

## MECHANISMS IN ENDOCRINOLOGY

# The crosstalk between thyroid gland and adipose tissue: signal integration in health and disease

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## Abstract

Obesity and thyroid diseases are common disorders in the general population and they frequently occur in single individuals. Alongside a chance association, a direct relationship between ‘thyroid and obesity’ has been hypothesized. Thyroid hormone is an important determinant of energy expenditure and contributes to appetite regulation, while hormones and cytokines from the adipose tissue act on the CNS to inform on the quantity of energy stores. A continuous interaction between the thyroid hormone and regulatory mechanisms localized in adipose tissue and brain is important for human body weight control and maintenance of optimal energy balance. Whether obesity has a pathogenic role in thyroid disease remains largely a matter of investigation. This review highlights the complexity in the identification of thyroid hormone deficiency in obese patients. Regardless of the importance of treating subclinical and overt hypothyroidism, at present there is no evidence to recommend pharmacological correction of the isolated hyperthyrotropinemia often encountered in obese patients. While thyroid hormones are not indicated as anti-obesity drugs, preclinical studies suggest that thyromimetic drugs, by targeting selected receptors, might be useful in the treatment of obesity and dyslipidemia.

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## Introduction

Obesity and thyroid diseases are common disorders in the general population and they frequently occur in single individuals.

Alongside a chance association, a direct relationship between ‘thyroid and obesity’ has been hypothesized

(1, 2, 3, 4, 5). Thyroid hormone is indeed an important determinant of energy expenditure and contributes to appetite regulation. On the other hand, secretory products from the adipose tissue act on the CNS to inform on the quantity of energy stores, and this may have an impact on

### Invited Author’s profile

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the activity of the hypothalamus–pituitary–thyroid axis (1, 2, 5).

An increase in body weight (on average 2.86 kg), which was reverted by treatment with thyroid hormone, was historically described in myxedematous patients (6). Yet, it was promptly recognized that a decrease in the fat free mass accounted for most of the body weight reduction (7). In line with this effect of thyroid hormones on body size, weight loss is historically reported among the main features of thyrotoxicosis (8).

Many attempts have been made to treat obese euthyroid subjects with thyroid hormones and/or their analogs in the effort to stimulate energy expenditure, especially during regimens of dietary restriction (1). The matter is a complex one, and it is further amplified by the fact that obese patients may display alterations in their thyroid function tests, thus raising the question of whether a specific substitution treatment is advisable.

Epidemiological data suggest that obesity might be associated with an increased incidence of thyroid cancer. This association, although still debated, prompted a discussion on the possible mechanisms underlying the effect of obesity on thyroid oncogenesis. This review article aims to analyze relevant data in the literature and to discuss current opinions on these topics.

## The thermogenic effect of thyroid hormones

Thyroxine ( $T_4$ ) is the major secretory product of the thyroid gland and it is a precursor of the active form of the hormone, the 3,5,3'-triiodothyronine ( $T_3$ ), which is mainly produced in peripheral tissues by 5'-deiodination of  $T_4$  (9). Thyroid hormone production is controlled by the thyroid-stimulating hormone (TSH) that is secreted by the anterior pituitary gland.  $T_3$  and  $T_4$  act directly on the pituitary and hypothalamus to regulate TSH production through a classical negative feedback loop (10).

Body weight regulation is achieved through a fine-tuning between energy intake and energy consumption, the latter being determined by resting energy expenditure (REE), non-exercise activity, and voluntary physical activity. In homeothermic species, such as humans,  $T_3$  has acquired a critical role in temperature homeostasis and is responsible for ~30% of REE (11). The  $T_3$ -induced thermogenic activity is exerted through the thyroid hormone receptor  $\alpha$  ( $TR\alpha$ ) (12, 13), while  $TR\beta$  is a key regulator of cholesterol metabolism (14). Mice lacking all TRs display a phenotype characterized by decreased basal metabolic rate, decreased body temperature, and cold intolerance (15). Besides its influence on thermogenesis,

$T_3$  might also influence REE by regulating the spontaneous motor activity. Indeed, shortly after the injection of  $T_3$  into the pre-optic region of hypothyroid rats, an increase in motor activity is observed (16).

Through an interaction with adipose tissue, the hypothalamic–pituitary–thyroid axis mediates the adaptations of both metabolism and thermogenesis by regulating: i) transcription factors involved in adipogenesis of white adipose tissue (WAT) and brown adipose tissue (BAT); ii) genes involved in lipid metabolism (lipogenesis and lipolysis) and oxidation; and iii) genes regulating thermogenesis in BAT (17). The TR isoforms  $\alpha 1$ ,  $\alpha 2$ , and  $\beta 1$  are expressed in WAT and BAT. In WAT,  $T_3$  affects the lipolytic activity (18), which is mediated by a cAMP-dependent mechanism and is synergized by the adrenergic system. Thermogenesis is also regulated by thyroid hormone at the hypothalamic level. The TR is expressed in the hypothalamus and modulates the sympathetic nervous output to BAT (19). This contributes to the negative energy balance occurring in the thyrotoxic status.

During cold exposure, the thyroid hormone-activating enzyme type 2 deiodinase (D2) increases the generation of  $T_3$  in BAT, thus promoting heat production (20). This is the core pathway of the so-called adaptive or facultative nonshivering thermogenesis. The thermogenic effect of  $T_3$  in BAT is mediated by the uncoupling protein 1 (UCP1) and possibly by the UCP3 via a proton leak through the inner membrane of the mitochondria. Additional mechanisms, such as increased turnover of calcium in the sarcoplasmic reticulum (11), are probably involved. No changes in BAT activity have been so far demonstrated in humans related to fasting or overfeeding (21). The presence of BAT was for a long time considered of negligible importance in humans. This concept has been recently revised because BAT activity was found to be impaired in obese subjects and significantly enhanced by cold exposure (22, 23, 24). The hypothesis postulating a relevant role for BAT in facultative thermogenesis and body weight regulation in humans is intriguing, but needs further proof. Recently, a new fat lineage named 'beige' adipose tissue has been described in rodents (25). Beige adipocytes were found to be inter-dispersed in WAT. The gene expression pattern of these cells is intermediate between white and brown fat (hereof the name). Beige adipose cells show low UCP1 mRNA levels and can be transformed into brown adipocytes by cAMP. It is not known whether  $T_3$  has any regulatory role on the activity of this fat cell lineage. Clarifying this issue would be important because in humans the previously identified

brown fat deposits were recently shown to be mainly composed by beige adipocytes (25, 26).

The pleiotropic effects of thyroid hormones on adipogenesis, fat metabolism, and thermogenesis raise the question of whether a primary dysfunction of the thyroid might result in a change in adipose mass.

### Feeding and thyroid hormone

The relationship of serum thyroid hormones with feeding was elegantly investigated over 30 years ago (27, 28, 29, 30, 31, 32) and most of the conclusions drawn by those pioneering works can still be considered valid. In lean subjects, the production rate of  $T_3$ , but not that of  $T_4$ , significantly increases during overfeeding. On the other hand, a caloric deficit, both in lean and in obese subjects, is characterized by a reduction in  $T_3$  and the concomitant increase in reverse  $T_3$  in the circulation. These effects appear related both to the caloric content and the composition of the diet.

The early studies already blamed the unjustified idea that obesity was related to thyroid dysfunction because of both the patients' and the physicians' desire of ascribing the increased adiposity to a disease that could exonerate them from responsibility and allow some form of treatment (32).

Experimental data advocate an important role for thyroid hormone and deiodinases in the regulation of feeding. In mammals, the peripheral administration of  $T_3$  has a catabolic effect and results in a decrease in body weight. However, when the thyroid hormone is injected into the hypothalamus, anabolic actions result, which include an increased appetite, and may thus favor body weight gain. In mice, fasting increases glial D2 activity and  $T_3$  local production in the arcuate nucleus (ARC), thus promoting mitochondrial proliferation and stimulation of NPY/AgRP orexigenic neurons (33). Furthermore,  $T_3$  exerts a negative feedback on the hypothalamic expression of type 4 melanocortin receptor (34), a pivotal mediator of the anorectic effects of leptin (35). Changes in the activity of hypothalamic deiodinase (D2 and D3) and of the local availability of  $T_3$  were shown to be major regulators of seasonal changes in body weight in hibernating mammals (36).

### The leptin–thyroid relationship

Leptin, an adipocyte-derived hormone, is a long-term regulator of body weight, acting through inhibition of food intake and stimulation of both energy expenditure (37) and locomotor activity (38).

Leptin receptors (Lep-Rb) are expressed primarily in the CNS, but also in peripheral organs such as lung, pancreas, and hematopoietic and immune cells (39, 40). Besides the ARC of the hypothalamus, which is considered the main action site of leptin, Lep-Rb have been found in the pituitary and on TRH-secreting neurons of the paraventricular nucleus (PVN) (41). Fasting is characterized by the fall of circulating leptin levels due to a reduction in fat mass and to a series of neuro-endocrine adaptations aimed at conserving energy. A down-regulation of the hypothalamus–pituitary–thyroid axis, mediated by low leptin levels, might play a role in this adaptation process.

In murine models of fasting, leptin administration reverses the reduced hypothalamic expression of TRH and increases the expression of D2 (42, 43), the effect on pituitary expression of TSH being less prominent. The action of leptin on TRH in the PVN occurs directly through an effect on TRH neurons expressing Lep-R and indirectly through  $\alpha$ -MSH production in POMC neurons of the ARC-targeting TRH neurons (44).

In lean healthy subjects, the circadian rhythms of TSH and leptin are superimposable (45), and the subcutaneous administration of leptin significantly blunts the fall of TSH secretion induced by prolonged fasting (46). These findings indicate that leptin has a regulatory effect on TSH secretion. Accordingly, leptin administration at physiological doses can partially reverse the fall of circulating thyroid hormones, which occurs during prolonged caloric restriction (47).

Taken together, these data support the view that a reduction in serum leptin levels acts as a peripheral signal capable of directly inhibiting the hypothalamus–pituitary–thyroid axis. This function, being exerted at the hypothalamic level through an inhibition of TRH expression and secretion, would be an ancestral one, aimed at saving energy in conditions of food shortage.

Partial central hypothyroidism was initially reported in patients with congenital lack of leptin (48), although this dysfunction was not confirmed in more recently described cases (49). Congenital lack of leptin does not affect the correct development of a normal hypothalamus–pituitary–thyroid axis, and in leptin-deficient patients it is unclear whether and to what extent leptin treatment influences thyroid function.

A large number of studies investigated the relationship between thyroid dysfunctions and circulating levels of leptin, but the reported results were highly conflicting both in basal conditions and after correction of the thyroid dysfunction (5, 50, 51). Overall, the evidence

supporting a direct action of  $T_4$  or  $T_3$  on leptin regulation is modest.

A bidirectional interaction is suggested by the intriguing observation that TSH receptors are expressed on adipocytes (52) and that the *in vivo* administration of recombinant human TSH at supra-physiological doses can induce the release of small but significant amounts of leptin which are proportional to the adipose mass (53). The latter finding confirms that functioning TSH receptors are expressed on the surface of white adipocytes. The physiologic and pathologic roles played by activation of TSH receptor in white adipocytes remain a matter of investigation. The possibility was also investigated that TSH, by binding to its receptor on brown adipocytes, may stimulate thermogenesis, thus preventing an excessive drop in body temperature in hypothyroidism (54, 55, 56, 57).

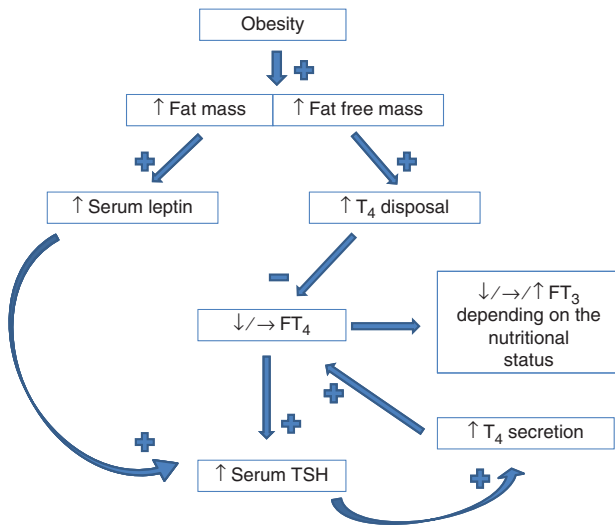
### Thyroid function and structure in obese subjects

Thyroid function has been extensively investigated in obese subjects with the purpose of relating the increase in body weight with an underlying thyroid disturbance. A recent review of 29 studies assessed the relationship between serum TSH and BMI in euthyroid subjects (58). Eighteen of these studies showed a positive correlation between the measures of adiposity and serum TSH. So far, these results have been confirmed in all available longitudinal studies. Data regarding the circulating concentrations of thyroid hormones are less univocal because the serum levels of  $FT_3$  were reported as increased, unchanged, or decreased. On the other hand, most studies reported a general trend toward low/normal levels of  $FT_4$  in obese subjects (59, 60, 61, 62, 63, 64, 65, 66). Lately, the relation between adiposity and serum TSH,  $FT_3$ , and  $FT_4$  was evaluated in a large, representative sample of the adult population from the National Health and Nutrition Examination Survey 2007–2008 (67). A significant positive association of serum TSH and, to a lesser degree,  $FT_3$  was observed with both BMI and waist circumference, while no association with  $FT_4$  could be demonstrated. The discrepant results obtained in the above reported studies can be attributed to the inclusion of patients with different degrees of obesity (i.e. patients with lower degrees of overweight and those with morbid obesity). Clinical and genetic evidence support the concept that obesity does not represent a continuous entity and that morbid obese patients are likely to harbor a different disease compared with subjects with milder forms of overweight (64). Examination of patients at different caloric intakes, either

while overeating or when on a hypocaloric diet, could also account for the discrepant results (1). The distribution of body fat, either subcutaneous or visceral, and insulin sensitivity were rarely taken into account. Age, sex, smoking, iodine intake, and definition of the upper-limit of serum TSH are additional confounders, which might modify the relationship between BMI and serum TSH. A recent meta-analysis confirmed that a high-normal serum TSH is associated with a high BMI (68). However, the design of analyzed studies does not allow clarifying whether the high-normal serum TSH is the consequence or the cause of overweight. This is a critical issue because in the latter case small variations in serum TSH levels, even within the normal reference range, might have negative consequences on body weight and eventually on metabolic and cardiovascular outcomes (69).

As a matter of fact the causes responsible for the increased serum levels of TSH in obese patients is still debated. The observation that the serum levels of TSH normalize after weight loss, resulting either from hypocaloric diet or from bariatric surgery (70, 71, 72), suggests that in obese patients the increased TSH is an adaptive response of the hypothalamus–pituitary–thyroid axis to weight gain. If the increase in TSH levels was the primary event of this response, an increase in serum thyroid hormones would also be expected. This is in contrast with most studies, showing low/normal levels of  $FT_4$  in obese subjects. As an alternative explanation, it should be considered that the turnover rate of  $T_4$  is proportional to body size (73) that is indeed a main determinant of the substitution dose of levothyroxine ( $L-T_4$ ) in hypothyroid subjects (74, 75). Thus, an increased rate of thyroid hormone disposal (resulting from a large body size) would be the causative event promoting an activation of the hypothalamus–pituitary–thyroid axis aimed at maintaining serum thyroid hormones within the euthyroid range. Eventually, this sequence of events would result in a low-normal serum  $FT_4$  associated with a slightly increased TSH level and a moderately enlarged thyroid gland. In this scenario, the serum levels of  $FT_3$  would be mainly related to the ongoing nutritional status (Fig. 1).

The possibility that chronic autoimmune thyroiditis could be the cause of the increased serum levels of TSH observed in obese patients has been evaluated in two recent studies. It was found that autoimmune hypothyroidism is more prevalent in patients with minor degrees of weight excess (66), whereas slightly increased serum levels of TSH, being unrelated to thyroid autoimmunity, predominate in morbidly obese patients (64). In morbid obese subjects, the serum concentration of



**Figure 1**

Tentative representation of the adaptive mechanisms leading to changes in serum thyroid hormones and TSH in obese subjects. +, Stimulation; -, inhibition; ↑, increased; ↓, decreased; →, unchanged.

cholesterol was lower than in lean controls having similar degrees of serum TSH elevation (76). This finding suggests that the higher serum TSH of morbid obese patients is not associated with peripheral hypothyroidism.

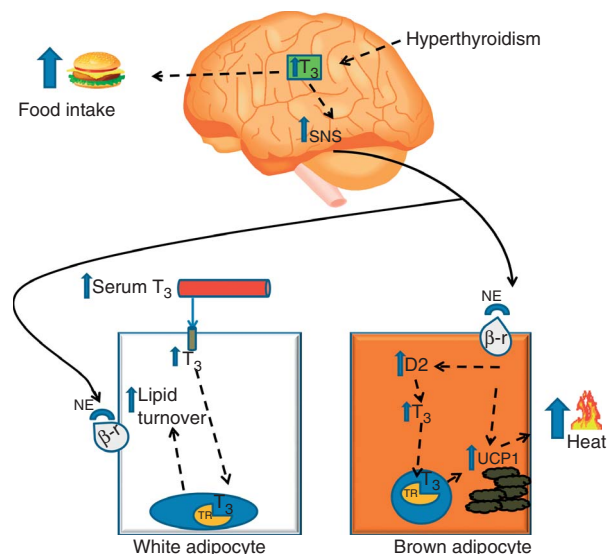
Although data regarding changes in thyroid structure in obese patients are scanty, the gland volume, as assessed by ultrasound (US), was found to be larger in obese compared with non-obese subjects. This difference was related to the amount of lean body mass rather than to body weight by itself (59). After weight loss, a reduction in thyroid volume was also observed (60). Studies on children and adults also demonstrated that obesity is associated with a thyroid hypo-echogenic pattern at US, which occurs independently from thyroid autoimmunity (77, 78). Indeed, among all patients with a thyroid hypo-echogenic pattern of the gland, only a minority of those with morbid obesity (20%) had serological evidence of thyroid autoimmunity (78). This figure was in contrast with the much greater prevalence (>80%) of thyroid antibodies in non-obese patients. Thus, thyroid US, a well-established tool for diagnosing thyroid autoimmune diseases (79), has a poor diagnostic accuracy in patients with morbid obesity.

## Hyperthyroidism and body weight

Despite increased appetite, hyperthyroidism is usually associated with a variable decrease in body weight, due to

a decline in both lean and fat mass, associated with an increase in total energy expenditure (Fig. 2) (19, 80, 81, 82, 83, 84). The latter phenomenon results from a reduced thermodynamic efficiency of the biologic machine with increased heat production (85). As a consequence, accelerated protein catabolism and skeletal muscle atrophy has been observed in experimental thyrotoxicosis (86). Furthermore, hyperthyroidism causes a negative calcium balance and reduced bone mineral density (87). The extent of these phenomena depends on the severity of the thyrotoxic state and the length of exposure. Occasionally, a paradoxical weight gain is observed in some thyrotoxic patients because, due to a greatly increased appetite, their caloric intake exceeds the augmented energy expenditure. Recovery of body weight is considered an early-positive response to the administration of anti-thyroid drugs. With time, the correction of hyperthyroidism may be responsible for excessive weight gain, independent of the treatment modality of thyrotoxicosis: surgery, radioiodine, or anti-thyroid drugs (88, 89, 90, 91, 92, 93).

The mechanisms responsible for excessive body weight gain after treatment of hyperthyroidism may include sub-optimal correction of hypothyroidism,



**Figure 2**

Role of thyroid hormone in thermogenesis and the interconnections with the brown adipose tissue and the adrenergic system during hyperthyroidism. ↑, Increased; ↓, decreased; D2, type 2 iodothyronine deiodinase; SNS, sympathetic nervous system; β-r, adrenergic β receptor; TR, thyroid hormone receptor; NE, norepinephrine; UCP1, uncoupling protein 1.

reduced energy expenditure due to incomplete recovery of the muscle mass, and/or greater energy intake than that required to maintain the individual's premorbid body weight. Recently, no change in body weight and resting energy metabolism has been observed in Graves' patients after the cessation of the block and replace therapy (i.e. anti-thyroid drugs plus L-T<sub>4</sub>) (94).

This treatment modality, although not generally recommended by the American Thyroid Association (95), may be employed when a satisfactory control of hyperthyroidism is not achieved by the administration of thionamides alone. Indeed, in Graves' disease, high levels of TSH receptor-stimulating antibody are often associated with a high T<sub>3</sub>/T<sub>4</sub> ratio and large goiters (96, 97). Administration of thionamides to these patients may be followed by a reduction in serum T<sub>4</sub> to the hypothyroid range, while serum T<sub>3</sub> remains elevated and TSH is undetectable. In these cases, the block and replace therapy allow the maintenance of serum thyroid hormones within the normal range, thus preventing a persistent hypermetabolic state that could eventually exert a detrimental effect on body weight.

### Hypothyroidism and body weight

In humans, overt hypothyroidism is associated with variable degrees of weight gain. While being a frequent complaint (weight excess was reported in 54% patients with overt hypothyroidism) (98), weight gain is usually of limited extent (99). In line with this concept, the BMI was not found to be greater in elderly women with subclinical hypothyroidism compared with euthyroid controls (100).

The alterations in body weight associated with hypothyroidism may reflect both the accumulation of body fat (83, 101), due to decreased REE and reduced physical activity, and the increased water content of the body (102), consequent to a reduced capacity of excreting free water (103). Hypothyroid subjects also have increased amounts of glycosaminoglycans that are responsible for the greater water-binding capacity, a condition that results in the typical 'myxedema' of hypothyroidism (102).

Restoration of euthyroidism is followed by an increase in REE and even small variations in serum TSH, induced by L-T<sub>4</sub> substitution, are associated with opposite changes in REE (104, 105). However, in spite of adequate substitution with L-T<sub>4</sub>, hypothyroid patients may experience only a modest and/or transient loss of weight during hormone treatment (81, 106). Excretion of excess body water, rather than reduction in fat mass, accounts for this change of body weight.

There is general agreement that an ideal body weight should be employed to calculate the final amount of hormone to be administered to hypothyroid patients. A study using dual-energy x-ray absorptiometry (DEXA) to assess body composition in normal-weight, overweight, and obese subjects provided evidence that lean body mass is the best predictor of the daily requirements for L-T<sub>4</sub> in hypothyroid patients (74). In that study, the age- and gender-related differences in the L-T<sub>4</sub> substitution dose reflected the different proportions of lean mass over the total body weight. Indeed, most metabolic processes of thyroid hormones, including type 3 inner-ring deiodination in skin (107), type 2 outer-ring deiodination in skeletal muscle (108), type 1 outer-ring deiodination, sulfation, and glucuroconjugation in liver (109), occur within the lean body compartment. No association was observed between L-T<sub>4</sub> requirement and serum leptin (74), suggesting that the mass of adipose tissue has a minor impact on L-T<sub>4</sub> needs in hypothyroid subjects.

### Obesity and thyroid autoimmunity

Susceptibility to autoimmune thyroid disease depends primarily on genetic determinants, both within the HLA and non-HLA loci (*CTLA4*, *CD40*, *PTPN22*, *TG*, and *TSH-R* genes), which may be influenced by diverse environmental stressors, such as iodine intake, chemical pollutants, stress, drugs, and infectious diseases (110). A causal link between obesity and thyroid autoimmunity has not been established so far, yet observational data from the general population suggest that obesity may increase the risk of developing allergies and several autoimmune diseases (111, 112), possibly through the chronic pro-inflammatory status resulting from the accumulation of WAT in the obese patients. In obesity, the immunological tolerance can be affected both directly and indirectly, via an altered secretion of adipokines (predominantly leptin, adiponectin, and visfatin) and/or cytokines (interleukin 6 (IL6), tumor necrosis factor alpha, and interleukin 10 (IL10)). The final result would be a shift from Th2 to Th1 immune response; the latter being more prone to produce autoimmune reactions (112, 113, 114). The visceral adipose tissue (VAT) contains resident macrophages, endothelial cells, and T cells with biased T cell receptors, which may contribute to mount an immune response by producing excessive amounts of pro-inflammatory cytokines (115). Moreover, VAT is a reservoir of regulatory T (Treg) cells, a small subset (5–15%) of the T cell compartment capable of controlling autoimmune reactions. *In vitro*, Treg cells have been shown to be influenced by leptin, which acts by

downregulating the proliferation of CD4<sup>+</sup>CD25<sup>+</sup> cells, a Treg subpopulation involved in the control of autoimmunity (116) and of thyroid cell apoptosis (117). Experimentally, the immune actions of leptin have been shown in several autoimmune rheumatic diseases (118).

A clear clinical association between obesity and autoimmune thyroid diseases is not established to date, and available studies assessing conventional markers of thyroid autoimmunity, such as thyroid peroxidase antibodies (TPOAb) and/or thyroid hypo-echogenicity, have provided discrepant results due to inherent issues of accuracy in the context of obesity.

Studies on pediatric populations suggest that obesity *per se* is associated with moderately elevated TSH levels in association with normal or slightly elevated FT<sub>4</sub> and/or FT<sub>3</sub> levels (119). Overall, this hormonal profile is observed in 7–23% of obese children (120). Similar data, indicating a higher prevalence of elevated serum TSH, were found both in European and North American populations when obese children were compared with normal-weight controls. These higher TSH levels were not related to autoimmune thyroiditis, iodine deficiency, or signs and symptoms of hypothyroidism (121, 122). Whether the raised serum levels of TSH in childhood obesity are an adaptive phenomenon, aimed at increasing the metabolic rate in the attempt to prevent further weight gain, or indicate subclinical hypothyroidism, or may be thyroid hormone resistance, is still debated. Although the first hypothesis is strongly supported by the observation that the serum levels of TSH normalize after substantial weight loss, an overall consensus has still to be reached. Other studies reported an increased prevalence of humoral signs of thyroid autoimmunity in childhood obesity. Radetti *et al.* (77) found high levels of TPOAb in nearly 24% of overweight or obese children. This prevalence is similar to that observed in children with type 1 diabetes mellitus (21.6%) (123) and outnumbers current epidemiologic data in iodine-sufficient schoolchildren, which indicate a TPOAb prevalence in the range of 3.4–4.6% (124, 125).

Moving to adults, in a large series of obese individuals referred for bariatric surgery, the prevalence of autoimmune thyroiditis was 17.1% and that of autoimmune hypothyroidism 12.3% (126). These prevalence rates are higher than those reported in the National Health and Nutrition Examination Survey (NHANES III), which was performed in an iodine-sufficient population (127). While data on body weight were not incorporated in NHANES III, the prevalence rate of positive TPOAb was 11.3%, the thyroid autoantibody being more prevalent in women and white people, and significantly associated with hypo-

hyperthyroidism. In the study by Marzullo *et al.* (66), which included patients younger than 50 years with moderate or severe obesity (grades II and III), a twofold greater prevalence of TPOAb (17%) was found compared with control subjects (7.6%,  $P < 0.01$ ). In order to explain the greater prevalence of TPOAb in obese individuals, an increased presentation of thyroid antigens to the immune system, possibly resulting from TSH stimulation of thyroid cells, was postulated, albeit not proven (121). At variance with these findings, in the study by Rotondi *et al.* (64), which was restricted to morbid obesity (grade III), patients with increased serum levels of TSH had a low prevalence of TPOAb and did not display the high female-to-male ratio that is typical of thyroid autoimmunity. Thus, the prevalence of autoimmune hypothyroidism was found to be low in this group of patients with morbid obesity. Based on the latter study, the likelihood that chronic autoimmune thyroiditis is the underlying cause of the mild TSH elevation observed in obese patients remains questionable.

Several limitations apply to currently available studies, such as a restricted number of population samples, biases in the selection of patients and controls, and differences in the study design. The imprecision deriving from the variability of commercially available assays for TPOAb should also be considered (128). Such limitations must be taken into account when considering the prevalence rate of TPOAb in the general and in the obese population (64, 66, 129, 130, 131, 132, 133, 134, 135, 136, 137).

As a matter of fact, the question of whether obesity prompts the development of autoimmune thyroid diseases remains unanswered and will require future large comparative studies. Yet, the possible association between obesity and thyroid autoimmunity remains an issue of concern because affected individuals would be at high risk of developing symptomatic hypothyroidism, which in turn would promote further weight gain or would hamper weight loss programs. In this regard, we would like to stress that the clinical meaning of the moderately raised serum TSH frequently observed in obese patients differs depending on its underlying cause. If 'true' hypothyroidism, as assessed by a concomitant diagnosis of chronic autoimmune thyroiditis is present, the adverse consequences will not differ from those of subclinical hypothyroidism occurring in normal-weight subjects (138, 139, 140, 141). On the other hand, when no primary cause of hypothyroidism is found and the alteration of serum TSH is probably due to obesity itself, the repercussions of this isolated hyperthyrotropinemia are not easily envisaged.

## Thyroid cancer in obese patients

Large prospective studies have shown a significant association of obesity with several types of cancer. The International Agency for Research on Cancer classified the evidence for a causal link as 'sufficient' for cancers of the colon, female breast (postmenopausal), endometrium, kidney, and esophagus. These assumptions, together with the worldwide rising trend in obesity, suggest that overeating might be the most common avoidable cause of cancer in nonsmokers (142).

The incidence of differentiated thyroid cancer (DTC) in the North American population nearly tripled in the last decades, with the most rapid period of increase being recorded between 1997 and 2006 (143). In the same timeframe, the prevalence of obesity doubled among adults in North America and tripled in children and adolescents (144). The question of whether the epidemics of obesity might be responsible for the increased incidence rate of DTC is thus an open matter of debate. A systematic review of prospective observational studies showed a positive association between BMI categories at diagnosis and the risk of developing DTC (HR=1.18 (95% CI, 1.03–1.35) for a 5 kg/m<sup>2</sup> increase) in both sexes and young adults (age range, 18–20 years) (145). More recently, a cross-sectional study has demonstrated that BMI is a significant predictor of DTC in women (OR, 1.63; 95% CI, 1.24–2.10) but not in men (OR, 1.16; 95% CI, 0.85–1.57) (146). Thus, it is conceivable to speculate that obesity might predispose to DTC, at least in females.

The mechanisms underlying this hypothetical association remain largely unclear, but the increased serum level of TSH, frequently observed in obese patients, might play a role. Indeed, TSH is a growth factor for thyroid cells and a predictor of malignancy in thyroid nodules (147, 148). As such, a recent meta-analysis showed that, in patients with nodular disease, higher concentrations of TSH, even within the normal range, are associated with higher odds of thyroid cancer (149). A potential role for insulin, insulin-like growth factor (IGF), growth hormone (GH) secretagogues, and adipokines was also postulated. The insulin–cancer hypothesis postulates that hyperinsulinemia, a common finding in obesity, would decrease the concentrations of IGF-binding protein 1 (IGFBP1) and IGFBP2, which, in turn, would increase the bioavailable free IGF1 levels (150). IGF1 has mitogenic and anti-apoptotic effects, thus it might generically favor tumor formation and progression. An overexpression of the insulin receptor A (IR-A) may also contribute to the activation of the IGF system, at least in poorly DTCs.

This effect would be mediated by the activation of an autocrine loop involving IGF2 and a paracrine loop involving IGF1 via the formation of IR/IGF1R hybrids (151).

In addition, an imbalance between estrogens (E2) and androgens, due to the action of aromatase in the adipose tissue, could contribute to thyroid carcinogenesis in obese patients, being responsible for different actions according to gender and age (152). In thyroid cancer cells, the biological effects of E2 are mediated by estrogen receptors  $\alpha$  (ER $\alpha$  (ESR1)) in an ERK1/2-related pathway (153).

Further potential links between obesity and DTC might be ghrelin, the GH-secretagogue receptor, and obestatin, which are expressed in cancer tissues (154). Although *in vitro* studies showed that ghrelin plays a role in several processes related to cancer progression, its effects largely vary across different cell types (155). In particular, a significant decrease in the proliferation of cell lines of human papillary carcinoma (N-PAP) was observed after *in vitro* treatment with ghrelin at concentrations ranging from 100 nM to 1  $\mu$ M (156). At variance with these data, a study in patients with papillary thyroid cancer found that the malignancy was associated with low circulating levels of ghrelin, a condition which is typically observed in obese individuals (155). These apparently discrepant *in vitro* and *in vivo* findings might be reconciled by hypothesizing that low levels of ghrelin would favor thyroid cell proliferation whilst supra-physiological doses would have an inhibitory effect.

The obesity-related adipocytokine network might also play a role in the development of thyroid cancer. Several *in vitro* studies investigated the effect of leptin on thyroid cancer cells, but the results were not univocal. All investigated thyroid cancer cell lines (the anaplastic ARO, the follicular WRO, and the papillary CGTH-W3 cell lines) were found to express long-form leptin receptors. Leptin was shown to promote cell migration in PTC cells, while inhibiting the migration of follicular and anaplastic thyroid cancer cells (157). Other *in vitro* studies demonstrated that leptin stimulates a more aggressive PTC phenotype by putative activation of the PI3K/AKT pathway (158), and also promotes the de-differentiation of thyroid tumor cells via the JAK2/STAT3 signaling pathway (159). The possibility that these effects might result in distinct tumor presentations and disease courses remains purely theoretical.

Abnormal micro-environment conditions such as hypoxia (through HIF1 $\alpha$  overexpression), chronic inflammation (through NF- $\kappa$ B activation and upregulation of pro-inflammatory genes), and oxidative stress (due to the presence of reactive oxygen species) are typically



observed in obesity, and might hypothetically favor the development of DTC and, in particular, a subgroup of cancers characterized by resistance to both  $^{131}\text{I}$  treatment and chemotherapy (160).

The possible association of obesity with autoimmune thyroid diseases might also play a role because of the reported association between chronic autoimmune thyroiditis and thyroid cancer (161).

In conclusion, epidemiologic and experimental data suggest that obesity might be a risk factor for DTC. However, this is still a matter of debate deserving specifically designed clinical and epidemiologic studies to be clarified.

### Thyroid hormone as a potential treatment for obesity

Weight loss up to 5–10% of the initial weight reduces the risk factors of cardiovascular disease, prevents the development of type 2 diabetes, and improves other health outcomes in obese patients. Unfortunately, bariatric surgery is at present the only effective method to rapidly induce weight loss in morbid obese patients (162).

For decades thyroid hormone preparations have been inappropriately added to dietary supplements with potential dangerous effects. The rationale for using thyroid hormones stems from the common experience that weight loss induced by a hypocaloric diet frequently fades over time, and among the possible causes for failure is the reduced metabolic rate resulting from a decrease in serum  $\text{FT}_3$  levels during a low-calorie diet (163). These changes of thyroid hormone metabolism are regarded as an adaptive process aimed at minimizing the waste of body protein. The administration of thyroid hormones (either  $\text{T}_3$  and/or  $\text{T}_4$ ) to euthyroid obese patients during a hypocaloric diet has been investigated for decades for its ability to enhance weight loss (164). Some studies also tried to establish the optimal dose of thyroid hormones that, while favoring weight loss, would prevent muscle wasting and adverse cardiac effects due to subclinical thyrotoxicosis (165, 166, 167). In 2009, a meta-analysis of the literature by Kaptein *et al.* (168) estimated the effectiveness and the risks of  $\text{T}_3$  and/or  $\text{T}_4$  therapy in obese patients. Weight loss, protein wasting, and cardiac function were evaluated. The review included randomized controlled trials and prospective observational studies evaluating the effects of  $\text{T}_3$  and/or  $\text{T}_4$  treatment in euthyroid adult obese subjects undergoing caloric deprivation. The results of this meta-analysis indicated no consistent increase in total weight loss during  $\text{T}_3$  or  $\text{T}_4$  therapy. A significant weight loss was only observed in 20%

of the studies employing  $\text{T}_3$  treatment. The effects of  $\text{T}_3$  or  $\text{T}_4$  on total weight loss did not correlate with the hormone dose, the length of treatment, and the duration of caloric deprivation. The effect of  $\text{T}_3$  on protein loss, as assessed by urinary 3-methylhistidine excretion and urinary nitrogen excretion, did not reach the level of statistical significance mainly due to the small sample size. However, even apparently physiologic doses of  $\text{T}_3$  were able to significantly reduce the serum levels of TSH (in 50% of the studies). These data indicate the development of subclinical thyrotoxicosis. In two studies, the administration of pharmacologic doses of  $\text{T}_3$  significantly increased urinary nitrogen excretion compared with caloric deprivation alone (169, 170). In a study specifically designed to evaluate the components of weight loss, 74% of extra weight loss in the  $\text{T}_3$  treated group was accounted for by loss of fat free tissue (171).

Despite the effect of  $\text{T}_3$  on heat generation, the hypothesis that  $\text{T}_3$  administration might lead to a negative energy balance and to a consequent reduction of lipid storage is questionable for several reasons. The greater REE produced by  $\text{T}_3$  administration can be counterbalanced by a simultaneous stimulation of appetite, which in turn results in increased energy intake. Moreover, the increased lipolysis induced by  $\text{T}_3$  is associated with the induction of lipogenesis.

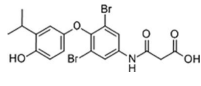
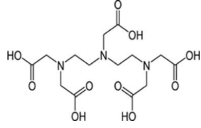
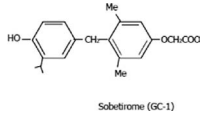
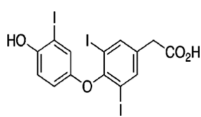
### Thyroid hormone mimetics as a future tool for the treatment of obesity and related co-morbidities?

The development of drugs selectively targeting the different isoforms of thyroid hormone receptor (TR) represents an emerging therapeutic tool aimed at improving weight loss, glucose tolerance, and dyslipidemia and at preventing atherosclerosis (Table 1) (172). The selective activation of different TR-mediated pathways is a promising strategy for treating lipid disorders and obesity (172, 173, 174, 175, 176). Indeed, studies on animals suggested that thyro-mimetics might be useful in the treatment of obesity, hepatic steatosis, and atherosclerosis (177).

In humans, many years ago, dextrothyroxine was used for the treatment of dyslipidemia (178). Despite the reduction in serum cholesterol levels, dextrothyroxine increased the overall mortality, due to a contamination of the drug preparation with the *l*-enantiomer.

Triiodothyroacetic acid (Triac) has a 3.5-fold higher affinity for  $\text{TR}\beta$  and a 1.5-fold higher affinity for  $\text{TR}\alpha$  compared with  $\text{T}_3$  (179). A study by Ladenson *et al.* showed that although Triac improved the lipid pattern in

**Table 1** Potential use of thyroid hormone analogs in humans.

Compound	TR isoform specificity $\beta > \alpha$	Structure	Favorable effects	Potential indications	Side effects
Eprotirome (KB 2115)	+		↓ LDL cholesterol ↓ LPA ↓ TGs	High cholesterol	Mild elevation in liver enzyme ↓ Serum T <sub>4</sub> chondrocyte loss (phase II discontinued)
DTPA 3,5 diiodo-acid	+/-		↑ CI ↓ SVR ↓ Cholesterol ↓ LPA ↓ TGs	Obesity Heart failure Statin synergy	↑ Marker of bone degradation ↓ T <sub>4</sub> , ↓ T <sub>3</sub> , and ↓ TSH
Sobetirome GC-1	++		↓ Fat mass ↓ LDL cholesterol ↓ LPA ↓ TGs	Obesity NAFLD FH	Not reported
Tiratricol TRIAC	++		↓ LDL cholesterol	Isolated pituitary resistance to thyroid hormones	↑ Bone resorption and turnover Symptoms of thyrotoxicosis ↓ T <sub>4</sub> and ↓ TSH

CI, cardiac index; SVR, systemic vascular resistance; LPA, apolipoprotein (a); TGs, triglycerides; NAFLD, nonalcoholic fatty liver disease; FH, familial hypercholesterolemia.

hypothyroid athyreotic patients, its use was associated with a negative effect on bone turnover (179).

Sobetirome (GC1), a THR $\beta$ -selective agonist, is able to bind TR $\beta$  with an affinity similar to T<sub>3</sub>, but has a tenfold lower affinity for the TR $\alpha$  isoform (180). In the study by Chiellini *et al.*, sobetirome decreased fat mass by 20% and improved the lipid profile without increasing food intake and affecting heart rate or bone mass (180). Treatment of rats with 3  $\mu$ g T<sub>3</sub>/100 g body weight and equimolar amounts of GC1 (3  $\mu$ g GC1/100 g body weight) resulted in a similar loss of fat mass. At variance with T<sub>3</sub>, which caused a loss of muscle mass, GC1 had no muscle wasting effect (181).

In 2010, a randomized, placebo-controlled, double-blind multicenter trial assessed the efficacy of KB2115 (eprotirome) in lowering the serum levels of LDL cholesterol. Eprotirome induced a 23–29% reduction in serum LDL cholesterol, a 22–38% decline in serum triglyceride, and a 37–45% decrease in lipoprotein(a) in patients with hypercholesterolemia who were already receiving simvastatin or atorvastatin, but still had serum LDL levels above 116 mg/dl (182). The drug had no adverse effects on the cardiovascular system or on bone mineral turnover. No significant change in serum TSH or T<sub>3</sub> was reported. Only a slight and transient increase in liver enzymes was observed. However, body weight did not change in patients receiving eprotirome.

GC24, a second-generation molecule, has a 40-fold higher affinity for TR $\beta$  than TR $\alpha$ . In rats, the drug reduces body fat accumulation, prevents liver steatosis, improves insulin sensitivity, and normalizes hypertriglyceridemia (183). These favorable actions can be obtained without significant changes in food intake or untoward cardiac effects.

In a recent preliminary study, two euthyroid human volunteers have been treated with 3,5-diiodo-L-thyronine (184). A significant 4% decrease in body weight was found, without significant changes in serum FT<sub>3</sub>, FT<sub>4</sub>, or TSH. Unfortunately, changes in fat mass were not evaluated in this study.

In summary, preclinical studies showed that thyromimetic drugs might be useful in treating obesity and dyslipidemia. The second generation of highly selective TR $\beta$  agonists or compounds with additional adipose tissue-specific effects might be promising in treating obesity.

## Conclusion

A continuous interaction between the thyroid gland and the adipose organ is important for human body weight control and maintenance of optimal energy balance. Thyroid dysfunctions may affect this equilibrium and always require proper treatment. Whether obesity has a pathogenic role in thyroid disease remains largely a matter of investigation.

Specifically, this review highlights the complexity in the identification of thyroid hormone deficiency in obese patients. Regardless of the importance of treating subclinical and overt hypothyroidism to improve the cardiovascular prognosis, at present there is no evidence to recommend a pharmacological correction of the isolated hyperthyrotropinemia often encountered in obese patients. While thyroid hormones are not indicated as anti-obesity drugs, preclinical studies suggest that thyromimetic drugs, by targeting selected receptors, might be useful in the treatment of obesity and dyslipidemia.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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