CLINICAL STUDY

TSH and free triiodothyronine concentrations are associated with weight loss in a lifestyle intervention and weight regain afterwards in obese children

Barbara Wolters, Nina Lass and Thomas Reinehr

*Department of Pediatric Endocrinology, Diabetes and Nutrition Medicine, Vestische Hospital for Children and Children Datteln, University of Witten/Herdecke, Dr F Steiner Street 5, D-45711 Datteln, Germany**(Correspondence should be addressed to T Reinehr; Email: t.reinehr@kinderklinik-datteln.de)*

Abstract

Objective: The impact of thyroid hormones on weight loss in lifestyle interventions and on weight regain afterwards is unknown. Therefore, we studied the relationships between TSH, free triiodothyronine (fT₃), free thyroxine (fT₄), and weight status, as well as their changes during and after a lifestyle intervention in obese children.

Materials and methods: We evaluated the weight status as BMI-SDS in 477 obese children (mean age 10.6 ± 2.7 years, 46% male, mean BMI 28.1 ± 4.5 kg/m²) participating in a 1-year lifestyle intervention in a 2-year longitudinal study. Changes in BMI-SDS at 1 and 2 years were correlated with TSH, fT₃, and fT₄ concentrations at baseline and their changes during the intervention.

Results: A decrease in BMI-SDS during the intervention period (-0.32 ± 0.38 ; $P < 0.001$) was significantly positively associated with baseline TSH and fT₃ in multiple linear regression analyses adjusted for age, sex, pubertal stage, and baseline BMI-SDS. An increase in BMI-SDS after the end of the intervention ($+0.05 \pm 0.36$; $P = 0.011$) was significantly related to the decreases in TSH and fT₃ during the intervention in multiple linear regression analyses adjusted for change in BMI-SDS during the intervention. In contrast to children with weight maintenance, children with weight regain after the end of the intervention demonstrated a decrease in their TSH levels (-0.1 ± 1.6 vs $+0.2 \pm 1.6$ mU/l; $P = 0.03$) and fT₃ (-0.2 ± 1.1 vs $+0.3 \pm 1.6$ pg/ml; $P < 0.001$) during the intervention.

Conclusions: The decreases in TSH and fT₃ concentrations during the lifestyle intervention were associated with weight regain after the intervention. Future studies should confirm that the decreases in TSH and fT₃ levels associated with weight loss are related to the change in metabolism such as resting energy expenditure.

European Journal of Endocrinology 168 323–329

Introduction

A moderate elevation of TSH concentrations, which is associated with triiodothyronine (T₃) values in or slightly above the upper normal range, is frequently found in obese humans (1, 2, 3, 4, 5, 6, 7, 8, 9). These changes are reversible in weight loss independent of whether weight loss is obtained through diet or bariatric surgery (2, 7, 8, 10, 11, 12). Furthermore, a positive correlation between weight gain during 5 years and a progressive increase in serum TSH has also been reported (13). These findings suggest that the increase in TSH and T₃ concentrations in obese subjects seems to be a consequence rather than a cause of obesity (1, 8, 10).

The underlying mechanisms of the increases in TSH and free T₃ (fT₃) levels in obesity are largely unknown (1, 14). For example, a derangement in the hypothalamic–pituitary axis, an impaired feedback due to a lowered number of T₃ receptors in the hypothalamus

(thyroid hormone resistance), and a decrease in peripheral deiodinase activity have been postulated (2). Furthermore, non-synonymous mutations in the *TSHR* gene have been reported as a cause of increased TSH levels in obesity, but these mutations are rare (15). Additionally, seronegative autoimmune thyroiditis has been suggested since thyroid hypoechogenicity at ultrasound has been reported and antithyroid antibodies are frequently negative in obese children with elevated TSH and fT₃ levels (2, 15, 16). However, cytological samples obtained in obese children with elevated TSH levels, hypoechogenicity in ultrasound, and negative for thyroid autoantibodies have been reported to be normal, and, thus, excluded an autoimmune disorder (16). A possible explanation for thyroid hypoechogenicity at ultrasound observed in obese children could be the existence of a low-grade inflammation, a known characteristic of obesity (2). However, the most favored hypothesis of increased TSH

levels in obesity is an increased leptin-mediated production of pro-TRH (1, 2).

It has been suggested that this moderate increase in TSH and consequently fT_3 levels in obesity is an adaptation process to increase resting energy expenditure (REE) (1, 2). It is well known that basal metabolic rate, total energy expenditure, and sleeping energy expenditure are positively correlated with the serum total or fT_3 concentrations, while the underlying pathways are not fully understood (1, 2, 8, 10, 12). As a consequence of the increased REE, the availability of accumulated energy for conversion into fat is diminished. Since weight loss is associated with a decrease in thyroid hormones (1, 3, 4, 7, 8, 10), the resulting decrease in REE may contribute toward difficulties in maintaining weight loss.

To support the hypothesis that a decrease in TSH and T_3 concentrations during a lifestyle intervention is associated with weight regain afterwards, we analyzed the impact of TSH and thyroid hormones and their changes during weight loss on the outcome of a lifestyle intervention in nearly 500 obese children. We hypothesize that increased basal TSH and T_3 levels are associated with greater weight loss in a lifestyle intervention since REE is increased in these children. Furthermore, we hypothesize that a decrease in TSH and T_3 concentrations during a lifestyle intervention is associated with difficulties in maintaining weight loss after the end of the intervention.

Materials and methods

The Local Ethics Committee of the University of Witten/Herdecke approved this prospective study. Informed consent was obtained from all subjects and their parents. This study is registered at ClinicalTrials.gov (NCT00435734).

We examined 477 obese children (mean age 10.6 ± 2.7 years, 46% male, mean BMI 28.1 ± 4.5 kg/m²) completing the lifestyle intervention 'Obeldicks'. Children with endocrine or metabolic disorders including goiter and autoimmune thyroiditis were excluded from the study. Furthermore, we excluded children with TSH levels >10 mU/l. Smokers and children taking any medication including oral contraceptives were also excluded. Weight status was determined at baseline, at the end of the 1-year intervention, and 1 year later (= 2 years after baseline). TSH, T_3 , and thyroxine (T_4) concentrations were examined at baseline and 1 year later (= end of the intervention). Our study protocol does not include a blood measurement at follow-up to avoid lost-to-follow-up rate after the end of the intervention.

Measurements

Weight status was determined as BMI. Height was measured to the nearest centimeter. Weight was

measured in underwear to the nearest 0.1 kg using a calibrated balance scale. The degree of overweight was quantified using Cole's least mean square method, which normalizes the BMI skewed distribution in childhood and expressed BMI as a BMI-SDS (17). Obesity was defined as BMI >97 th percentile according to the definition of the International Obesity Task Force (18) using population-specific reference data for German children (19).

Pubertal stage according to Marshall and Tanner was determined by well-trained physicians. Pubertal developmental stage was categorized into three groups based on breast and genital stages (prepubertal: boys with genital stage I, girls with breast stage I; early pubertal: boys with genital stages II and III, girls with breast stages II and III; late/postpubertal: boys with genital stage $>III$, girls with breast stage $>III$).

TSH, fT_3 , and free T_4 (fT_4) concentrations were determined in the fasting status. TSH, fT_3 , and fT_4 were measured by high-specific, solid-phase technique chemiluminescence immunoassays (Immulite; DPC, Los Angeles, CA, USA). Intra- and interassay variations were $<10\%$. The normal values range between 0.2 and 3.0 mIU/l for TSH, between 3.0 and 5.4 pg/ml for fT_3 , and between 0.9 and 2.3 ng/dl for fT_4 .

In all children with TSH levels >3 mU/l, autoimmune thyroiditis was excluded by measuring antithyroidal peroxidase and thyroglobulin antibodies.

Intervention

The 1-year lifestyle intervention 'Obeldicks' has been described in detail elsewhere (20, 21). Briefly, this intervention is based on physical exercise, nutrition education, and behavior therapy including the individual psychological care of the child and its family. Exercise therapy consists of sports, instructions in physical exercise as part of all-day life, and in the reduction of the amount of time spent watching television. The nutritional course is based on the prevention concept of the 'Optimized mixed diet' which is both fat and sugar reduced containing 30% energy intake (E) of fat, 15 E% proteins, and 55 E% carbohydrates including 5 E% sugar.

Statistical analysis

Statistical analysis was performed using WinSTAT for Excel. All variables were normally distributed as tested by the Kolmogorov-Smirnov test. Correlations were calculated by Pearson's correlation. Multiple linear regression analyses were calculated with a reduction in BMI-SDS during the intervention or with a change in BMI-SDS between the end of the intervention and 1 year later as dependent variables, and age, sex, pubertal stage, baseline BMI-SDS, and TSH, fT_3 , and fT_4 respectively as independent variables. Sex was used as a classified variable. *T*-tests for paired observations were

used to compare the variables. The changes in TSH and thyroid hormones were analyzed separately for children with and without a reduction of >0.5 BMI-SDS in the lifestyle intervention since this amount of overweight reduction was associated with an improvement in cardiovascular risk factors (22, 23). Furthermore, children were divided into children with weight regain defined by an increase in BMI-SDS after the end of the intervention and children with weight maintenance defined by stable or decreasing BMI-SDS after the end of the intervention. Corrections for multiple testing were performed by Bonferroni's adjustment. A $P < 0.05$ was considered as statistically significant. Data are presented as means and s.d.s.

Results

At baseline, 39% of the children demonstrated TSH levels above 3.0 mIU/l for TSH, 5.1% of the subjects showed fT_3 concentrations >5.4 pg/ml, while only 1.2% had fT_4 levels >2.3 ng/dl (see also Table 1). None of the children with TSH levels >3 mIU/l had fT_3 or fT_4 levels below the normal range. A total of 20 children (11%) with TSH levels >3 mIU/l had $fT_3 >5.4$ pg/ml and one child (0.5%) with TSH levels >3 mIU/l had fT_4 levels >2.3 ng/dl. A total of 20 children (83%) with $fT_3 >5.4$ pg/ml showed TSH levels >3 mIU/l and one child (17%) with fT_4 levels >2.3 ng/dl demonstrated TSH levels >3 mIU/l.

The changes in weight status during the 1-year intervention period and in the course of 1 year after the end of the intervention are demonstrated in Table 1. Children had a significant reduction in their BMI-SDS in the intervention period (-0.32 ± 0.38 ; $P < 0.001$). After the end of the intervention, BMI-SDS increased significantly ($+0.05 \pm 0.36$; $P = 0.011$). The BMI-SDS 2 years after baseline was significantly lower compared with baseline (-0.27 ± 0.49 ; $P < 0.001$). The changes in BMI-SDS during the intervention period were significantly negatively associated with the changes in BMI-SDS between the end of the intervention and 1 year later ($r = -0.14$; $P < 0.001$), which means that children with a higher degree of weight loss tend to increase their BMI-SDS after the end of the intervention.

In the entire study population, TSH and thyroid hormones did not change significantly during the lifestyle intervention (see Table 1). The 119 children with a decrease in BMI-SDS >0.5 in the intervention period (baseline BMI-SDS, 2.48 ± 0.39 ; change in BMI-SDS during the intervention, -0.78 ± 0.27) demonstrated a significant decrease in their TSH (-0.4 ± 1.7 mIU/l; $P = 0.014$) and fT_3 (-0.3 ± 1.4 pg/ml; $P = 0.018$) concentrations, while fT_4 levels remained stable ($P = 0.507$). Children with a decrease in BMI-SDS <0.5 in the intervention period (baseline BMI-SDS, 2.49 ± 0.40 ; change in BMI-SDS during the intervention, -0.15 ± 0.22) showed no significant changes in their TSH and thyroid hormone concentrations during the intervention period.

The 119 children with a reduction in BMI-SDS >0.5 in the intervention period demonstrated significantly higher TSH and fT_3 concentrations at baseline when compared with the 358 children without a BMI-SDS reduction >0.5 , while fT_4 levels did not differ significantly between these groups (see Fig. 1).

The changes in BMI-SDS in the intervention period were significantly associated with baseline TSH ($r = 0.21$; $P < 0.001$) and fT_3 ($r = 0.22$; $P < 0.001$), but not with fT_4 ($r = 0.05$; $P = 0.151$). The associations between TSH and thyroid hormones at baseline and changes in weight status during the intervention in multiple linear regression analyses adjusted for age, sex, pubertal status, and baseline BMI-SDS are presented in Table 2. Higher baseline TSH and fT_3 concentrations were significantly related to a greater BMI-SDS reduction in the intervention period.

The changes in BMI-SDS during the intervention period were significantly related to the changes in TSH ($r = 0.21$; $P < 0.001$) and fT_3 ($r = 0.22$; $P < 0.001$), but not to the changes in fT_4 ($P = 0.150$).

Children with weight regain after the end of the intervention demonstrated a decrease in TSH and fT_3 concentrations during the lifestyle intervention in contrast to children with weight maintenance after the end of the intervention, while fT_4 levels did not differ significantly between these groups (see Fig. 2).

The changes in TSH and thyroid hormone concentrations during the intervention period were significantly negatively related to the changes in BMI-SDS

Table 1 Changes in weight status (as BMI-SDS) and TSH, fT_3 , and fT_4 concentrations in 477 obese children participating in the 1-year lifestyle intervention 'Obeldicks' in the course of 2 years. Data are presented as mean and s.d. Values that are significant after multiple testing corrections are highlighted in bold.

	Baseline	1 year	2 years	<i>P</i> value (BL compared with 1 year)	<i>P</i> value (BL compared with 2 years)	<i>P</i> value (1 year compared with 2 years)
BMI-SDS	2.49 ± 0.40	2.17 ± 0.53	2.22 ± 0.59	<0.001	<0.001	0.011
TSH (mIU/l)	3.0 ± 1.4	3.0 ± 1.5	ND	0.947	—	—
fT_3 (pg/ml)	4.2 ± 0.8	4.3 ± 1.1	ND	0.630	—	—
fT_4 (ng/dl)	1.2 ± 0.3	1.2 ± 0.4	ND	0.563	—	—

ND, not determined; BL, baseline.

Figure 1 Baseline TSH, fT₃, and fT₄ levels in the 477 obese children subjected to weight loss in the lifestyle intervention (data as mean and s.d., substantial weight loss defined by BMI-SDS reduction >0.5).

after the end of the intervention (TSH, $r = -0.11$; $P = 0.010$; fT₃, $r = -0.16$; $P < 0.001$; fT₄, $r = -0.06$; $P = 0.101$). The associations between the changes in TSH and thyroid hormone levels in the intervention period and the changes in weight status after the end of the intervention in multiple linear regression analyses adjusted for age, sex, pubertal status, and the changes in BMI-SDS during the intervention are presented in Table 3. A greater decrease in TSH and fT₃ levels during the intervention was significantly related to a greater increase in BMI-SDS after the end of the intervention.

Discussion

This is the first longitudinal study in obese children analyzing the associations between TSH and thyroid hormones and weight status respective weight regain during and after a lifestyle intervention. In accordance with previous studies, obese children in our study demonstrated frequently slightly elevated TSH and fT₃ levels at baseline, while substantial weight loss (decrease in BMI-SDS >0.5) was associated with a normalization of TSH and fT₃ (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 24). We demonstrated that the BMI-SDS reduction during the lifestyle intervention was associated with a reduction in TSH and fT₃ concentrations according to a study in adults reporting a positive correlation between weight gain during 5 years and a progressive increase in serum TSH (13). Most importantly, baseline TSH and fT₃ levels were positively related to BMI-SDS reduction in the lifestyle intervention period and a decrease in TSH and fT₃ levels during this intervention was associated with an increase in BMI-SDS after the end of the intervention in our study.

These findings suggest that TSH and fT₃ concentrations and their changes predict in part weight changes during and after a lifestyle intervention. This relationship may be explained by the impact of thyroid hormones on REE. Increased thyroid hormones as in childhood obesity are associated with increased REE. Thyroid hormones, especially T₃, regulate both the resting metabolic rate and thermogenesis and lead to lipolysis (25, 26, 27, 28). An increase in energy expenditure reduces the availability of energy for conversion into fat. When TSH and fT₃ concentrations decrease in a parallel manner to a reduction of overweight as demonstrated in many studies (1, 3, 4, 7, 8, 10), then we can also expect a reduction in energy expenditure. Indeed, a decrease in energy expenditure due to weight loss has been shown in several studies in children and adults (1, 29, 30, 31) and may represent one of the causes of the difficulties in maintaining weight loss. It has been reported that a decrease of

Table 2 Associations between TSH, fT₃, and fT₄ levels at baseline and weight changes during a 1-year lifestyle intervention in the 477 obese children. The b-estimators were derived from linear regression models (adjustment for age (linear), sex, pubertal stage, and baseline BMI-SDS). Values that are significant after multiple testing corrections are highlighted in bold. Positive values of the effect size for the changes (Δ) indicate a reduction in BMI-SDS.

	TSH (mU/l)	fT ₃ (pg/ml)	fT ₄ (ng/dl)
Δ BMI-SDS b-estimator	0.05	0.06	0.01
95% CI	0.03, 0.07	0.02, 0.06	-0.09, 0.11
P value	1.18×10^{-5}	0.002	0.795
r ²	0.13	0.11	0.08

For each thyroid hormone effect size (b-estimators), their 95% confidence interval (95% CI), the P values, and the r² are listed.

Figure 2 Changes in TSH, fT₃, and fT₄ levels during the lifestyle intervention in the 477 obese children subjected to weight regain after the lifestyle intervention in the course of 1 year (data as mean and 95% confidence interval, weight regain defined by BMI-SDS increase, and weight maintenance defined by stable or decreasing BMI-SDS).

1 IU/l of serum TSH concentrations, within normal range limits, is accompanied by a reduction in energy expenditure of 75 ± 150 kcal/day. This reduction corresponds to 8 ± 17 g stored fat, equivalent to several kilograms over a period of years (32).

Since i) the decrease in BMI-SDS in the lifestyle intervention was associated with the decrease in TSH and ii) fT₃ levels and the BMI-SDS reduction during the lifestyle intervention were a predictor of weight regain

after the end of the intervention, one might speculate whether weight regain after the lifestyle intervention is caused by greater weight loss and not by the decrease in TSH and fT₃ levels. However, even after adjustment for changes in BMI-SDS in the intervention period in multiple linear regression analyses, the decrease in TSH and fT₃ concentrations during the intervention was related to weight regain after the end of the intervention.

We need to keep in mind that the explained variances of BMI-SDS change during the intervention and of BMI-SDS increase after the end of the intervention by thyroid changes were only low to moderate in multiple linear regression analyses, suggesting that other factors such as eating and exercise behavior, social or genetic background might be more important for the outcome of a lifestyle intervention. However, the significant relationships between TSH and fT₃ concentrations and their changes and the changes in BMI-SDS during and after a lifestyle intervention are an important finding: no success in a lifestyle intervention and weight regain is not only caused by the behavior of obese children but also by their metabolism. Therefore, it is not adequate to blame unsuccessful participants of lifestyle interventions.

Interestingly, fT₄ levels or their changes were not related to the changes in BMI-SDS during or after the end of the intervention in contrast to fT₃ and TSH levels. Furthermore, fT₄ levels did not decrease in substantial weight loss in contrast to TSH and fT₃ levels. These findings suggest an increase in reverse T₃ (rT₃) in weight loss. It has been reported that fT₃ levels are increased in obesity also due to changes in the monodeiodination pathway (1). Approximately 80% of the circulating T₃ is derived by extrathyroidal monodeiodination of T₄, whereas rT₃ is almost completely produced by extrathyroidal T₄ monodeiodination. In normal-weight humans, monodeiodination of T₄ produces approximately equal amounts of T₃ and rT₃. However, in obesity, production of rT₃ is decreased, while production of T₃ is increased (1).

Table 3 Associations between the changes in TSH, fT₃, and fT₄ concentrations during the intervention and weight regain after the end of the lifestyle intervention in the 477 obese children. The b-estimators were derived from linear regression models (adjustment for age (linear), sex, pubertal stage, and change in BMI-SDS during the intervention). Values that are significant after multiple testing corrections are highlighted in bold. Negative values of the effect size for the changes (Δ) indicate a weight regain (=increase in BMI-SDS after the end of the intervention).

	ΔTSH (mU/l)	ΔfT ₃ (pg/ml)	ΔfT ₄ (ng/dl)
ΔBMI-SDS b-estimator	-0.02	-0.04	-0.04
95% CI	-0.03, -0.01	-0.06, -0.02	-0.09, 0.01
P value	0.009	0.003	0.176
r ²	0.04	0.05	0.03

For each thyroid hormone effect size (b-estimators), their 95% confidence interval (95% CI), the P values, and the r² are listed.

Since other mechanisms than obesity *per se* are discussed to be the underlying mechanisms of the increase in TSH and thyroid hormone levels, we need to consider that the relationships between TSH, fT_3 , and weight change may represent an epiphenomenon caused by a third factor. For example, if inflammation is the driver of changes in TSH and thyroid hormone levels in obesity as discussed (2), then a change in weight status is likely to be associated with a change in the grade of inflammation and may explain the relationships between the change in weight status and TSH respective thyroid hormones.

The strengths of this study are the longitudinal design including not only the intervention period but also a follow-up period after the end of the intervention as well as the large study sample. However, this study has a few potential limitations. First, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measurement of adiposity. Measurement of body composition would be ideal. However, the gold standards such as dual-energy X-ray absorptiometer or indirect calorimetry are very difficult to perform in a large collection of obese children. We evaluated changes in BMI in relation to TSH and thyroid hormones, whereas it might have been more appropriate to evaluate, or at least include, measurements of lean body mass. Lean body mass appears to be a major determinant of thyroxine requirement (33). Furthermore, we did not measure REE, which is very laborious in a large collection of children. Second, we did not perform ultrasound measurement to exclude seronegative autoimmune thyroiditis. However, a recent study has excluded autoimmune disorders by cytological samples obtained in obese children with elevated TSH levels and hypoechogenicity in ultrasound (16). Finally, we did not differentiate the effect of diet, increased physical exercise, and weight loss on TSH and thyroid hormones and weight regain due to our study protocol. In contrast to exercise-induced weight loss, diet-induced weight loss has been reported to be associated with changes in thyroid hormone production (34).

In summary, we found moderately increased TSH and fT_3 concentrations in obese children, which normalized in substantial weight loss. Since both baseline TSH and fT_3 levels as well as the decrease in these hormones during weight loss were associated with changes in BMI-SDS, we put forward the hypothesis that increased TSH and T_3 concentrations may represent an adaptation process of obesity, increasing the REE to reduce the availability of energy for conversion to fat. Future studies should confirm that the decrease in TSH and T_3 during a successful lifestyle intervention is associated with a decrease in REE, representing a negative predictive factor for weight maintenance after the lifestyle intervention.

Declaration of interest

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

Funding

T Reinehr and B Wolters received grant support from the 'Kompetenznetz Adipositas (Competence Network for Adiposity)' funded by the German Federal Ministry of Education and Research (FKZ: 01GI1120A). The hypothesis development, analysis, interpretation, and conclusions contained in this study are those of the authors alone.

Author contribution statement

T Reinehr developed the study design and wrote the first draft of the paper and performed the statistical analyses. N Lass and B Wolters performed the anthropometrical measurements. All authors discussed the findings.

Acknowledgements

We thank the children who participated in this study.

References

- 1 Reinehr T. Obesity and thyroid function. *Molecular and Cellular Endocrinology* 2010 **316** 165–171. (doi:10.1016/j.mce.2009.06.005)
- 2 Reinehr T. Thyroid function in the nutritionally obese child and adolescent. *Current Opinion in Pediatrics* 2011 **23** 415–420. (doi:10.1097/MOP.0b013e328344c393)
- 3 Shalitin S, Yackobovitch-Gavan M & Phillip M. Prevalence of thyroid dysfunction in obese children and adolescents before and after weight reduction and its relation to other metabolic parameters. *Hormone Research* 2009 **71** 155–161. (doi:10.1159/000197872)
- 4 Marras V, Casini MR, Pilia S, Carta D, Civolani P, Porcu M, Ucheddu AP & Loche S. Thyroid function in obese children and adolescents. *Hormone Research in Paediatrics* 2010 **73** 193–197. (doi:10.1159/000284361)
- 5 Dekelbab BH, Abou Ouf HA & Jain I. Prevalence of elevated thyroid-stimulating hormone levels in obese children and adolescents. *Endocrine Practice* 2010 **16** 187–190. (doi:10.4158/EP09176.OR)
- 6 Grandone A, Santoro N, Coppola F, Calabro P, Perrone L & Del Giudice EM. Thyroid function derangement and childhood obesity: an Italian experience. *BMC Endocrine Disorders* 2010 **10** 8. (doi:10.1186/1472-6823-10-8)
- 7 Reinehr T, de Sousa G & Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3088–3091. (doi:10.1210/jc.2006-0095)
- 8 Reinehr T, Isa A, de Sousa G, Dieffenbach R & Andler W. Thyroid hormones and their relation to weight status. *Hormone Research* 2008 **70** 51–57. (doi:10.1159/000129678)
- 9 Rotondi M, Leporati 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? *European Journal of Endocrinology* 2009 **160** 403–408. (doi:10.1530/EJE-08-0734)
- 10 Reinehr T & Andler W. Thyroid hormones before and after weight loss in obesity. *Archives of Disease in Childhood* 2002 **87** 320–323. (doi:10.1136/adc.87.4.320)

- 11 Sari R, Balci MK, Altunbas H & Karayalcin U. The effect of body weight and weight loss on thyroid volume and function in obese women. *Clinical Endocrinology* 2003 **59** 258–262. (doi:10.1046/j.1365-2265.2003.01836.x)
- 12 Rotondi M, Magri F & Chiovato L. Thyroid and obesity: not a one-way interaction. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 344–346. (doi:10.1210/jc.2010-2515)
- 13 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. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4019–4024. (doi:10.1210/jc.2004-2225)
- 14 Legrady G, Emerson CH, Ahima RS, Flier JS & Lechan RM. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. *Endocrinology* 1997 **138** 2569–2576. (doi:10.1210/en.138.6.2569)
- 15 Rapa A, Monzani A, Moia S, Vivenza D, Bellone S, Petri A, Teofoli F, Cassio A, Cesaretti G, Corrias A *et al.* Subclinical hypothyroidism in children and adolescents: a wide range of clinical, biochemical, and genetic factors involved. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2414–2420. (doi:10.1210/jc.2009-0375)
- 16 Radetti G, Kleon W, Buzi F, Crivellaro C, Pappalardo L, di Iorgi N & Maghnie M. Thyroid function and structure are affected in childhood obesity. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4749–4754. (doi:10.1210/jc.2008-0823)
- 17 Cole TJ. The LMS method for constructing normalized growth standards. *European Journal of Clinical Nutrition* 1990 **44** 45–60.
- 18 Cole TJ, Bellizzi MC, Flegal KM & Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000 **320** 1240–1243. (doi:10.1136/bmj.320.7244.1240)
- 19 Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiß HC, Hesse V, von Hippel A, Jaeger U, Johnsen D, Korte W *et al.* Percentiles of body mass index in children and adolescents evaluated from different regional German studies. *Monatsschrift für Kinderheilkunde* 2001 **149** 807–818. (doi:10.1007/s001120170107)
- 20 Reinehr T, Kersting M, Wollenhaupt A, Alexy U, Kling B, Ströbele K & Andler W. Evaluation of the training program “OBELDICKS” for obese children and adolescents. *Klinische Pädiatrie* 2005 **217** 1–8. (doi:10.1055/s-2004-816246)
- 21 Reinehr T, Temmesfeld M, Kersting M, de Sousa G & Toschke AM. Four-year follow-up of children and adolescents participating in an obesity intervention program. *International Journal of Obesity* 2007 **31** 1074–1077. (doi:10.1038/sj.ijo.0803637)
- 22 Wunsch R, de Sousa G, Toschke AM & Reinehr T. Intima-media thickness in obese children before and after weight loss. *Pediatrics* 2006 **118** 2334–2340. (doi:10.1542/peds.2006-0302)
- 23 Reinehr T, Kiess W, Kapellen T & Andler W. Insulin sensitivity among obese children and adolescents, according to degree of weight loss. *Pediatrics* 2004 **114** 1569–1573. (doi:10.1542/peds.2003-0649-F)
- 24 Pacifico L, Anania C, Ferraro F, Andreoli GM & Chiesa C. Thyroid function in childhood obesity and metabolic comorbidity. *Clinica Chimica Acta* 2012 **413** 396–405. (doi:10.1016/j.cca.2011.11.013)
- 25 Blennemann B, Leahy P, Kim TS & Freahe HC. Tissue-specific regulation of lipogenic mRNAs by thyroid hormone. *Molecular and Cellular Endocrinology* 1995 **110** 1–8. (doi:10.1016/0303-7207(95)03509-6)
- 26 Roti E, Minelli R & Salvi M. Thyroid hormone metabolism in obesity. *International Journal of Obesity and Related Metabolic Disorders* 2000 **24** (Suppl 2) S113–S115. (doi:10.1038/sj.ijo.0801293)
- 27 Shin DJ & Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein-2 (SREBP-2). *Journal of Biological Chemistry* 2003 **278** 34114–34118. (doi:10.1074/jbc.M305417200)
- 28 Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Annals of Internal Medicine* 2003 **139** 205–213.
- 29 Kiortsis DN, Durack I & Turpin G. Effects of a low-calorie diet on resting metabolic rate and serum tri-iodothyronine levels in obese children. *European Journal of Pediatrics* 1999 **158** 446–450. (doi:10.1007/s004310051117)
- 30 Heshka S, Yang MU, Wang J, Burt P & Pi-Sunyer FX. Weight loss and change in resting metabolic rate. *American Journal of Clinical Nutrition* 1990 **52** 981–986.
- 31 Hill JO, Sparling PB, Shields TW & Heller PA. Effects of exercise and food restriction on body composition and metabolic rate in obese women. *American Journal of Clinical Nutrition* 1987 **46** 622–630.
- 32 al-Adsani H, Hoffer LJ & Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 1118–1125. (doi:10.1210/jc.82.4.1118)
- 33 Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, Valeriano R, Giannetti M, Taddei D, Centoni R, Scartabelli G *et al.* Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 124–127. (doi:10.1210/jc.2004-1306)
- 34 Katzell HL & Selgrad C. Maintenance of thyroid hormone production during exercise-induced weight loss. *American Journal of Physiology* 1991 **261** E382–E388.

Received 23 September 2012

Accepted 3 December 2012