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Review article

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The complexity of the relationship between thyroid disease and body weight

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Abstract

The factors influencing the control of body weight are numerous and include many hormones. Even though levels of thyroid hormone might not always be the major factor affecting weight, in the sense that large changes in weight can occur despite a euthyroid state, there are notable changes in weight, appetite and body composition associated with excesses and deficiencies of thyroid hormone. Exploring the effect of thyroid hormone on weight is facilitated by studying the disease states of hypothyroidism and hyperthyroidism, the development and treatment of which can be associated with substantial changes in body weight. As is illustrated in the ensuing discussion, hypothyroidism is associated with modest increases in body weight and accompanying changes in body composition, with reversal of these alterations with its treatment. By contrast, hyperthyroidism can be accompanied by profound weight loss with reversal of the weight loss with restoration of euthyroidism. Using iatrogenic hyperthyroidism, whether during treatment for hypothyroidism or during off-label use in euthyroid individuals, has not proven to be an effective weight loss strategy.

Sections

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Key points

- There is a complex relationship between levels of thyroid hormone and body weight and body composition.
- Development of hypothyroidism is generally accompanied by a mild to modest weight gain.
- Reversal of hypothyroidism is not always associated with a reduction in weight.
- Hyperthyroidism is associated with weight loss with decreases in adipose tissue mass, muscle mass and bone mass.
- The change to euthyroidism with treatment of hyperthyroidism is accompanied by increases in adipose tissue mass, muscle mass and bone mass.
- Resolution of hyperthyroidism is typically associated with a net increase in body weight over time, to a weight substantially above the pretreatment baseline.

Introduction

The goal of this Review is to summarize the relationship between thyroid dysfunction and weight changes, while acknowledging that reversal of thyroid dysfunction is not universally associated with a return to baseline weight, but is, in fact, more commonly associated with gradual weight gain. Questions to be considered include whether this weight gain is due to the many other hormonal and non-hormonal factors that affect body weight and interact with thyroid status, or whether it could be linked to suboptimal treatment of thyroid disorders, such as not using liothyronine therapy. Given the prevalence of thyroid disorders, this trend towards weight gain has notable consequences for overall population health. Based on the positive effect of weight loss in reducing cardiometabolic risk factors and the negative effect of weight gain, weight changes of <5% could be considered mild, whereas changes of 5–10% could be considered modest, and weight changes of >10% are probably clinically significant[1].

Thyroid hormone is one of the important hormones involved in weight regulation[2]. However, large changes in weight can occur in individuals who exhibit a euthyroid state, defined as one in which serum levels of thyroid-stimulating hormone (TSH) and thyroid hormone levels fall within the normal reference interval. This observation illustrates that there are many factors, other than thyroid status, that can cause body weight alterations[3]. Moreover, there is redundancy in the hormonal systems that control body weight, as illustrated by the fact that manipulation of a single hormonal system with drug therapy might have only a relatively modest effect on body weight[4]. An example is the gut-derived peptides, which, although they have an important role in appetite control, appear to be a system in which there is a high level of redundancy with no one particular gut-derived peptide having a controlling role in appetite regulation[5].

As is the focus of this Review of the literature (Box 1), there are substantial changes in weight, appetite, energy expenditure and body composition associated with the development of thyroid disorders. Thyroid disorders are also related in a complex manner to the development of metabolic syndrome[6–8]. The profound effect that levels of thyroid hormone can have on body weight regulation is illustrated by the disease states of hypothyroidism and hyperthyroidism, conditions in which TSH levels are above and below the reference interval, respectively. Both the development of these disorders and their treatment can be accompanied by clinically significant changes in body weight. For example, hypothyroidism is associated with modest increases in body weight and alterations in body composition, such as increased BMI and waist circumference. These changes are reversed by treatment of hypothyroidism. Hyperthyroidism can have an even greater effect on body weight and composition, and be accompanied by profound weight loss, which is reversed by treatment that restores a euthyroid state. However, intentional iatrogenic thyrotoxicosis, in which exogenous thyroid hormone is provided in a dose that suppresses TSH, has not proven to be effective as a weight loss approach. This fact is true regardless of whether thyroid hormone is being utilized for treatment of hypothyroidism or being used in individuals without a diagnosis of hypothyroidism, who are striving for weight loss or body composition changes that might be potentially beneficial for body image or in certain sports.

Alterations in thyroid function associated with alterations in weight

Epidemiological studies suggest that different weights or BMIs within a euthyroid population can be associated with differences in thyroid function tests. Perhaps the most pronounced among these findings are trends for increases in serum levels of TSH with increasing BMI. A 2025 meta-analysis identified 21 studies for quantitative analysis of the association between concentrations of TSH, concentrations of free tetraiodothyronine (T_4) and BMI[9]. Most of these studies were cross-sectional with fewer longitudinal studies, and most were conducted in Europe, with fewer studies from Asia and Oceania. The cross-sectional studies showed an estimate of 0.21 kg/m^2 increase in BMI (95% CI 0.09–0.32 kg/m^2) per 1 mIU/l increase in concentrations of TSH[9]. There was a 0.14 kg/m^2 (95% CI −0.23 to −0.05 kg/m^2) decrease in BMI for each picomole per litre increase in free T_4 concentration.

Individual cross-sectional studies, such as one in the USA examining National Health and Nutrition Examination Survey (NHANES) data, have shown an increase in TSH values for every quartile increase in BMI in euthyroid men and women[10]. Similarly, a Danish database showed a positive association between BMI and TSH category (TSH values divided into five different concentration-based groups), such that, in euthyroid individuals, the lowest versus highest TSH values were associated with a BMI difference of 1.9 kg/m^2 (ref. 11). In addition, TSH values at the higher end of the normal range appear to be associated with adverse health outcomes, such as high blood pressure, elevated levels of cholesterol and metabolic syndrome[12]. It is possible that the effect of weight on TSH levels could be mediated via leptin through the effects of leptin in regulating the hypothalamic–pituitary–thyroid axis and the release of TSH[13]. The data regarding thyroid hormone levels are more variable across the different studies, as opposed to the consistency of the TSH findings. With respect to longitudinal studies, increasing TSH concentrations were associated with weight gain, whereas increasing free T_4 concentrations were associated with weight loss[9]. However, not all studies are consistent. For example, in a population of 784 individuals in Spain studied at baseline and 6 years later, higher free T_4 and higher free triiodothyronine (T_3) values were associated with greater weight gain at follow-up. The authors hypothesized that the changes in thyroid hormone were a consequence rather than a cause of the weight gain[14]. However, in a different prospective study, lower levels of free T_3 but not lower levels of free T_4 were associated with greater weight gain[15].

In keeping with the previously mentioned studies, in which weight increases were accompanied by increases in levels of TSH, weight loss is associated with decreases in serum concentrations of TSH. One example is a study in 256 patients who achieved a weight loss of 28% from baseline 1 year after bariatric surgery, who had an accompanying decline in concentrations of TSH from a median of 2.33 mIU/l to a median of 1.82 mIU/l[16]. In another study, weight loss was associated with a statistically significant decrease in the mean 24-h serum concentration of TSH[17]. Another example of the interaction between thyroid hormones and weight changes is the finding that, in a trial evaluating weight loss in euthyroid individuals, higher levels of free T_4 and free T_3 at baseline were associated with greater weight loss over 6 months[18]. In another trial evaluating weight loss in individuals with overweight or obesity, levels of TSH and total T_3 at baseline were positively correlated with fat mass. A mean weight loss of 6.5% was achieved in the 47 individuals being studied, and was associated with a statistically significant decrease in levels of total T_3, perhaps suggesting a decrease in peripheral conversion from T_4 to T_3 (ref. 19).

Based on these studies, it is clear that there is a complex relationship between thyroid hormones and weight that, in euthyroid individuals, appears more likely to be due to changes in weight affecting concentrations of thyroid hormones, rather than the changes in thyroid hormones actually causing the weight changes.

Box 1 | Description of literature search

- References for this article were identified through searches of PubMed for articles published in English from 1 January 1985 to 30 January 2025.
- The Medical Subject Headings (MeSH) terms 'hypothyroidism', 'hyperthyroidism', 'subclinical hypothyroidism', 'subclinical hyperthyroidism', 'thyroid disease', 'thyroid stimulating hormone', 'thyroid hormone', 'thyroxine', 'free thyroxine', and 'triiodothyronine' in combination with the terms 'weight loss and weight gain' were used.
- Relevant articles were also identified through searches in the author's personal files.
- Articles resulting from these searches and relevant references cited in those articles were reviewed.
- It is important to note that although meta-analyses were cited where available, many of the identified articles were small, retrospective studies or case series, leading primarily to hypothesis-generation, and limiting the ability to draw conclusions and attribute causation.

Weight changes despite a euthyroid state

In addition to the many hormonal control mechanisms that influence body weight, multiple non-hormonal factors are also important regulators of body weight, including calorie intake, food marketing, exercise frequency and intensity, stress, genetic factors, epigenetics, gut microbiome, sleep dysregulation, medications, gastrointestinal disorders, psychiatric disorders and age, to mention but a few[3,20,21] (Fig. 1). Individuals can undergo substantial changes in weight while maintaining a euthyroid state. This finding illustrates the complexity of the mechanisms that govern body weight regulation. It is also a difficult concept to incorporate into understanding of the well-established relationship between thyroid status and weight changes. Patients with weight derangements being treated for thyroid disorders and their clinicians, understandably, suspect out of range thyroid function as the most probable explanation for the weight change. Moreover, despite demonstration of euthyroidism, a role for thyroid disorders in weight changes is still often invoked and sought for by patients and physicians, even after being ruled out. Three illustrations of some of the situations in which weight changes occur while euthyroidism is maintained are discussed below.

Weight changes with age

An important trend seen with normal ageing is weight changes that occur despite the absence of a thyroid disorder. Weight gain with age can be more pronounced in women than in men[22,23]. In general, there is an increase in weight as an individual ages, and this weight gain in later life is associated with an increased risk of chronic diseases[24]. However, this trend for weight gain can be modified by other factors such as general health, mobility and comorbidities, such that there can instead be a decline in weight associated with sarcopenia, particularly at older ages.

Weight changes with menopause

A major contribution to weight changes in women involves the increase in weight and change in body composition that can accompany menopause[23], despite maintenance of a euthyroid state. Typically the transition into menopause is associated with increased weight and increased adiposity, compared with the premenopausal period[25,26]. It is interesting in this regard that ovariectomy in mice leads to weight gain, perhaps via an effect of oestrogen on the ventromedial nucleus of the hypothalamus (VMH)[27], possibly implying that menopause-related weight gain could be at least partially associated with oestrogen deficiency. In support of this association with oestrogen, premenopausal women undergoing hysterectomy experience more weight gain than control women with an intact uterus and ovaries, with a weight gain of greater than 4.5 kg occurring in 23% of the oestrogen-deficient women who had undergone hysterectomy[28]. Despite these findings, hormone replacement therapy has not been established as an effective means of remediating menopause-associated weight gain[29].

Weight changes in native versus levothyroxine-treated euthyroidism

There are some data that suggest that patients who have undergone thyroidectomy can subsequently gain more weight than age-matched and sex-matched euthyroid control individuals without thyroid disease, despite the patients being maintained in a euthyroid state with levothyroxine[30]. The weight gain over 1 year in one study was 3.1 kg in euthyroid patients who had undergone thyroidectomy, compared with 1.3 kg in euthyroid patients without thyroid disease[30]. A study in patients who had undergone thyroidectomy for thyroid cancer showed that weight gain following surgery occurs despite TSH suppression therapy. Female thyroid cancer survivors had a weight gain of 0.46 kg per year after thyroidectomy, whereas their male counterparts gained 0.94 kg per year. This weight gain was greater than in an age-matched general population from the National Health Examination Follow-up Study (NHEFS), in which both men and women gained on average 0.23 kg per year[31]. If confirmed, such findings have the practical implication that patients should be advised of these data prior to surgery and attempts should be made to mitigate subsequent weight gain. However, a meta-analysis of 11 studies in patients undergoing thyroidectomy and receiving levothyroxine-replacement did not document a greater weight gain in the thyroidectomized individuals than was seen

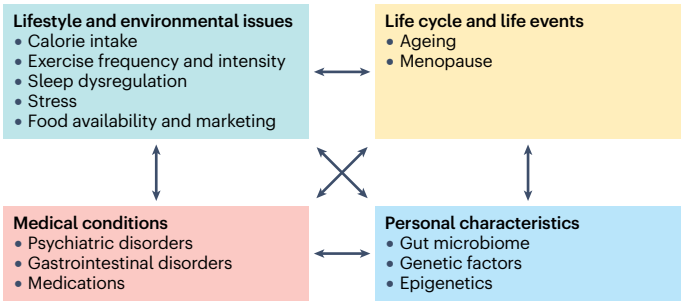

Fig. 1 | Non-hormonal factors affecting body weight. Some of the multiple non-hormonal factors that can substantially influence body weight are shown. These factors are intertwined with each other. The factors are presented in a juxtaposed manner and any combination of these factors can be relevant at any one time.

in euthyroid individuals being followed without surgery for thyroid nodules[32]. An additional meta-analysis of 17 studies in patients undergoing thyroidectomy concluded that there is a small degree of weight gain after thyroidectomy, which is most notable in those undergoing thyroidectomy for hyperthyroidism, compared with those undergoing surgery for goitre or thyroid cancer[33] (Box 2).

The mechanisms by which thyroid hormones contribute to weight regulation

Thyroid hormone contributes to weight regulation by both peripheral and central mechanisms. The peripheral mechanisms involve regulation of basal metabolic rate, energy expenditure and oxygen consumption. The central mechanisms involve regulation of appetite, food preferences and activity level (Figs. 2, 3). The net effect of perturbation of these mechanisms is that hypothyroidism leads to decreased energy expenditure, weight gain and intolerance to cold[34], whereas hyperthyroidism leads to hypermetabolism, weight loss and intolerance to heat[35].

Peripheral mechanisms

T_4 undergoes controlled conversion via the activity of deiodinases to its active metabolite, T_3, which then contributes to weight regulation through several different peripheral avenues (Figs. 2, 3). T_3 modulates basal metabolic rate, energy expenditure, oxygen consumption, calorigenesis, metabolic efficiency and thermogenesis[36]. T_3 also regulates lipid turnover in adipocytes and thereby counteracts lipid accumulation, reduces levels of cholesterol and increases lipid metabolism, including via lipolysis and free fatty acid oxidation[2]. T_3 also appears to be involved in protein metabolism[37].

T_3 regulates basal metabolic rate by both genomic and non-genomic mechanisms that affect mitochondrial biogenesis[6]. Thyroid hormones stimulate mitochondrial respiration by enhancing the expression of genes involved in oxidative phosphorylation, with glycerol phosphate oxidation being increased in both liver and kidney mitochondria. This effect on mitochondria includes increasing the expression of the gene encoding the Na^+–K^+ ATPase, resulting in increased ATP availability and oxygen consumption. T_3 induces the expression of uncoupling proteins, leading to heat production instead of ATP synthesis, a process known as thermogenesis[38]. This uncoupling leads to the increased thermogenesis characteristic of hyperthyroidism and, when reversed, the decreased thermogenesis seen in hypothyroidism. Through the above mechanisms, thyroid hormone determines basal metabolic rate and oxygen consumption[39], induces thermogenesis, including in brown adipose tissue (BAT)[38,40], and permits the generation of heat to maintain body temperature[41].

With respect to heat generation in animal studies, T_3 directly stimulates the expression of genes involved in fatty acid oxidation and mitochondrial respiration in cultured mouse adipocytes, thereby facilitating thermogenesis[42]. T_3 also permits metabolic inefficiency by inducing the mitochondrial uncoupling protein (UCP1) and allowing heat generation[43]. Interestingly, in individuals on a very low-energy diet and undergoing rapid weight loss, there is both a decrease in serum concentrations of T_3 and a reduced resting metabolic rate[44]. The reduced resting metabolic rate was reversed in this study by thyroid hormone treatment with levothyroxine and liothyronine[44]. The same changes of decreased metabolic rate and decreased levels of T_3 are also seen with sustained fasting[45]. In an animal study, food restriction led to decreased type 1 deiodinase activity, decreased T_3 levels and lowered metabolic rate, but T_4 replacement did not normalize metabolic rate in this case[46].

As mentioned above, thyroid hormone regulates thermogenesis via its actions on BAT[47–51], possibly with a role for selenium in regulating deiodinase activity under some circumstances[52]. The type and amount of thermogenic adipose tissue varies widely between individuals, with the amount being affected by cold exposure, age and leanness[48,53–56]. Brown adipocytes contain multiple lipid droplets with numerous mitochondria, and are important for heat production[57]. Thyroid hormone is a key factor in influencing BAT activity. In response to thyroid hormone[58], BAT is activated in situations that perturb energy regulation such as in response to a high-fat diet or cold exposure, in order to protect the organism from weight gain and hypothermia, respectively. Induction of type 2 deiodinase expression in BAT promotes local conversion of T_4 to T_3, and activation of the transcription of target genes involved in thermogenesis[59]. Increased type 2 deiodinase activity is associated with increased levels of uncoupling proteins and heat generation[60]. In addition to the necessary role of T_3 in activating BAT and thermogenesis, sympathetic nervous stimulation is also required for full activation of these mechanisms[61,62]. Thyroid hormone also appears to have a role in regulating deiodinase expression and thermogenesis in white adipose tissue (WAT), although less is known about the relative importance of thyroid hormone actions in WAT compared with BAT[63].

Central mechanisms via thermogenesis

The central effect of thyroid hormones on metabolism, energy homeostasis and thermogenesis can be investigated by studying responses to cold exposure and fasting, which has been conducted primarily in rodent models. Several hypothalamic nuclei including the dorsomedial hypothalamic nucleus, the VMH, the preoptic area, the arcuate nucleus and the paraventricular nucleus (PVN) have been shown to interact with thyroid hormones[35,64,65]. Thyroid hormone receptor-α (TRα) in the VMH mediates sympathetic nervous system output, increasing thermogenesis and energy expenditure[64,66]. Thyroid hormones have a role in altering obligatory thermogenesis, but also in adapting facultative thermogenesis. During exposure to low temperatures, heat-sensitive neurons in the preoptic area are inactivated, which causes an increase in input to the dorsomedial nucleus and activation of WAT, BAT, liver and skeletal muscle to increase thermogenesis. Associated with this response to cold is an increase in thyroid-releasing hormone (TRH), TSH and thyroid hormones. This hormonal response stimulates lipolysis, glucose production and provision of substrates to combat the cold.

Other studies in rodents suggest a role of the PVN in inducing metabolic and behavioural changes[67,68]. Cold exposure and TRH administration into the PVN increase both body temperature and locomotor activity, thus providing a defence against cold. However, during fasting there is reduced inhibition of the type 2 deiodinase by leptin, reduction of TRH from the PVH, and decreased TSH and thyroid hormone production[67,68]. Under these conditions, there is less activation of WAT, BAT, liver and muscle, and reduced resting energy expenditure. During the hypothyroid state, there is increased production of TRH and TSH, but, despite TSH stimulation of lipolysis, there is insufficient sympathetic drive associated with the thyroid hormone deficiency to allow fuel consumption, and so the potential for decreased core body temperature ensues. With hyperthyroidism, TRH and TSH production is decreased and the action of thyroid hormone on the VMH causes heat production via effects on the liver and adipose tissue.

Central mechanisms via appetite regulation

Regarding appetite, thyroid hormone might have an effect on appetite primarily by central effects[69,70] (Figs. 2, 3). Other hormones such as leptin[5] and the central melanocortin system[71,72] might also interact with thyroid hormone and have substantial roles in the control of food intake. In experimental animal models, knockdown of the thyroid hormone receptor-β (TRβ) in the VMH results in hyperphagia and reduced energy expenditure[73]. Ultimately this loss of TRβ results in severe obesity. Injection of T_3 into the VMH of rats produces a fourfold increase in food intake over an hour[74], although other studies suggest a more substantial role of the arcuate nucleus[75,76]. In addition to the VMH, the PVN and the arcuate nucleus also appear to be involved in T_3-mediated appetite regulation[69]. Additional studies support a role of the arcuate nucleus in T_3-stimulated feeding behaviour[64,75,76] via TRα[76]. The arcuate nucleus contains two distinct neuronal populations, one expressing pro-opiomelanocortin and the other expressing neuropeptide Y and agouti-related protein. It appears from animal studies that T_3 increases appetite via stimulation of neuropeptide Y. Fasting appears to be associated with T_3 production in the arcuate nucleus and rebound feeding following food deprivation[75].

Weight gain accompanying hypothyroidism

The 2025 *Lancet* Commission on Obesity, which defines clinical obesity as a condition characterized by excess adiposity with or without abnormal distribution or function of adipose tissue, highlights hypothyroidism as a secondary form of obesity that can be ruled out with specific blood tests[77]. The development of hypothyroidism is generally accompanied by weight gain (Table 1), with decreased energy expenditure and decreased thermogenesis. Other factors potentially contributing to weight gain when individuals are in a hypothyroid state include fatiguability[78], reduction of physical activity[79] and accumulation of glycosaminoglycans, which in the skin interstitium are associated with increased fluid accumulation and oedema[80,81]. Perplexingly, a return to the baseline body weight with treatment of hypothyroidism can be elusive. This might be partly due to a new set point associated with the higher weight, combined with the incomplete normalization of metabolic rate.

Newly diagnosed subclinical hypothyroidism

Subclinical hypothyroidism occurs when levels of TSH are elevated, but levels of thyroid hormones remain within the normal range and can be associated with metabolic syndrome[82]. A trend for weight gain has been described for increases in TSH values even within the normal range in a population in Denmark[11]. Another study in Norway observed that increasing TSH within the reference range of 0.3–3.5 mIU/l was associated with weight gain, and conversely weight loss was associated with a lower TSH value[83]. In data from the Framingham Offspring Study, baseline weight increased progressively from the lowest to highest TSH quartile within the range of 0.5–5.0 mIU/l[84]. Similarly, an increasing TSH value within the reference range was positively associated with BMI ($p < 0.001$) and with the prevalence of obesity ($p < 0.005$) in another study conducted in Norway[85].

In a Danish study in which the TSH reference range was 0.4–3.6 mIU/l, the group that had a TSH greater than 3.6 mIU/l (median TSH 4.5 mIU/l), and thus had subclinical hypothyroidism, had the greatest 5-year weight gain[11]. For the previously mentioned Framingham Offspring Study, in addition to the positive association between TSH and BMI at baseline, at the 3.5-year follow-up, more women in the highest decile of weight change had high TSH concentrations (serum concentrations of TSH >5.0 mIU/l) compared with the rest of the sample (9.2% versus 5.7%)[84]. In another study, patients with subclinical hypothyroidism and a mean TSH concentration of 13 mIU/l had a mean BMI of 25.3 ± 4.3 kg/m^2, compared with a BMI of 23.5 ± 3.5 kg/m^2 in a euthyroid control group with a TSH of 1.6 mIU/l (BMI differences $p < 0.01$)[86]. However, despite these studies, an association between subclinical hypothyroidism and weight gain is not always documented, particularly in studies with smaller patient numbers. For example, in a small study in patients with newly diagnosed subclinical hypothyroidism, BMI values were no different from those in euthyroid controls (BMI 25 ± 4 kg/m^2 versus 24 ± 4 kg/m^2; *p* value not significant)[79].

Box 2 | The effect of thyroidectomy on body weight as shown in two meta-analyses

Huynh et al. (2021) meta-analysis[33]

- A meta-analysis of 17 studies showed a weight gain of 2.1 kg over approximately 2 years following thyroidectomy[33].
- In the same meta-analysis, the greatest weight gain of 5.19 kg occurred in patients undergoing thyroidectomy for hyperthyroidism, compared with 1.3 kg and 1.55 kg in those who underwent thyroidectomy for cancer and goitre, respectively[33].

Singh Ospina et al. (2018) meta-analysis[32]

- A meta-analysis of nine studies showed similar weight gain over 1–2 years in three groups of patients; that is, those undergoing surgery for thyroid cancer, those undergoing surgery for thyroid nodules, and those being followed for thyroid nodules without surgery[32].
- In this second meta-analysis, at 1–2 years of follow up, the weight gain following thyroidectomy for thyroid cancer was 0.94 kg, compared with 1.07 kg in those undergoing surgery for benign disease and 0.51 kg in patients with benign thyroid nodules followed without surgery[32].

To conclude from these meta-analyses and the individual studies included within them, there is weight gain over time after thyroidectomy, but it does not appear to be substantially more than the weight gain occurring in control groups, except within specific individual studies or populations.

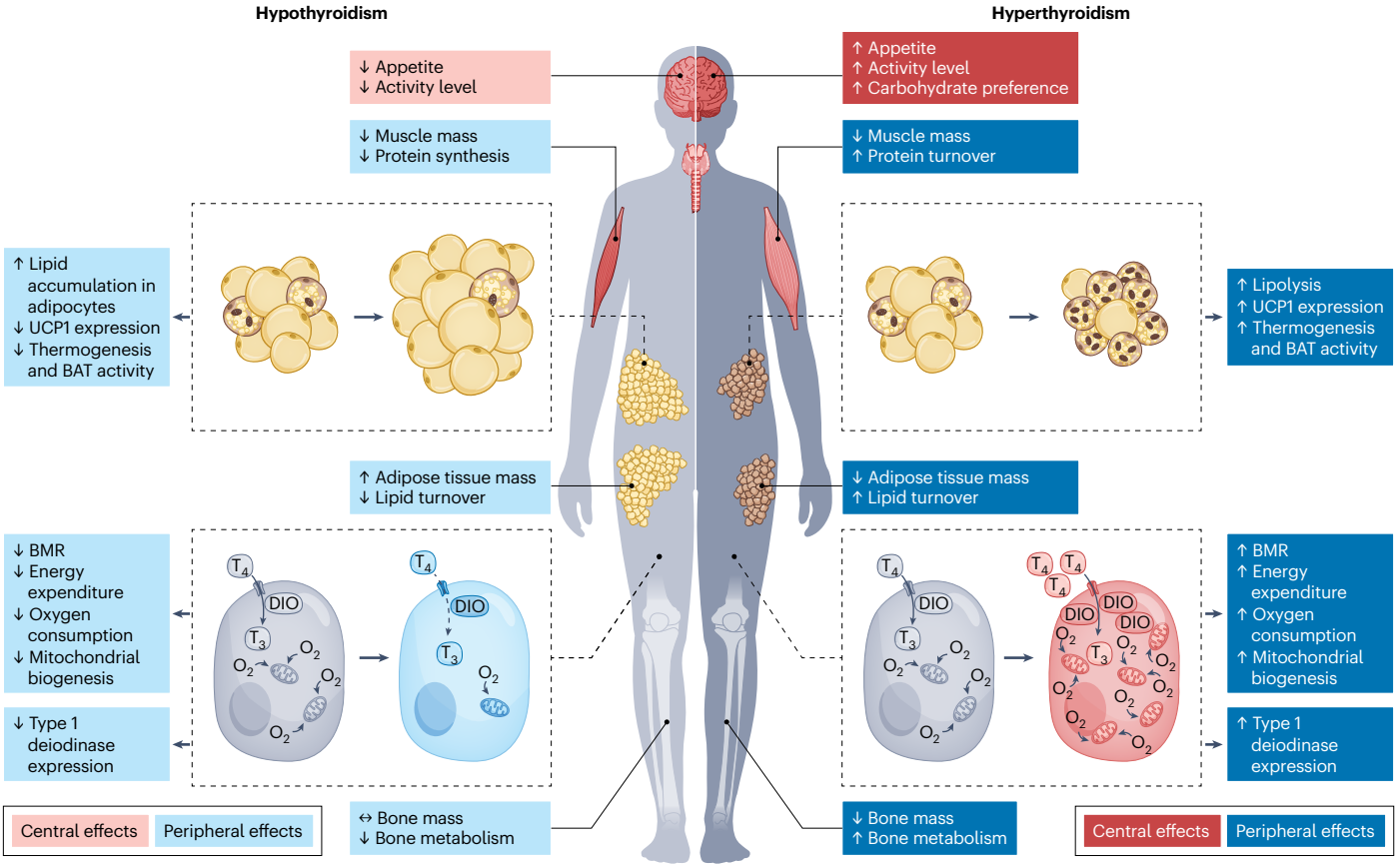

Fig. 2 | Mechanisms through which thyroid hormone controls body weight. Mechanisms are divided into central and peripheral mechanisms. For each mechanism the effect is in the opposite direction for hypothyroidism versus hyperthyroidism. Opposite effects on appetite and metabolic rate are given as examples. BAT, brown adipose tissue; BMR, basal metabolic rate; DIO, deiodinase; T_3, triiodothyronine; T_4, thyroxine; UCP1, uncoupling protein 1.

The modest or absent weight changes with the development of subclinical hypothyroidism could suggest either that the patient uses compensatory behaviours or strategies to prevent a greater degree of weight gain, or that various physiological control mechanisms are deployed, or that there is a TSH and free T_4 concentration threshold before weight gain manifests. Furthermore, the absent or minor weight reduction with treatment of subclinical hypothyroidism (see later section 'Weight changes with treatment of hypothyroidism') could be due to the previously discussed mechanisms causing weight gain despite a euthyroid state.

Newly diagnosed overt hypothyroidism

Overt hypothyroidism, typically caused by thyroid peroxidase antibodies and known as autoimmune hypothyroidism, occurs when there is both an increase in levels of TSH and a reduction in thyroid hormone levels below the reference interval. This condition is associated with obesity, which appears to manifest gradually as the hypothyroidism progresses. In addition to autoimmune hypothyroidism being associated with obesity, it also appears that the metabolic issues associated with obesity can be associated with the presence of autoimmune thyroid disease[87] and with non-autoimmune thyroid dysfunction[88], although causation has not been established. In the case of non-autoimmune thyroid dysfunction the so-called lipotoxicity mechanism has been promulgated by one particular group[89]. The weight gain that can be associated with newly diagnosed overt hypothyroidism has not been well documented in comparison with a control group. However, weight gain is a symptom reported by patients with hypothyroidism, and it has a positive predictive value of 70.6% for the diagnosis[86]. In one study of patients with hypothyroidism with a mean TSH of 52 mIU/l and a low T_3 level (0.7 nmol/l), the mean BMI was 27.2 ± 3.2 kg/m^2, compared with 23.5 ± 3.5 kg/m^2 in a euthyroid control group with a TSH of 1.6 mIU/l ($p < 0.001$)[86]. However, in a small study of patients with newly diagnosed hypothyroidism, BMI values were no different from those in euthyroid controls (BMI 27 ± 5 kg/m^2 versus BMI 24 ± 4 kg/m^2; p value not significant)[79].

Rapid-onset overt hypothyroidism

Hypothyroidism of rapid onset, as opposed to the gradual onset seen with spontaneous hypothyroidism, can primarily occur under two circumstances. It occurs in individuals who remain untreated for hypothyroidism with levothyroxine after undergoing thyroidectomy. Rapid-onset hypothyroidism can also occur during protocols involving withdrawal from thyroid hormone in patients with post-surgical hypothyroidism who are being prepared for radioactive iodine treatment for thyroid cancer. Under the latter specific circumstance, in a 2015 study, weight gain was 1.0 ± 1.9 kg in those withdrawn from thyroid hormone

compared with a weight loss of 1.4 ± 1.6 kg in those who underwent a recombinant human TSH protocol involving two injections of recombinant TSH while remaining on thyroid hormone[90]. Both groups followed a low-iodine diet and the weight loss in the recombinant human TSH group was attributed to this diet. Interestingly, in another study of the weight gain during a thyroid hormone withdrawal protocol, 69% of patients reported a gain in weight, whereas only 35% of participants in a comparison group who were also prescribed probiotics gained weight[91]. The authors suggested that the modified gut flora associated with the consumption of probiotics reduced the weight gain associated with hypothyroidism. It also appears that the weight gain experienced during the withdrawal from thyroid hormone had the additional consequence of being associated with greater weight gains at 3–4 years following radioactive iodine treatment compared with those who were treated with a recombinant human TSH protocol. The weight gain over 3–4 years was significant at 0.7 kg ($p < 0.001$) compared with baseline for the withdrawal group compared with no weight gain ($p = 0.55$) in the recombinant human TSH group[92]. The weight gain was greatest (1.5 kg) in the patients in the thyroid hormone withdrawal group who were aged less than 40 years.

The generally clinically significant weight increases occurring with development of overt hypothyroidism reinforce the role of thyroid hormone in weight regulation and perhaps also suggest that, with the greater magnitude of thyroid hormone deficiency than in subclinical hypothyroidism, other systems are less effective in rectifying the weight increase.

Weight changes with treatment of hypothyroidism

Perhaps surprisingly, weight loss following treatment of hypothyroidism with levothyroxine is typically quite modest[93] (Table 1). In one study of individuals with moderately severe hypothyroidism, with a mean TSH of 102 mIU/l, initiation of thyroid hormone treatment was associated with normalization of TSH to 2.2 mIU/l. Once these individuals achieved euthyroidism, their weight decreased from a mean of 83.7 ± 16.4 kg to 79.4 ± 16.0 kg ($p < 0.002$)[94]. However, the weight loss was not due to a change in fat mass, but was entirely due to a decrease in the weight of the lean mass subcompartment. The lack of alteration in fat mass was observed despite increases in resting energy expenditure and physical activity with achievement of euthyroidism. In keeping with the theory that weight loss can occur due to reversal of myxoedematous changes, in a study in which skin biopsies were performed before and after treatment of hypothyroidism with desiccated thyroid extract, the deposition of mucopolysaccharides, hyaluronic acid and chondroitin sulfate was decreased by treatment[81]. In a study of 17 patients with a milder degree of hypothyroidism (mean TSH concentration 23.99 mIU/l) in whom euthyroidism was restored (mean TSH concentration 3.27 mIU/l), mean weight decreased from 70.9 ± 10.1 kg to 68.7 ± 10.1 kg (mean difference 2.3 ± 2.0 kg; $p < 0.001$). Statistically significant differences were also observed between patients' baseline BMI (27.07 ± 3.22 kg/m^2) and final BMI (26.22 ± 3.36 kg/m^2; mean difference 0.86 ± 0.77 kg/m^2; $p < 0.001$)[95].

In another study in individuals with a moderate degree of hypothyroidism (mean TSH concentration 48–61 mIU/l), there was no weight change reported with restoration of euthyroidism[96]. Similarly, in a study in patients with hypothyroidism (mean TSH concentration 17 mIU/l, range 10.8–53 mIU/l), who were treated with levothyroxine, BMI did not change (25.3 versus 25.0 kg/m^2), despite the fact that TSH normalization was associated with restoration of cold-induced thermogenesis[97]. Treatment of hypothyroidism with levothyroxine in 25 patients with a mean TSH concentration of 18.7 mIU/l (95% CI 10.3–26 mIU/l) did not result in a statistically significant weight loss at 1 year. The mean weight loss in these patients was 0.6 kg (95% CI −2.2 to +1.1 kg)[98]. Another study of levothyroxine treatment in patients with subclinical hypothyroidism resulted in normalization of TSH from 8 mIU/l to 3.4 mIU/l, but was not associated with reduction in percentage lean body mass or BMI[99]. Patients with treated hypothyroidism, especially those with autoimmune thyroid disease, report more inability to exercise and more exercise intolerance than control individuals without hypothyroidism, which could contribute to weight loss difficulties, even once euthyroidism has been restored[100].

The fact that weight loss with treatment of hypothyroidism does not reach the anticipated pre-hypothyroidism baseline could indicate that, once a higher weight has been established, the body defends this weight as the new set point. This defence could involve mechanisms that have been invoked in the thrifty phenotype theory, in which there is hard wiring to allow potentially protective weight gain[101]. Other

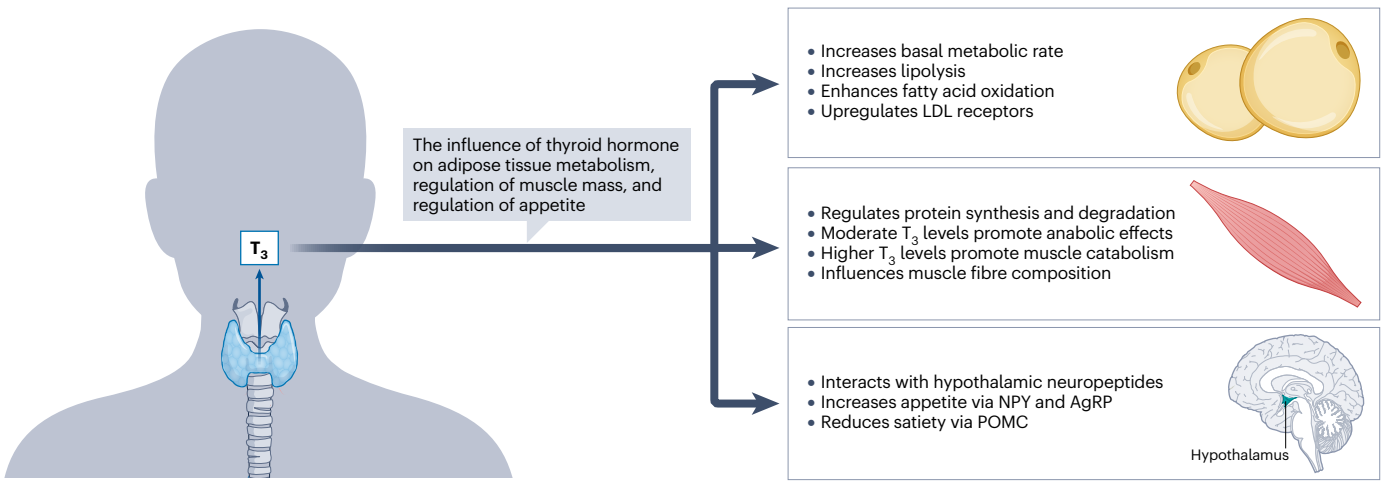

Fig. 3 | The influence of thyroid hormone on adipose tissue metabolism, regulation of muscle mass and regulation of appetite. Triiodothyronine (T_3) promotes adipose tissue metabolism, increases protein catabolism when T_3 levels rise above normal, and interacts with other hypothalamic neuropeptides to stimulate appetite and reduce satiety. AgRP, agouti-related protein; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

Table 1 | Weight changes with development of hypothyroidism and hyperthyroidism and their treatments

Thyroid disorder	At diagnosis[a]	With treatment	Comments
Subclinical hypothyroidism	Mild to no weight gain or increase in BMI	Mild weight loss or BMI decrease	–
Newly diagnosed overt hypothyroidism	Mild to moderate weight gain or increase in BMI	Moderate to no weight loss or decrease in BMI	Weight loss due to decreased weight of the lean body compartment
Rapid onset hypothyroidism	Mild weight gain	Mostly reversion to previous weight	Future weight gain if previous weight is not achieved when euthyroidism achieved
Subclinical hyperthyroidism	Mild to no weight loss or decrease in BMI	No change or return to baseline weight and BMI	With treatment, weight and BMI can overshoot from baseline
Overt hyperthyroidism	Moderate to significant weight loss	Return to at least baseline weight and BMI; however, generally weight overshoots Increase in both lean mass and fat mass	The degree of weight and BMI gain is affected by the modality used to treat hyperthyroidism. Weight gain is greater with definitive therapies

[a]Weight changes of <5% could be considered mild, whereas changes of 5–10% could be considered modest, and weight changes of >10% are probably clinically significant.

theories exist regarding set points promoting lipid storage, in which leptin probably has an important role[102]. One small study suggested that the metabolic response to a carbohydrate load was not fully normalized by levothyroxine therapy for hypothyroidism[103]. Similarly, levothyroxine treatment to restore a normal TSH concentration was associated with a lower resting energy expenditure than in a healthy control group[104]. Furthermore, three different TSH concentration targets among the patients being treated for hypothyroidism did not alter resting energy expenditure between the groups[105]. Interestingly, combination therapy with both levothyroxine and liothyronine did not assist with weight loss during treatment of hypothyroidism, despite patients' hope that it would do so[106]. Only two studies of combination therapy have demonstrated achievement of weight loss. One was a study in which levothyroxine and liothyronine were administered at a ratio of 5:1, which exceeds the physiological ratio of 14:1 (ref. 107). Another was the first of two studies investigating the use of desiccated thyroid extract[108], with the weight loss not being replicated in a second study by the same authors[109]. The most recent of the randomized controlled trials of combination therapy published in 2025 confirmed the findings of previous studies, that weight loss is not achieved with such treatment[110]. However, of note, monotherapy with liothyronine is associated with a modest weight loss of 3%[111,112].

Weight loss accompanying hyperthyroidism

Both subclinical and overt hyperthyroidism can be accompanied by weight loss[113] (Table 1). Subclinical hyperthyroidism, in which TSH levels are low but thyroid hormone levels remain normal, is generally accompanied by no weight change or mild to moderate weight loss. Overt hyperthyroidism, characterized by low levels of TSH and elevated thyroid hormone concentrations, is most commonly accompanied by substantial weight loss[114–117]. This weight loss is thought to include loss of fat mass, muscle mass and bone mass. Whether weight loss occurs and the degree of weight loss can vary greatly, probably based on the complexity of individual responses to the elevated thyroid hormone levels, and possibly due to the degree of T_3 thyrotoxicosis. The extent of weight loss in each patient can depend on the balance of the effects of thyroid hormone on basal metabolic rate, lipid metabolism, activity level, appetite and food preferences, and the effect on the gastrointestinal system with respect to the occurrence of hyperdefaecation and diarrhoea.

Appetite changes with hyperthyroidism

Development of hyperthyroidism is associated with an increased appetite[118]. One of the many factors that is thought to affect the magnitude of weight loss after development of hyperthyroidism is the degree of appetite stimulation. Ghrelin levels increase as patients with Graves disease are treated for their hyperthyroidism, which could be one of the factors involved in modulating hunger and satiety signals[119]. Some individuals with hyperthyroidism might not lose weight[114,120], perhaps due to the co-existent appetite stimulation. Altered food preferences can also be seen following development of hyperthyroidism[121]. In one study this change in food preference manifested as increased consumption of carbohydrates, but not protein or fat[121]. These changes in food preferences could potentially help protect against severe weight loss.

Weight changes with treatment of hyperthyroidism

There is a compelling literature demonstrating that there are weight gain and other alterations in body composition parameters after treatment of hyperthyroidism[120] (Table 1). Furthermore, many studies suggest a rebound effect, such that weight after treatment is higher than the weight believed to be present prior to the development of hyperthyroidism. Generally, patients experience greater weight gain following treatment of hyperthyroidism with definitive treatments such as thyroidectomy and radioactive iodine ablation than with the use of antithyroidal agents[122,123]. This finding also extends to the subset of patients with obesity at the time their hyperthyroidism was diagnosed[114]. However, many other factors can affect the amount of weight gain, including whether there is an intervening period of iatrogenic hypothyroidism after therapy is started and before thyroid hormone therapy is initiated[123,124]. As an example of the weight gain that occurs following treatment of hyperthyroidism, in a study in 17 patients who received an unspecified treatment for hyperthyroidism, the mean weight of the patients increased from 65.5 ± 11.6 kg to 68.4 ± 12.8 kg (increase 2.9 ± 3.0 kg; $p = 0.001$) following restoration of euthyroidism. The mean BMI of these patients also increased upon restoration of euthyroidism, from an initial mean BMI of 26.4 ± 4.4 kg/m^2 to a post-treatment BMI of 27.6 ± 5 kg/m^2 (mean increase 1.2 ± 1.2 kg/m^2; $p = 0.001$)[95]. Weight gain has also been documented in paediatric patients with Graves disease[125]. With respect to treatment of subclinical hyperthyroidism, BMI has been found to increase in individuals whose initial TSH values were less than 0.1 mIU/l, but not in those whose initial TSH values were in the 0.1–0.39 mIU/l range[126].

Weight changes with specific therapies for hyperthyroidism

Thyroidectomy and radioactive iodine treatment are considered definitive therapy for Graves disease, in that the hyperthyroidism is fully reversed and most patients ultimately need levothyroxine treatment for

the resultant hypothyroidism. In one study in 160 patients with hyperthyroidism, who mostly had Graves disease and were primarily treated with radioactive iodine, the median weight gain after therapy was 5.0 kg at 6 months and 9.0 kg at 12 months, with stabilization at 12 kg after 24 months[122]. A study in 65 patients with hyperthyroidism compared the weight gain at 1 year after each of three therapies for hyperthyroidism. The mean weight gains were 5.4 kg (95% CI 3.6–7.2 kg) following carbimazole treatment, 6.3 kg (95% CI 3.4–9.2 kg) following thyroidectomy, and 7.4 kg (95% CI 5.2–9.6 kg) following radioactive iodine treatment. There were no statistically significant differences in weight gain between treatment groups but, in each of the three groups, the weight gains from baseline to 1 year after treatment initiation were statistically significant ($p < 0.001$)[98]. By contrast, in a study in 162 patients treated for hyperthyroidism, patients treated with thyroidectomy gained more weight than those treated with thionamides or radioactive iodine (10.27 ± 2.56 kg in the thyroidectomy group; $p = 0.007$ for compared with the other two groups)[123]. In the entire group of patients in this study undergoing treatment of any type, the weight gain at one year was 3.95 ± 0.40 kg and 9.91 ± 1.62 kg at 4 years. Any period of hypothyroidism was also associated with substantially more weight gain (Fig. 4).

In a study in which hyperthyroid patients received surgery, radioactive iodine or methimazole, those in whom euthyroidism was not restored following therapy and who required levothyroxine treatment for hypothyroidism gained more weight (10.1–10.4 kg) than those in whom euthyroidism was restored by hyperthyroidism therapy (3.9–4.1 kg)[127]. In another study in patients who received antithyroidal medication, surgery or radioactive iodine, patients gained weight after treatment, but additionally women, those with a higher pretreatment BMI and those who received definitive therapy with surgery or radioactive iodine gained more weight[114]. A further study confirming these concerns found that weight gain was of a greater magnitude with radioactive iodine treatment than with antithyroid agents, and was also associated with any period of high TSH levels and the need for thyroid hormone replacement. The predicted overall weight gain in this study was 1.8 kg[124] (Fig. 4).

Anthropometric and metabolic changes with therapy for hyperthyroidism

Interestingly, in a group of 75 patients treated for hyperthyroidism with radioactive iodine therapy, the increase in BMI at 5 years was mostly attributable to an increase in lean body mass of 7.2 kg ($p = 0.0004$)[128]. However, increases in fat mass also occur with hyperthyroidism treatment, as demonstrated, for example, in another study[129]. In a study in 50 patients with Graves disease, anthropometric indices were measured at baseline and then at 6 and 12 months after treatment with methimazole. Body weight at baseline was 59.02 ± 11.11 kg and increased to 64.29 ± 9.70 kg at 6 months, and then to 65.78 ± 9.51 kg at 12 months ($p < 0.001$)[129]. There were similar changes in BMI, which was 22.44 ± 3.12 kg/m^2 at baseline, 24.53 ± 3.09 kg/m^2 at 6 months and 25.08 ± 2.78 kg/m^2 at 12 months. There were also statistically significant increases in visceral and subcutaneous fat area at 6 months and at 12 months.

In another study in 35 patients with hyperthyroidism treated with carbimazole, on restoration of euthyroidism, weight had increased from 51.15 ± 8.50 kg to 55.74 ± 8.74 kg ($p < 0.001$), accompanied by significant increases in lean body mass and fat mass ($p < 0.001$). The patients also showed a decrease in insulin resistance as measured by HOMA-IR from a median of 1.35 (interquartile range (IQR) 1.02–1.72) to a median of 0.73 (IQR 0.52–0.93; $p < 0.001$), and a decrease in leptin levels from a median of 17 ng/ml (IQR 7–36 ng/ml) to a median of 11 ng/ml (IQR 4.6–28 ng/ml; $p = 0.03$)[130]. These data could suggest that, despite causing weight loss, hyperthyroidism is associated with insulin resistance. Ghrelin levels have been reported to be reduced in patients with hyperthyroidism and to return to higher levels similar to those in control individuals after treatment with antithyroidal agents[131]. In a 2016 Chinese study in 24 women with Graves disease, restoration of euthyroidism following treatment with thionamides resulted in a significant increases in body weight (52.6 ± 9.0 kg to 55.3 ± 9.4 kg; $p < 0.001$) and fat mass (14.3 ± 6.9 kg to 16.8 ± 6.5 kg; $p = 0.005$)[132]. These changes were accompanied by a decrease in resting energy expenditure. In another study in 20 patients with Graves disease, medical therapy resulted in significant decreases in resting energy expenditure, and concomitant increases in body weight, muscle mass and lean body mass at 1, 3 and 6 months after therapy initiation[133], and fat mass at 1 and 3 months.

In a small group of nine patients with hyperthyroidism treated with surgery, radioactive iodine or antithyroid drugs, weight, body composition and tissue areas were documented at 3 and 12 months after restoration of euthyroidism[117]. Body weight had increased at both time points, accompanied by decreases in basal metabolic rate and energy intake. Body adipose tissue area had increased at 12 months, with increases in both subcutaneous and intraperitoneal adipose tissue area, whereas fat-free mass had increased at both 3 and 12 months. These findings led the authors to suggest that replenishment of skeletal muscle was prioritized with resolution of hyperthyroidism. Another study in patients with Graves disease treated with thyroidectomy also suggested that skeletal muscle mass increases with normalization of thyroid function[134]. In another study, treatment of hyperthyroidism was associated with decreased resting energy expenditure but no change in cold-induced thermogenesis[135].

Although it is reassuring that muscle mass is increased as a hallmark of the recovery from hyperthyroidism, the gains in fat mass are of concern. Taken together, these studies suggest the importance of patient education, avoidance of iatrogenic hypothyroidism and other lifestyle measures to avoid weight gain above pretreatment baseline values and then continued weight gain following initial therapy for hyperthyroidism[124].

Thyroid hormone as a weight loss drug

Thyroid hormone has an unconvincing track record as a weight loss drug[136]. This finding is true regardless of whether thyroid hormone is used in individuals who do not have a diagnosis of hypothyroidism,

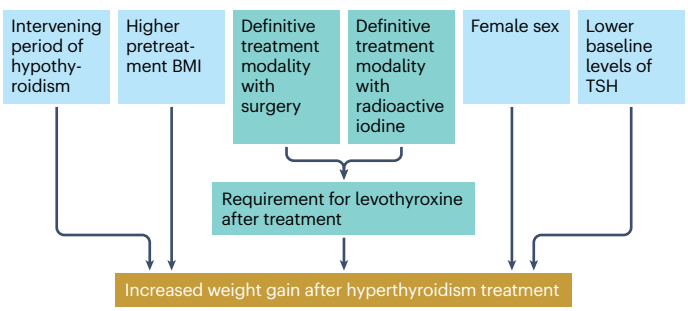

Fig. 4 | Hyperthyroidism treatment: factors causing weight gain following treatment. Each of these factors can potentially contribute to a greater weight once euthyroidism has been restored after treatment for hyperthyroidism. Among the most important factors seem to be the definitive therapies of surgery and radioactive iodine along with the need for levothyroxine initiation after hyperthyroidism treatment. TSH, thyroid-stimulating hormone.

or whether iatrogenic hyperthyroidism is achieved in those who are being treated for hypothyroidism. An example of lack of effectiveness is weight gain, rather than weight loss, in patients with thyroid cancer treated with TSH-suppressive doses of levothyroxine[31]. Despite the lack of evidence to support the use of thyroid hormone for weight loss purposes, there is still a belief among physicians that it has potential utility for this purpose[137]. Doses of thyroid hormone that actually are associated with weight loss are often accompanied by concerning adverse effects of thyrotoxicosis such as cardiac arrhythmias[138].

There has been interest in selective thyromimetic agents, which act on the thyroid hormone receptor. These drugs could potentially be harnessed for their positive effects of lowering body weight and improving metabolic dysfunction via their hepatic action, without detrimental effects on the cardiac and skeletal systems[7,139,140]. However, historically one of these agents, 3,5-diiodothyropropionic acid, despite achieving weight loss and reduced levels of LDL cholesterol, was also associated with adverse effects on the skeleton[141] and did not show promise when tested for potential cardiac benefits[142]. In a randomized controlled trial evaluating the effect of the thyromimetic agent eprotirome on LDL cholesterol levels in patients with statin-treated hypercholesterolaemia, eprotirome lowered LDL cholesterol levels without any effect on weight[143]. A phase III trial of eprotirome for the treatment of familial hypercholesterolaemia was halted because of an increase in levels of liver enzymes observed in trial participants, and a report of cartilage damage in animal studies[144]. More recently, resmetirom has been tested as a potential treatment for metabolic dysfunction-associated steatotic liver disease (MASLD)[145] and for its lipid-lowering capabilities. Not only does hypothyroidism increase the risk of MASLD via a decreased metabolic rate, lipid accumulation and weight gain[146], but MASLD-associated metabolic disturbances might also impair thyroid function. Resmetirom improves lipid profile and liver fibrosis[147] and is FDA-approved for such uses[148,149]. However, it has no effect on body weight[147], in contrast to other agents which seem to improve metabolic dysfunction via an effect on weight[150,151]. Other thyromimetic agents are currently under investigation.

Conclusions

The importance of this Review is the demonstration that the relationship between thyroid hormones and weight and body composition is complex and intertwined with many other control mechanisms. The profound and far-reaching effects of thyroid disease on body weight and body composition more than justify the classification of thyroid diseases as non-communicable diseases with a major public health effect on obesity, metabolic disease and cardiovascular disease[152].

Although the development of hypothyroidism is associated with weight gain and the development of hyperthyroidism with weight loss, the trend that is most evident after treatment of these diseases is one of weight gain over time. Development of hypothyroidism is generally accompanied by a mild to modest weight gain, but reversal of hypothyroidism is not universally associated with a reduction in weight. Hyperthyroidism, however, is commonly associated with weight loss, with decreases in adipose tissue (fat) mass, muscle mass and bone mass. As treatment to lower thyroid hormone levels is initiated, the change from hyperthyroidism to euthyroidism is accompanied by an increase in adipose tissue mass, muscle mass and bone mass. However, the resolution of hyperthyroidism typically is associated with a net increase in body weight and BMI that appear to rebound substantially above their hyperthyroid baselines. Thus, although thyroid dysfunction and its treatment appear to be intimately linked to inexorable weight gain, manipulation of the thyroid axis does not appear to hold promise as a means of limiting or reversing weight gain. Other hormones such as leptin, ghrelin and glucagon-like peptide agonists, combined with neuropeptides such as those in the melanocortin pathways, might have more substantial roles in weight regulation. Owing to the co-occurrence of thyroid disease and weight gain, it appears that restoring euthyroidism and optimal management of thyroid diseases has a major role in weight management. However, other approaches including lifestyle modification, efficacious weight loss medications and bariatric surgery[34] might also need to be used to reduce the harmful effects of obesity on health and to improve quality of life.

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