Thyroid Function And Child And Adolescent Obesity

ebook.ecog-obesity.eu/chapter-clinics-complications/thyroid-function-and-child-and-adolescent-obesity

Éva Erhardt
Department of Paediatrics, University of Pécs, Pécs, Hungary
H-7623 Pécs, József a. Str. 7.
erhardt.eva@pte.hu

Introduction

Obesity occurs when energy intake exceeds energy expenditure. Energy balance, hunger and satiety are regulated by neurotransmitters synthezised by the brain, into the region called the hypothalamus. Energy expenditure is regulated mainly by pituitary hormones, especially thyroid hormones. . Energy expenditure has three components: resting metabolic rate (RMR), thermogenesis and energy consumption by physical activity. Energy required for growth is below 2 % of TEE beyond childhood (see corresponding chapters). All of these can be altered by defective (hypthyroidism) or excessive (hyperthyroidism) thyroid hormone synthesis and action.

Adipose tissue and other organs, such as the gut, take part in a ”brain-gut axis” which influences the hypothalamic regulation of energy balances through the secretion of several hormones including leptin, the synthesis of which is enhanced in obesity (see corresponding chapter). (1, 2)

The causes of obesity are shown in Table 1. Secondary causes of obesity is less then 5 % of the cases, so most obese children have so-called ’primary obesity’.

Table 1 Aetiological Classification Of Obesity

1. Primary obesity (’Exogene obesity’)

- *Socieconomic factors*
- *Lifestyle factors*

(decreased physical activity, increased energy intake /fatty food/)

- *Genetic factors* (susceptibility genes)

2. Secondary obesity

- *Neuroendocrine causes*

  (hypothalamic insufficiency or tumor,, hypothyroidism, growth hormone deficieny, Cushing syndrome,)
- *Neuromuscular diseases*
- *Psychiatric diseases*
- *Iatrogenic origin*
- *Genetic causes*

  Abnormal chromosomes number

  Rare syndromes associated with obesity

  Monogenic obesities

Hypothyroidism is often thought to contribute to obesity, however severe obesity is rarely explained by it.
Thyroid hormones modulate several cellular processes that are relevant for REE (3, 4), but the exact mechanisms in humans are still unclear. Because of this, patients with thyroid disease often exhibit changes in body weight, thermogenesis and lipolysis in adipose tissue. Hypothyroidism is usually associated with modest weight gain, decreased thermogenesis and metabolic rate.

In recent years numerous studies have been conducted in order to elucidate the link between the dysfunction of the thyroid gland and fatness in obese children and adolescents. The first reports of mild thyroid stimulating hormone (TSH) elevation of obese children were published in Germany (5,6). The mild elevation of TSH in obese children is usually not associated with changes in total thyroxine (T4) and free T4 (FT4) plasma concentrations, but it's associated with moderately increased total triiodothyronine (T3) and free T3 and with an increased thyroid volume. The mechanism underlying these alterations are not clear, although several theories have been proposed (Table 2.) (7).

Table 2. Causes of thyroid hormonal changes in obese children

- **Subclinical hypothyroidism**
  - Iodines deficiency
  - Autoimmune thyroiditis
- **Autoimmunity (cytokines)**
- **Mutations in the thyroid stimulating hormone receptor (TSH-R) gene**
- **Hypothalamic-pituitary axis**
  - Role of leptin
  - Thyroid hormone resistance
- **Mitochondrial dysfunction**
- **Adaptive process to increased energy expenditure**

Subclinical hypothyroidism (SH) is suggested (8,9) when a slightly elevated serum level of TSH is associated with normal peripheral thyroid hormone concentrations. Weight gain, dyslipidaemia and ischemic heart disease may be due to obesity. SH can be caused by iodine deficiency, autoimmune thyroiditis or a mutation in thyroid stimulating hormone receptor (TSH-R) gene. Another potential pathway is the increased leptin-mediated production of pro-thyrotropin-releasing hormone (TRH). Thyroid hormone resistance due to disturbed negative pituitary feedback and an increased deiodinase activity have also been suggested (7). A study (10) suggests that impaired mitochondrial function plays a role in the significant increase in TSH. The thyroid dysfunction may also represent an adaptive process to increase energy expenditure (4, 11). Another explanation could be the inflammatory state that

characterizes obesity. The adipose tissue secretes inflammatory cytokines (tumor necrosis factor α (TNF α), interleukin -1 (IL1) and interleukin-6 (IL6) which have been proven to inhibit sodium/iodide symporter (NIS) mRNA expression and iodide uptake activity in human thyroid cells. This may in turn explain the compensatory raised TSH level, the tissue resistance to TSH and its reversibility after weight loss in obese individuals (7,12, 13,14). Together these findings indicate that moderately elevated TSH levels are rather a consequence than a cause of obesity.

Acquired Hypothyroidism

Autoimmune (Hashimoto's) thyroiditis is the most common cause of acquired hypothyroidism in the Western world (15, 16). It's more common in adolescent girls and there may be a family history. Autoantibodies are present in 95% of cases. The thyroid gland can be enlarged or atrophic. It can be associated with other autoimmune diseases such as celiac disease, type 1 diabetes mellitus, Addison's disease, alopecia and vitiligo. Clinical signs of hypotyhroidism are shown in Table 3.

Table 3. Clinical signs of hypothyroidism

- Weight gain - obesity
- Constipation
- Tiredness
- Proximal muscle weakness
- Cold intolerance
- Dry skin
- Pallor
- Vitiligo
- Short stature
- Delayed puberty
- Menstrual irregularity
- Decreased school performances
- Family history of thyroid or other autoimmune disease

The principal symptoms of hypothyroidism are tiredness, constipation, weight gain and in children decreased height velocity. FT4 and TSH measurement are required, for diagnosis together with thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) antibodies. Whenever a goiter is present, it's usually diffuse and non-tender, although it can be nodular and occasionally tender. Ultrasound is needed to determine the location and size of the thyroid gland as well as presence of cysts or nodules, and helps in differentiating between non-autoimmune and autoimmune hypothyroidism (17).

Acquired hypothyroidism can be secondary or tertiary. TSH and thyroid releasing hormone (TRH) deficiency is associated with hypothalamo-hypophyseal dysfunction. TSH measurements of these patients are unhelpful, FT4 and FT3 measurements are needed.

Treatment of autoimmune thyroiditis with hypothyroidism is based on thyroxine at a final single daily dose of 2-5 μg/body weight, The target dosage has to be reached gradually over a period of 2-3 months. In a case of secondary or tertiary hypothyroidism doses of thyroxine should be titrated against FT4 levels. Whether euthyroid children with subclinical (compensated autoimmune) thyroiditis should be treated or not is controversial. One approach is to give thyroxine therapy if the TSH value is above 15 mU/l, or if the TSH is above 6 mU/l when the patient has a goiter. The prognosis is very good and the outlook partly depends on whether the child develops other autoimmune diseases (16).

The obese children may have an ultrasound pattern of thyroid gland which is suggestive of Hashimoto's thyroiditis, but without circulating thyroid autoantibodies. A thyroid fine-needle biopsy did not show any lymphocytic infiltrate excluding an autoimmune process. A possible theoretical explanation may be the existing low-grade inflammation due to obesity. The above mentioned cytokines (TNF-α, IL-1, IL-6) may induce vasodilation and increase the permeability of blood vessels in the thyroid gland thus causing local swelling of the parenchyma and the ultrasound findings. A genuine Hashimoto's thyroiditis may develop in obese children, but in these cases the autoantibodies are usually present (18).

Thyroid Gland And The Metabolic Consequences Of Obesity

The metabolic changes (obesity, dyslipidaemia, hypertension, hyperglycaemia, insulin resistance) described in metabolic syndrome (MS) are very similar to the changes associated to hypothyroidism, Hypercholesterolemia in hypothyroidism is characterized by increased levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B, the catabolism of which is decreased because of a reduction of the LDL receptors on liver cells surface. This process is controlled by T3. T3 directly affects the systemic vascular resistance by increasing tissue thermogenesis and metabolic activity. In hypothyroidism the hepatic triglyceride (TG) lipase activity is decreased, and triglyceride plasma concentrations increased, because of the reduced removal rate of TG from plasma. This may contribute to the development of non-alcoholic fatty liver (NAFLD) and steatohepatitis (NASH). However, data about the relationships between thyroid function and lipids remain scarce in obese children .

Thyroid hormones are important determinants of glucose homeostasis: they increase the inhibtion of hepatic glucose production by insulin and increase glucose uptake in muscle. In adults an association between TSH, fasting insulin and insulin sensitivity has been reported in patients with type 2 diabetes mellitus. However there are some

results that after adjustment for BMI there were no significant relationships between thyroid hormones and insulin resistance.

Previous studies in euthyroid children reported that increasing levels of TSH were associated with increasing insulin resistance. Another study reported that in obese children, the decrease of elevated TSH during weigth loss predicts the decrease of fasting insulin plasma concentrations and insulin resistance independently of changes in body weight or body fat. These data are conflicting with another report of the lack of association between decreased TSH levels and changes in insulin resistance after weight loss in another group of obese children. Further investigations are required in order to determine whether elevated TSH plasma concentrations in obese children reflect an adaptation to the increased metabolic rate or a SH which contributes to lipid and/or glucose disturbances (7).

Conclusion

Several studies report altered thyroid function in obese children. An estimated 7 to 23 % of obese children were reported to have moderately elevated TSH levels together with normal FT4 or slightly elevated FT4 and/or FT3, but the mechanisms underlying these changes are not clear. Hypothyroidism should be ruled out whenever TSH concentrations are slightly elevated by measuring peripheral thyroid hormones (FT4, FT3). The diagnosis of Hashimoto"s thyroiditis when a pathological thyroid is suspected by ultrasound requires the presence of elevated anti-thyroid antibodies. Thyroid hormone treatment, should not be used in simple obesity . Further studies are needed in order to establish whether higher TSH in childhood obesity is adaptive to an increased metabolic rate or reflects a subclinical hypothyroidism thereby contributing to lipids and glucose metabolism disturbances.

References

1. Krotkiewski M Thyroid hormones in the pathogenesis and treatment of obesity Eur J Pharmacol 2002; 440: 85-98
2. Fisher DM, Gruetters A. Thyroid disorders in childhood and adolescence. In Sperling MA eds. Pediatric Endocrinology 3rd ed Philadelphia, USA Saunders, Elsevier 2008; 227-254
3. Onur S, Haas V, Bosy-Westphal A et al. L-Tri-iodothyronine in a major determinant of resting energy expenditure in underweight patients with anorexia nervosa and during weight gain. Eur J Endocrinol 2005; 152: 179-184
4. Reinehr T. Obesity and thyroid function Mol Cell Endocinol 2010; 316: 165-171
5. Stichel H, Allemand L, Gruter A. Thyroid function and obesity in children and adolescents. Horm Res 2000; 54: 14-19
6. Reinehr T, Andler W. Thyroid hormones before and after weight loss in obesity. Arch Dis Child 2002; 87: 320-323
7. Pacifico L, Anania C, Ferraro F, Andreoli GM, Chiesa C. Thyroid function in childhood obesity and metabolic comorbidity. Clin Chim Acta 2012; 413: 396-405
8. Rotondi M, Laporati P, La Manna A et al. Raised serum TSH levels in patientswith morbid obesity; is it enough to diagnose subclinical hypothyroidism ? Eur J Endocrinol 2009; 160(3): 403-408.
9. Reinehr T, de Sousa G, Andler W. Hyperthyrotropinaemia in obese children reversible after weight loss and is not related to lipids. J Clin Endocrinol Metab 2006; 91: 3088-3091
10. Wilms L, Larsen J, Pedersen PL, Kvetny J. Evidence of mitochondrial dysfunction in obese adolescents. Acta Paediatr. 2010; 99: 906-911.
11. Reinehr T. Thyroid function int he nutritionally obese child and adolescent . Curr Opin Pediatr 2011; 23: 415-420
12. Chrousos GP. The hypothyalamic-pituitary- adrenal axis and immun-mediated inflammation. N Engl J Med 1995; 332: 1351-1362
13. Radetti G, Kleon W, Buzi F et al. Thyroid function and structure are affected in childhood obesity. J Clin Endocrinol Metab 2008; 12: 4749-4754
14. Duntas LH, Biondi B. The interconnections between obesity, thyroid function, and autoimmunity: the multifold role of leptin. Thyroid 2013; 23(6): 646-653
15. Bhowmick SK, Dasari G, Levens KL, Rettig KR. The prevalence of elevated serum thyroid-stimulating hormone in childhood/adolescent obesity and of autoimmun thyroid diseases in a subgroup. J Nat Med Assoc 2007; 99(7): 773-776.
16. Raine JE, Donaldson MD, Gregory JW, Savage MO, Hintz RL. Acquired hypothyroidism. In Raine JE … Practical Endocrinology and Diabetes in children 2nd ed. Oxford, UK Blackwell Publishing 2006; 98-100.

17. Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013; 5(Suppl 1): 40-44
18. Bursell JDH, Warner JT. Interpretation of thyroid function in children. Ped Child Health 2007; 17 (9(: 361-366

~ About the Authors ~

Éva Erhardt

Éva Erhardt was born and educated in Pécs, studied Medicine at the University of Pécs. After her graduation she was trained in Paediatrics and then Paediatric Endocrinology and Diabetology. Since 2009 she is the Head of the Division of Endocrinology and Diabetology at the Department of Paediatrics, University of Pécs. Throughout her career, she has been highly involved not only in clinics, but also in research mainly focusing on genetic background and consequences of childhood obesity, such as impaired glucose tolerance, type 2 diabetes mellitus and insulin resistance. One book chapter, twenty-two original papers and number of abstracts, which can be cited, have been published (impact factor: 69,381, citations: 310). She is a member in several national and international societies, she takes part in the work of European Childhood Obesity Group (ECOG) since 1993. She was the Vice-President of ECOG between 2010-2013, now she is also a Board Member as Scientific Advisor. She was the President of Endocrine Working Group of Hungarian Paediatric Society between 2012-2014.

~ How To Use This article ~

You are **free to use, share and copy this content** by quoting this article as follow:

Erhardt E (2015). Thyroid Function And Child And Adolescent Obesity. In M.L. Frelut (Ed.), The ECOG's eBook on Child and Adolescent Obesity. Retrieved from ebook.ecog-obesity.eu

Also make sure to **give appropriate credit** when using this content. Please visit ebook.ecog-obesity.eu/terms-use/summary/ for more information.

~ Final Word ~

Thank you for reading this article.

If you have found this article valuable, please share it with someone that will be interested in.

Also make sure to visit ebook.ecog-obesity.eu to read and download more childhood obesity-related articles.