

Thyroid Function and Obesity

Peter Laurberg^a Nils Knudsen^b Stig Andersen^a Allan Carlé^a
Inge Bülow Pedersen^a Jesper Karmisholt^a

^aDepartment of Endocrinology, Aalborg Hospital, Aalborg, and ^bMedical Clinic I, Bispebjerg Hospital, Copenhagen, Denmark

Key Words

Obesity · Weight control · Thyroid function · Hypothyroidism · Hyperthyroidism · Graves' disease · Liothyronine therapy · Levothyroxine therapy

Abstract

Important interaction exists between thyroid function, weight control, and obesity. Several mechanisms seem to be involved, and in studies of groups of people the pattern of thyroid function tests depends on the balance of obesity and underlying thyroid disease in the cohort studied. Obese people with a normal thyroid gland tend to have activation of the hypothalamic-pituitary-thyroid axis with higher serum TSH and thyroid hormones in serum. On the other hand, small differences in thyroid function are associated with up to 5 kg difference in body weight. The weight loss after therapy of overt hypothyroidism is caused by excretion of water bound in tissues (myxoedema). Many patients treated for hyperthyroidism experience a gain of more weight than they lost during the active phase of the disease. The mechanism for this excessive weight gain has not been fully elucidated. New studies on the relation between L-T₃ therapy and weight control are discussed. The interaction between weight control and therapy of thyroid disease is important to many patients and it should be studied in more detail.

Copyright © 2012 European Thyroid Association
Published by S. Karger AG, Basel

The obesity epidemic is a major threat to health in most countries [1], although the increase in the prevalence of obesity seems to have stopped in some countries according to recent investigations [2, 3]. The international focus on obesity has led to a steep increase in the number of studies dealing with possible interactions between obesity and other diseases as well as the relation between obesity and physiology and pathophysiology of the various organs and tissues of the body.

In thyroidology, there have been studies of weight and thyroid cancer showing a borderline positive association between the risk of cancer and body mass index (BMI) [4] similar to the association demonstrated for a number of other types of cancer [5], and maybe there is a more aggressive behaviour of thyroid cancer in obese people [6]. On the other hand, it has been suggested that obesity may protect against thyroid nodules [7].

However, the most straightforward scientific and practical clinical question in the thyroid and obesity field is the potential association between thyroid function and weight control, and the issue has been addressed in many studies. The present review discusses data suggesting that even rather small differences in thyroid function within a population are associated with differences in BMI and with the prevalence of obesity. The association is complex, because overeating with accumulation of fat and the development of obesity seems to activate the hypothy-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 European Thyroid Association
Published by S. Karger AG, Basel
2235-0640/12/0013-0159\$38.00/0
Accessible online at:
www.karger.com/etj

Peter Laurberg, MD
Department of Endocrinology and Medicine
Aalborg Hospital, Aalborg University
DK-9000 Aalborg (Denmark)
E-Mail peter.laurberg@rn.dk

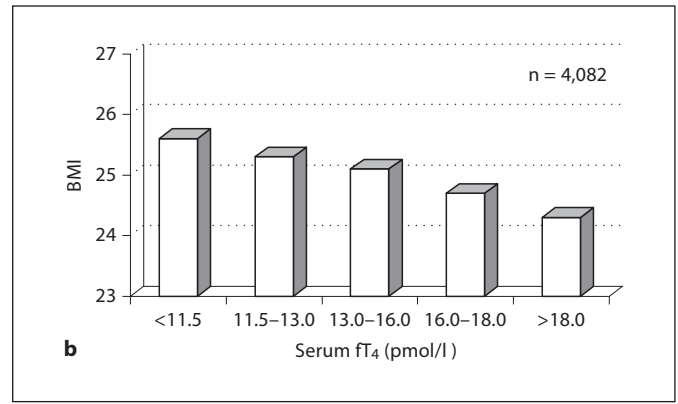
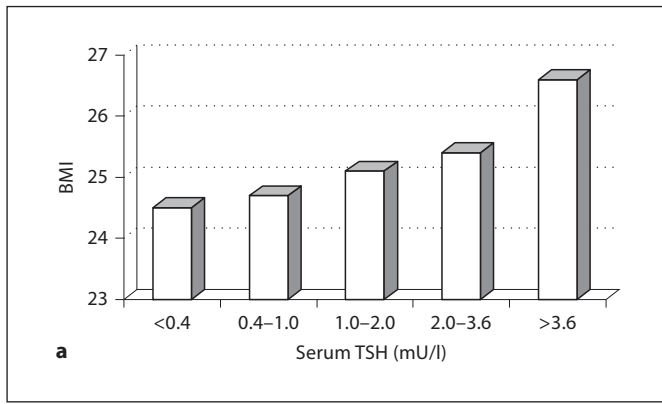


Fig. 1. The association between BMI and serum TSH (a) or fT₄ (b) in 4,082 participants of the DanThyr 1997–1998 population cohort [13, 14]. Participants with previous (n = 151) or present (n = 77) treatment for thyroid disease, with overt hypothyroidism (TSH >3.6 and fT₄ <9.8 pmol/l) (n = 16) or overt hyperthyroidism (TSH <0.4 mU/l and fT₄ >20.4 pmol/l or fT₃ >6.9 pmol/l) (n = 26),

pregnant women (n = 60), women with a pregnancy within 12 months (n = 78) and participants with missing values (n = 159) had been excluded. In calculations, adjustments were made for age, sex, and tobacco smoking in multivariate models. $p < 0.001$ for TSH and BMI, and for fT₄ and BMI. Data from Knudsen et al. [14].

lamic-pituitary-thyroid axis leading to changes in thyroid function tests overlapping with the abnormalities seen in primary thyroid disease.

A special area of practical concern is the common complaint from patients treated for thyroid disease that therapy has led to ‘irreversible’ gain of weight – or that the weight increase occurring in association with the disease did not reverse upon therapy.

Finally, a few comments will be added on new studies that may add a new role for L-T₃ replacement in control of body weight independent of energy expenditure.

Inverse Correlation between Thyroid Function and Body Weight in the Population

Resting energy expenditure (REE), which comprises around 60% of total energy expenditure in adult man [8], is high in overt hyperthyroidism and low in overt hypothyroidism [9]. However, measurable differences in REE have been described also with smaller variation in thyroid function. al-Adsani et al. [10] found changes in REE of 7–8% when the dose of L-T₄ to hypothyroid patients was modified to change serum TSH by a factor of 10, corresponding to the difference from the lower to the upper limit of the laboratory reference range for serum TSH (0.4–4.0 mU/l). Based on data from many studies, Eisenberg and Distefano [11] developed a model on the association between the absorbed doses of L-T₄ given as sup-

plement to a thyroidectomized patient and serum TSH. In this model, a change in serum TSH from 4.0 to 0.4 mU/l corresponds to a quite substantial (approx. 40%) increase in the absorbed dose of L-T₄.

A 7–8% difference in REE corresponds to a daily difference in metabolism of around 10 g of lipid. Thus, assuming unaltered energy intake and energy expenditure from exercise as well as unaltered food intake and thermoregulation, differences in thyroid function tests within the normal laboratory range might theoretically be associated with several kilogram loss or gain of weight per year.

Notably, results of a thyroid function test being within the ‘normal’ laboratory reference range may not be normal for an individual. Individual variation in thyroid function tests is considerably narrower than the broad laboratory reference range, and around 50% of this ‘normal’ range is not normal for the individual person [12].

Figure 1 illustrates the association between thyroid function tests and BMI in the Danish DanThyr 1997–1998 population cohort [13]. Small differences in thyroid function over the whole range of test results were associated with differences in BMI when studying this population. With higher levels of TSH, even within the laboratory reference range, BMI was higher, also after adjusting for many relevant confounding factors [14]. Moreover, the opposite association was observed between serum fT₄ and BMI, whereas no association was observed between fT₃ in serum and BMI [14]. Participants were selected to

have fT_4 and fT_3 within laboratory reference ranges. In the group of participants with serum TSH >3.6 mU/l, the odds ratio for obesity with BMI >30 was 2.1 compared with the group with serum TSH of 1–1.99 mU/l. The estimated difference in weight between an average woman with a serum TSH of 0.28 mU/l and one with TSH of 4.5 mU/l was 5.5 kg, and a significant association was observed between retrospectively recorded weight gain over the last 5 years and serum TSH [14].

Higher serum TSH with lower fT_4 and less affected fT_3 is the typical picture of low-degree thyroid failure. The patterns observed in the DanThyr study suggest that the association between thyroid function variables and BMI is primarily driven by differences in thyroid hormone-dependent energy expenditure. A number of other studies have observed a negative association between serum fT_4 and BMI as well as markers of the metabolic syndrome [15–18].

However, as discussed below, other studies of the association between body weight and thyroid function parameters have come up with different main conclusions based on patterns that are to some degree overlapping with those shown above, but considerably different in some details.

Obesity and Pituitary-Thyroid Activation

Thyroid function tests in people who are morbidly obese may differ from those in a comparable group of lean people, with a serum TSH that is higher in the obese, but with no tendency of thyroid hormones in serum to be low in the obese. On the contrary, fT_3 and also in some studies fT_4 in serum tends to be higher in obese people [19–21]. The pattern has been most clearly observed in overweight children and adolescents (fig. 2) [22], where the frequency of underlying thyroid disease in the population is much lower than in adults. Characteristically, weight reduction by change of lifestyle and diet [22, 23] or following gastric banding [24] or gastric bypass surgery [25] tends to ameliorate the small aberration in thyroid function tests in the majority of obese patients.

Thyroid hormones are important regulators of metabolism, and conversely metabolism modifies the system of hypothalamic-pituitary-thyroid-peripheral activation/inactivation effect of thyroid hormones. It is well known that such interaction may have effects on the thyroid function test used to evaluate patients for the presence of thyroid disease [26].

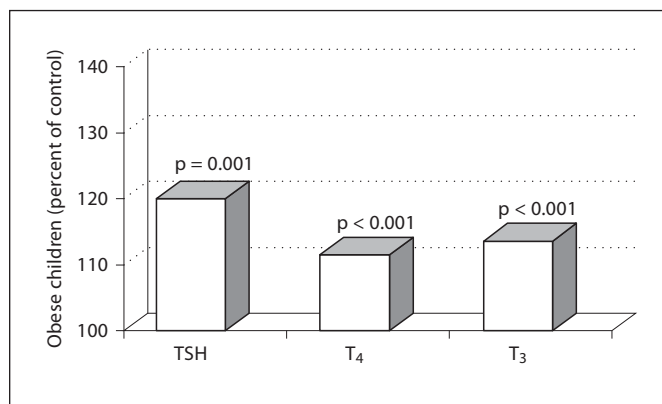


Fig. 2. Serum TSH, T_4 and T_3 in a group of obese children ($n = 118$), median age 11.5 years, BMI Z-score $+3.2$, in percent of values in a group of lean children ($n = 107$), with median age 11.3 years, median BMI Z-score -0.5 . Serum TSH, T_4 and T_3 were statistically significantly higher in the obese children. In the group of obese children TSH, T_4 and T_3 correlated significantly with BMI ($p \leq 0.002$). Data from Reinehr and Andler [22].

The exact mechanisms involved in the energy intake-dependent variations in the thyroid system are only partly known but probably quite complex [27]. Signs of low activity of the thyroid system are not only found during short-term fasting, but characteristically also in chronic caloric deprivation such as anorexia nervosa [28]. On the other hand, morbid obesity leads to signs of an elevated activity with slightly elevated TSH, and free thyroid hormones in serum (fig. 2). In the complex system of hypothalamic regulation, the factor favoured by most authors when discussing the cause for activation of the thyroid in overweight is activation of hypothalamic centres by leptin released from adipocytes in fat tissue [19, 29–31]. There is a complex interaction between the thyroid hormones and adipose tissue where TSH and thyroid hormones may participate in adipocyte differentiation [32] and lipolysis regulation [33], whereas various adipocyte cytokines may interact with the hypothalamic-pituitary-thyroid axis [34–36].

Compiling the Effects of Thyroid Function Aberration on Energy Balance with Those of Obesity-Induced Thyroid Activation

Obesity is now very common in most populations with 32.2% of adult USA citizens being obese in the 2003–2004 National Health and Nutrition Examination Survey

(NHANES) [37], and health care providers are seeing many more obese children and adults now than previously.

In a population with few thyroid abnormalities, but much obesity, it is to be expected that the predominant pattern of association between thyroid function tests and BMI will be activation of the thyroid axis with a positive association between body weight and elevated TSH and thyroid hormones in serum, as illustrated in the study of obese and lean children (fig. 2). On the other hand, in a study such as DanThyr with less obesity, but a more common occurrence of small thyroid function abnormalities, the findings will be those of a negative association between BMI and thyroid function as shown in figure 1.

In many population studies, only the positive association between serum TSH and BMI has been reported and thyroid hormones in serum were not measured [38–40]. From this, it is not possible to judge if the main factor involved is a change in body weight secondary to a change in thyroid function or an increase in TSH caused by obesity. Likely, both mechanisms would to some degree be involved in all studies.

A good example is a recent study of the 2003–2004 NHANES cohort [41] where serum TSH correlated positively with BMI as in many other studies. In addition, a significant positive association was observed between serum fT_3 and BMI pointing to an important role of thyroid axis activation by obesity in this cohort with >30% obese people [37]. On the other hand, serum fT_4 correlated negatively with BMI, which may suggest an additional role of higher BMI with a lower thyroid function. In the 1997–1998 DanThyr cohort illustrated in figure 1, the prevalence of obesity was considerably lower (12.8%) [3] than in the USA study.

A similar suggestion for the differences in results between studies was given in an Italian report investigating morbidly obese patients [20]. The authors found little evidence for thyroid failure being the cause for mildly elevated TSH in their group of severely obese patients.

Other methodological differences between studies might be involved. For example, the absolute differences in results of thyroid function tests between groups having different BMI are relatively small, around the magnitude of day-to-day variation in assays. In some studies, it is not indicated if serum samples from different groups of participants (e.g. obese patients and lean controls) were analysed in random order in the same batch. If not, this may have induced bias. Moreover, if samples have been kept at room temperature for more than short periods, free fatty

acids from lipolysis may alter the results of free thyroid hormone assays [26], the magnitude being dependent on concentration of lipids in blood.

Therapy of Obese Patients with Elevated Serum TSH?

As discussed above, as well as in several recent reviews [19, 29, 30], obesity tends to increase serum TSH and nothing suggests that an isolated slightly elevated TSH in a morbidly obese person is more abnormal to the person than a low serum T_3 in a person with severe underweight. It is an adaptation and the appropriate therapy is adjustment of energy balance and body weight.

Patients should not be treated with thyroid hormone replacement unless there are other signs of thyroid disease. Therapy of obese patients with pharmacologic doses of thyroid hormones leading to hyperthyroidism might reduce their weight, but side effects of the hyperthyroidism may be severe, and currently there is no indication for such therapy [42].

Body Weight in Overt Hypothyroidism and Changes after Replacement Therapy

Because of the low metabolic rate, it is generally assumed that patients with longstanding overt hypothyroidism are overweight and clearly, body weight tends to increase during the development of severe hypothyroidism. In a recent case-control study of patients with newly diagnosed overt autoimmune hypothyroidism identified in a population study versus age-, gender- and inhabitan-
cy-matched euthyroid controls from the same background population, the patients weighed on average 7 kg more than the controls [43]. The main mechanism behind such increase in body weight seems not to be fat as might be anticipated, but an expanded water compartment.

Two studies have examined body composition using dual-energy X-ray absorptiometry (DXA) before and after L- T_4 replacement therapy of overtly hypothyroid patients [44, 45]. The main result was the same: the loss of weight after therapy is caused by a decrease in lean body mass and not in fat mass, as illustrated in figure 3. Severe hypothyroidism leads to accumulation in skin and other tissues of water-binding glycosaminoglycans, which is a main factor in giving the myxoedematous character of hypothyroid patients. With therapy, tissue composition

normalizes and the excess water is excreted. Thus, during the initial phase of therapy there may be excessive diuresis [46].

The notion that overt hypothyroidism does not cause morbid overweight and that most, if not all, of the gain in weight is caused by retention of water in tissues was already brought forward by Plummer [47] in 1940. Plummer published a number of patient photos illustrating the difference in myxoedematous appearance with excess body water before and after therapy (fig. 4). Based on the weights of the 200 hypothyroid patients (with an average basal metabolic rate of -32.3%) whom Plummer had seen, he judged that the average gain of weight in untreated patients was 4.6 kg, and that this was all water.

An interesting question is, if the difference in body weight observed with relatively small differences in thyroid function in studies of populations (fig. 1) might to some degree be caused by differences in body water content or if it is entirely caused by a difference in the amount of body fat.

When discussing weight gain in patients with hypothyroidism, it is of clinical importance to remember the large increase in risk of developing overt autoimmune hypothyroidism during the first 2 years after stop of tobacco smoking. Weight gain is common after smoking cessation [48]. In a 10-year study, weight gain attributable to smoking cessation was on average 4–5 kg. [49]. However, any patient complaining of weight gain after quitting smoking should have thyroid function tested to exclude that this is caused by hypothyroidism, because there is a 6- to 7-fold increase in the risk of developing autoimmune hypothyroidism after quitting smoking [43].

Weight Changes after Therapy of Patients with Hyperthyroidism

Hoogwerf and Nuttall [50] studied a group of 87 patients treated for hyperthyroidism with radioiodine and/or antithyroid drugs and who had been followed for a mean of 7.5 years after therapy. The setting was a USA military veteran clinic and 84% of the patients were men. Most of the patients had had their body weight recorded already before they became hyperthyroid, and body weight just before and during follow-up after therapy was systematically recorded. At the time of treatment, body weight was 16% below the baseline recorded before the disease, and only 1 patient had no loss of weight in association with the disease. After therapy, weight started to increase and at 24 months after initial therapy patients

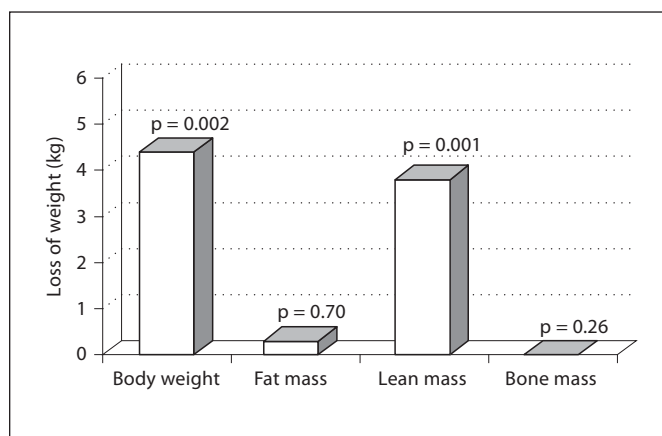


Fig. 3. Mean loss of total body weight, fat mass, lean mass, and bone mass measured by DXA in 12 severely hypothyroid patients (mean age = 55 years, serum TSH = 102 mU/l, fT_4 = 4.5 pmol/l, BMI = 28.5) over 1 year of L-T₄ replacement therapy. After 1 year, TSH was 2.2 mU/l, fT_4 was 18 pmol/l and BMI was 26.8. Data from Karmisholt et al. [45].

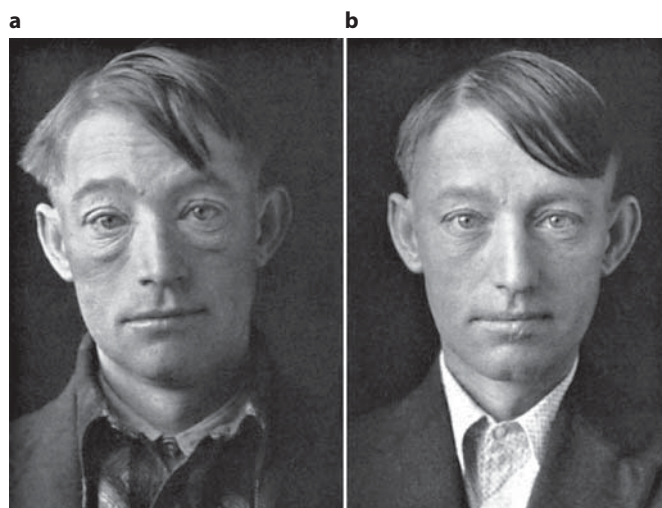


Fig. 4. Photo of a 36-year-old man before (a) and 41 days after start of therapy with thyroid extract (b). Basal metabolic rate was -38% before and -1% after therapy. Body weight decreased from 70.5 to 65.9 kg during the 41 days of therapy. Note the disappearance of facial oedema during therapy. The case and photo was presented by Dr. William A. Plummer, The Mayo Clinic, Rochester, Minn., USA, at the 1940 meeting of the American Association for the Study of Goiter (now the American Thyroid Association) [47]. We are grateful to Dr. Jeffrey R. Garber, Endocrine Division, Harvard Vanguard Medical Associates, Boston, Mass., USA, for drawing our attention to this publication.

had on average the same weight as before they became hyperthyroid. Body weight continued to increase slightly and 8 years after therapy it was on average 1.7 kg higher.

In general, this study, which was published in 1984, suggests that there are few problems with weight gain after therapy of hyperthyroidism, and the authors concluded that in the absence of significant metabolic derangement, body weight is regulated within narrow limits over many years. The conclusion followed the concept of a set point for body weight regulation proposed by Nisbett in 1972 [51].

The idea of 'body weight autoregulation' has been severely challenged by the current obesity epidemic and a number of studies have subsequently indicated that a considerable proportion of patients experience excessive weight gain after therapy of hyperthyroidism [52–59]. In a questionnaire-based follow-up study of 235 Swedish patients previously treated for hyperthyroidism, Berg et al. [54] found that weight gain was a problem in 79% of the individuals, and O'Malley et al. [55] found 69% of patients experiencing more weight gain than previous weight loss after therapy of hyperthyroidism.

de la Rosa et al. [60] reported that a considerable part of the initial weight gain after therapy of hyperthyroidism consisted of lean body mass. This is in accordance with a longitudinal study performed by Lönn et al. [61]. Based on serial investigations using DXA and CT scan they concluded that initial gain of weight after therapy of hyperthyroidism was mostly caused by an increase in muscle mass, whereas the continued gain in weight was caused by accumulation of fat. On the other hand, Zimmermann-Belsing et al. [62] found that increases in lean mass and fat mass measured by DXA were nearly parallel over 12 months after therapy of hyperthyroidism.

In another follow-up study, Dale et al. [56] found that pre-existing obesity, Graves' disease, prior weight loss, and development of hypothyroidism predicted excessive gain in weight. Similarly, Brunova et al. [57] found the main factors associated with weight gain to be the need for replacement therapy and poor control of thyroid function.

The exact reason for the excessive weight gain encountered by many patients after therapy of hyperthyroidism is not clear. Jansson et al. [53] hypothesized that hyperthyroidism may induce a long-lasting disturbance in the neurochemical regulation of appetite and weight. Common suggestions have been a psychological delay in adapting food intake to the fall in energy expenditure after therapy. Another suggested mechanism is low energy expenditure caused by overtreatment of hyperthyroidism with induction of hypothyroidism [63]. In a study on the

effect of dietary advice in patients being treated for hyperthyroidism, Alton and O'Malley [64] found that patients with no dietary advice gained 16% in weight during the period of normalisation of thyroid function from carbimazole therapy. The group advised by a dietician gained 9.8% ($p < 0.05$).

Triiodothyronine and Body Weight Regulation

An interesting speculation is on the role of T_3 in body weight regulation. T_3 has important effects in hypothalamic centres apart from the feedback effects on the pituitary-thyroid axis. A study performed in rats concluded that changes in energy balance in hyperthyroidism mostly occurred via T_3 regulation of lipid metabolism in the hypothalamus, leading via the sympathetic nervous system to induction of brown adipose tissue [65], and animals with profound circannual biological rhythms of food intake and reproduction show no cycles if hypothalamic T_3 content is kept stable [66]. Thus, the annual variations in food intake driven by changes in hours of daylight seem to be mediated by hypothalamic T_3 content. Moreover, in rats, direct T_3 stimulation of food intake via hypothalamic effects has been demonstrated [67]. However, when the same investigators performed an experiment in 11 healthy normal weight men, a short-term 45% increase in serum T_3 after oral intake of 10 μg L- T_3 did not affect subsequent food consumption [68].

A recent carefully controlled study may even suggest that T_3 has an appetite reducing effect in humans. Celi et al. [69] studied the metabolic effects of L- T_3 in hypothyroidism by performing a randomized double-blind crossover trial of full replacement with L- T_3 versus L- T_4 . Medication was split over 3 daily doses to avoid the large fluctuation in serum T_3 associated with once daily administration, and doses of L- T_3 and L- T_4 were carefully adjusted to give the same normal level of serum TSH. Each treatment period was 4–5 months. Quality of life, REE, insulin sensitivity and cardiovascular function were studied in detail, but with no difference between groups. However, L- T_3 therapy was associated with a significant weight loss of 2.1 kg compared with L- T_4 therapy, and also with significant reductions in serum low-density lipoprotein cholesterol and apolipoprotein B. The weight loss despite unaltered REE may suggest a decrease in food intake during L- T_3 therapy. On the other hand, the fall in serum cholesterol and a concomitant increase in serum sex-hormone-binding hormone suggest an effect on liver metabolism.

Interestingly, a randomized Dutch 15-week study on the effect of L-T₄ + L-T₃ combination therapy in two ratios versus L-T₄ alone for hypothyroidism [70] observed an L-T₃ dose-dependent decrease in body weight during the combined therapy. Furthermore, such an effect was statistically significant (although of small absolute magnitude) in a meta-analysis of studies evaluating L-T₄ + L-T₃ therapy [71].

A relatively more profound effect of L-T₃ versus L-T₄ on body weight even if TSH in serum is the same, may be one cause for the observed increase in weight in patients kept euthyroid with L-T₄ alone after total thyroidectomy [72] even if this is not a universal finding [73]. It may also be a mechanism involved in the excessive weight loss in Graves' disease where thyroidal T₃ production from T₄ is excessive [74] – and the subsequent excess in weight gain in patients who become hypothyroid and are replaced with L-T₄.

The effect of L-T₃ on body weight adds new fuel to the fire of discussion between experts who claim that pure L-T₄ replacement therapy of hypothyroidism is optimal, and the patients who insist that preparations with high T₃ content such as desiccated thyroid makes them feel healthier [75].

Clearly, more long-term intervention studies are needed to expand our knowledge on the association between body weight and different types of thyroid hormone replacement therapy.

Disclosure Statement

The authors declare no conflicts of interest.

References

- 1 Caballero B: The global epidemic of obesity: an overview. *Epidemiol Rev* 2007;29:1–5.
- 2 Aeberli I, Ammann RS, Knabenhans M, Molinari L, Zimmermann MB: Decrease in the prevalence of paediatric adiposity in Switzerland from 2002 to 2007. *Public Health Nutr* 2010;13:806–811.
- 3 Svendstrup M, Knudsen NK, Jørgensen T, Rasmussen LB, Ovesen L, Perrild H, Laurberg P: Stagnation in body mass index in Denmark from 1997/1998 to 2004/2005, but with geographical diversity. *Dan Med Bul* 2011;58:1–5.
- 4 Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, Tjønneland A, Halkjaer J, Lukanova A, Kaaks R, Bergmann MM, Boeing H, Trichopoulos A, Zylis D, Valanou E, Palli D, Agnoli C, Tumino R, Polidoro S, Mattiello A, Bas Bueno-de-Mesquita H, Peeters PH, Weiderpass E, Lund E, Skeie G, Rodríguez L, Travier N, Sánchez MJ, Amiano P, Huerta JM, Ardanaz E, Rasmuson T, Hallmans G, Almquist M, Manjer J, Tsilidis KK, Allen NE, Khaw KT, Wareham N, Byrnes G, Romieu I, Riboli E, Franceschi S: Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* 2012;131:E1004–E1014.
- 5 Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M: Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–578.
- 6 Kim HJ, Kim NK, Choi JH, Sohn SY, Kim SW, Jin SM, Jang HW, Suh S, Min YK, Chung JH, Kim SW: Associations between body mass index and clinico-pathological characteristics of papillary thyroid cancer. *Clin Endocrinol* 2012, E-pub ahead of print.
- 7 Cappelli C, Pirola I, Mittempergher F, De Martino E, Casella C, Agosti B, Nascimbeni R, Formenti A, Roei EA, Castellano M: Morbid obesity in women is associated to a lower prevalence of thyroid nodules. *Obes Surg* 2012;22:460–464.
- 8 Toth MJ: Energy expenditure in wasting diseases: current concepts and measurement techniques. *Curr Opin Clin Nutr Metab Care* 1999;2:445–451.
- 9 Kim B: Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid* 2008;18:141–144.
- 10 al-Adsani H, Hoffer LJ, Silva JE: Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab* 1997;82:1118–1125.
- 11 Eisenberg M, Distefano JJ: TSH-based protocol, tablet instability, and absorption effects on L-T₄ bioequivalence. *Thyroid* 2009;19:103–110.
- 12 Andersen S, Pedersen KM, Bruun NH, Laurberg P: Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab* 2002;87:1068–1072.
- 13 Laurberg P, Jørgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB, Rasmussen LB, Carlé A, Vejbjerg P: The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol* 2006;155:219–228.
- 14 Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, Jørgensen T: Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab* 2005;90:4019–4024.
- 15 Shon HS, Jung ED, Kim SH, Lee JH: Free T₄ is negatively correlated with body mass index in euthyroid women. *Korean J Int Med* 2008;23:53–57.
- 16 Makepeace, AE, Bremner AP, O'Leary P, Leedman PJ, Feddema P, Michelangeli V, Walsh JP: Significant inverse relationship between serum free T₄ concentration and body mass index in euthyroid subjects: differences between smokers and nonsmokers. *Clin Endocrinol* 2008;69:648–652.
- 17 Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C, Stamatelopoulos K: Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. *Eur J Endocrinol* 2009;161:459–465.
- 18 Garduño-García JJ, Alvirde-García U, López-Carrasco G, Mendoza MEP, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas A: TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *Eur J Endocrinol* 2010;163:273–278.

- 19 Reinehr T: Obesity and thyroid function. *Mol Cell Endocrinol* 2010;316:165–171.
- 20 Rotondi M, Leparati P, La Manna A, Pirali B, Mondello T, Fonte R, Magri F, Chiovato L: Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? *Eur J Endocrinol* 2009;160:403–408.
- 21 De Pergola G, Ciampolillo A, Paolotti S, Tretolot P, Giorgino R: Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. *Clin Endocrinol* 2007;67:265–269.
- 22 Reinehr T, Andler W: Thyroid hormones before and after weight loss in obesity. *Arch Dis Child* 2002;87:320–323.
- 23 Reinehr T, de Sousa G, Andler W: Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. *J Clin Endocrinol Metab* 2006;91:3088–3091.
- 24 Dall'Asta C, Paganelli M, Morabito A, Vedani P, Barbieri M, Paolisso G, Folli F, Pontiroli AE: Weight loss through gastric banding: effects on TSH and thyroid hormones in obese subjects with normal thyroid function. *Obesity* 2010;18:854–857.
- 25 Fazylov R, Soto E, Cohen S, Merola S: Laparoscopic Roux-en-Y gastric bypass surgery on morbidly obese patients with hypothyroidism. *Obes Surg* 2008;18:644–647.
- 26 Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, Livolsi VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry: Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003;13:3–126.
- 27 Lechan RM, Fekete C: Central mechanisms for thyroid hormone regulation. *Am J Psychiatry* 2006;163:1492.
- 28 Warren MP: Endocrine manifestations of eating disorders. *J Clin Endocrinol Metab* 2011;96:333–343.
- 29 Biondi B: Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab* 2010;95:3614–3617.
- 30 Rotondi M, Magri F, Chiovato L: Thyroid and obesity: not a one-way interaction. *J Clin Endocrinol Metab* 2011;96:344–346.
- 31 de Moura Souza A, Sichiari R: Association between serum TSH concentration within the normal range and adiposity. *Eur J Endocrinol* 2011;165:11–15.
- 32 Obregon MJ: Thyroid hormone and adipocyte differentiation. *Thyroid* 2008;18:185–195.
- 33 Endo T, Kobayashi T: Expression of functional TSH receptor in white adipose tissues of hyt/hyt mice induces lipolysis in vivo. *Am J Physiol Endocrinol Metab* 2012;302:1569–1575.
- 34 Feldt-Rasmussen U: Thyroid and leptin. *Thyroid* 2007;17:413–419.
- 35 Boelen A, Wiersinga WM, Fliers E: Fasting-induced changes in the hypothalamus-pituitary-thyroid axis. *Thyroid* 2008;18:123–129.
- 36 Sainsbury A, Zhang L: Role of the hypothalamus in the neuroendocrine regulation of body weight and composition during energy deficit. *Obes Rev* 2012;13:234–257.
- 37 Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW: Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab* 2009;94:1853–1878.
- 38 Nyren A, Jorde R, Sundsfjord J: Serum TSH is positively associated with BMI. *Int J Obes* 2006;30:100–105.
- 39 Fox CS, Pencina MJ, D'Agostino RB, Muraibito JM, Seely EW, Pearce EN, Vasan RS: Relations of thyroid function to body weight. *Arch Intern Med* 2008;168:587–592.
- 40 Svare A, Nilsen TIL, Bjoro T, Åsvold BO, Langhammer A: Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. *Clin Endocrinol* 2011;74:769–775.
- 41 Kitahara CM, Platz EA, Ladenson PW, Mondul AM, Menke A, Berrington de González A: Body fatness and markers of thyroid function among US men and women. *PloS One* 2012;7:1–6.
- 42 Kaptein EM, Beale E, Chan LS: Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab* 2009;94:3663–3675.
- 43 Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jørgensen T, Laurberg P: Smoking cessation is followed by a sharp but transient rise in the incidence of overt autoimmune hypothyroidism – A population-based case-control study. *Clin Endocrinol* 2012, E-pub ahead of print.
- 44 Sánchez A, Carretto H, Ulla MR, Capozza R: Body composition of patients with primary hypothyroidism evaluated by dual-energy X-ray absorptiometry and its changes after treatment with levo-thyroxine. *Endocrinologist* 2004;14:321–327.
- 45 Karmisholt J, Andersen S, Laurberg P: Weight loss after therapy of hypothyroidism is mainly caused by excretion of excess body water associated with myxoedema. *J Clin Endocrinol Metab* 2011;96:99–103.
- 46 Fenwick EH: The diuretic action of fresh thyroid juice. *BMJ* 1891;2:798–799.
- 47 Plummer WA: Body weight in spontaneous myxedema; in American Association for the Study of Goiter: Transactions of the American Association for the Study of Goiter. Rochester, Western Journal of Surgery, Obstetrics and Gynecology 1940, pp 88–98.
- 48 Parsons AC, Shraim M, Inglis J, Aveyard P, Hajek P: Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev* 2009;21:CD006219.
- 49 Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM: The influence of smoking cessation on the prevalence of overweight in the United States. *N Engl J Med* 1995;333:1165–1170.
- 50 Hoogwerf BJ, Nuttall FQ: Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. *Am J Med* 1984;76:963–970.
- 51 Nisbett RE: Hunger, obesity, and the ventromedial hypothalamus. *Psychol Rev* 1972;79:433–453.
- 52 Pears J, Jung RT, Gunn A: Long-term weight changes in treated hyperthyroid and hypothyroid patients. *Scott Med J* 1990;35:180–182.
- 53 Jansson S, Berg G, Lindsted G, Michanek A, Nyström E: Overweight – a common problem among women treated for hyperthyroidism. *Postgrad Med J* 1993;69:107–111.
- 54 Berg G, Michanek A, Holmberg E, Nyström E: Clinical outcome of radioiodine treatment of hyperthyroidism: a follow-up study. *J Intern Med* 1996;239:165–171.
- 55 O'Malley B, Hickey J, Nevens E: Thyroid dysfunction – weight problems and the psyche: the patients' perspective. *J Hum Nutr Diet* 2000;13:243–248.
- 56 Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA: Weight gain following treatment of hyperthyroidism. *Clin Endocrinol* 2001;55:233–239.
- 57 Brunova J, Bruna J, Joubert G, Koning M: Weight gain in patients after therapy for hyperthyroidism. *S Afr Med J* 2003;93:529–531.
- 58 Ariza MA, Loken WM, Pearce EN, Safer JD: Male sex, African American race or ethnicity, and triiodothyronine levels at diagnoses predict weight gain after antithyroid medication and radioiodine therapy for hyperthyroidism. *Endocr Pract* 2010;16:609–616.
- 59 van Veenendaal NR, Rivkees SA: Treatment of pediatric Graves' disease is associated with excessive weight gain. *J Clin Endocrinol Metab* 2011;96:3257–3263.
- 60 da la Rosa R, Hennessey JV, Tucci JR: A longitudinal study of changes in body mass index and total body composition after radioiodine treatment for thyrotoxicosis. *Thyroid* 1997;7:401–405.
- 61 Lönn L, Stenlöf K, Ottosson M, Lindroos A, Nyström E, Sjöström L: Body weight and body composition changes after treatment of hyperthyroidism. *J Clin Endocrinol Metab* 1998;83:4269–4273.
- 62 Zimmermann-Belsing T, Dreyer M, Holst JJ, Feldt-Rasmussen U: The relationship between the serum leptin concentrations of thyrotoxic patients during treatment and their total fat mass is different from that of normal subjects. *Clin Endocrinol* 1998;49:589–595.

- 63 Jacobsen R, Lundsgaard C, Lorenzen J, Toubro S, Perrild H, Krog-Mikkelsen I, Astrup A: Subnormal energy expenditure: a putative causal factor in the weight gain induced by treatment of hyperthyroidism. *Diabetes Obes Metab* 2006;8:220–227.
- 64 Alton S, O'Malley BP: Dietary intake in thyrotoxicosis before and after adequate carbimazole therapy; the impact of dietary advice. *Clin Endocrinol* 1985;23:517–520.
- 65 López M, Varela L, Vázquez MJ, Rodríguez-Cuenca S, González R, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R, Martínez de Morentin PB, Tovar S, Nogueiras R, Carling D, Lelliott C, Gallego R, Orešič M, Chatterjee K, Saha AK, Rahmouni K, Diéguez C, Vidal-Puig A: Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nat Med* 2010;16:1001–1008.
- 66 Murphy M, Jethwa PH, Warner A, Barrett P, Nilaweera KN, Brameld JM, Ebling FJ: Effects of manipulating hypothalamic triiodothyronine concentrations on seasonal body weight and torpor cycles in Siberian hamsters. *Endocrinology* 2012;153:101–112.
- 67 Kong WM, Martin NM, Smith KL, Gardiner JV, Connoley IP, Stephens DA, Dhillon WS, Gbatei MA, Small CJ, Bloom SR: Triiodothyronine stimulates food intake via the hypothalamic ventromedial nucleus independent of changes in energy expenditure. *Endocrinology* 2004;145:5252–5258.
- 68 Martin NM, Small CJ, Lee JL, Ellis S, Dhillon WS, Smith KL, Kong WM, Frost GS, Bloom SR: Low-dose oral tri-iodothyronine does not directly increase food intake in man. *Diabetes Obes Metab* 2007;9:435–437.
- 69 Celi FS, Zemskova M, Linderman JD, Smith S, Drinkard B, Sachdev V, Skarulis MC, Kozolsky M, Csako G, Costello R, Pucino F: Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind crossover trial of liothyronine versus levothyroxine. *J Clin Endocrinol Metab* 2011;96:3466–3474.
- 70 Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM: Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. *J Clin Endocrinol Metab* 2005;90:2666–2674.
- 71 Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L: Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2006;91:2592–2599.
- 72 Jonklaas J, Nsouli-Maktabi H: Weight changes in euthyroid patients undergoing thyroidectomy. *Thyroid* 2011;21:1343–1351.
- 73 Weinreb JT, Yang Y, Braunstein GD: Do patients gain weight after thyroidectomy for thyroid cancer? *Thyroid* 2011;21:1339–1342.
- 74 Laurberg P, Vestergaard H, Nielsen S, Christensen SE, Seefeldt T, Helleberg K, Pedersen KM: Sources of circulating 3,5,3'-triiodothyronine in hyperthyroidism estimated after blocking of type 1 and type 2 iodothyronine deiodinases. *J Clin Endocrinol Metab* 2007;92:2149–2156.
- 75 Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MPJ: 2012 ETA Guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J* 2012;1:55–71.