Effect of Metformin on TSH Levels in Patients with Morbid Obesity and Diabetes *Mellitus*

Efeito da Metformina nos Níveis Séricos de TSH em Doentes com Obesidade Mórbida e Diabetes Mellitus

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Abstract

Introduction: Morbid obesity is associated with elevated TSH levels. Several studies have suggested that, in patients with hypothyroidism, metformin reduces TSH.
Objectives: To evaluate the effect of metformin on thyroid function in patients with morbid obesity and diabetes.
Material and Methods: We evaluated 244 patients with morbid obesity and diabetes undergoing bariatric surgery, without history of thyroid disease and with serum levels of TSH and free T4 within the reference range. We analyzed the effect of metformin treatment on thyroid function before and after bariatric surgery.
Results: Among the patients with morbid obesity and diabetes, 76.3% were on metformin. Patients on metformin had significantly lower levels of TSH. After bariatric surgery, there was a more marked decrease in TSH among patients not treated with metformin. One year after surgery, TSH levels were similar in both groups.
Conclusions: Treatment with metformin was associated with lower levels of TSH in patients with morbid obesity and diabetes. Our results suggest that the normalization of TSH promoted by bariatric surgery in patients with morbid obesity may be mimicked by treatment with metformin.

Keywords: metformin, thyroid function, morbid obesity, diabetes, bariatric surgery

Resumo

Introdução: A obesidade mórbida associa-se a elevação dos níveis de TSH. Vários estudos têm sugerido que, em doentes com hipotiroidismo, a metformina reduz a TSH.
Objetivos: Avaliar o impacto da metformina na função tiroideia de doentes com obesidade mórbida e diabetes.
Material e Métodos: Avaliamos 244 doentes com obesidade mórbida e diabetes submetidos a cirurgia bariátrica, sem história de doença tiroideia e com níveis séricos de TSH e T4 dentro do intervalo de referência. Analisamos o impacto do tratamento com metformina na função tiroideia antes e após a cirurgia bariátrica.

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Recebido/Received: 02/11/2017; Aceite/Accepted: 15/12/2017.

Resultados: Dos doentes com obesidade mórbida e diabetes, 76,3% estavam medicados com metformina. Os doentes sob metformina apresentavam níveis significativamente inferiores de TSH. Após a cirurgia bariátrica observou-se uma diminuição mais marcada da TSH no grupo de doentes não tratados com metformina pelo que, um ano após a cirurgia, os níveis de TSH foram sobreponíveis nos dois grupos.
Conclusões: O tratamento com metformina associou-se a níveis mais baixos de TSH em doentes com obesidade mórbida e diabetes. Os nossos resultados sugerem que a normalização da TSH promovida pela cirurgia bariátrica em doentes com obesidade mórbida pode ser mimetizada pelo tratamento com metformina.

Palavras-chave: metformina, função tiroideia, obesidade mórbida, diabetes, cirurgia bariátrica

> INTRODUCTION

Obesity is a disease with an increasing incidence in Portugal [1] and worldwide [2], being associated with significant morbidity and mortality [3]. A high incidence of type 2 diabetes mellitus [4] and a significant frequency of dysfunction of multiple endocrine systems [3], including changes in thyroid function, are observed in morbid obesity [5]. The relationship between thyroid function, morbid obesity and diabetes has been evaluated by several studies [6-16]. Although it is established that thyroid dysfunction may contribute to the development of morbid obesity [5] and diabetes [17], the effect of morbid obesity and diabetes on thyroid function is less clear.
Several studies have shown elevated TSH levels in patients with morbid obesity [18-20]. The elevation of TSH in this context may constitute a compensatory mechanism of activation of the hypothalamic-pituitary-thyroid axis in response to peripheral mediators, particularly leptin [21, 22], or a compensatory response to some degree of resistance to thyroid hormones [23]. Among the mechanisms underlying resistance to thyroid hormones, the reduction of insulin sensitivity and the visceral obesity have been proposed as relevant mechanisms [24]. Previous studies have suggested that treatment with metformin promotes a reduction of TSH in patients with hypothyroidism [25-27]. In addition, the elevated TSH levels in morbid obesity tend to normalize after bariatric surgery [6-9, 28], and there is a significant correlation between the percentage of weight loss and the reduction of TSH one year after surgery [29].
The effect of metformin on thyroid function in patients with diabetes and morbid obesity remains unknown. Thus, our goal was to evaluate the effect of metformin treatment on thyroid function in patients with diabetes and morbid obesity.

> METHODS

Study Design and Participants

We performed a retrospective observational study evaluating 244 patients with morbid obesity and diabetes undergoing bariatric surgery (adjustable gastric band, roux-en-Y gastric bypass or sleeve gastrectomy) at Centro Hospitalar de São João between January 2010 and June 2015. We only included patients without history of thyroid disease, without levothyroxine or antithyroid treatment and with serum levels of TSH and free T4 (FT4) within the reference range (TSH 0.35-4.94 mU/L and FT4 0.70-1.48ng/dL). Patients missing TSH or FT4 levels before surgery or TSH levels one year after surgery were also excluded.

Clinical Variables

The following preoperative variables were evaluated: age, sex, weight, body mass index (BMI), waist circumference, TSH and FT4 levels, history of diabetes and treatment with metformin. Diabetes was defined by fasting plasma glucose ≥126mg/dL, glycated hemoglobin ≥6.5%, 2-h plasma glucose after a 75-g oral glucose tolerance test ≥200 mg/dL, or the use of antihyperglycemic drugs. TSH levels and treatment with metformin were re-evaluated one year after surgery.

Statistical Analysis

We compared TSH levels of patients with morbid obesity and diabetes treated with metformin with those not treated with metformin. The variation of TSH after bariatric surgery was evaluated among patients treated with metformin and among patients not treated with metformin. We also evaluated TSH levels one year after surgery according to treatment with metformin before surgery and after surgery.
We used independent t-tests (for comparison between groups) and paired t-tests (for comparison within the same group at different times) for continuous variables. The results are presented as mean ± standard deviation for continuous variables and as percentage for categorical variables. Statistical analysis was performed using Stata, version 14.1 (StataCorp). A p-value of less than 0.05 was considered statistically significant.

> RESULTS

Baseline Characteristics

Among the 244 patients with morbid obesity and diabetes, 81.1% were female and the mean age was 47.3 ± 9.0 years. Patients had a mean pre-surgery weight of 115.8 ± 19.0 kg and a mean BMI of 44.8 ± 5.9 kg/m^2, with a waist circumference of 125.5 ± 12.9 cm. Most patients underwent roux-en-Y gastric bypass (58.2%), followed by adjustable gastric band (26.2%) and sleeve gastrectomy (15.6%). Fasting plasma glucose was 126.6 ± 46.6 mg/dL, with an HbA1c of 6.7 ± 1.3%. Among the patients evaluated, 76.3% were treated with metformin (Table I).

Table I - Clinical characteristics of the study population.

	Study population (n=244)
Sex	
Male	18.9%
Female	81.1%
Age, years	47.3 ± 9.0
Weight, kg	115.8 ± 19.0
BMI, kg/m^2	44.8 ± 5.9
Waist circumference, cm	125.5 ± 12.9
Type of surgery	
Adjustable gastric band	26.2%
Roux-en-Y gastric bypass	58.2%
Sleeve gastrectomy	15.6%
Fasting glucose, mg/dL	126.6 ± 46.6
HbA1c, %	6.7 ± 1.3
Treatment with Metformin	
Yes	76.3%
No	23.7%
TSH, mIU/L	1.97 ± 0.84
FT4, ng/dL	1.06 ± 0.13

Effect of Metformin on TSH Levels Before Surgery

Preoperative TSH levels were 1.97 ± 0.84 mIU/L (Table I). We observed a statistically significant difference between TSH levels in patients receiving metformin and TSH levels in patients not treated with metformin (p = 0.023). TSH levels in the metformin group were 1.91 ± 0.77 mIU/L and in the non-metformin group were 2.20 ± 1.02 mIU/L (Figure 1).

We did not observe significant differences in FT4 levels according to treatment with metformin (1.03 ± 0.13 vs 1.06 ± 0.13 ng/dL, p = 0.140).

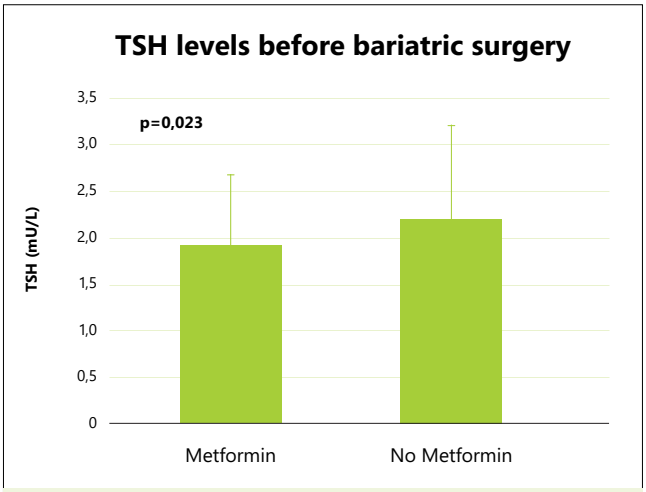

Figure 1 - TSH levels before bariatric surgery according to treatment with metformin.

TSH Variation After Surgery According to Treatment with Metformin

We observed a weight loss after bariatric surgery of 31.5 ± 14.0 kg (before 115.8 ± 19.0 kg vs after 84.4 ± 17.1, p <0.001). The reduction of TSH one year after surgery was 0.18 ± 0.75 mIU/L in the total group of patients. Patients not receiving metformin had a significantly greater reduction of TSH comparing with patients receiving metformin (0.34 ± 0.66 vs. 0.12 ± 0.77, p = 0.046) (Figure 2).

TSH Levels One Year After Surgery According to Treatment with Metformin

One year after surgery, TSH levels were not significantly different according to metformin treatment at that time or before surgery (Figure 3). TSH levels one year after surgery were 1.85 ± 0.87 mIU/L in subjects not treated with metformin prior to surgery and 1.79 ± 0.79 mIU/L in subjects treated with metformin prior to surgery (p = 0.597). The difference between groups was also not statistically significant when dividing patients according to metformin treatment one year after surgery (1.83 ± 0.87 vs. 1.80 ± 0.74 mIU/L, p = 0.795).

> DISCUSSION

We observed, in patients with morbid obesity and diabetes, an association between treatment with metformin and lower levels of TSH. In addition, the TSH reduction in patients with diabetes not treated with metformin was greater than in patients receiving metformin. This

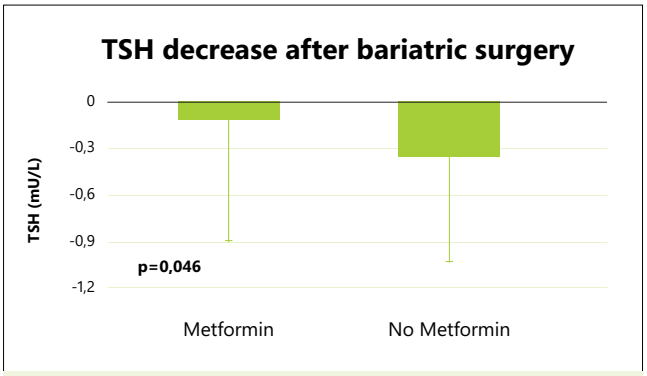

Figure 2 - TSH decline one year after bariatric surgery according to treatment with metformin.

patients not treated with metformin suggests a more significant dysregulation of thyroid axis in this group. This difference also suggests that the normalization of TSH by bariatric surgery may be dependent on mechanisms, at least in part, overlapping those promoted by metformin. This hypothesis is reinforced by the absence of significant differences in TSH levels one year after surgery between metformin treatment groups.

The mechanism underlying TSH reduction by metformin remains uncertain. Some authors suggested that metformin increases sensitivity to thyroid hormones [26]. Alternatively, metformin may modulate the hypothalamic-pituitary feedback of thyroid hormones [33] or enhance the dopaminergic tone in TSH secretion [34].

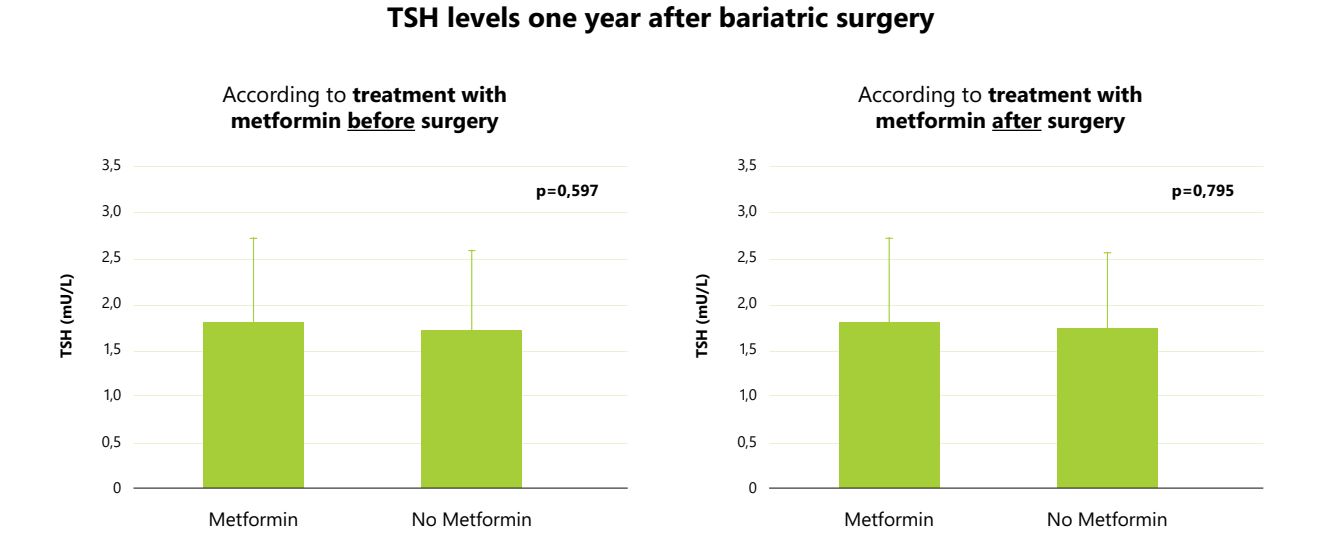

Figure 3 - TSH levels one year after bariatric surgery according to treatment with metformin (before and after surgery).

suggests that the effect of normalization of TSH by bariatric surgery may be, at least partially, mimicked by treatment with metformin.

The description of lower levels of TSH in patients receiving metformin is consistent with several previous studies [25-27, 30, 31] and with a meta-analysis that showed a reduction of TSH in patients with clinical and subclinical hypothyroidism [32]. In this meta-analysis, the reduction of TSH was not statistically significant in euthyroid patients. The fact that we observed lower levels of TSH in morbidly obese patients treated with metformin suggests that, in morbid obesity, elevations of TSH within the reference range may represent a dysregulation of the thyroid axis potentially correctable with metformin.

The greater reduction of TSH after bariatric surgery in

In summary, our study highlights that, in patients with morbid obesity and diabetes, metformin is associated with a decrease in TSH levels contributing to the normalization of the hypothalamic-pituitary-thyroid axis. The clarification of the mechanisms and consequences associated with the elevation of TSH in patients with morbid obesity and diabetes may contribute to an improvement in the therapeutic approach to these patients. <

Conflict of interests

The authors declare that they have no conflict of interests, nor any source of external financing in the realization of this work.

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