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

Inês Ferreira Barros [a,*], Mariana Barbosa [a], Vera Fernandes [a], Cláudia Matta-Coelho [a], Ana Margarida Monteiro [a], Marta Alves [a], Selma Souto [a], Maria Lopes Pereira [a]

[a] *Endocrinology Department, Hospital de Braga, Braga, Portugal.*

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

* Autor Correspondente / Corresponding Author.
E-Mail: barros.ines@gmail.com (Inês Ferreira Barros)
Sete Fontes, São Victor, 4710-243 Braga, Portugal

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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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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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