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Should we treat subclinical hypothyroidism in obese children?

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Thyroid function tests are often requested when investigating obese or overweight children. Slightly raised thyrotropin (TSH) with normal free thyroxine—subclinical hypothyroidism (hyperthyrotropinaemia)—is a common finding. An isolated raised thyrotropin is best described as hyperthyrotropinaemia rather than subclinical hypothyroidism and by definition excludes people with clinical symptoms, positive thyroid antibodies, goitre, or associated thyroidal illness.^{1 2} The adult consensus guideline defines it as a thyrotropin value between the upper limit of the local normal range and 10 mIU/L.¹ Paediatric reviews have adopted a similar definition and thresholds.³ Reference ranges vary with the laboratory but are typically 0.45–4.5 mIU/L.¹ In paediatric practice, as in adults, thyrotropin >10 mIU/L is potentially indicative of overt hypothyroidism.⁴

An isolated increase in thyrotropin is more common in overweight children, with a reported prevalence of 7–23% in obese children compared with only 2% in normal weight children.^{4 5} Thus it is unclear whether raised thyrotropin is a cause or consequence of obesity and whether thyroxine should be used to help manage these children's weight.

What is the evidence of the uncertainty?

To ascertain the association between obesity and hyperthyrotropinaemia in children, we searched the Medline, Embase, and Cochrane databases until February 2015 using the keywords “subclinical hypothyroidism”, “hyperthyrotropin(a)emia”, “obesity”, and “treatment” in various combinations. Because of the paucity of paediatric data we also examined the literature on adults. We found several cross sectional and longitudinal studies on the association between thyroid dysfunction and obesity in adults and children and one systematic review of adult studies, but no randomised controlled trials evaluating interventions and no systematic reviews of paediatric studies.

Subclinical hypothyroidism in obese children: cause or effect?

Evidence on the association between an isolated raised thyrotropin and obesity is more limited in children than in adults, but it still supports a link between weight gain and hyperthyrotropinaemia. A recent review identified 12 mostly cross sectional studies, some of which had a longitudinal component, which found a positive association between increasing thyrotropin and increasing weight.⁴ In these cohorts 7–23% of obese children had moderately raised thyrotropin with normal free thyroxine and normal or slightly raised free triiodothyronine,⁴ compared with 0.3–2.0% in normal weight controls. Several large longitudinal studies have examined the effect of weight loss on thyrotropin. In one study of 246 obese children, thyrotropin was initially raised. Thyrotropin values dropped significantly in the 49 children who subsequently lost weight ($P=0.035$) but not in the 197 children who did not lose weight.⁶ Other cohort studies also showed normalisation of thyrotropin values after weight loss.^{5 2} These studies concluded that hyperthyrotropinaemia is caused by increased weight, perhaps representing an adaptive process to increase basal energy expenditure, rather than predisposing to weight gain in children.^{5 2}

What's the evidence in adults?

Because of the limited paediatric data it is useful to look at the adult literature. In a recent systematic review of 29 cross sectional and longitudinal studies in adults, 18 showed a positive correlation between serum thyrotropin and measures of adiposity.⁷ A study of 15 000 Norwegians found that, over a five year period, weight gain correlated with increased thyrotropin and weight loss with reduced thyrotropin.⁸ It has been suggested that the increase in thyrotropin is an adaptive

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What you need to know

- Hyperthyrotropinaemia comprises an isolated raised thyrotropin (>4.5 mIU/L but <10 mIU/L) without clinical symptoms, thyroid antibodies, goitre, or associated thyroidal illness
- It is common in obese children but seems to be a consequence rather than the cause of obesity and may normalise after weight loss
- Offer lifestyle measures to promote weight loss because there is no evidence to justify thyroxine treatment for subclinical hypothyroidism with obesity. However monitor thyrotropin and free thyroxine every 6-12 months in view of the unlikely but possible progression to overt hypothyroidism

response of the hypothalamic-pituitary axis to weight gain in an attempt to enhance resting energy expenditure,⁹ rather than subclinical hypothyroidism causing the weight gain. In support of this, two small observational studies (11 and 72 patients, respectively) showed normalisation of thyrotropin after weight loss (due to dieting or bariatric surgery).^{10 11} Although most studies suggest that raised thyrotropin is a consequence rather than the cause of obesity, there have been reports of bidirectional effects. However, these studies included patients with differing degrees of obesity and did not adjust for confounding factors such as age, sex, iodine intake, and distribution of body fat, making interpretation difficult.⁹

What's the role of thyroxine treatment?

The only study to evaluate the role of thyroxine treatment for hyperthyrotropinaemia in obese children was a prospective cohort study in which 15 children received 1-2 µg/kg of thyroxine as an adjunct to a lifestyle intervention programme versus 26 untreated children who received the same lifestyle intervention programme.¹² All children lost weight and their previously raised thyrotropin values fell. No statistically significant difference was seen between the thyroxine treated and untreated groups with regard to effect on body weight, body mass index, linear growth, or lipid profile.¹² Although the lack of appropriately powered, high quality studies leaves us with insufficient direct evidence regarding thyroxine treatment in obese children with hyperthyrotropinaemia, the limited evidence available suggests that it has no benefit.

In adults, a recent narrative review of six randomised controlled trials reported no significant difference in body mass index or weight with levothyroxine treatment compared with placebo in subclinical hypothyroidism.¹³

Is ongoing research likely to provide relevant evidence?

We reviewed the clinical trials.gov database and found no current studies that are looking at this specific question.

What should we do in the light of the current uncertainty?

Raised thyrotropin, which is seen in 7-23% of overweight children, is probably a consequence rather than a cause of obesity because thyrotropin tends to normalise after weight loss.⁴ There is no evidence to support treatment with thyroxine in otherwise well children if thyrotropin is <10 mIU/L.¹² Most children with hyperthyrotropinaemia, with or without obesity, do not progress to develop overt hypothyroidism. In a population study of 120 000 children, 79% of those with an initially raised thyrotropin showed normal values at five year follow-up and only 0.4% of the cohort developed overt hypothyroidism requiring treatment.¹⁴ Thus, in obese children with hyperthyrotropinaemia (thyrotropin >4.5 mIU/L but <10 mIU/L):

- Exclude the presence of goitre or clinical features of thyroid disease (tiredness, dry skin, cold skin or feeling colder, constipation, slower thinking, poor memory)
- Exclude the presence of thyroid autoantibodies
- Offer lifestyle measures, but not thyroxine treatment, to promote weight loss
- We suggest that it is prudent to monitor thyrotropin and free thyroxine every six to 12 months.

Thyrotropin levels >10 mIU/L fall outside the definition of hyperthyrotropinaemia and may indicate thyroid disease requiring referral to a paediatric endocrinologist for further assessment and investigation.¹ Children with clinical symptoms of thyroid disease, positive thyroid antibodies, or goitre also require specialist assessment.

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Recommendations for further research

Adequately powered randomised controlled trials with:

- Population: obese and overweight children with hyperthyrotropinaemia (raised thyrotropin with normal free thyroxine)
- Intervention and comparison: thyroxine treatment versus placebo
- Outcome: weight loss and normalisation of thyrotropin taking into consideration confounding factors such as age, sex, smoking, iodine intake, and markers of adiposity (body mass index, degree of obesity, lean body mass, distribution of body fat, waist circumference, and insulin sensitivity)⁹

What patients need to know

- Mild thyroid hormone abnormality—where the thyroid hormone level is normal but the signalling hormone level (thyrotropin) is slightly high—is common in obese children and is called hyperthyrotropinaemia
- This is a consequence rather than the cause of obesity and may become normal after weight loss
- There is no evidence to justify thyroid hormone treatment in obese children with hyperthyrotropinaemia, which is managed with lifestyle measures that promote weight loss. However, thyroid hormone levels need to be monitored every 6-12 months because of the unlikely but possible progression to overt hypothyroidism (underactive thyroid gland)

How patients were involved in the creation of this article

This article was submitted before we asked authors to involve patients and report any contributions.

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