Revista Brasileira de Obesidade, Nutrição e Emagrecimento
ISSN 1981-9919 ***versão eletrônica***

Periódico do Instituto Brasileiro de Pesquisa e Ensino em Fisiologia do Exercício

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ANALYZING THE EFFECTS OF TREATING HYPOTHYROIDISM AND SUBCLINICAL HYPOTHYROIDISM ON BODY MASS

Ana Cristina Diniz Silva[1]
Hiang Leng Tan[2]
Nada Rawof[3]
Bongiwe Vilakazi[4]

ABSTRACT

Hypothyroidism and subclinical hypothyroidism (SCH) are common endocrine dysfunctions, mostly affecting females. The prevalence of overt hypothyroidism is estimated in 2%, whereas SCH may affect as much as 3-15% of the population. Both conditions evolve with near similar symptoms and one of the commonest presentations is weight gain. The goal of the standard thyroid replacement therapy is to achieve euthyroidism, both clinically and biochemically, which is assessed by the circulating thyroid stimulating hormone (TSH) within the normal range of reference. Although patients tend to correlate their overweight/obesity with overt or subclinical hypothyroidism, it remains difficult to determine how much of the weight gain can be attributed to these conditions, as their onset is not always clear. In addition, despite highly expected, weight loss following hormonal replacement therapy cannot be assured, according to the current evidence. The aim of this article is to evaluate the relationship between TSH levels and weight, and the effects of treating hypothyroidism and SCH on body mass, specifically looking at weight loss, through a detailed review of the available literature.

Key words: Hypothyroidism. Subclinical hypothyroidism. Obesity. BMI. Overweight. Thyroid Hormone.

RESUMO

Hipotireoidismo e hipotireoidismo subclínico (SCH) são disfunções endócrinas comuns, que afetam principalmente as mulheres. As prevalências de hipotireoidismo clínico e subclínico são estimadas em 2% e 3-15%, respectivamente. Ambos evoluem com sintomas bastante semelhantes, sendo o ganho de peso uma das apresentações mais frequentes. O objetivo da terapia de reposição hormonal com hormônio tireoidinano é atingir o estado de eutireoidismo, clínica e bioquimicamente, que é avaliado pela dosagem periódica do hormônio tíreo-estimulante (TSH), o qual deve estar dentro da faixa normal de referência. Embora os pacientes tendam a correlacionar o excesso de peso ou mesmo a obesidade com o hipotireoidismo clínico ou subclínico, ainda não se pode estabelecer ao certo, de acordo com as evidências disponíveis, o ganho de peso atribuível a essas condições. Também incerta é a associação entre o início do ganho de peso e o início da disfunção endócrina, não sendo possível, portanto, assegurar perda de peso com a terapia hormonal. Tais dúvidas tornam esse tema controverso e polêmico. O objetivo desta revisão é avaliar a relação entre os níveis de TSH e peso, e os efeitos do tratamento do hipotireoidismo clínico e subclínico sobre a massa corporal, focando, especificamente, na perda de peso.

Palavras-chave: Hipotiroidismo. Hipotireoidismo Subclínico. Obesidade. IMC. Excesso de Peso. Hormônio da Tiroide.

1-Tribunal de Justiça de Minas Gerais, Brasil.
2-North Bristol NHS Trust, Reino Unido.
3-Sydney Metabolic Surgery/Nepean Hospital, Australia.
4-University of South Wales, Reino Unido.

E-mails dos autores:
anacristina@sernobre.com.br
hiangleng@doctors.org.uk
nada.rawof@gmail.com
bongiwe.vilakazi@gmail.com

Revista Brasileira de Obesidade, Nutrição e Emagrecimento
ISSN 1981-9919 ***versão eletrônica***

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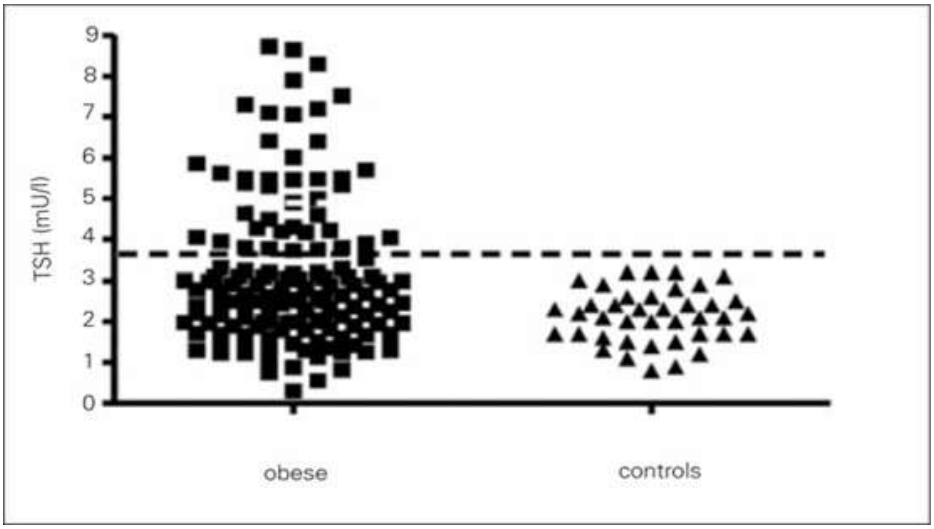
INTRODUCTION

Obesity impacts negatively on metabolic process, increasing the probability of the development of diabetes (DM) and cardiovascular disease (CVD). In obesity, thyroid structural and functional changes, which improve with weight loss, have been described. However, it remains unclear whether these changes are sequential to increased adiposity or the cause thereof (Longhi e Radetti, 2013).

It is widely accepted that hypothyroidism causes weight gain associated with a decrease in basal metabolic rate (BMR) and thermogenesis, and that there is a perceived association between thyroid hormones and body composition. This emanates from the function of the thyroid gland in the regulation of basal metabolism and thermogenesis, thereby affecting energy intake, and the glucose and lipid metabolism (Longhi e Radetti, 2013).

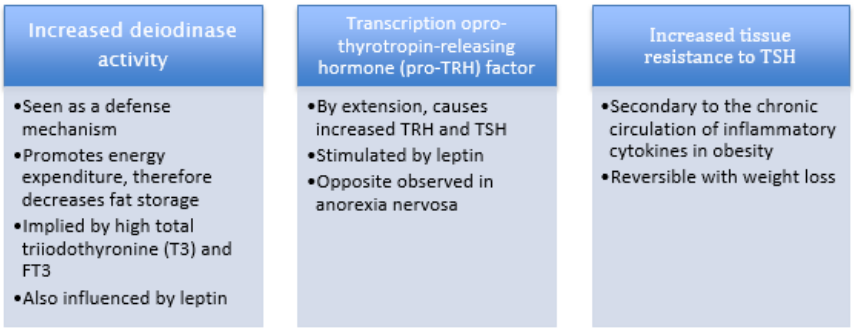
Further strengthening the relationship between weight and thyroid function is the observed inverse correlation between free thyroxine (FT4) and body mass index (BMI), and the high levels of thyroid-stimulating hormone (TSH) observed in obese children, depicted in Figure 1 (Longhi e Radetti, 2013).

Less understood are the mechanisms for these alterations in thyroid function. Longhi e Radetti (2013) postulate that such thyroid dysfunction could be consequence of some events, which are represented in Figure 2.



Source: Longhi e Radetti (2013).

Figure 1 - Thyroid-stimulating hormone (TSH) serum levels in a group of 143 obese children and in normal-weight children.



Adapted from: Longhi e Radetti (2013).

Figure 2 - The mechanisms that may explain the alterations in thyroid function encountered in overweight and obesity.

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MATERIALS AND METHODS

To build up this article, we have systematically reviewed the literature using online search tools and the PubMed database. The search process included clinical trials, reviews and guidelines published from January 2001 to December 2015. The used key terms were “hypothyroidism”, “subclinical”, “obesity”, “TSH”, “weight loss”, and their combinations. The results were then filtered through the analysis of the title and abstract. Finally, the full papers have been retrieved from the online library of the University of South Wales.

The evidence-based relationship between thyroid dysfunction and weight change

Thyroid hormone (TH) assumes a major role in the regulation of metabolism and thermogenesis. In the event of excess TH, patients present with hyperthyroidism, detected biochemically with a suppressed TSH and an excess of thyroid hormones (T4 and T3) (Skugor, 2014). From a weight perspective, hyperthyroidism is associated with unintentional weight loss, despite an increased appetite due to higher BMR (Enrique, 2003). However, following treatment for hyperthyroidism, there is evidence that the majority of patients will gain weight (Dale and collaborators, 2001). In a 24-month period following treatment, there was overall documented weight gain of 5.42kg and increase in BMI of 8.49 in a cohort of 162 patients with hyperthyroidism. Patients who had undergone thyroidectomy gained the most weight, with similar weight gain in both thionamides and radioiodine group (Dale and collaborators, 2001).

An analysis of the body composition, muscle mass and TH essays of healthy male subjects, with no history of thyroid disease or treatment, was undertaken to assess if the association between TH and body composition, as observed in thyroid dysfunction, existed in euthyroid subjects (Roef and collaborators, 2012). The findings (Table 1) showed positive associations between the circulating levels of thyroid hormones and BMI, fat mass, insulin resistance and leptin, and a negative association with muscle area and lean mass, leading to the curious conclusion that a less favorable body composition and metabolic function correlated with higher T3 and T4 levels in healthy euthyroid men (Roef and collaborators, 2012).

In primary hypothyroidism, serum TSH is elevated and thyroid hormone levels are subnormal (Kostoglou-Athanassiou and Ntalles, 2010). The signs and symptoms of primary hypothyroidism are varied (Table 2) and are dependent on the severity of the disease (Kostoglou-Athanassiou and Ntalles, 2010).

Table 1 - Standardized estimates of mixed effects model describing the relationship between thyroid hormones (independent) and body composition (dependent), with parameters of glucose metabolism and leptin. Data presented as standardized estimate +/- S.D. Results from mixed effects model to account for family structure and adjusted for age, height and weight, except models for weight (age, height), and BMI (age).

	TT3 (ng/dL)		**TT4 (µg/dL)**	
		P value		P value
Weight (kg)	0.14 ± 0.03	<0.0001	0.04 ± 0.03	0.2
BMI (kg/m2)	0.15 ± 0.03	<0.0001	0.03 ± 0.03	0.3
Whole body fat mass (kg)	0.06 ± 0.02	0.0005	0.10 ± 0.02	<0.0001
Trunk fat mass (kg)	0.05 ± 0.02	0.0005	0.07 ± 0.02	<0.0001
Whole body lean mass (kg)	-0.05 ± 0.01	0.0003	-0.09 ± 0.01	<0.0001
CSMA Radius 66% (mm2)	0.03 ± 0.03	0.3	-0.10 ± 0.03	0.0001
CSMA Tibia 66% (mm2)	-0.08 ± 0.03	0.003	-0.05 ± 0.03	0.08
Glucose (mg/dl)	0.06 ± 0.03	0.08	0.02 ± 0.03	0.6
Insulin (µU/ml)	0.12 ± 0.03	<0.0001	0.06 ± 0.03	0.03
HOMA IR	0.13 ± 0.03	< 0.0001	0.07 ± 0.03	0.03
Leptin (µg/l)	0.08 ± 0.02	0.0002	0.12 ± 0.02	<0.0001

Legends: CSMA = cross sectional muscle area. **Source:** Roef and collaborators (2012).

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Table 2 - Percentage of symptoms and signs in clinical hypothyroidism.

Symptoms	Percentage (%)	**Signs**	Percentage (%)
Fatigue	88	Dry coarse skin	90
Cold intolerance	84	Voice hoarseness	87
Dry skin	77	Facial periorbital oedema	76
Decreased hearing	40	Slowed movements	73
Sleepiness	68	Mental impairment	54
Impaired memory	66	Bradycardia < 60/min	10
Weight gain	72	Bradycardia > 60/min	90
Paraesthesia	56		
Constipation	52		
Hair loss	41		

Source: Kostoglou-Athanassiou and Ntalles (2010).

DISCUSSION

Apart from weight gain, primary hypothyroidism has also been associated with abnormal fat redistribution causing central adiposity (Esmail and collaborators, 2013). The authors demonstrated that the mean waist-to-hip ratio before treatment was significantly higher compared to controls, then significantly declined after TSH normalisation with levothyroxine (L-T4) treatment. The limitation of this study was that participants were exclusively men, recruited from a Veterans Affairs Medical Centre. A large cohort involving women would be necessary to demonstrate these findings in females, as primary hypothyroidism is 3-5 times more common in the female population (Kostoglou-Athanassiou and Ntalles, 2010).

In the spectrum of hypothyroidism is subclinical hypothyroidism (SCH), defined as a combination of elevated serum TSH and normal FT4 levels (Nyrnes and collaborators, 2006). Thyroid hormone replacement might be useful in SCH, particularly in the overweight or obese, as recent research has demonstrated a negative impact of SCH on morbidity and mortality indices, especially in association with dyslipidemia and CVD (Nyrnes and collaborators, 2006). Nevertheless, the indications and the opportune time for treatment remain unclear.

Several studies have investigated the relationship between TSH and BMI. A longitudinal trial revealed that increased TSH was associated with higher BMI in nonsmokers, even after adjusting for age (Nyrnes and collaborators, 2006). Another trial demonstrated a BMI difference of 1.9kg/m2 (correspondent to 5.5kg) when the group with the highest TSH levels was compared with the group with the lowest levels, in the absence of alterations in FT4 levels (Knudsen and collaborators, 2005).

Although not all studies confirm an association between weight gain and SCH, there is mounting evidence that even slight dysfunctional changes within the laboratory reference ranges negatively affect adiposity and fat distribution (Biondi, 2010). For instance, when patients with normal TSH levels were evaluated with regard to weight gain, a positive, strong and linear association was observed in both genders (Fox and collaborators, 2008).

The evidence-based analysis of effects of thyroid hormonal therapy on body mass

As weight gain is commonly reported to be associated with primary hypothyroidism, patients would be expected to lose weight following treatment with L-T4. However, the lack of weight loss on treatment has negated this popular belief (Hoogwerf and Nuttall, 1984; Lee and collaborators, 2014). A study by Lee and collaborators (2014) demonstrated no significant change in weight following treatment with L-T4 in patients with primary hypothyroidism. The authors observed that 52% of the investigated patients lost weight, with a median weight loss of 3.8kg following treatment. However, taking into account all patients, the overall weight change was only -0.1kg. An earlier clinical trial showed that in 18 hypothyroid patients, there was an initial weight loss within the first six months of treatment, but by 24 months, patients had reverted to their pre-treatment weight (Hoogwerf and Nuttall, 1984).

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Although L-T4 is considered the mainstay of primary hypothyroidism treatment, combination therapy adding liothyronine (L-T3) has been used in selected group of patients (Chakera and collaborators, 2012). The combined therapy was associated with more weight loss compared to monotherapy with L-T4 (Bente and collaborators, 2005). However, it had a TSH endpoint below the reference range, which is not recommended, as there is a linear correlation of suppressed TSH with cardiovascular dysfunction and decreased bone mineral density (Kostoglou-Athanassiou and Ntalles, 2010).

The American Thyroid Association (ATA) recommends levothyroxine as the first choice treatment in hypothyroidism due to its proven efficacy, ease of administration, good absorption, low index of adverse events and low costs. The treatment goal is the maintanance of a normal TSH level (0.45-4.50 mIU/L) (Sawka and Jonklaas, 2015).

This guideline also recommends targeting age-specific TSH levels, e.g., for people older than 65yr, TSH concentrations up to 6 mIU/L may be acceptable, with concern to the possible comorbidities. Moreover, FT4/FT3 are recommended neither as screening, nor as follow-up tests in the management of hypothyroidism (Sawka and Jonklaas, 2015).

There is no evidence that targeting lower TSH or higher T3 concentrations with hormonal therapy would benefit overweight hypothyroid patients (Jonklaas and collaborators, 2014).

Parameters such as body weight, lean body mass, pregnancy, TSH, age and the general clinical context should be considered prior to commencing treatment (Jonklaas and collaborators, 2014).

To investigate the impact of body composition on the dose of L-T4, 75 patients in an endocrine unit were assessed employing the DEXA scan. On average the daily dose of L-T4 was lower in normal-weight versus overweight and obese participants, and a stronger correlation was shown between L-T4 and lean body mass ($p<0.001$, $r=0.667$) as opposed to fat mass ($p<0.023$, $r=0.26$). Furthermore, the peripheral lean mass was shown to have the highest correlation to L-T4, with no correlation observed for peripheral fat mass (Santini and collaborators, 2004).

ATA recommends against treating obese euthyroid patients with L-T4. Experts argue that it is difficult to determine the cause-effect association between weight-gain and elevated serum TSH levels, as autoimmunity itself may predispose to obesity, whereas overweight may trigger thyroid dysfunction. Furthermore, after obese patients lose weight, TSH levels tend to normalize (Jonklaas and collaborators, 2014).

Interestingly, most of the overweight observed in hypothyroid patients is secondary to fluid retention. Even in severe hypothyroidism, after proper treatment, a significant loss of fat mass is not observed, despite the improvement in BMR. Additionally, there is no evidence that body weight is substantially affected by L-T4 in patients with SCH.

Therefore, more than ineffective, L-T4 administration in euthyroid/SCH patients may cause negative nitrogen balance and serious cardiovascular and skeletal adverse effects (Jonklaas and collaborators, 2014).

In the specific cases of SCH, Krotkiewski (2002) suggested a consideration for hormonal replacement for obese patients with dyslipidemia; in these specific cases, small doses of T3 are preferred.

Another meta-analysis (Pearce and collaborators, 2013) reported that overt hypothyroidism causes downregulation of glucose transporters located in the cell membrane, and affect insulin production and clearance, thus resulting in reduced insulin sensitivity.

By extension, SCH may correlate with insulin resistance and metabolic syndrome as well. Therefore, the authors recommend considering L-T4 therapy only in patients with type 2 diabetes, whose glycemic control has worsened in correspondence with the onset of SCH. Treatment success is then assessed by the improvement of the glycemic control (Pearce and collaborators, 2013).

CONCLUSION

In this paper, the aim was to review the available literature on the analysis of the effects of treating hypothyroidism and SCH on body mass. As a preamble to the review, a relationship between thyroid function and body mass was analyzed. The evidence suggests that such a relationship is in existence. High TSH levels were shown to be significantly associated with high BMIs, whilst FT4 was

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inversely associated with body mass. Increased leptin levels and insulin resistance accompanied this profile. This association has led to the unsubstantiated use of thyroid hormone in the treatment of obesity in euthyroid subjects.

Even in light of the close relationship between thyroid function and body mass, cause and effect could not be clearly or directly demonstrated in any of the studies reviewed, as there are other predisposing factors involved in the etiopathogenesis of obesity in those patients, yet to be revealed. For instance, autoimmunity itself may predispose to obesity, whereas overweight may trigger thyroid dysfunction.

There is no evidence that body weight is substantially affected by L-T4 replacement in patients with SCH. More than ineffective, L-T4 administration in euthyroid or SCH patients may cause negative nitrogen balance and serious cardiovascular and skeletal adverse effects. Experts agree that thyroid hormonal therapy should be reserved for obese patients with overt hypothyroidism.

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Received for publication in 17/03/2016
Accepted in 27/08/2016