Thyroid Function in Human Obesity: Underlying Mechanisms

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Abstract
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Obesity is associated with several metabolic and endocrine disorders; and changes in plasma concentrations, secretion patterns, and clearance of various hormones are observed in obese patients. In this context, recent research has shown that overweight can influence the function of the thyroid gland, usually leading to increased thyrotropin concentrations and changes in the ratio between the hormones triiodothyronine and thyroxine, though within the normal range. The etiology of these changes is still unclear; however, several mechanisms have been proposed including the adaptive process to increase energy expenditure, hyperleptinemia, changes in the activity of deiodinases, the presence of thyroid hormones resistance, chronic low-grade inflammation, and insulin resistance. Although the clinical implications have not been clarified, studies suggest that these changes in the thyroid function of obese individuals may contribute to the worsening of metabolic complications and the development of diseases in the thyroid gland.

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Introduction
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Obesity is a chronic disease characterized by excessive accumulation of body fat resulting from the interaction between environmental and genetic factors, and a positive energy balance. This condition leads to adipocyte hypertrophy with resultant dysfunction of white adipose tissue, resulting in the development of hypoxia, oxidative stress, and inflammation [1,2].

Due to the endocrine role of adipose tissue and its importance in homeostasis, the dysfunction of this tissue in obesity contributes to metabolic alterations in various organs and systems [3,4]. In this respect, endocrine disorders stand out, and changes are observed in plasma levels, secretion patterns, and clearance of various hormones in obese individuals [5,6].

Regarding thyroid function, research has revealed the existence of a positive correlation between adiposity parameters and serum thyrotropin (TSH) and triiodothyronine (T3) in euthyroid individuals, suggesting a possible influence of obesity on the functioning of the hypothalamus-pituitary-thyroid axis and the activity of deiodinases [7–11].

Changes in thyroid function, even within the normal range, may contribute to the worsening of metabolic complications and the development of diseases in the thyroid gland. In this context, it is worth mentioning that high levels of TSH and T3 have been positively associated with components of metabolic syndrome, and specifically higher serum TSH levels have been linked to increased risk of thyroid cancer [12–16].

Thus, considering the complexity of the pathogenesis of obesity and the impact of this disease on the function of the thyroid gland and thyroid hormone metabolism, this review aims to bring forward up-to-date information on the possible mechanisms involved in the changes in thyroid function in obese individuals.

Thyroid Hormone Metabolism
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Thyroid hormones are synthesized by follicular cells of the thyroid gland from thyroglobulin molecules. First, iodide is taken up by these cells via the sodium/iodide symporter in a process dependent on the electrochemical gradient generated by Na^+/K^+-ATPase. In thyroid follicles, iodide is incorporated into the phenolic ring of tyrosine residues of thyroglobulin protein; the enzyme thyroid peroxidase and appropriate concentrations of hydrogen peroxide (H_2O_2) are

required for this reaction [17, 18]. As the molar ratio of thyroxine (T4) to T3 in human thyroglobulin is 15:1, T4 is the main product secreted by the thyroid gland, and T3 is mainly produced from T4 deiodination in other tissues [19].

Deiodination involves the removal of an iodine atom from iodo-thyronine molecules and the reaction is catalyzed by deiodinase enzymes D1, D2, and D3. This process regulates plasma and tissue concentrations of thyroid hormones, controlling the synthesis of T3 as well as inactivation of these hormones in the body. D1 catalyzes iodine removal from T4 phenolic ring, thus activating it, or from its tyrosyl ring, leading to its inactivation. This enzyme provides T3 for circulation, and is also involved in the process of thyroid hormone clearance and recycling of iodine. D2 is present intracellularly and is primarily responsible for the conversion of T4 to T3 in the tissues. D3 only catalyzes the inactivation of thyroid hormones [20].

In cells, thyroid hormones exert their physiological effects via binding to their specific nuclear receptors (TRα and TRβ) or to other receptors in mitochondria, in the cytoplasm or at the plasma membrane, which regulate cell signaling pathways, including intracellular mitogen-activated protein kinase (MAPK 1 and 2) and phosphatidylinositol-3-kinase (PI3K). It is important to mention that T3 is the major contributor to genomic actions, as nuclear receptors for these hormones have 10–15 times higher affinity for T3 than for T4. In turn, T4, considered as a pro-hormone, plays an important role in non-genomic actions [21, 22].

Thyroid hormones have complex mechanisms of homeostatic control involving multiple feedback loops, which act to maintain serum T3 levels within the normal range and are influenced by various genetic, physiological, pathological, and environmental factors. The classic feedback mechanism refers to the negative control exerted by plasma T3 concentrations and that derived from the hypothalamic and pituitary deiodination of T4 on the expression and secretion of TRH in the hypothalamic paraventricular nucleus and TSH by thyrotrophs in the anterior pituitary [19, 23, 24]. TSH acts by regulating the thyroid gland function and has as one of its actions promoting the D1 synthesis and activity through increasing intracellular cAMP concentrations. This effect also seems to be exerted on the D2 enzyme activity in other peripheral tissues that have functional receptors for this hormone, such as brown adipose tissue and bone [23, 25]. Other feedback loops involve the inhibitory effect that TSH has on its own secretion, as well as various mechanisms of peripheral regulation of thyroid hormones that control bioavailability and cellular bioactivity [23, 26].

Etiology of Changes in Thyroid Status in Obesity
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The relationship between obesity and the thyroid is complex and bidirectional. In the literature, it is well established that dysfunction in this gland (hypothyroidism or hyperthyroidism) results in changes in body weight because of the participation of thyroid hormones in the control of thermogenesis and appetite. However, recent research has shown that excess weight can also influence thyroid function, with the presence of hyperthyrotropinemia, with or without changes in T3 and T4 concentrations, generally being observed in euthyroid obese subjects [27, 28]. ⊙ Table 1 and ⊙ Fig. 1 present the main results of human studies evaluating thyroid function in obesity.

However, it is not possible to establish whether these changes in thyroid function are primary or secondary to obesity [8, 53]. In

this regard, several studies suggest that dysfunction of adipose tissue is the main factor responsible for changes in the homeostasis of thyroid hormones, which is borne out by the observation that weight loss reverses or mitigates these changes [10, 11, 54, 55].

Notably, longitudinal studies have established the relationship between the concentrations of thyroid hormones and changes in body weight over time. Bjergved et al. [29] observed that an increase of 1 mU/l of TSH was associated with a weight gain of 0.6 kg for women and 0.7 kg for men. Soriguer et al. [30] reported a relative risk of becoming obese of 2.94 and 3.06 in euthyroid individuals with higher levels of T3 and T4, respectively, when compared with patients in the lowest quartile.

The etiology of these changes on hypothalamic-pituitary-thyroid axis in obesity is still unclear. However, several mechanisms have been proposed, among which are those related to the adaptive process to increase energy expenditure, the influence of leptin, changes in the activity of deiodinases, the presence of central or peripheral resistance to thyroid hormones, the chronic low-grade inflammation, and the presence of insulin resistance. ⊙ Fig. 2 shows a schematic of the main mechanisms suggested.

Energy expenditure
The literature suggests that the increase in serum TSH and T3 levels observed in obese individuals occur so as to increase energy expenditure and minimize weight gain [56, 57]. This assumption is justified by the role of thyroid hormones in the acceleration of energy metabolism and ATP turnover, especially in the induction of thermogenesis by stimulating the expression and activity of energy uncoupling protein (UCP) [27, 57, 58].

In this scenario, it is worth mentioning that levels of resting energy expenditure rise in obesity, probably due to the concomitant increase in fat-free mass [59]. However, studies conducted in euthyroid obese individuals revealed no association between energy expenditure and concentrations of serum TSH, and free T3 and T4 [60, 61]. One possible explanation for this is the impairment of thyroid hormones action to induce thermogenesis in obesity because adipose tissue, in these individuals, especially the visceral, has reduced expression of thyroid hormone receptors, D2 and D3 enzymes, β2 and β3 adrenergic receptors, and UCP-2 [62].

Hyperleptinemia
In obesity, the presence of hyperleptinemia is another important factor for the manifestation of changes in the hypothalamic-pituitary-thyroid axis. This is due to the regulatory role of leptin, which by promoting TRH expression and synthesis in paraventricular hypothalamic nucleus (direct route) and arcuate nucleus (indirect route), stimulates TSH secretion by the pituitary gland that may favor an increase in the serum levels of this hormone in obese individuals [63].

In the paraventricular hypothalamic nucleus, leptin, through its ObRb receptor, activates phosphorylation of the transcription factor STAT3 (signal transducer and activator of transcription 3), favoring its binding to promoter region of the gene coding for TRH. In the arcuate nucleus, leptin activates a subpopulation of neurons expressing proopiomelanocortin (POMC), while inhibiting neurons that synthesize Agouti-related protein (AgRP) and neuropeptide Y (NPY). This action leads to increased production of α-melanocyte stimulating hormone (α-MSH), which, in turn, is able to stimulate TRH expression by hypothalamic neurons by binding to the melanocortin 4 receptor (MC4-R) [64, 65].

Table 1 Studies on the status of thyroid hormones in euthyroid obese adults (2005–2015).

Author (year) Country	Study	Results
Prospective cohort studies		
Bjergved et al. (2014) [29] Denmark	F: 1577/M: 367, age 18–65 years Average follow-up: 11.2 years	– Significant association between changes of TSH and BMI: increase of 1 mU/l in TSH was associated with weight gain of 0.6 kg for women and 0.7 kg for men.
Soriguer et al. (2011) [30] Spain *	F: 479/M: 305, age 18–65 years Follow-up: 6 years	– No significant difference in TSH, fT3, and fT4 concentrations between the obese and normal weight group (baseline). – Subjects who became obese had higher concentrations of fT3 and fT4 than non-obese (after follow-up). – Positive correlation between fT3 and weight gain (after follow-up).
Ortega et al. (2007) [31] United States	F: 42/M: 47, age 18–65 years Average follow-up: 4 years	– Positive correlation between TSH, weight and body fat percentage. – Inverse association between fT3 initial levels and weight change percentage.
Knudsen et al. (2005) [32] Denmark	n=4082, aged 18–65 years Average follow-up: 5 years	– Positive association between TSH and BMI. – Negative association between BMI and fT4. – Significant association between TSH (the end of follow-up) and weight gain. – BMI difference of 1.9 kg/m² (1st quintile vs. 5th quintile of TSH.).
Cross-sectional studies		
Bétry et al. (2015) [33] France	F: 554/M: 246 Obese only, mean age 44±0.5 years	– Positive association of TSH with BMI and leptin (1st quartile vs. 4th quartile TSH). – TSH was positively correlated with body weight, BMI, and leptin.
Lambrinoudaki et al. (2015) [9] Greece	F: 194 (postmenopausal women), mean age 55.5±6.4	– ↓ fT4 levels and a ↑ fT3/fT4 ratio predicted ↑ subcutaneous fat mass. – ↑ fT3 predicted ↑ preperitoneal fat mass. – Positive association between fT3 and subcutaneous fat mass only among women with higher BMI and waist/hip ratio. – Positive independent association between BMI and TSH.
Bakiner et al. (2014) [34] Turkey	Groups: control (n=150), overweight (n=133), obese (n=330) and morbid obese (n=166), aged 18–65 years	– No significant difference in TSH concentrations between groups. – Positive correlation of TSH with BMI and body weight observed only in men with excess weight. – Positive correlation between TSH and WC observed only in the morbidly obese group.
Ren et al. (2014) [11] China	F: 470/M: 395, age 31–53 years	– ↑ fT3 in the group of individuals with overweight (BMI≥25 kg/m²), no significant difference in fT4. – Positive correlation of fT3 with adiposity parameters (BMI, WC, HC, waist-hip ratio, and body fat percentage), fasting insulin and HOMA-IR. – Percentage of body fat and HOMA-IR were independently associated with fT3 concentrations.
Roef et al. (2014) [14] Belgium *	F: 1138/M: 1177, age 33–55 years	– Positive correlation of fT3 and fT3/fT4 ratio with BMI, WC and waist-hip ratio. – Negative correlation of fT4 with BMI, WC, and waist/hip ratio.
Sakurai et al. (2014) [35] Japan *	F: 993/M: 1044, age 36–55 years	– Positive association of TSH with BMI and WC only in nonsmoking men (1st quartile vs. 4th quartile of TSH).
Shinkov et al. (2014) [36] Bulgaria *	F: 1176/M: 977, mean age 48.3±14.4 (F) and 45.9±14.4 (M) years, with or without metabolic syndrome	– There was no correlation between TSH, BMI, and WC.
Kouidhi et al. (2013) [37] Tunisia	Groups: control (n=25), overweight (n=19) and obese (n=24), age 45–65 years	– ↑ TSH and ↓ fT4 in the overweight/obesity group. – Positive correlation of TSH with BMI and WC in the overweight/obesity group. – Negative correlation of fT4 with BMI, and WC in the overweight/obesity group.
Milionis and Milionis (2013) [38] Greece	F: 616/M: 118, mean age 52.5±15.4 years	– T4 total was considered BMI predictor: increase of 1 ug/dl. T4 was related to increased BMI in 0.608 kg/m². – For each increase of 1 ng/ml in total T3, obesity chance (grade I) increased by 2.1 times. – For each increase of 1 ug/dl in total T4, obesity chance (>35 kg/m²) increased by 40.9%. – For each increase of 1 ng/dl in fT4, obesity chance (>35 kg/m²) decreased by 22.4%.
Muscogiuri et al. (2013) [10] Italy	F: 36/M: 24, mean age 50.4±17.1 years Groups: control (n=28) and overweight/obese (n=32)	– ↑ TSH in the overweight/obesity group, no significant difference in fT3 and fT4. – Positive correlation of TSH with BMI, and volume of subcutaneous and visceral adipose tissue (computed tomography scan). – Volume of visceral adipose tissue was identified as a predictor of TSH concentrations.
Oh et al. (2013) [13] Korea	F: 2760, age 18–39 years	– Positive correlation of TSH with BMI and WC.

Table 1 Continued

Author (year) Country	Study	Results
Solanki et al. (2013) India [39]	Groups: underweight (n = 25), normal weight (n = 147), overweight (n = 100) and obese (n = 145), age 18–60 years	– ↑ TSH in the overweight and obese groups.
Kitahara et al. (2012) [8] United States	F: 1 491/M: 1 623, age 20 years and older	– ↑ TSH and fT3 of each quartile of BMI and WC, with no significant difference for free T4.
Tarcin et al. (2012) [40] Turkey	F: 187/M: 24; mean age, 39.7 ± 11.7 years, with or without metabolic syndrome	– Positive correlation of total T3 with BMI, WC, and HOMA-IR.
Eray et al. (2011) [41] Turkey	Groups (F): control (n = 31), mean age 38.6 ± 12.9 years and obese (n = 98), mean age 40.5 ± 11.4 years	– No significant difference in TSH, fT3, and fT4 levels between groups. – ↑ thyroid volume in obese women. – Positive correlation of thyroid volume with BMI, leptin, and TSH in the group of obese women.
Lee et al. (2011) [42] Korea *	F: 3 102/M: 4 168, mean age 43.4 ± 9.8 (F) and 44.2 ± 8.7 (M) years, with or without metabolic syndrome	– ↑ TSH in the group of obese men with only a tendency among women.
Ambrosi et al. (2010) [43] Italy	F: 436/M: 145 Overweight and obese only, mean age 39.8 ± 13.7 years	– Positive correlation of TSH with BMI and WC.
Nam et al. (2010) [44] Korea	F: 136/M: 41, mean age 34.69 ± 11.25 years	– Positive correlation of the total T3 with: total, visceral, and subcutaneous adipose tissue area; WC; BMI and body fat percentage. – T3 was considered an independent predictor of visceral fat.
Alevizaki et al. (2009) [45] Greece	F: 181/M: 122, mean age 42.9 ± 8.8 years	– Positive correlation of total T3 with abdominal subcutaneous fat, pre-peritoneal fat, weight, BMI, and WC. – Free T4 was considered a predictor of abdominal subcutaneous fat and the ratio of abdominal subcutaneous fat and preperitoneal (negative association).
Rotondi et al. (2009) [46] Italy	F: 256/M: 94, mean age 46.2 ± 12.2 years	– ↑ TSH and ↓ fT4 and fT3 in the group of obese individuals, but no correlation with BMI.
Shon et al. (2008) [47] Korea	F: 1 572, mean age 46.2 ± 11.2 years	– ↓ fT4 in the group of obese women. – Negative correlation between fT4 and BMI.
Bastemir et al. (2007) [48] Turkey *	Groups (F): control (n = 39), mean age 40 ± 9 years and overweight/obese (n = 226), mean age 43 ± 12 years	– ↑ TSH in the group of obese women. – Positive correlation of TSH with BMI and WC.
Pergola et al. (2007) [49] Italy	F: 201 with overweight and obese, age 18–68 years	– Positive correlation between TSH and WC. – Positive correlation of fT3 with BMI and WC.
Manji et al. (2006) [50] United Kingdom	F: 361/M: 40, mean age 48.2 years	– No significant difference between obese and non-obese groups for TSH and fT4 levels.
Michalaki et al. (2006) [51] Greece *	Groups: control (n = 77), mean age 33.54 ± 7.37 years and morbidly obese (n = 78), mean age 34.27 ± 9.68 years	– ↑ TSH, fT3 and fT4 in the morbidly obese group, but no correlation with BMI, WC, fat mass and lean mass.
Iacobellis et al. (2005) [52] United States	Groups: control (n = 45) and obese (F) (n = 87), mean age of 34.7 ± 9 years	– ↑ TSH in the group of obese women, no significant difference in T4 and fT3. – Positive correlation between TSH and BMI.

F: Female; M: Male; TSH: Thyrotropin; fT3: Free triiodothyronine; fT4: Free thyroxine; HOMA-IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference
* Studies that mentioned the inclusion of subjects with type 2 diabetes in the sample
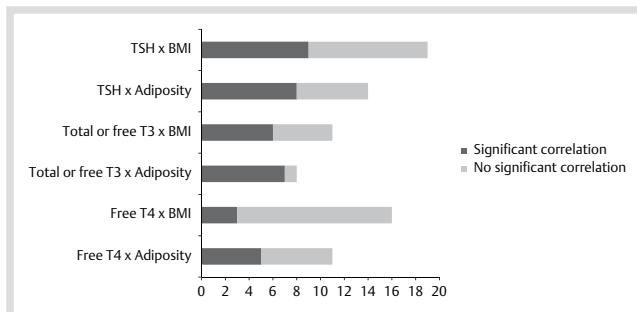
Fig. 1 Number of cross-sectional studies that evaluated the correlation between thyroid hormones, BMI, and adiposity markers in euthyroid obese adults (2005–2015). For TSH and T3: significant correlations were positive. For free T4: significant correlations were negative. Adiposity markers: waist circumference, waist-hip ratio, subcutaneous and preperitoneal fat layers, subcutaneous and visceral adipose tissue volume, subcutaneous and visceral adipose tissue area.
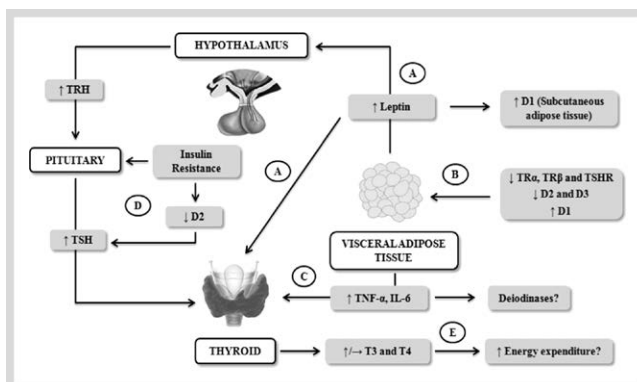
Fig. 2 Etiology of changes in thyroid hormones levels in obesity. **a** Hyperleptinemia stimulates the synthesis and secretion of TRH and TSH while simultaneously modulating the responsiveness of the thyroid gland to TSH, inhibiting the iodide uptake and expression of symporter sodium/ iodide and thyroglobulin. In addition, leptin influences the activity of dei- odinases, in particular D1 in subcutaneous adipose tissue. **b** The change in the expression and activity of deiodinases enzymes, TRα and TRβ receptors and TSHR promote a resistance state to the action of thyroid hormones. **c** The inflammatory adipokines compromise thyroid function, contributing to morphological changes in the gland. In addition, there is the assumption that these adipokines may also alter the activity of deio- dinases. **d** The insulin resistance in obesity seems to contribute to the D2 activity reduction in thyrotrophic cells, leading to tissue hypothyroidism and subsequent increase in TSH synthesis. **e** All of these mechanisms lead to changes in serum TSH, T3, and T4, which may lead to increase energy expenditure and affect the metabolic regulation of body tissues.

However, due to the presence of selective leptin resistance in the arcuate nucleus of the hypothalamus in obesity, the main route of modulation of the hypothalamic-pituitary-thyroid axis is through the direct action of this adipokine on the paraventricu- lar nucleus [66–68]. In addition, leptin also promotes the syn- thesis of TRH at the post-translational level by inducing, via STAT3, expression of the enzymes prohormone convertases 1 (PC1/3) and 2 (PC2), which participate in the proteolytic cleav- age of pro-TRH to its biologically active form [69].

In this context, studies have shown a positive correlation between serum TSH concentrations and leptin in obese individ- uals, which remained significant even after adjustment for body mass index (BMI), suggesting that high TSH values seem to be more related to energy balance than to adiposity [30,33,52].

Leptin also appears to influence the metabolism of thyroid hor- mones by regulating the activity of deiodinase enzymes in dif- ferent tissues [70]. In this regard, it is worth mentioning that changes in the activity of these enzymes may occur in obesity, with increase in D1 activity in the liver, kidney, and thyroid, and reduction of D2 activity in brown adipose tissue and the pitui- tary being observed [71,72]. In particular, animal and human studies have shown a positive relationship between leptin and D1 expression and/or activity in white adipose tissue [73,74]. In a study by Ortega et al. [74], high expression of D1 was observed in adipose tissue, which correlated positively with lep- tin expression, particularly in subcutaneous adipose tissue. These results suggest that leptin, which is synthesized by adipo- cytes, seems to stimulate the expression and local activity of D1, increasing the intracellular production of T3 in adipocytes, and thereby modulating the metabolism of this tissue. However, it is noteworthy that thyroid hormone receptor expression is reduced in adipocytes, which can impair the local action of T3, as explained below.

It is also important to stress that binding of TSH to its receptors on adipocytes appears to promote leptin secretion by these cells, suggesting the existence of a complex positive feedback mecha- nism between these 2 hormones [75,76]. Furthermore, T3 also appears to modulate leptin gene expression in cultured adipo- cytes as demonstrated by Oliveira et al. [77].

Thyroid hormones resistance

Resistance to thyroid hormones is a genetic disorder in which there is a reduction of the affinity for T3 of thyroid receptor ligands associated with irreversible interaction of co-repressors to these receptors. The most common form involves mutations in β receptors (TRβ) characterized by elevated serum levels of T3 and T4, and normal or slightly increased TSH concentrations. On the other hand, mutations in α receptors (TRα) promote increase in serum T3, while TSH and T4 remain normal, and are associ- ated with increased cholesterol and BMI [24].

Several studies have correlated the presence of certain genetic polymorphisms in thyroid receptors or molecules in its signaling pathway to the obesity risk [56,57]. Accordingly, Fernandez-Real et al. [78], analyzing 2 types of polymorphisms in TRα, found that individuals with the G allele related to the polymorphism rs1568400 (−635 A/G) had increased BMI, waist circumference, and levels of cholesterol and triglycerides, with a 2.3 times higher incidence of obesity in homozygotes. Another less fre- quent polymorphism, rs12939700 (A/C), was also associated with obesity in a group considered at high cardiovascular risk. These genetic factors indicate that resistance to thyroid hor- mones is related to the etiology of obesity. However, recent research suggests that this disease can also induce a resistance to these hormones, characterized by changes in expression of thyroid receptors in adipocytes. These alterations seem to be more pronounced in visceral adipose tissue, but may also be present in other tissues [55,62,79,80].

In this context, the study by Nannipieri et al. [55] on morbid obe- sity has verified the lowered TSH receptor (TSHR) expression in adipose tissue, particularly visceral fat, and a tendency towards reduction of TRα1 expression. The expression of these receptors is inversely correlated with BMI, so that weight loss favored increased expression of both receptors in subcutaneous adipose tissue. The authors suggest the presence of peripheral resistance to thyroid hormones, which could have led to increased plasma concentrations of TSH and free T3 in these individuals, and that

this condition can be reversed by weight loss. In accordance with this hypothesis, Kurylowicz et al. [62] found reduced expression of TRα in visceral adipose tissue and TRβ in visceral and subcutaneous adipose tissue of morbidly obese patients.

On the other hand, Lu et al. [81] found elevated expression of TSHR in adipocytes of subcutaneous adipose tissue of the cervical region in overweight individuals, and observed a trend towards increased expression of this receptor with increasing BMI. These conflicting results may be due to the location of the adipose tissue evaluated and show the complexity of the regulatory action of thyroid hormones in the body.

Inflammation

Chronic low-grade inflammation, a characteristic of obesity, also appears to be related to thyroid dysfunction. In the study of Roef et al. [14] on euthyroid adults, a positive correlation was observed between free T3/T4 ratio and serum concentrations of interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP), regardless of body weight and waist circumference. Chen et al. [82] found a positive correlation between the BMI of children and adolescents and the volume of the thyroid, which also showed a positive correlation with hs-CRP concentrations.

In this regard, investigations have shown that inflammatory cytokines such as tumor necrosis factor α (TNF-α) and IL-1 and 6, can inhibit the mRNA expression of symporter sodium/iodide thus compromising iodide uptake activity in human thyroid cells [83–85]. These adipokines can still induce vasodilation and increased permeability of blood vessels in the thyroid that may contribute to morphological changes in this gland [85–87].

Rotondi et al. [87] found morphological changes in thyroid patients with morbid obesity, characterized by the presence of a hypoechogenic pattern on ultrasound in the absence of thyroid abnormalities. In the study conducted by Eray et al. [41], the volume of the thyroid was positively correlated with BMI, serum leptin and TSH concentrations, with reduction in the volume of the gland being observed 6 months after weight loss intervention.

With regard to the leptin role in chronic inflammation and, consequently, in morphological changes of the thyroid gland, a study with cultured thyroid cells in rats showed that this adipokine, as well as inflammatory cytokines, are capable of inhibiting iodide uptake and expression of the sodium/iodide symporter and thyroglobulin induced by TSH. This action suggests the presence of a modulating effect of leptin on responsiveness of thyroid cells to TSH, which may partially explain the changes in thyroid hormones concentrations in obese individuals [88].

Another important aspect is that inflammation may also affect thyroid function by regulating the expression and/or activity of deiodinases in different body tissues, as shown by studies investigating the action of inflammatory cytokines in models of acute or chronic infectious inflammation [89–91]. However, the mechanisms involved in the regulation of deiodinases by chronic inflammation present in obese individuals are not yet clarified.

Insulin resistance

Insulin resistance is a common disorder in obesity and is characterized by impaired insulin action in metabolically active organs and tissues. The relationship between this metabolic disorder and thyroid hormones levels has been widely investigated because of the strong association of thyroid hormones and glucose homeostasis and also because of the insulin influence in the function of brain target regions such as the hypothalamus [24,92,93].

Some studies in humans have revealed the existence of a positive association between serum TSH and insulin resistance markers [37,43,48,94]. However, the mechanisms involved in the insulin action on the hypothalamic-pituitary-thyroid axis have not yet been elucidated. According to some authors, the insulin resistance in obesity seems to contribute to the D2 activity reduction in thyrotrophic cells, leading to tissue hypothyroidism and subsequent increase in TSH synthesis [51,93,94]. This hypothesis was proposed from results of an in vitro study that showed the role of insulin in promoting the activity of deiodinase in hepatocytes from fasted rats [95].

It is noteworthy that the positive association between TSH and insulin resistance in obesity appears to be mediated by adipose tissue [8,10]. In this regard, the increase in serum TSH levels may stimulate the synthesis of inflammatory cytokines by adipocytes and thus indirectly promote this metabolic disorder [96]. A recent study showed that TSH inhibits insulin-stimulated Akt phosphorylation in differentiated human adipocytes, which also may contribute to the insulin resistance observed in obesity [97]. Concerning the relationship between free T3 and glucose homeostasis in obesity, some studies show a positive correlation between serum concentrations of this hormone and insulin resistance markers [11,40]. It is known that T3 regulates the metabolic processes of gluconeogenesis and insulin secretion and function; however, the precise mechanisms by which the concentrations of this hormone could influence glucose homeostasis in obese individuals have not yet been elucidated [24].

Final Considerations
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The metabolism of thyroid hormones in obesity is influenced by several factors that alter their homeostatic control, which is reflected by changes in their serum levels. These changes probably occur in specific tissues, influencing the metabolism of every organ and system differently. Although several mechanisms have been proposed to explain the changes in thyroid hormone concentrations in obesity, its etiology is still unclear, and it is not possible to define the long-term clinical implications for obese individuals. From this perspective, it is necessary to perform longitudinal studies that seek to investigate the influence of obesity on thyroid function and its relationship with the risk of developing diseases.

Conflict of Interest
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The authors declare no conflict of interest.

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