfócitos T), que aumentam o risco de apresentar estas doenças.[5]

Caso Clínico

Mulher de 45 anos, autónoma, agricultora, com história pregressa de hipotiroidismo medicado com L-tiroxina (T4L 13,6 pmol/L, TSH 0,06 mIU/L). Sem antecedentes familiares relevantes.

Recorreu ao hospital, via consulta externa para exérese de lipoma na face medial da coxa esquerda, com mau estado geral, prostrada, asténica, adinâmica e com emagrecimento recente de cerca de 10 kg em 45 dias. Apresentou também dor abdominal difusa, vómitos bidiários, dejeções diarreicas diárias nas últimas 3 semanas, assim como débito urinário diminuído. Sem noção de febre e sem toma de outros fármacos, chás ou quaisquer produtos tóxicos.

Ao exame objetivo, a doente apresentava um desconforto abdominal difuso sem sinais de defesa ou irritação peritoneal e uma hiperpigmentação cutânea não habitual. Sem alterações ao exame físico neurológico.

Neste contexto, foi internada no serviço de cirurgia geral para estudo complementar.

Ao final do primeiro dia de internamento, por hipotensão sustentada (tensão arterial sistólica de 55 mmHg), hiperlactacidemia, associada a lesão renal aguda de provável etiologia pré-renal (creatinina 4,6 mg/dL e ureia 107 mg/dL), hiponatremia (127 mg/dL), hipercaliemia (8,7 mg/dL) e hipoglicemia (58 mg/dL), foi ativada equipa de Medicina Intensiva. Foram iniciadas, de imediato medidas de ressuscitação volémica com fluidoterapia e de correção hidroeletrolítica e glicémica (Tabela 1).

Tabela 1. Perfil analítico à admissão e à alta

Bioquímica	À admissão	À alta
Glicose (74-106 mg/dL)	58 mg/dL	71 mg/dL
Ureia (<50 mg/dL)	107 mg/dL	27 mg/dL
Creatinina (0,6-1,1 mg/dL)	4,6 mg/dL	0,9 mg/dL
Sódio (135-147 mEq/L)	127 (mEq/L)	143 (mEq/L)
Potássio (3,7-5,1 mEq/L)	8,7 (mEq/L)	3,3 (mEq/L)
Cloretos (96-106 mEq/L)	92 (mEq/L)	109 (mEq/L)

Foi admitida no Serviço de Medicina Intensiva com os diagnósticos de choque hipovolémico e provável insuficiência suprarrenal, pelo que foi iniciada corticoterapia com hidrocortisona em perfusão e suporte aminérgico por hipotensão sustentada.

Após melhoria do perfil tensional, correcção dos distúrbios hidroelectrolíticos, normalização do perfil glicémico e melhoria da função renal, a doente foi transferida para enfermaria ao final de 48 horas.

No curso diagnóstico, a prova de tetracosídeo aos 0` (cortisol = 0,4 mcg/dL, ACTH > 2000) e aos 60` (cortisol = 0,3 mcg/dL) foi compatível com insuficiência suprarrenal primária. O doseamento dos anticorpos anti 21-OH hidroxilase, anticorpos anti-tiroglobulina e anti-tiroideperoxidase foi positivo e o estudo de DM autoimune negativo (Tabela 2). Realizou tomografia computorizada (TC) toraco-abdomino-pélvica para exclusão de possível lesão ocupante de espaço, que mostrou apenas derrame pleural bilateral de pequeno volume (2 cm) e uma TC crânio-encefálica sem alterações.

Tabela 2. Estudo imunológico

Imunologia	Resultado
Atc anti-transglutaminase IgG (<10 U/mL)	0,3 U/mL
Atc IgA anti-gliadina IgG (<7 U/mL)	0,2 U/mL
Atc IgA anti-gliadina desaminada (<7 U/mL)	0,6 U/mL
Atc anti-tireoglobulina (<40 UI/mL, negativo)	523 UI/mL
Atc anti-tiroide peroxidase (<25 UI/mL, negativo)	61 UI/mL
Atc anti-suprarrenal	Negativo

Após o diagnóstico de síndrome poliglandular autoimune tipo II, foi iniciada terapêutica com hidrocortisona per os 40 + 20 mg/dia e levotiroxina 25 mcg/dia. Teve alta hospitalar ao 10º dia de internamento, clinicamente bem e sem disfunção de orgão. Foi referenciada para consulta externa, medicada com hidrocortisona 10+5+5 mg, fludrocortisona 0,05 mg/dia e levotiroxina 100 mcg/dia.

Discussão

A SPGA tipo 2 consiste numa insuficiência suprarrenal autoimune associada a disfunção tiroideia autoimune e/ou DM tipo I. Pode também coexistir com outras doenças autoimunes *minor*, nomeadamente gastrite autoimune, hipogonadismo primário, vi-

tiligo, alopecia, hepatite autoimune, doença celíaca, síndrome de Sjögren, entre outras.[1,4]

Os autores descrevem o caso de uma síndrome de Schmidt numa mulher adulta, que chega ao hospital via consulta externa, com sintomas típicos de insuficiência suprarrenal, nomeadamente astenia, adinamia, fadiga intensa, náuseas e vómitos, mas não tão comumente, em choque e, portanto, necessidade de suporte vasopressor. A hiperpigmentação cutânea foi também um achado observado.[3]

Dada a forma exuberante de apresentação e sua gravidade, esta necessitou de cuidados em ambiente de Medicina Intensiva.

Em concordância com o descrito, constataram-se desequilíbrios hidroeletrolíticos com hiponatremia e hipercaliemia, associado a hipoglicemia grave, corrigidos progressivamente após terapêutica médica. A literatura aponta que a corticoterapia seja semelhante à de libertação endógena, tal como hidrocortisona 100 mg 6/6 horas.[6]

Sivarajah et al diz-nos que a terapêutica de reposição tiroideia pode precipitar uma insuficiência suprarrenal, inclusivamente num contexto ameaçador de vida. Desta forma, embora não possamos inferir nenhum nexo de causalidade, aponta-se o facto de tratar-se de uma doente com patologia tiroideia previamente conhecida e medicada com suplementação tiroideia.[7]

Em casos de hipotiroidismo recém-diagnosticados, a terapia de reposição tiroideia deve ser protelada até avaliação da função suprarrenal. Como a corticoterapia inicial, por si só, pode causar melhoria da função tiroideia, optou-se por terapêutica única com corticóide.[7]

A suplementação tiroideia na dose habitual foi apenas iniciada após estabilização completa da doente, tendo em mente o possível efeito secundário referido anteriormente.[6]

À data da alta, a doente foi medicada com um glicocorticóide, hidrocortisona 10+5+5 mg, associado a um mineralocorticóide em dose terapêutica, fludrocortisona 0,05 mg/dia e levotiroxina 100 mcg/dia, em concordância com o sugerido.

A evolução desta síndrome mostra-se muito imprevisível, pelo que é recomendado um seguimento a longo prazo, regular e personalizado para cada doente, tendo em conta os antecedentes familiares, a autoimunidade de cada individuo e a correlação entre as patologias constatadas, tendo em vista a relação custo/benefício de cada atitude na redução da morbi-mortalidade de cada patologia envolvida.[5]

Trata-se de uma situação rara e de difícil diagnóstico pelo elevado número de possibilidades diagnósticas, que complicam o enquadramento numa síndrome primária. Neste caso, o diagnóstico foi obtido numa fase limite e com necessidade de intervenção rápida. Destaca-se a importância do diagnóstico precoce, com a necessidade de criação de protocolos de diagnóstico e seguimento/orientação dos doentes com patologia autoimune, para melhoria da sobrevida e da qualidade de vida.

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Caso Clínico

Continuous Glucosee Monitoring in Real Time in Premature Infant: A Challenge

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A B S T R A C T

Neonatal diabetes mellitus is a rare disorder defined as persistent treatment-requiring hyperglycemia during the first six months of life. Diagnosis and management can be challenging, especially in transient cases. We present a case of an extremely low birth weight premature infant with transient neonatal diabetes mellitus. In the first days of life he developed persistent hyperglycemia requiring the need to start an insulin infusion. It was difficult to adjust insulin doses due to the small quantities with variable requirements, so real-time continuous glucose monitoring was initiated. This system showed a good correlation with capillary glycemia, allowing adjustments of insulin perfusion and consequently normalizing the infant's blood glucose levels. This report highlights the usefulness of real-time continuous glucose monitoring for monitoring insulin therapy in patients with transient neonatal diabetes mellitus, particularly in those with comorbidities as in this case.

Keywords:
Blood Glucose;
Hyperglycemia;
Infant, Newborn;
Infant, Premature;
Monitoring, Physiologic.

Monitorização Contínua da Glicose em Tempo Real no Prematuro: Um Desafio

R E S U M O

A diabetes *mellitus* neonatal é uma entidade rara definida como uma hiperglicémia persistente que requer tratamento e ocorre nos primeiros seis meses de vida. O diagnóstico e o tratamento podem ser desafiantes, principalmente nos casos transitórios. Apresentamos o caso de um prematuro de extremo baixo peso com diabetes *mellitus* neonatal. Nos primeiros dias de vida apresentou hiperglicemia persistente com necessidade de iniciar uma perfusão de insulina. Foi difícil de ajustar as doses de insulina devido às pequenas quantidades e necessidades variáveis, por isso foi iniciada a monitorização contínua da glicose em tempo real. Este sistema mostrou uma boa correlação com a glicémia capilar permitindo uma ajuste da perfusão de insulina e consequente normalização da glicémia. Este caso clínico destaca a utilidade da monitorização contínua da glicose em tempo real para monitorizar a insulinoterapia em pacientes com diabetes *mellitus* neonatal, principalmente naqueles com comorbilidades como o caso apresentado.

Palavras-chave:
Glicemia;
Hiperglicemia;
Monitorização Fisiológica;
Recém-Nascido;
Recém-Nascido Prematuro.

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Introduction

Hyperglycemia is a symptom present in some neonates, especially in the preterm or low birth weight (LBW) infant. Typical causes for hyperglycemia in this group include an immature pancreas, increased parenteral glucose administration, infection, insulin resistance, increased counter-regulatory hormones due stress, and medications, such as steroids.[1] Additionally, neonatologists should consider neonatal diabetes mellitus (NDM), a rare condition where hyperglycemia is persistently greater than 250 mg/dL (13,88 mmol/L)[1] for longer than two weeks, in the absence of other predisposing factors.[2,3]

NDM is defined as persistent treatment-requiring hyperglycemia occurring in the first six months of life.[4,5] Its frequency varies between different populations, in Europe the incidence rate ranged between 1 in 90 000 and 1 in 500 000.[6,7] This condition can either be permanent neonatal diabetes mellitus (PNDM), requiring lifelong treatment, or transient neonatal diabetes mellitus (TNDM).[2,8] TNDM represents about 50% of NDM cases[5,9] and is biphasic: usually remit spontaneously within one to 18 months, but often recurs during adolescence or early adulthood.[7,8,10]

NDM is a heterogeneous disease predominantly monogenic.[11-13] It is recommended to perform a genetic test in infants with NDM because identifying the genetic cause has many clinical benefits: first, it can help to select the best treatment (some individuals with a specific mutation may be successfully treated with sulfonylureas); secondly, it can predict the development of some extrapancreatic features; finally, to provide genetic counselling to the family.[7]

Obtaining and maintaining a good glycemic control is important to prevent adverse neurological outcomes. But, the close monitoring, results in numerous blood glucose tests which can be technically demanding for caregivers and traumatic for infants.[14,15]

Therefore, the advent of real-time continuous glucose monitoring (RT-CGM) systems enables the optimization of metabolic control. RT-CGM consists of a small monitoring device that receives a signal by Bluetooth from a sensor inserted into the subcutaneous layer. The sensor using the glucose in the interstitial fluid, produces a small electrical current that is proportional to the glucose concentration. Calibration algorithms convert sensor signals into RT-CGM output (glucose value). Calibration blood sugar measurements are required to convert electrical current into meaningful RT-CGM output. After initial calibration, it is recommended that RT-CGM devices be calibrated two times a day.[16] Data are monitored and showed in real time on the monitor. RT-CGM (Paradigm™ Veo™, Medtronic MiniMed), an insulin pump enhanced with RT-CGM, was the device used to control the blood glucose level (BGL) in the case described.

This device provides information not only about the current interstitial glucose level but also glucose trends, which are important to anticipate therapeutic measures, when metabolic control is a challenge.

Clinical Case

In this report, we present a case of an extremely LBW infant with NDM.

At 24 weeks' gestation, a 21-year-old woman pregnant with twins was admitted to the hospital after threatened preterm labor. There was no maternal history of gestational diabetes or hypertension. Maternal serologic screening was negative and the prenatal ultrasounds were normal. Parents were nonconsanguineous and no history of diabetes in the family was reported. The mother received a complete cycle of antenatal corticosteroids and she delivered two infants at 25 weeks' gestation by cesarean section. The first twin did not survive. The second twin was a male with weight 765 g (<3rd centile), length 34 cm (<3rd centile) and head circumference 23 cm (<3rd centile), according to Fenton growth charts. He was intubated in the delivery room.

On the first day of life, the newborn was under mechanical ventilation and hemodynamically stable. Blood tests (arterial blood gas, blood count, C-reactive protein, glucose) were normal and he initiated antibiotic prophylaxis. On the second day of life, under parenteral nutrition with 5.9 mg/kg/min of glucose, he developed hyperglycemia with BGL persistently >300 mg/dL (16.65 mmol/L) despite a decrease in the glucose infusion rate of 3.1 mg/kg/min. After five boluses of insulin (0.05 units/kg/dose), the BGL remained high, >250 mg/dL (13.88 mmol/L), and according to our departmental protocol, the newborn started an insulin infusion with a dose 0.01 units/kg/hour. The dose was then adjusted to achieve normoglycemia (insulin infusion maximum dose was 0.01 units/kg/hour) and the BGL dropped down to <200 mg/dL (11.1 mmol/L). Insulin doses were reduced gradually and finally discontinued on day 16, when he was normoglycemic on full feeds (180 mL/kg/day of breast and premature milk).

On the 29th day of life he was extubated, after corticotherapy, and developed again hyperglycemia, >400 mg/dL (22.2 mmol/L). Laboratory results showed C-peptide level of 2.1 ng/mL (normal, 1-7.6 ng/mL), and insulin level of 3.7 uIU/mL (normal, <30 uIU/mL), further reflecting relative insulin deficiency (both drawn when the serum glucose level was 200 mg/dL (11.1 mmol/L). We restarted an insulin infusion with a dose of 0.009 units/kg/hour, (insulin

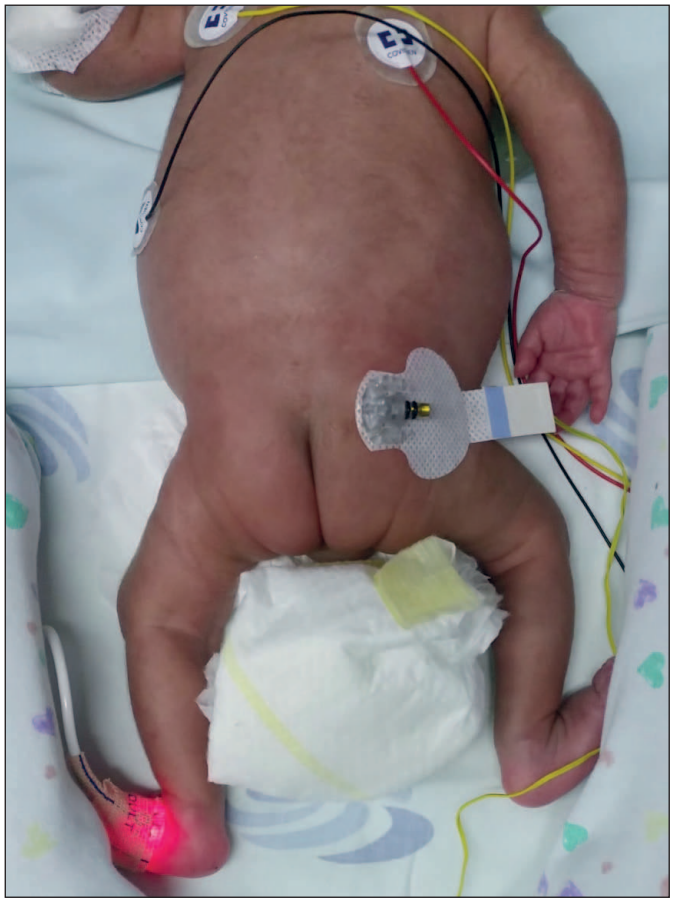

Figure 1. Real-time continuous glucose monitoring sensor inserted into the subcutaneous layer of the patient.

infusion maximum dose was 0.01 units/kg/hour) but this time with marked difficulty in dose due to the small quantities of insulin with variable requirements.

Pediatric endocrinologist suggested initiating RT-CGM at this time. The sensor was inserted into the subcutaneous layer in the upper buttock area (Fig. 1). We defined the target serum glucose levels between 70 mg/dL (3.9 mmol/L) and 140 mg/dL (7.8 mmol/L), being 50 mg/dL (2.8 mmol/L) the cut-off for hypoglycemia. Alarms for thresholds, >250 mg/dL (13.9 mmol/L) or <70 mg/dL (3.9 mmol/L) were introduced in the system. Due to minute doses of insulin required, 1:10 insulin dilution was necessary. Twice a day the nurse calibrated glucose measurements. The sensor was changed every seven days. Two weeks of continuous glucose monitoring trace (Fig. 2) showed fluctuations in interstitial glucose concentrations varying with the meals. We adjusted the insulin perfusion to this glucose profile. Initially, there was a needed to increase the insulin perfusion after the meal (for two hours), and decrease the insulin perfusion before the meal (one hour earlier). Then the insulin perfusion was suspended for one hour a day (before one meal in the afternoon). When the alarm was activated, a capillary blood sampling was performed to confirm the glycemia value: confirmed hypoglycemia led to stop insulin infusion temporarily and one hour later performed a new capillary blood sampling; confirmed hyperglycemia led to increasing the insulin infusion.

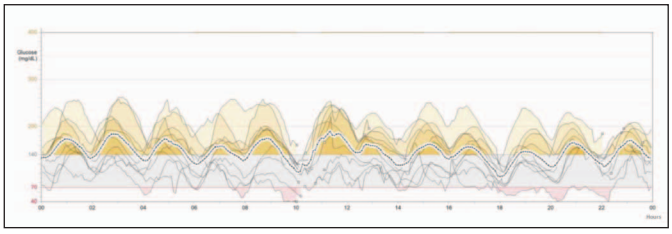

Figure 2. Two weeks continuous interstitial glucose monitoring trace. The mean glucose concentration was 144 ± 36 (standard deviation) mg/dL (7.9 ± 2 mmol/L)

The RT-CGM showed a strong correlation with capillary glycemia (correlation coefficient of 0.817) allowing adjustment of insulin perfusion with normalization of BGL (Fig. 3). During use of RT-CGM the mean of capillary BGL was 118±20 mg/dL (6.5±1.1 mmol/L) and the mean of sensor glucose levels was 126±18 mg/dL (6.9±1 mmol/L) , time in range was 78.1% of total, and time in hypoglycemia was 0.4% of total.

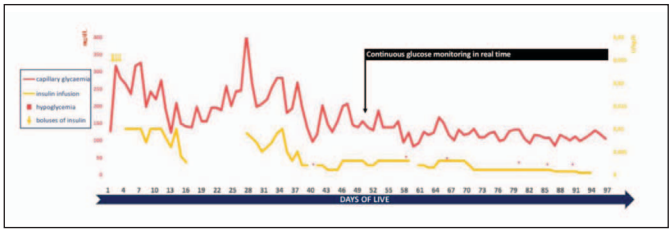

Figure 3. Evolution of capillary glycemia and insulin infusion of the patient. The red line represents the daily mean of capillary glycemia; the yellow line represents intravenous insulin infusion. The cutoff for hypoglycemia was 50 mg/dL (2.8 mmol/L)

This system allowed to reduce the number of daily capillary blood samples from eight to two, and no complications, such as bleeding, edema or local infection, were described. There was no severe hypoglycemia. Overall insulin requirement decreased, treatment was progressively reduced and stopped on day 95, with the infant remaining normoglycemic ever since, consistently with TNDM.

The infant was discharged home after a lengthy hospital stay due to other complications: a peri-intraventricular hemorrhage (PIVH) grade 3; late-onset *sepsis* (*Staphylococcus Haemolyticus*) treated with vancomycin; and he was also diagnosed with bilateral retinopathy of prematurity grade III.

On discharge, 117 days of live (five days corrected age), he was feeding well with normal BGL and showed a catch-up growth. He is followed by the pediatric endocrinology team and remains asymptomatic without treatment until now. The parents refused to perform the genetic test.

Discussion

Insulin plays a critical role in promoting growth in the fetus.[14] Patients with NDM are more likely to have intrauterine growth retardation because they have lower insulin levels during fetal life. According to Besser *et al*,[17] reduced birth weight in patients with NDM is well-described and prematurity can result from early elective delivery due to poor fetal growth. The patient presented a metabolic profile consistent with TNDM, which can justify his LBW and the associate prematurity.

PIVH was one of the prematurity-related complications present in the infant. In LBW infants hyperglycemia was associated with increased risk for PIVH grade 3-4.[18] However recent randomized trials did not show any benefit of continuous insulin infusion for PIVH in hyperglycemic preterm infants.[19,20] Other risk factors, such as LBW, low Apgar score, and postnatal complications have been associated with PIVH.[21] The PIVH present in our premature is probably due to these risk factors, but possibly persistent hyperglycemia in the first days of life also has a contribution.

Our case demonstrates the complex management of diabetes in an extremely preterm with associated comorbidities. At first, the diagnosis can be challenging because there are alternative causes of hyperglycemia in the preterm or LBW infant, in whom hyperglycemia occurs in 40%–80% in the neonatal intensive care unit.[22] Secondly, insulin therapy in these infants can be problematic, as they require ultra-small doses to cover the small carbohydrate intake, meaning that insulin dilution may be necessary and that is technically difficult and associated with an increased risk of error.[11] Due to the paucity of subcutaneous fat and muscles in these tiny LBW newborns, regular insulin is routinely used intravenously, which usually leads to the dilemma of either hypoglycemia or hyperglycemia again after stopping insulin, as happened in our case.[23] Furthermore, in these infants, the increased need for some medications or the highest risk of infections contributes even more to the fluctuation of BGL. We faced this situation after stopping insulin infusion, due to hypoglycemia episodes. The patient gradually developed hyperglycemia, which was exacerbated by corticotherapy, requiring the need to initiate insulin infusion again. Galal *et al*[23] faced the same frustrating cycle of hyperglycemia followed by hypoglycemia and vice-versa. Finally, the need for monitoring the BGL requires repeated blood draws or manipulation of central lines which should be avoided to reduce the risk of infections and anemia.[24,25]

As described above, managing LBW with NDM presents many problems, therefore achieving a metabolic control and also avoiding potentially dangerous hypoglycemic events can be very difficult. In the patient, when the glycemic control became very difficult to achieve with a consequent need of frequent invasive blood sampling, we started to use the RT-CGM device. Its use in infants is off-label, being only approved in children older than 4 years with type 1 diabetes.[26] Due to this, some aspects should be carefully considered for its use in the neonatal population. For instance RT-CGM devices

use algorithms based on interstitial glucose–blood glucose kinetics in adults, which have not been tested specifically or rigorously in neonates.[27] An important limitation of the RT-CGM instrument is to provide measurements of glucose only in a large range and preterm infants require accuracy for management of glucose concentrations. Still, some studies conclude that using RT-CGM is safe and reliable in preterm infants.[24] They also demonstrated that glucose results correlate well with BGL with minimal bias,[28] so its use (even off-label) is very important to make therapeutic decisions.

RT-CGM devices use a fine needle sensor inserted into the subcutaneous tissue. Unlike the subcutaneous administration of rapid acting insulin that has to be administered several times per day, the sensor inserted into the subcutaneous tissue is changed every seven days. Furthermore the minute doses of insulin required to make the subcutaneous administration of insulin are even more difficult. Therefore in our neonate intravenous insulin infusion was preferred. Currently, there are available RT-CGM systems integrated with continuous subcutaneous insulin pumps. They have an automated algorithm-driven insulin dosing that liberates the patient/caregiver from managing insulin therapy.[29] It is an available option if the patient requires a long insulin-treatment and his weight is appropriated to an adequate insulin dose.

Despite off-labell use, the application of the sensor appeared to be safe and well tolerated as established by Beardsall *et al*.[28] Other two studies[24,30] also reported that needle sensors were well tolerated, even in infants weighing <1500 g. The lowest birth weight reported in these two studies[24,30] was 579 g. There have been no reports of local complications, such as infection, edema, bleeding or bruising.[31]

The interstitial subcutaneous glucose concentration mirrors the BGL, reflecting even more rapid changes.[15] Consequently, RT-CGM devices provide information about the current interstitial glucose level and glucose trends,[26] allowing the adjustment of insulin. The use of RT-CGM in LBW infants has the potential to minimize the incidence and severity of hypoglycemia and hyperglycemia with a non-invasive monitoring of glucose profiles, improving glucose stability by adjusting its intake and insulin perfusion in real-time according to individual metabolic requirements.[27,31] Uettwiller *et al*[30] compared RT-CGM with intermittent blood glucose monitoring in very LBW infants and found that RT-CGM reduced the median duration of hypoglycemic episodes by 50% and the number of capillary blood samples by 25%. This was attributed primarily to earlier detection of episodes by RT-CGM more than by regular intermittent capillary blood glucose testing.[31]

The infant presented a metabolic profile consistent with TNDM, which is mainly caused by mutations in the genes *KCNJ11* and *ABCC8*.[13] Mutations in these genes may be treated with oral sulfonylureas, instead of subcutaneous insulin, improving glycemic control and increasing the quality of life.[1] Since TNDM often recurs during adolescence or early adulthood, a genetic cause identified could orientate the treatment in the future.

RT-CGM was crucial achieving euglycemia in the infant, allowing clinicians to keep glucose concentrations within a narrower range, and no complications were reported. This newborn was the smallest premature with NDM managed with RT-CGM described in our country.

Responsabilidades Éticas

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Caso Clínico

Long-term Survival in a Patient with Metastatic Medullary Thyroid Carcinoma and Multiple Endocrine Neoplasia Type 2A: A Case Report

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Carcinoma Medular;
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Neoplasias da Tiroide.

A B S T R A C T

Multiple endocrine neoplasia type 2 A (MEN2A) is an autosomal dominant disorder characterized by the development of medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. The genetic defect involves the RET proto-oncogene. We report a 58-year-old female with MEN2A syndrome with bilateral pheocromocytoma and metastatic MTC with 30 years of follow-up. At the age of 27 she was admitted to an intensive care unit due to hypertensive crisis, caused by catecholamine excess. Pheocromocytoma were present in both adrenal glands and there were metastases in the lungs and liver. Patient was submitted to bilateral adrenalectomy, but with incomplete excision. Biopsy of liver nodules revealed metastatic MTC. Lung biopsy was not performed. Neck ultrasound showed thyroid nodules with microcalcifications. Analysis of the RET proto-oncogene revealed the exon *11 Cys634Arg* mutation. The thyroid nodules and biochemical markers remained stable, with a slight increase of metastatic disease. This case is representative of a MEN2A syndrome with a life-threatening presentation yet with an indolent progression.

Longa Sobrevida num Doente com Carcinoma Medular Metastático e Neoplasia Endócrina Múltipla Tipo 2A

R E S U M O

A síndrome de neoplasia endócrina múltipla tipo 2 A (MEN2A) é uma condição autossómica dominante caracterizada por carcinoma medular da tiróide (CMT), feocromocitoma (FEO) e hiperparatiroidismo primário. O defeito genético envolve o proto-oncogene RET. Apresentamos o caso de uma mulher de 58 anos com MEN2A, feocromocitoma bilateral e CMT metastático com 30 anos de seguimento. Aos 27 anos foi admitida na unidade de cuidados intensivos por crise hipertensiva por excesso catecolaminérgico. Apresentava lesões em ambas as suprarrenais, pulmões e fígado. Foi submetida a adrenalectomia bilateral mas com excisão incompleta do tumor à direita. A biópsia dos nódulos hepáticos era compatível com metástases de CMT. Não foi realizada biópsia do pulmão. A ecografia cervical mostrava nódulos tiroideus suspeitos. A análise do proto-oncogene RET revelou uma mutação no exão *11 Cys634Arg*. Durante um período de 30 anos, manteve marcadores bioquímicos estáveis, com ligeiro aumento da doença metastática. Este caso é representativo de um MEN2A com apresentação grave, ainda assim, com progressão tumoral lenta.

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Introduction

Multiple endocrine neoplasia syndrome type 2 A (MEN2A) is an autosomal dominant disease, characterized by the development of medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO) and primary hyperparathyroidism.[1] The genetic defect involves, the *RET* proto-oncogene, in 95% of cases due to the codon 634 mutations.[1,2] In the presence of codon 634 mutations, PHEO occurs in 50% of cases, hyperparathyroidism in 25% and amyloid cutaneous lichen in 10% of cases, typically located in the interscapular region.[3] The risk of developing MTC is close to 100%, and at 13 years of age, 25% of patients already have this diagnosis.[4] For the clinical surveillance of MTC patients, calcitonin-doubling time correlates with tumour survival and recurrence rates, providing an excellent survival predictor.[5,6] For the treatment of metastatic disease, there are only two approved drugs, vandetanib and cabozantinib, which have a significant impact on the progression-free survival.[7,8] However, tyrosine kinase inhibitors (TKI) often induce side effects, affecting the quality of life, and resistance to these drugs usually occurs and disease progresses.[7,8] We report a 58-year-old woman with MEN2A syndrome with bilateral PHEO and metastatic MTC with 30 years of follow-up, in whom active surveillance has been chosen as the most appropriate approach.

Case Report

We report a case of a 58-year-old woman with a personal history of laryngeal chondroma submitted to surgical excision at the age of 23. Her mother had a history of essential hypertension and microfollicular thyroid adenoma, treated with total thyroidectomy, and her three sisters had goiter. At 27 years of age (in 1988), she started to complain of headaches, palpitations, chest tightness, abdominal pain and diarrhea, and on May 28th 1988, she was admitted to the intensive care unit of Hospital Santa Maria in Lisbon due to abdominal pain, hypertensive crisis (blood pressure 260/150 mmHg) and tachycardia (140 bpm). The electrocardiogram showed sinus rhythm, negative T waves and high serum creatine kinase-MB suggesting myocardial ischemia. A computerized tomography (CT) scan of chest and abdomen revealed tumours in both adrenal glands suggestive of PHEO, as well as multiple lung and hepatic nodules suspicious of malignancy. Urinary metanephrines levels were high at 22 mg/24 hours (NR <0.6). After the institution of medical therapy with an alpha-blocker (phenoxybenzamine) and beta-blocker (propranolol) the patient underwent bilateral adrenalectomy, however, with incomplete excision of the right tumour (due to local invasion of the abdominal vessels). During this surgery, a biopsy of the hepatic nodules was performed, which revealed amyloid deposition and positivity for calcitonin in the immunohistochemistry, thus, being compatible with MTC metastases. In the cervical ultrasound the thyroid gland was multinodular, with a dominant 10 mm nodule located at the lower pole of the left lobe, with no suspicious cervical lymph nodes. Later, at the age of 36, the patient was referred to the Instituto Português Oncologia of Lisbon. At the initial appointment, the patient reported palpitations, dysphonia, and diarrhea. A small goiter was palpable. She was normotensive (under alpha- and beta-blockers) and had a normal heart rate. Blood tests revealed calcitonin 1229 pg/mL (NR <8.5), carcinoembryonic antigen (CEA) 91.8 µg/L (NR 3 <µg/L), urinary metanephrines 3.1 mg/24 hours (NR <1.0), total calcium 8.9 mg/dL (NR 8.5-10.2) and parathyroid hormone (PTH) 47 pg/mL (NR <65). Laryngoscopy disclosed a paralysis of the right vocal cord. At this time, a thoracoabdominal CT scan showed a heterogeneous thyroid gland with bilateral nodules, the largest with 10 mm and macrocalcifications, without lymphadenopathies. She also presented extensive and bilateral pulmonary involvement (the largest lesions with 60 mm), multiple liver metastases (the largest with 35 mm) and persistence of PHEO in the right adrenal bed with 20 mm. Genetic analysis of the *RET* proto-oncogene revealed a mutation at codon 634 (TGCàCGC) of exon 11, Thus, the diagnosis of MEN 2A was admitted. This mutation was not present in her parents and in her three sisters. The patient had no children. Since the patient remained asymptomatic, active surveillance was considered as the most appropriate approach to the patient. Over a 30-year follow-up, the largest nodule of MTC on the thyroid gland increased from 10 mm to 18 mm, no lymph-node metastases have been documented (Fig. 1), PHEO increased of about 20 mm in maximal diameter (Fig. 2), and multiple pulmonary metastases, probably

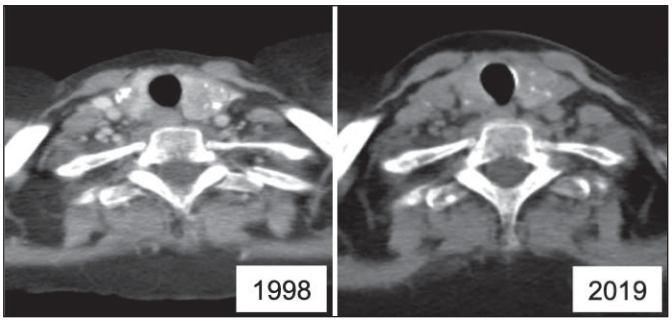

Figure 1. Cervical CT scan showing the left thyroid nodule (medullary thyroid cancer).

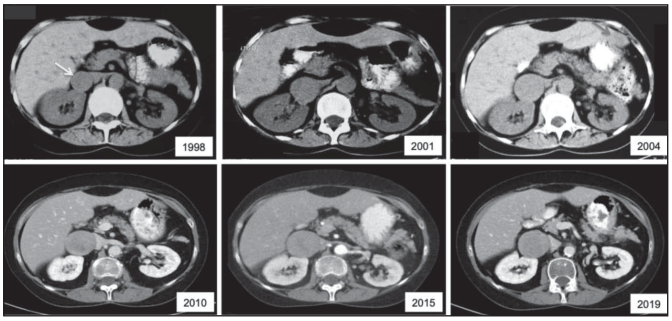

Figure 2. Abdominal CT scan showing the partially resected right pheochromocytoma.

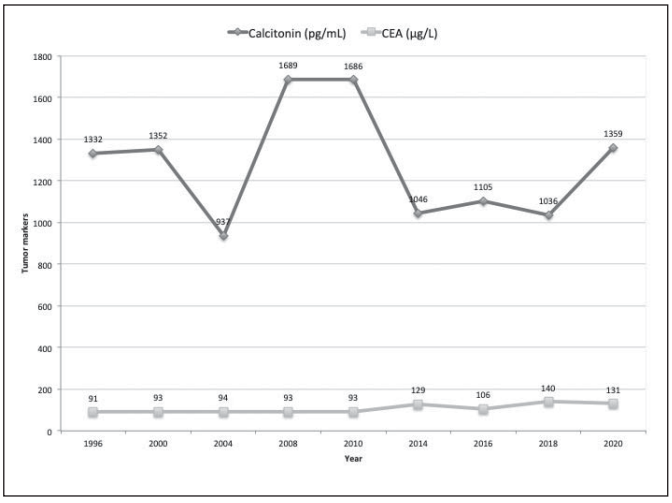

Figure 3. Evolution of tumour markers (calcitonin and CEA) in the last 24 years.

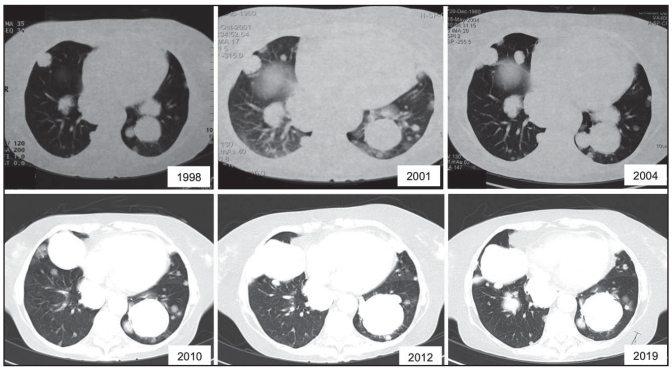

Figure 4. CT scans showing the indolent progression of lung metastases.

from MTC, have increased at a slow pace (Fig. 3). Tumour markers (calcitonin and CEA) have remained stable over the years, as shown in the Fig. 4. Serum calcium and PTH levels have been normal over the years.

High blood pressure has been controlled with phenoxybenzamine 50 mg daily, nifedipine 30 mg qd, atenolol 50 mg qd, and diabetes mellitus, secondary to excess catecholamines, developed 11 years after diagnosis, without no vascular complications until now, under therapy with metformin and insulin. Currently, she is 58-years-old, with a performance status (PS) of 1 (non-productive cough and tiredness for mild efforts).

Discussion and Conclusion

The absence of major complications over 30 years of follow-up proved that active surveillance was probably the most appropriate decision regarding the patient treatment. The decision to not perform the thyroidectomy was due to the small size of the goiter in the presence of large metastatic disease, the absence of cervical compressive symptoms, and the risk of bilateral vocal cord paralysis with surgery. The patient also shared the decision-making.

Considering the PHEO, therapy with MIBG could have been an option but it is usually of little benefit in these tumors[9] and high blood pressure was well controlled by medication. Systemic chemotherapy should only be considered for patients with unresectable and rapidly progressive PHEO.[10] Peptide receptor radioligand therapy is not yet approved for malignant pheochromocytoma.[11]

Considering the metastatic CMT, currently, treatment with TKI (vandetanib, cabozantinib) can be considered, given the extent of the disease. However, these drugs have a high risk of adverse side effects such as hypertensive crises, thromboembolic events and left ventricular dysfunction, which are particularly relevant in a patient with concomitant PHEO, and the patients current PS is only 1, which has allowed to delay its administration.

Responsabilidades Éticas

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Caso Clínico

Precocious Menarche: Functional Ovarian Cystadenoma?

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A B S T R A C T

Precocious menarche is rare and should be investigated when not consistent with pubertal development.
Seven-years-old girl with painful bilateral breast button and menarche. Analytically with slightly elevated estradiol, normal endocrinological study and negative tumor markers. Ultrasound showed a large right ovary cystic lesion compatible with an ovarian cystadenoma. Magnetic resonance imaging showed an enlarged right ovary with a medullary cystic lesion and parenchymal preservation, suggestive of an ovarian cystadenoma. Multidisciplinary follow-up showed breast reduction, absence of vaginal hemorrhages or other signs of puberty. One year later, ultrasound showed spontaneous resolution of the ovarian cystadenoma.
This case describes a large functional cystadenoma with spontaneous resolution. Non-invasive approach may be safe but clinical close surveillance is imperative.

Palavras-chave:
Cistoadenoma;
Criança;
Menarca;
Neoplasias dos Ovários;
Puberdade Precoce.

Menarca Precoce: Cistoadenoma Funcionante do Ovário?

R E S U M O

A menarca precoce é uma condição rara que deve ser investigada quando ocorre em não consonância com o desenvolvimento pubertário.
Menina de 7 anos com botão mamário doloroso bilateral e menarca. Analiticamente com estradiol ligeiramente elevado, estudo endocrinológico normal e marcadores tumorais negativos. Ecografia apresentou lesão cística de grandes dimensões do ovário direito compatível com cistoadenoma do ovário. Ressonância magnética revelou ovário direito aumentado com lesão medular cística e preservação do parênquima, sugestiva de cistoadenoma do ovário. Seguimento multidisciplinar com redução do tamanho da mama, ausência de hemorragia vaginal ou outros sinais de puberdade. Repetiu ecografia um ano depois onde se constatou resolução espontânea do cistoadenoma do ovário.
Este caso descreve um cistoadenoma funcionante do ovário de grandes dimensões com resolução espontânea. A abordagem não invasiva pode ser segura, mas é necessário a vigilância apertada.

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Introduction

Precocious puberty (PP) in caucasian girls is defined as the development of secondary sexual characteristics before the age of 8 years and may range from normal variants of pubertal development to pathological processes.[1] Most cases of PP are due to normal variants of pubertal development and do not require treatment. All cases of PP should be carefully evaluated, mainly those occurring at younger age. Vaginal bleeding before the age of 8 years or not consistent with pubertal development requires additional evaluation and prompt referral to a pediatric endocrinologist.

Pediatric cystic abdominal masses have several etiologies and can occur in almost every intra-abdominal organ. Differential diagnosis should be made with abscess, teratomas and necrotic or cystic changes in tumors.[2]

In girls, pediatric tumors of the genital tract are rare, and among them, ovarian tumors are the most frequent.3 Its incidence increases with age, and most cases are benign or physiologic, such as functional cysts.[3-5] Germ cell tumors are the most frequent ovarian tumors in children, and within these, about 10%-17% are epithelial tumors.[4-6] The majority of ovarian epithelial tumors are mucinous or serous cystadenomas.[2] Childhood epithelial tumors are usually unilateral, and a minority (12%) can be malignant.[2] Malignant tumors can be up to 10% of ovarian masses and are more frequent during premenarchal age.[3,4]

Ovarian tumors usually present with abdominal pain, increased abdominal volume, nausea, vomiting or symptoms that result from surrounding compression of urinary or intestinal organs. Rarely, they can present with PP or menarche due to hormonal disorders. Ovarian cysts can also present as asymptomatic abdominal mass or incidental imaging finding.

After the diagnosis of an ovarian mass, it is important to establish the malignant potential since it will determine the therapeutic approach and consequently the prognosis. The diagnosis is based on ultrasound and magnetic resonance image (MRI). Ultrasound criteria can differentiate benign from malignant tumors. Tumor markers, such as, cancer antigen 125 (CA-125), alpha-fetoprotein (α-FP), beta-human chorionic gonadotropin (β-hCG), carcinoembryonic antigen (CEA), inhibin, lactate dehydrogenase (LDH) and cancer antigen 19-9 (CA 19-9) are useful, but nonspecific.[3,4] The presence of tumor markers, along with abdominal ultrasound data such as size, homogeneity, and presence of solid components, raise the suspicion of malignancy. The absence of tumor markers does not exclude the diagnosis since they can be positive in only 54% of cases.[3]

Treatment of ovarian epithelial tumors, such as cystadenomas, remains controversial. The therapeutic approach of ovarian tumors is mostly surgical and should be evaluated by a multidisciplinary team that includes Pediatrics, Gynecology and Pediatric Surgery. The preservation of the ovary is very important to maintain fertility.

The aim of this paper was to describe the presentation of a benign tumor of the ovary and its evolution to spontaneous resolution. Written informed consent was obtained from the patient's legal guardian for the publication of this case.

Case Report

We report the case of a 7-years-old caucasian girl referenced to Pediatric Endocrinology consultation due to suspected precocious puberty. The child´s mother reported the appearance of painful bilateral breast button with 1-month-evolution but without pubic or axillary hair, without apocrine odor and without capillary or cutaneous oil. Menarche occurred in the previous week with a catamenium duration of 4 days. There was no phytosterols intake, consumption of medicines or use of cosmetic products

There was a maternal notion of increase in growth velocity, but there were no measurements to prove it.

The child was lactose intolerant and had previous complaints of abdominal pain and diarrhea that resolved with lactose-free milk. Her growth was regular, with height at 75th percentile and weight at 25-50th percentile. There was no family history of puberty alterations. Her target family height was 169.5 cm (75-90th percentile). Remaining past history was unremarkable.

At the consultation, she presented the following anthropometric data: weight 22.8 kg (50th percentile), height 127.3 cm (75-90th percentile) and body mass index of 14.5 kg/m^2 (15-50th percentile). On examination, there were no dysmorphia, breasts were palpable bilaterally with 2-3 cm of diameter and without nipple elevation or enlargement, and there were no vulvar alterations. The remaining examination was unremarkable.

Bone age was similar to chronological age. Pelvic ultrasound showed the presence of an image adjacent to the right ovary with 40x27 mm, convex and with anechoic morphology, suggestive of a cystic formation. Analytically: normal blood count, normal erythrocyte sedimentation rate, LDH 442 U/L (reference range 142-290 U/L), normal lipid profile and transaminases. Endocrinological study: normal thyroid function, estradiol 22.3 pg/mL (reference value <15 pg/mL), FSH <0.3 mUI/mL, LH<0.1 mUI/mL, total testosterone <20 ng/dL and normal cortisol (13.7 ug/dL). Four days later, she repeated the pelvic ultrasound that confirmed the presence of a 51x25 mm cystic lesion in the right ovary in relation to a probable ovarian cystadenoma (Fig. 1). Uterus with

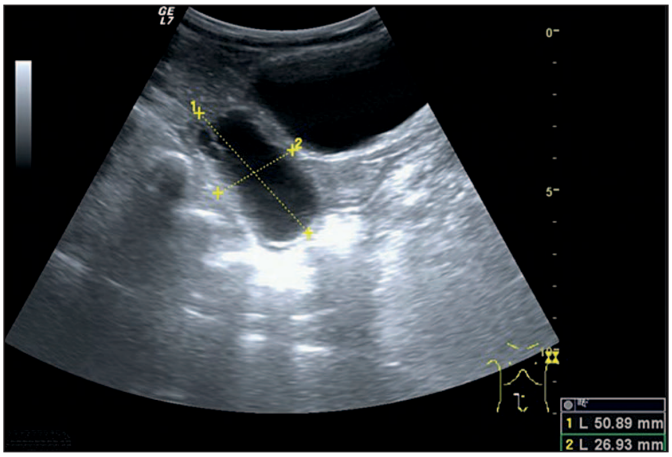

Figure 1. Ultrasound showing cystic lesion in the right ovary

preserved morphology, measuring 24x12x40 mm (TxAPxL), left ovary with normal morphology, without adnexal lesions. Tumor markers, such as CA-125, prolactin, α-FP, β-hCG and CEA were within the normal limits. Two months later, a pelvic MRI was performed, and showed an enlarged right ovary with a cystic lesion measuring 19x22x33 mm centered on the medullary region of the ovary, with preservation of the ovarian parenchyma, suggesting an ovarian cystadenoma (Fig. 2). Left ovary and uterus with dimensions and morphology appropriate to the age group.

Due to the apparent size reduction of the cystic formation, surgery was postponed. Multidisciplinary follow-up was maintained

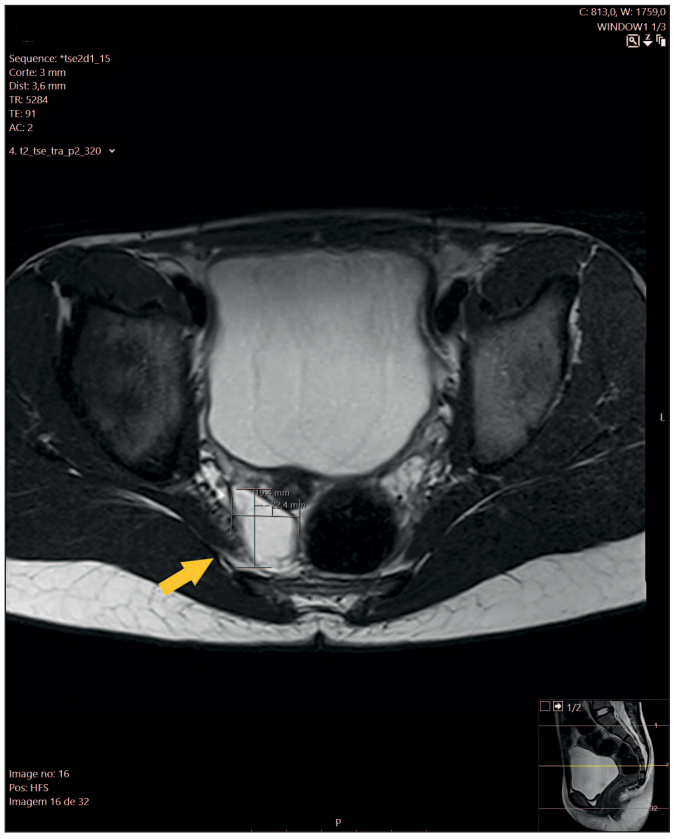

Figure 2. Pelvic MRI showing cystic lesion in the right ovary

with regular pediatric surgery and pediatric endocrinology consultations. During follow-up, she presented regular growth velocity, breast size reduction, and there were no new episodes of vaginal hemorrhage or other signs of puberty.

One year later, pelvic ultrasound was repeated and showed uterus with normal shape and dimensions for the age group, measuring 3.6x1.5 cm, and right ovary with 18 mm longitudinal diameter and left ovary with 16 mm, without any cystic formations. Analytical reassessment of the tumor marker CEA came back negative.

Despite the spontaneous regression and the presumptive diagnosis of a functioning ovarian cystadenoma, multidisciplinary follow-up was maintained.

Conclusion

Ovarian masses may be cystic, complex, or solid. Most ovarian cysts, whether occurring in the prepubertal phase or in the pubertal phase, are physiological. Most ovarian tumors are benign, with cystadenomas being the most common type.[8] An early diagnosis of ovarian mass is necessary to reduce the risk of complications, such as ovarian torsion, and to improve the prognosis if a malignant neoplasm is diagnosed.

This case reports an unusual pathology in prepubertal girls, with clinical and imaging features suggestive of ovarian cystadenoma. Most pediatric ovarian cysts are functional and usually regress spontaneously.[7] According to the literature, ovarian masses measuring more than 8 cm rarely resolve spontaneously, with the majority requiring surgical removal.[8] This girl presented a cystic lesion compatible with cystadenoma, without unequivocal ultrasonographic criteria of functional cyst. Spontaneous resolution, particularly in large-volume lesions as in this case, is not common, and is not described in the literature. This raises the hypothesis that an expectant attitude can be maintained if there are unremarkable clinical and analytical findings along with benign ultrasonographic characteristics. In those cases, an expectant attitude includes careful clinical follow-up and imaging control. However, if puberty continues to progress, surgery is mandatory, even if clinical, analytical or imaging findings are suggestive of benignity.

Ovarian masses can have a variable and nonspecific presentation, ranging from diffuse abdominal pain, increased abdominal volume, asymptomatic abdominal mass or hormonal disorders.[5] In this case, the initial presentation was a precocious puberty. The presence of bilateral breast button and the slightly elevated estradiol levels should raise the suspicion of either central or peripheral stimulation. Since gonadotropins are non doseable, the hypothesis of central stimulation is ruled out and the presence of an estradiol-secreting tumor or a physiologic cyst should be considered.

Although this girl has negative tumor markers, it is very important to maintain a careful clinical, analytical and imaging follow-up, since negative tumor markers do not exclude the existence of malignancy. Also, a small percentage of cystadenomas can become malignant.[3]

Pediatric population with adnexal tumors should be followed by a multidisciplinary team that includes Pediatrics, Gynecology and Pediatric Surgery. When necessary, surgery should be carefully programmed in order to preserve the ovary and maintain fertility.

The absence of follow-up protocols for this type of pathology makes research in this area important. Clinical and therapeutic approach should be based not only on individual experiences but on robust scientific evidence.

The presentation of this case aims to contribute to a better understanding of this unusual pathology in the pediatric age.

Responsabilidades Éticas

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Imagens em Endocrinologia

Thyroglossal Duct Cyst Embracing Thyroid Gland and Trachea

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INFORMAÇÃO SOBRE O ARTIGO

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O Quisto Tireoglosso que Abraça a Tiróide e a Traqueia

Palavras-chave:
Quisto Tireoglosso

Thyroglossal duct cysts (TGDC) are the most common form of congenital cervical anomalies. They represent epithelial remnants of the thyroglossal tract and can form anywhere along the thyroid route of migration. Characteristically, TGDC present as a 20 mm midline nontender neck mass at the level of the thyrohyoid membrane, closely associated with the hyoid bone, although other locations may occur.[1-3]

Most patients with TGDC are children or adolescents, but up to one third of patients affected are adults: males and females are equally affected.[1,2] The differential diagnosis includes dermoid cysts, sebaceous cysts and thyroid ectopia. Computed tomography (CT) of the neck and cervical ultrasonography (US) are the preferred imaging modalities.[1-3] for the diagnosis.

We report a case of a healthy 42 year-old woman presented with a neck mass, causing aesthetic concerns. Ultrasonography (US) revealed what seemed to be a cystic nodule that compassed all thyroid gland (Fig. 1). Thyroid function was within the normal age. US-guided aspiration of the cyst was performed, with inconclusive cytological results (Result: scarce number of cells in the fluid). After simple aspiration, there was full restitution of the cyst. CT of the neck showed a 57 mm cystic mass surrounding the thyroid gland and compressing adjacent structures (Fig. 2) and, therefore, a surgical approach was decided. The patient underwent surgical removal of the cystic mass alone (full thyroid tissue was kept intact), with a histology described as a thyreoglossal cyst (result: histological and immunohistochemical studies (CD31 and CK7) strongly suggesting thyreoglossal cyst). There were no complications after surgery. In the last follow-up, US shows no signs of cyst formation and thyroid function is normal without levothyroxine replacement.

All incidental detected cystic masses on head and neck imaging should be investigated, and TGDC should be considered. Before surgery is planned, it is important to determine whether patients with a TGDC have thyroid tissue in the normal site or any ectopic thyroid tissue (All cases of thyroid ectopia should have thyroid function tests, ultrasonography, and a thyroid scan performed to locate additional functioning thyroid tissue), as this can be involved with benign or malignant thyroid disease. If there is not normal thyroid tissue, the patient faces the possibility of lifelong hypothyroidism after surgery. There are no other major risks, reported with this procedure. After surgery, the prognosis is excellent, with around 10% risk of lifelong recurrence of the TGDC.[1,2]

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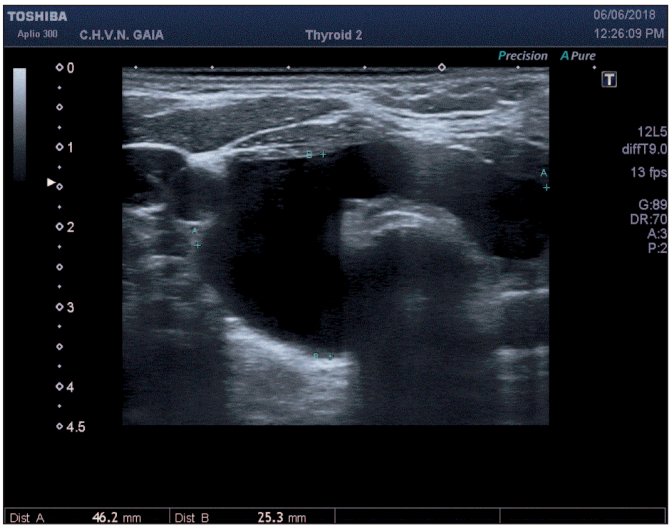

Figure 1. US transversal plan, showing an enlarged cyst around and compressing thyroid gland.

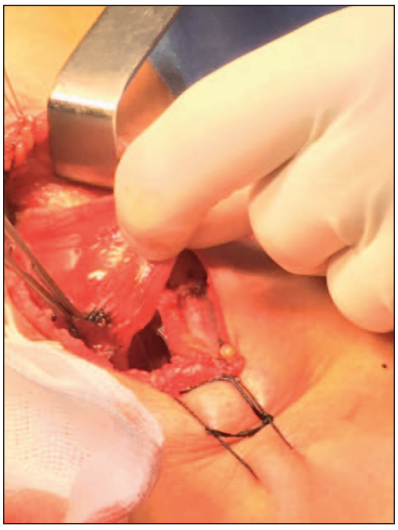

Figure 2. Thryreoglossal cyst surgical removal: the cyst, beeing held in the picture by the surgion, has a thin membrane with transparent liquid content.

During follow-up, the patient has been shown no signs of cyst recurrence and is now under ultrasound surveillance, every 6 months.

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Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
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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 **Maio 2017**