ORIGINAL ARTICLE

Thyroid hormones before and after weight loss in obesity

T Reinehr, W Andler

Arch Dis Child 2002;**87**:320–323

See end of article for authors' affiliations

Correspondence to: Dr T Reinehr, Vestische Kinderklinik, University of Witten-Herdecke, Dr F Steiner Str. 5, 45711 Datteln, Germany; TIReinehr@aol.com

Accepted 23 May 2002

Background: Little is known about changes in thyroid function in obese children. An influence of leptin on thyroid hormone synthesis has been proposed.
Aims: To examine thyroid function and leptin concentrations in obese children.
Methods: Triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), and leptin were measured in 118 obese children (aged 4.5–16 years); thyroid function was also determined in 107 healthy children of normal weight. T3, T4, and TSH were analysed in 55 obese children who had achieved weight reduction and in 13 obese children who had not achieved weight reduction after one year based on normal energy diet.
Results: TSH, T3, and T4 were significantly higher in obese children compared to those of normal weight. Twelve per cent of the obese children had TSH, 15% had T3, and 11% had T4 concentrations above the twofold standard deviation of normal weight children. The degree of overweight correlated with T3, T4, and TSH. Thyroid hormones did not correlate significantly with leptin. A reduction in overweight showed a significant decrease in T3, T4, and leptin serum concentrations, but there was no significant change in TSH.
Conclusion: Peripheral thyroid hormones (T3, T4) and TSH are moderately increased in obese children; weight reduction leads to a long term decrease in the peripheral thyroid hormones but not in TSH. There is no necessity to treat the increased serum TSH.

There are hardly any studies concerning thyroid functioning in obese children. Experiments on animals have shown a correlation between thyroid hormones and changes in weight.[1] Studies on thyroid hormones in obese adults are inconsistent.[2–4] There has been discussion as to whether leptin influences the production of thyroid hormones.[5–7] Long term changes in thyroid hormones caused by a reduction in weight have not been studied in depth.

We therefore analysed thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and leptin in obese children before and after weight reduction based on normal energy diet, compared to healthy children of normal weight.

MATERIALS AND METHODS

We examined all children with non-syndromal obesity, defined by a body mass index (BMI) above the 97th centile who attended the intervention programme "Obeldicks"[8] for obese children between 1999 and 2000. Reference data from Rolland-Cachera and colleagues[9] were used, as proposed by the European childhood obesity group.

Thyroid hormone parameters (T3, T4, TSH), leptin, degree of overweight as a z score from the BMI according to the LMS method,[9 10] which includes an age dependent factor controlling for variation and skewness of the BMI distribution, as well as age, sex, and stage of puberty according to Tanner were established. After one year the same parameters were determined for all those taking part in the intervention programme "Obeldicks". These data were compared to thyroid function (T3, T4, TSH) of 107 non-obese healthy children with constitutional or familial short or tall stature and a BMI below the 90th centile.[9]

TSH, total T3, and total T4 were determined by solid phase technique—chemiluminescence—immunoassays (Immulite). The norm values for the respective age range were between 0.2–0.4 and 5.4–6.1 mIU/l for TSH, between 0.6 and 3.1–3.5 nmol/l for T3, and between 46–54 and 160–178 nmol/l for T4. Leptin was measured with an enzyme immunoassay (DRG). The intraassay coefficients of variation were 3.9% for TSH, 5.4% for T3, and 6.3% for T4. The interassay coefficients of variation were 8.0% for TSH, 7.1% for T3, and 6.7% for T4.

In all children, autoimmune thyroiditis was excluded by measuring antimicrosomal and thyroglobulin antibodies for TSH concentrations above 5 mU/l or above the twofold standard deviation based on the 107 normal weight children (see table 1) and for goitre. Children with endocrine or metabolic disorders were excluded from the study. Smokers and children taking any medication including oral contraceptives were also excluded. Growth hormone deficiency was excluded in all children with short stature.

The reduction in weight was achieved through the intervention programme "Obeldicks" for obese children based on a one year therapy with behavioural components, physical exercise, and normal energy diet.[9]

Statistical analysis was performed by the Statistical Package for Social Sciences (SPSS). Stastically significant differences were tested by the non-parametric Mann-Whitney U test, paired observation by the non-parametric Wilcoxon test, correlations by the Spearman rank test, and dependent variables by partial correlation.

RESULTS

A total of 119 obese children presented for participation in the intervention programme "Obeldicks". One child was excluded because of autoimmune thyroiditis. In the last three months before schooling no child had had a change in weight.

Obese children showed significantly higher serum concentrations of TSH, T3, and T4 than the non-obese children (see table 1). The group of obese children did not differ with respect to age, sex, or stage of puberty from the group of non-obese children. TSH serum concentrations were above the

Abbreviations: BMI, body mass index; MAK, microsomal autoantibodies; rT3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TAK, thyroide activating autoantibodies; TRAK, thyroglobulin autoantiboides; TSH, thyroid stimulating hormone

Table 1 Age, gender, degree of overweight (z score BMI), and serum TSH, T3, and T4 in obese and non-obese children

	Non-obese	Obese	p value
Number	107	118	
Gender	43% girls	47% girls	0.586
Age (y)	11.3 (4.0–16.0)	11.5 (4.5–16.0)	0.938
z score BMI	–0.5 (–1.8 to +1.3)	+3.2 (+1.9 to +4.8)	<0.001
TSH (mIU/l)	2.0 (0.2–4.8) SD 1.46	2.4 (0.8–10.5) SD 1.41	0.001
T3 (nmol/l)	2.2 (1.4–3.4) SD 0.43	2.5 (1.5–6.1) SD 0.62	<0.001
T4 (nmol/l)	103 (55–184) SD 21	116 (24–172) SD 23	<0.001

Data expressed as median (range). SD, standard deviation.

Table 2 Correlation of thyroid hormones to degree of overweight (z score BMI) in 118 obese children

TSH	r=0.21	p=0.002
T3	r=0.27	p=0.0001
T4	r=0.25	p=0.002

twofold standard deviation based on the 107 normal weight children in 14 (12%) of the 118 obese children, T3 serum concentrations in 18 (15%), and T4 serum concentrations in 13 (11%) obese children. There was no correlation between TSH, T3, and T4 serum concentrations, and age, sex, or stage of puberty. No child had a goitre. The thyroid hormones correlated with the degree of overweight (z score BMI; see table 2). The thyroid hormones did not correlate significantly with leptin (T3: $r = 0.07$, $p = 0.46$; T4: $r = -0.05$, $p = 0.60$; TSH: $r = 0.16$, $p = 0.11$). As both leptin[11] and the thyroid hormones correlated with the degree of overweight, partial correlation adjusted to the degree of overweight was used.

Two obese children without goitre had TSH values above 5 mIU/l (child 1: 10.5 mIU/l; child 2: 7.8 mIU/l) and normal autoantibodies (microsomal (MAK), thyroglobulin (TRAK), and thyroid activating autoantibodies (TAK)). T3 of these children was 3.8 (child 1) and 3.1 nmol/l (child 2); T4 was 130 nmol/l (child 1) and 102 nmol/l (child 2). They had no clinical signs of hyperthyroidism or hypothyroidism.

Sixty eight obese children took part in the intervention programme "Obeldicks". Fifty five (81%) finished the training programme successfully with a reduction of their z scores BMI by at least 0.1 (median loss 0.50, range 0.20–1.90; see table 3). The group of successful children did not differ from that of the unsuccessful children as to age (median 11.3 years, range 4.5–15 years compared to median 11.9 years, range 6–15 years), sex (44% compared to 54% girls), or degree of overweight (z score BMI). Compared to their initial concentrations the successful children showed a significant decrease in serum T3, T4, and leptin (see table 3) but not in TSH, even if patients with TSH above twofold standard deviation based on the 107 normal weight children are excluded (TSH: $p = 0.761$; T3: $p = 0.002$; T4: $p < 0.0001$). The thyroid hormones of the 13 children who did not lose weight successfully after a year did not change significantly compared to their initial values (see table 4).

DISCUSSION

In obese children, serum concentrations of thyroid hormones (TSH, T3, T4) were on average above those of the children of normal weight, and decreased (T3, T4) after weight loss from a normal energy diet; this points to a reversible increase of thyroid hormones in obesity.

These changes of TSH and T3 are not caused by other influencing factors, as without weight loss in a collective of obese

Table 3 Degree of overweight (z score BMI), thyroid hormones, and leptin before and one year later after weight loss in 55 obese children

	Before weight loss	After weight loss	p value
z score BMI	+3.1 (+1.9 to +4.1)	+2.4 (+0.8 to +3.9)	<0.001
TSH (mIU/l)	2.34 (0.80–7.81)	2.24 (0.98–6.33)	0.491
T3 (nmol/l)	2.30 (1.69–6.14)	2.15 (1.31–3.69)	0.001
T4 (nmol/l)	114 (73–157)	101 (24–137)	<0.001
Leptin (ng/ml)	20.8 (2.2–124.0)	14.8 (1.0–54.0)	<0.001

Data expressed as median (range).

Table 4 Degree of overweight (z score BMI), thyroid hormones, and leptin before and one year later in 13 obese children without weight loss

	Before weight loss	After unsuccessful weight loss	p value
z score BMI	+2.7 (+2.2 to +3.7)	+2.9 (+2.2 to +4.0)	0.166
TSH (mIU/l)	2.15 (1.09–5.06)	2.01 (0.67–4.05)	0.115
T3 (nmol/l)	2.00 (1.54–3.38)	2.46 (1.51–3.23)	0.914
T4 (nmol/l)	110 (83–145)	101 (64–132)	0.055
Leptin (ng/ml)	27.0 (2.0–93.0)	25.3 (7.0–54.0)	0.167

Data expressed as median (range).

children of the same age, gender, and degree of overweight, there was no change in thyroid status over the same time period.

As both TSH and the peripheral thyroid hormones (T3 and T4) are increased in obesity, there is no necessity for treatment of the increased TSH serum concentrations,[13] as T3 is the biologically active thyroid hormone and is crucial for metabolism.

A moderate rise in total and free T3 and TSH serum concentrations of obese children, as in our group, has been shown in a number of other studies.[12–15] The cause of the increased thyroid hormone concentrations in obesity is unclear. In a study in children, the increase in TSH serum concentrations was not accounted for by iodine deficiency or autoimmune thyroiditis.[13] Increased thyroid hormone concentrations could point to hormone resistance, similar to insulin resistance in obesity.[16] In support of this theory is the fact that in obesity T3 receptors are decreased,[17] and the negative feedback between TSH and the peripheral thyroid hormones (T3, T4) is decreased, as both TSH and the peripheral thyroid hormones are increased in obesity. The patients with the highest serum TSH concentrations had high serum T3 concentrations. To determine whether pituitary responsivity is altered in obese children, a TRH test would be useful.

As the thyroid hormones—especially T3—regulate both the resting metabolic rate and thermogenesis and lead to lipolysis,[12 18 19] changes in thyroid hormones could also point to an adaptation process in obesity. When the peripheral thyroid hormones decrease after a reduction of overweight, we can also expect a reduction in resting metabolic rate and consequently a reduction in energy expenditure. This decrease in energy expenditure as a result of weight loss has been shown in several studies in children.[12 20]

Production of TSH is also regulated by transmitters and hormones which regulate body weight and satiation, such as neuropeptide Y, α melanocyte stimulating hormone, and the agouti related peptide innervating hypophysiotropic TRH neurones.[21] These transmitters are also influenced by leptin,[22] which correlates with the degree of adipose tissue.[11] Some studies have described a correlation between leptin and TSH[2 6 7]; indeed leptin has even been considered the mediator responsible for the increase in the production of TSH.[5 7] However, in our study as well as in one further study,[4] no significant correlation between TSH and leptin could be identified, although in our analysis we used partial correlation adjusted to the degree of overweight, as both leptin and TSH correlated with the degree of overweight. As such there seems to be no direct connection between leptin and the thyroid hormones.

Surprisingly in our sample there was no significant decrease in TSH serum concentrations through weight loss as there was in most other studies.[12 23 24] The non-decrease of TSH despite weight loss could point to a neuroendocrine dysfunction as a cause of obesity, producing a bioinactive TSH[25] owing to a derangement in the hypothalamic-hypophysial axis, which also regulates body weight.[15] Further causes for the non-decrease of TSH may be attributed to the small samples, to insufficient weight loss, to an improvement in the down regulated negative feedback from TSH to the peripheral thyroid hormones in obesity, or to the observations having taken place over too short a period of time. As the capacity of binding proteins of thyroid hormones changes with the state of nutrition,[26] the decrease in total concentration of T4 and T3 with unchanged TSH serum concentrations could therefore be a result of changes in the transport proteins, leaving the free amounts of peripheral thyroid hormones unchanged. In order to clarify this point, the free amounts of peripheral thyroid hormones and the transport proteins throughout long term weight reduction need to be determined.

Some studies have described a decrease in serum T3 concentrations a few weeks after weight loss,[12 27 28] while others reported constant T4 serum concentrations after weight loss.[12 23 24] All these studies dealt merely with short term changes after a few weeks on a low energy diet, indicating that a low energy diet leads to an increase in the production of biologically inactive rT3.[24 27 28] As both T3 and T4 decreased in our sample after weight loss on a normal energy diet, increased production of rT3 cannot be assumed. On the other hand, in our study total T4 decreased—but not significantly—even in the group of children not achieving weight loss. This points to other influencing factors of total T4. For example, the individuals in our study progressed into puberty during the course of the year, influencing thyroid binding.

Children taking any medication or having a medical condition which can affect binding proteins were excluded from the study. Measurement of total T3 and total T4 concentrations is therefore a good method to assess thyroid hormone status as measurement of free T3 in the obese showed the same results.[4 13]

In summary, moderately increased TSH, total T3, and T4 serum concentrations are frequently found in obese children. There is no necessity for treatment of the increased thyroid hormones. A normal energy diet induces a long term decrease in the peripheral thyroid hormones as opposed to TSH. As in our study leptin showed no correlation with the thyroid hormones, it is doubtful that leptin is important as a mediator in thyroid changes. There is still a need for further research into the causes of the changes in thyroid hormones (especially TRH test, TSH, free T3, and T4) in obesity and weight loss.

Authors' affiliations

T Reinehr, W Andler, Vestische Kinderklinik, University of Witten-Herdecke, Datteln, Germany

REFERENCES

1 **Koritschoner NP**, Alvarez-Dolado M, Kurz SM, *et al.* Thyroid hormone regulates the obesity gene tub. *EMBO Rep* 2001;**2**:499–504.
2 **Pinkney JH**, Goodrick SJ, Katz J, *et al.* Leptin and the pituitary-thyroid axis: a comparative study in lean, obese, hypothyroid and hyperthyroid subjects. *Clin Endocrinol (Oxf)* 1998;**49**:583–8.
3 **Rosenbaum M**, Hirsch J, Murphy E, *et al.* Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr* 2000;**71**:1421–32.
4 **Tagliaferri M**, Berselli ME, Calo G, *et al.* Subclinical hypothyroidism in obese patients: relation to resting energy expenditure, serum leptin, body composition, and lipid profile. *Obes Res* 2001;**9**:196–201.
5 **Cegradi G**, Emerson CH, Ahiana RS, *et al.* Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribo-nucleic acid in neurons of the hypothalamic paraventricular nucleus. *Endocrinology* 1997;**138**:2569–76.
6 **Kautzky-Willer A**, Ludwig C, Nowotny P, *et al.* Elevation of plasma leptin concentrations in obese hyperinsulinaemic hypothyroidism before and after treatment. *Eur J Clin Invest* 1999;**29**:395–403.
7 **Kim MS**, Small CJ, Stanley SA, *et al.* The central melanocortin system affects the hypothalamo-pituitary thyreoid axis and may mediate the effects of leptin. *J Clin Invest* 2000;**105**:1005–11.
8 **Reinehr T**, Kersting M, Chahda C, *et al.* Ambulante Schulung "Obeldicks" für adipöse Kinder and Jugendliche. *Kinder- and Jugendmedizin* 2001;**82**:33–6.
9 **Rolland-Cachera MF**, Cole TJ, Sempe M, *et al.* Body mass index variations: centiles from birth to 87 years. *Eur J Clin Nutr* 1991;**45**:13–21.
10 **Cole TJ**. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr* 1990;**44**:45–60.
11 **Blum WF**, Englaro P, Attanasio AM, *et al.* Human and clinical perspectives on leptin. *Proc Nutr Soc* 1998;**57**:477–85.
12 **Kiortis DN**, Durack I, Turpin G. Effects of a low-calorie diet on resting metabolic rate and serum triiodothyronine levels in obese children. *Eur J Pediatr* 1999;**158**:446–50.
13 **Stichel H**, l'Allemand D, Gruters A. Thyroid function and obesity in children and adolescents. *Horm Res* 2000;**54**:14–19.
14 **Bray GA**, Chopra IJ, Fischer DA. Relation of thyroid hormones to body-weight. *Lancet* 1976;**I**:1206–8.
15 **Maccario M**, Oleandri SE, Valetto MR, *et al.* Pituitary-thyroid axis in obesity. *Int J Obes* 1998;**22**: P175.
16 **Srinivasan SR**, Myers L, Berenson GS. Temporal association between obesity and hyperinsulinemia in children, adolescents, and young adults: the Bogalusa Heart Study. *Metabolism* 1999;**48**:928–34.
17 **Burman KD**, Latham KR, Djuh YY, *et al.* Solubilized nuclear thyroid hormone receptors in circulating human mononuclear cells. *J Clin Endocrinol Metab* 1980;**51**:106–16.

18 **Ravussin E**, Burnard B, Schutz Y, *et al*. Twenty-four-hour energy expenditure and resting metabolic rate in obese, moderately obese, and control subjects. *Am J Clin Nutr* 1982;**35**:566–73.
19 **Toubro S**, Sorensen TIA, Ronn B, *et al*. Twenty-four-hour energy expenditure: the role of body composition, thyroid status, sympathetic activity and family membership. *J Clin Endocrinol Metab* 1996;**81**:2670–4.
20 **Zwiauer KFM**, Mueller T, Widhalm K. Resting metabolic rate in obese children before, during and after weight loss. *Int J Obes* 1992;**16**:11–16.
21 **Mihaly E**, Fekete C, Tatro JB, *et al*. Hypophysio-tropic thyrotropin-releasing hormone-synthesizing neurons in the human hypo-thalamus are innervated by neuropeptide Y, agouti-related protein, and alpha-melanocyte-stimulating hormone. *J Clin Endocrinol Metab* 2000;**85**:2596–603.
22 **Rohner-Jeanraud F**, Jeanraud B. The discovery of leptin and its impact in the understanding of obesity. *Eur J Endocrinol* 1996;**135**:649–50.
23 **Barrows K**, Snook JT. Effect of a high-protein, very low calorie diet on resting metabolism, thyroid hormones, and energy expenditure of obese middle-age women. *Am J Clin Nutr* 1987;**45**:391–8.
24 **Hill JO**, Sparling PB, Shields TW, *et al*. Effects of exercise and food restriction on body composition and metabolic rate in obese women. *Am J Clin Nutr* 1987;**46**:622–30.
25 **Winter WE**, Signorio MR. Review: molecular thyroidology. *Ann Clin Lab Sci* 2001;**31**:221–44.
26 **Ekins R**. Measurement of free hormones in blood. *Endocr Rev* 1990;**11**:5–46.
27 **Spaulding SW**, Chopra IJ, Sherwin RS, *et al*. Effect of caloric restriction on serum T3 and reverse T3 in man. *J Clin Endocrinol Metab* 1976;**42**:197–200.
28 **O'Brian JT**, Bybee DE, Burman KD, *et al*. Thyroid hormone homeostasis in states of relative caloric deprivation. *Metabolism* 1980;**29**:566–73.

ARCHIVIST

Blood pressure after repair of coarctation

Adults who have had coarctation of the aorta repaired in childhood are at increased risk of hypertension compared with the general population. In most published follow up series the age at coarctation repair was quite high and it is known that late repair increases the risk of hypertension. Now data have been reported from a cohort in Newcastle upon Tyne (JJ O'Sullivan and colleagues. *Heart* 2002;**88**:163–6) whose coarctations were repaired early.

From a cohort of 166 children born between 1983 and 1992 with coarctation of the aorta 119 survivors were followed up with full data. Mean age at repair was 0.2 years and at follow up 12 years. All were thought to have had a satisfactory repair. At follow up echocardiography 70 children were considered to have no arch obstruction and 49 mild obstruction. Of those with no arch obstruction 15 (21%) had a high (>95th centile) casual systolic blood pressure (mean of three readings) and 13 (19%) had a high mean 24 hour systolic blood pressure. For those with mild arch obstruction the corresponding figures were 19/49 (39%) and 23/49 (49%). High systolic blood pressure on casual readings was 66% sensitive and 88% specific for high mean 24 hour systolic blood pressure.

Systolic hypertension is common in later childhood after early repair of coarctation of the aorta even in the absence of significant residual arch obstruction. There is uncertainty about the need for treatment of this hypertension. Its cause also seems uncertain.