

## Alterations of thyroid function in overweight and obese children: An update

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### ABSTRACT

**Background:** Children with simple overweight and obesity may have alterations in the function of various endocrine organs. Abnormal function of the thyroid gland is seen in about one-fifth of children with obesity. The underlying mechanisms of obesity-associated thyroid dysfunction are still unclear, and hence, the specific treatment with levothyroxine (LT4) is controversial. This review discusses the causes of thyroid dysfunction and its management in pediatric obesity. **Methods of Evidence Acquisition:** The literature search for this narrative review was performed using international databases including PubMed/Medline, EMBASE, SCOPUS, and Google Scholar and relevant information was extracted from articles on thyroid dysfunction in obesity with an emphasis on the most recent studies. **Results:** The most common thyroid function abnormality in children with obesity is an isolated increase in thyroid-stimulating hormone (TSH) followed by minor changes in the ratios of triiodothyronine (T3) and thyroxine (T4). Several mechanisms have been proposed for the thyroid dysfunction in obesity, but none explains it fully, and hence, the clinical implications remain unclassified, and the specific treatment with levothyroxine is controversial. There are a few studies in children with obesity-related thyroid dysfunction and the effect of normalization of thyroid function on weight. However, there are limited data on the effect of normalization of thyroid function by either weight loss or levothyroxine (LT4) treatment on the various metabolic consequences closely associated with thyroid dysfunction in obesity. **Conclusions:** Further research is needed to elucidate the exact mechanisms of thyroid dysfunction in childhood obesity. In addition, larger studies are required to understand the beneficial effects of specific LT4 treatment on weight and on the other thyroid related metabolic derangements in childhood obesity, especially in view of the recent findings of induction of browning of white adipose tissue by thyroid hormones. Until new research establishes its benefits, specific LT4 treatment of thyroid dysfunction in childhood obesity should be avoided.

**Key words:** Children, Mechanisms, Obesity, Thyroid dysfunction, Treatment

Over the past few decades, childhood obesity has emerged as a major public health problem in the developed as well as developing countries [1]. It is associated with several physical, psychological, metabolic, and hormonal disturbances [2,3]. Children with obesity may manifest metabolic problems such as dyslipidemia, hypertension, impaired glucose tolerance, insulin resistance (IR), hypoferrremia, polycystic ovarian syndrome, and non-alcoholic steatohepatitis which contribute to the risk of cardiovascular diseases and diabetes in later life [2-5]. These metabolic problems are attributed to the excess of adipose tissue, which works as an endocrine organ [6]. The hormonal problems due to obesity result in changes in the plasma concentrations, secretory patterns and clearance of various hormones [6]. Of the various hormonal disturbances observed in childhood obesity, thyroid dysfunction in the form of isolated hyperthyrotropinemia is the most common and is often regarded as an adaptive response to reduce body weight by increasing the metabolic rate [6]. The hyperthyrotropinemia usually reverses after weight loss and does not require any specific treatment [6,7]. However, patients are

often initiated on levothyroxine (LT4) due to a widely prevalent belief among clinicians that LT4 treatment along with other obesity interventions results in normalization of body weight [6]. In this review, we discuss the current evidence on prevalence, mechanisms, and the current understanding of replacement therapy with LT4 in thyroid dysfunction due to simple obesity in children.

### MAGNITUDE OF THE PROBLEM

The average prevalence of thyroid dysfunction in children and adolescents with obesity is about 14% (range, 9.2–22.2%) [7-12]. A higher prevalence of 17% and 22.2% has been reported from Germany and Israel, respectively [7,8], whereas studies from Nigeria and Denmark have reported a lower prevalence of about 10% [9,12]. In the two studies from Turkey, the prevalence of isolated hyperthyrotropinemia in childhood obesity was found to be 9.2% and 15.3% [10,11]. These studies on thyroid dysfunction have included preschool and school going children as well as adolescents with age range of 3–18 years (7–12). There is a

scarcity of data from developing countries in the prevalence of thyroid dysfunction in pediatric obesity [13].

## NORMAL METABOLISM OF THYROID HORMONES

The synthesis of thyroid hormones occurs through several enzymatic steps in the thyroid gland to secrete thyroxine (T4) as the main product. The more active triiodothyronine (T3) is mainly produced from deiodination of T4 in peripheral tissues. The homeostatic control involves multiple feedback loops and are in turn influenced by various genetic, physiological, pathological, and environmental factors; the end result of all these is to maintain serum T3 concentrations within the normal range. The classic feedback mechanism is the negative control exerted by T3 concentrations in plasma as well as in hypothalamus and pituitary on the expression and secretion of thyrotropin-releasing hormone (TRH) in the hypothalamus and thyroid-stimulating hormone (TSH) in the anterior pituitary. TSH regulates the function of thyroid gland and promotes the synthesis and activity of Type I deiodinases (D1) as a part of its actions. A similar effect is also exerted on the activity of Type II deiodinases (D2) in other peripheral tissues which have functional TSH receptors, such as brown adipose tissue (BAT) and bone [14]. However, the full thermogenic identity of the brown adipocyte is provided by the D2-dependent pathways. The BAT requires D2-dependent production of T3 for its function and adipogenesis [14]. Therefore, thyroid hormone-mediated activation of the BAT especially in adolescents and adults has a potential role in the treatment of obesity [14]. Several other feedback loops include the inhibition of its own secretion by TSH and peripheral regulation of thyroid hormones that control bioavailability and cellular bioactivity.

## PRINCIPAL EFFECTS OF ABNORMAL THYROID FUNCTION ON BODY WEIGHT

A close relationship exists between thyroid function and body composition. Thyroid hormones are involved in the regulation of basal metabolism and thermogenesis and have a significant role in lipid and glucose metabolism, food intake, and fat oxidation [15]. Thyroid dysfunction, therefore, affects body weight and composition, body temperature, and resting energy expenditure (REE), and total EE independent of physical activity [15]. In adults, untreated subclinical hypothyroidism may lead to significant changes in body weight and is considered as a risk factor for overweight and obesity [13]. Even minor variations in serum TSH due to changes in dosage of levothyroxine during treatment of hypothyroidism are associated with significant changes in REE [16]. There is, however, a scarcity of data regarding the extent of weight gain due to thyroid dysfunction and the extent of weight loss attributable to LT4 treatment in hypothyroidism [13].

## PROPOSED MECHANISMS OF THYROID DYSFUNCTION IN OBESITY

Several mechanisms have been proposed for the alterations in thyroid function in obese patients. However, it is not established whether these alterations in thyroid function are primary or

secondary to obesity [6,13]. Changes in thyroid function are primarily driven by the dysfunction of adipose tissue as weight loss is associated with reversal or mitigation of thyroid dysfunction [17]. Conversely, longitudinal studies have shown that even minor thyroid dysfunction such as isolated TSH increase leads to weight gain and are associated with a significant risk of becoming obese [6,18]. The proposed mechanisms for thyroid dysfunction in obesity are briefly discussed below. A schematic presentation of the main mechanisms is given in Fig. 1.

### Adaptive Response to Increase EE

Thyroid hormones play an important role in energy metabolism and ATP turnover, especially in inducing thermogenesis by stimulating energy uncoupling protein (UCP) [19]. This can partly explain the commonly proposed mechanism that the increase in TSH and T3 in obese children is an adaptive process to increase EE and minimize further weight gain [20]. The mechanism is also supported by clinical observations that minor changes in serum TSH during treatment of hypothyroidism cause significant changes in REE [16]. However, the increase in REE may also be due to a concomitant increase in fat-free mass in obese individuals [21]. Furthermore, recent data suggests that there is no association between EE and concentrations of serum TSH, and free T3 and T4 in euthyroid obese individuals [22]. This may be due to the impaired thyroid hormone action to induce thermogenesis in obese individuals. The adipose tissue especially the visceral adipose tissue is shown to have decreased expression of thyroid hormone receptors, deiodinases, adrenergic receptors, and UCP in patients with obesity [23]. The reduced reactivity to hormonal and adrenergic stimuli in adipose tissues leads to a lower potential to activate thermogenesis in these patients [23]. With weight loss, the concentrations of T3 and TSH also decrease and cause a decrease in REE as well as TEE which partly explains the difficulties in maintaining the weight loss [7].

### Hyperleptinemia Due to Increased Leptin Secretion by Adipose Tissue

Leptin is mainly produced by adipocytes and has a major role in food intake and energy storage [24,25]. It is involved in the regulation of body weight through inhibition of food intake and stimulation of EE and locomotor activity. The serum concentrations of leptin increase proportionally to the increase in body adiposity [24,25]. The consequent hyperleptinemia influences the hypothalamic-pituitary-thyroid axis by promoting TRH expression and synthesis in paraventricular hypothalamic nucleus by a direct action and in arcuate nucleus indirectly leading to an increase in TSH secretion by the pituitary gland [25]. Leptin also activates proopiomelanocortin neurons and inhibits Agouti-related protein and neuropeptide Y neurons in the arcuate nucleus. As a result, the production of  $\alpha$ -melanocyte stimulating hormone increases which stimulates the expression of TRH in hypothalamic neurons by binding to the melanocortin 4 receptor [26]. Leptin also induces the expression of enzymes involved in proteolytic

cleavage of pro-TRH to its biologically active form [25]. Leptin may also act directly on pituitary to increase TSH secretion as leptin receptors are found in the pituitary gland as well. The net result of all these actions of leptin on hypothalamic-pituitary axis is the increased production of TSH from the pituitary. The increased TSH, in turn, may stimulate leptin secretion (TSH helps in differentiation of preadipocytes into adipocytes) through its receptors on the adipose tissue thus creating a vicious cycle of hyperleptinemia and hyperthyrotropinemia [27]. Recent studies also indicate the existence of a complex positive feedback mechanism between these two hormones [28].

In addition to its actions on the hypothalamic-pituitary axis, leptin also influences the metabolism of thyroid hormones by altering the activity of deiodinases in various tissues; increase in D1 activity in the liver, kidney, and thyroid, and reduction of D2 activity in BAT and the pituitary gland [25,28]. Hence, while leptin seems to increase the local production of T3 in the adipose tissue it should be remembered that the reduced expression of thyroid hormone receptors in obesity may hamper the local actions of T3.

### Resistance to Thyroid Hormones

Obesity may induce a state of resistance similar to genetic form of thyroid hormone resistance. The changes in thyroid hormone receptors (TR) are primarily observed in the adipose tissue but are also present in other tissues [29]. A relative pituitary resistance to T3 resulting in increased concentrations of both TSH and T3 is also observed in obesity [24]. The decreased tissue responsiveness explains the usual findings of increased TSH and T3 in an attempt to overcome peripheral resistance [29]. However, recent research in this regard has shown conflicting results. The expression of TSH receptor and TR $\alpha$ 1 in adipose tissue was found to be inversely correlated with body mass index (BMI) [29]. The increase in the severity of obesity increased the peripheral resistance to thyroid hormones leading to an increase in concentrations of TSH and T3, and weight loss increased the expression of receptors and a consequent fall in hormone concentrations [29]. Similar findings of reduced expression of TRs in adipose tissue were observed in another study [23]. In contrast to these two studies, a recent study showed increased TSH receptor expression in adipocytes of overweight individuals and a trend toward increased expression of this receptor with increasing BMI [30]. The discrepancies in the findings of these studies may be related to the location of the adipose tissue studied or an indication of the complexity of regulatory actions of thyroid hormones [6].

### Increased Concentrations of Inflammatory Cytokines

Obesity is characterized by chronic low grade inflammation as evidenced by increase in concentrations of high sensitivity C-reactive protein and other inflammatory cytokines [3,31]. A positive correlation has indeed been documented between markers of inflammation and thyroid function and morphology in obese subjects [31]. The underlying mechanism is inhibition of mRNA expression of sodium/iodide symporter by inflammatory

cytokines such as tumor necrosis factor  $\alpha$ , interleukin-1, and interleukin-6, resulting in reduced iodide uptake in thyroid cells [32]. These adipokines may also induce morphological abnormalities in thyroid gland [24]. The role of chronic inflammation in the regulation of deiodinases in different tissues is also speculated but the mechanisms are unclear at present [33].

### Influence of Thyroid Autoimmunity

Thyroid autoimmunity may lead to the common finding of subclinical hypothyroidism in obesity [34]. The frequent finding of a hypoechogenic pattern on thyroid ultrasonography in obese patients was thought to be the manifestation of a seronegative autoimmune thyroid disease (AITD) that may precede the generation of thyroid autoantibodies [34]. Another study concluded that obesity is a risk factor for thyroid autoimmunity and main cause of acquired thyroid failure in obesity [35]. Leptin was suggested as main determinant of autoimmunity, leptin concentrations were associated with AITD independent of bio-anthropometric variables [35]. This study also noted an increased prevalence of hypothyroidism and thyroid autoantibodies in obese subjects as compared to controls [35]. A greater prevalence of thyroid autoantibodies in obese children as compared to their controls have also been observed in other studies [36-38]. However, not all patients with autoantibody positivity show evidence of thyroid dysfunction; a majority of patients with obesity-related thyroid dysfunction do not have autoantibodies [36-39]. Furthermore, observations in morbidly obese patients suggest that thyroid autoimmunity may not be a major cause of hypothyroidism [40]. The antibody positivity rate was found to be much lower in obese patients with untreated hypothyroidism as compared to controls (32.1 vs. 66.1%) in this study [40]. Thus, the role of thyroid autoimmunity in inducing thyroid dysfunction in obesity remains unresolved.

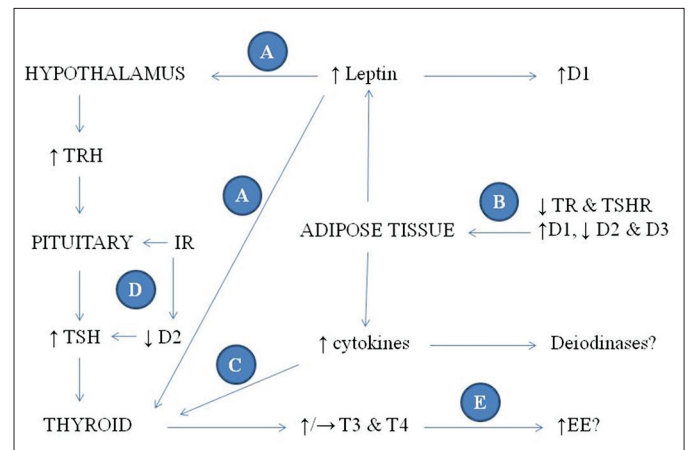
### Role of IR

IR is commonly observed in patients with simple overweight and obesity [41] similar to patients with secondary obesity [42,43]. The hyperinsulinemia stimulates leptin release from adipocytes leading to hyperleptinemia which is closely associated with features of IR [44,45]. Although a positive association between markers of IR and serum TSH has been observed, the underlying mechanisms are not clear [44]. The hypothalamic-pituitary-thyroid axis may be affected by IR in different ways. IR may reduce D2 activity in thyrotrophs causing tissue hypothyroidism and an increased TSH synthesis [46]. The increased TSH may also stimulate the synthesis of inflammatory cytokines by adipocytes and promote IR [17]. The increase in T3 concentrations is also positively associated with IR [47]. Although T3 is known to regulate the metabolic processes of gluconeogenesis, insulin secretion and function, the underlying mechanisms of how it influences the glucose homeostasis are unclear [6].

## CURRENT CONTROVERSIES RELATED TO LT4 TREATMENT OF THYROID DYSFUNCTION

In the wake of current understanding that thyroid dysfunction may lead to several other metabolic and endocrine alterations in obesity, specific therapy with LT4 appears desirable, at least theoretically. There is also a widely prevalent belief among clinicians that LT4 treatment may be beneficial in normalization of body weight [24]. The specific treatment may also help overcoming the difficulties in maintaining the weight loss by keeping the REE and TEE higher which usually fall as a result of fall in the concentrations of T3 and TSH after weight loss [7]. However, clinical studies of LT4 supplementation in obesity-associated thyroid dysfunction have failed to demonstrate beneficial effects on body weight [48,49]. In a study in children with acquired hypothyroidism, LT4 treatment showed no effect on body weight and BMI even after normalization of TSH concentrations [50]. A systematic review concluded that there is not enough data on the effectiveness of LT4 therapy to enhance weight loss and subclinical hyperthyroidism may occur as a complication of such therapy [51]. While the data on LT4 supplementation to treat thyroid dysfunction in obesity remains scarce, there are several studies which have shown a normalization of this dysfunction with weight loss only [7,24,52-55]. The findings and limitations of the major interventional studies are summarized in Table 1. The normalization of TSH after weight loss without LT4 therapy has also been shown to have beneficial effects on insulin sensitivity and leptin levels [55]. The European Thyroid Association and several pediatric thyroid societies recommend that the decision to initiate LT4 treatment in children

with TSH <10 mU/L and normal T4 concentrations should be taken on an individual basis as there is insufficient evidence for the need for such treatment [56,57].



**Figure 1: Proposed mechanisms for alterations in thyroid hormone levels in obesity.** (a) Increased leptin secretion by adipose tissue stimulates hypothalamus to increase thyrotropin releasing hormone (TRH) which increases thyroid-stimulating hormone (TSH) from pituitary. Leptin modulates thyroid gland's responsiveness to TSH, inhibits iodide uptake and expression of sodium/iodide symporter and thyroglobulin. Leptin also increases the activity of deiodinases (D1). (b) There is a change in the activity of deiodinases (D1, D2, and D3) and receptors which promote a state of thyroid hormone resistance. (c) The increased adipokines released by the adipose tissue affect thyroid gland as well as deiodinases. (d) Insulin resistance may reduce deiodinase activity (D2) and increase TSH production from the pituitary. (e) The net result is the alterations in thyroid hormones concentrations leading to changes in energy expenditure and metabolic regulations of body tissues

**Table 1: Summary of interventional studies on thyroid dysfunction in childhood obesity**

Authors, year, country and reference No	Study subjects (mean age)	Results and conclusions	Limitations
Reinehr T <i>et al.</i> , 2002, Germany (52)	118 obese and 107 controls (10.9±2.9 yr)	55 obese children who achieved weight reduction showed normalization of T3 and T4 but not TSH, without use of thyroxine	Small sample size and observation period
Reinehr T <i>et al.</i> , 2006, Germany (7)	246 obese children (9.5±2.0 yr) and 71 controls	Hyperthyrotropinemia improved in 49 obese children who showed significant weight loss after 1 yr intervention based on exercise, behavior therapy, and nutrition education	None
Eliakim A <i>et al.</i> , 2006, Israel (49)	41 obese children (10.6±0.2 yr) 15 received thyroxine	Hyperthyrotropinemia improved in majority of children who participated in weight reduction intervention, irrespective of thyroxine use	Small sample size
Grandone A <i>et al.</i> , 2010, Italy (54)	64 of 398 children (10.3±2.6 yr) participated in weight reduction program	23 out of 64 children showed weight loss and concomitant reduction of hyperthyrotropinemia indicating no requirement of additional levothyroxine	Small sample size
Marras V <i>et al.</i> , 2010, Italy (53)	43 out of 109 obese children with thyroid dysfunction underwent lifestyle intervention	The thyroid hormone levels of obese children who underwent weight reduction program for 6 months were compared with normal weight controls. Moderate weight loss over 6 months improved thyroid dysfunction without use of thyroxine in obese children	Selection of non-obese controls
Matusik P <i>et al.</i> , 2015, Poland (48)	51 children (10.0±3.1 yr), 25 received thyroxine	Normalisation of TSH was similar in children treated by dietary-behavioral management as compared to those given additional levothyroxine	Retrospective design

## RECOMMENDATIONS FOR FUTURE RESEARCH

There are a number of studies on the effect of weight loss on thyroid dysfunction in childhood obesity [7,24,52-54]. However, there is limited data on the effect of weight loss on different metabolic alterations such as hyperleptinemia, IR, and dyslipidemia in obesity which may have a link with the thyroid dysfunction [7,55]. In particular, the effect of specific treatment of thyroid dysfunction with LT4 on these metabolic changes has not been evaluated. There is, thus, a need for acquisition of more data to draw conclusions about the beneficial effects of LT4 supplementation in childhood obesity. A recent study has suggested that thyroid hormones induce browning of white adipose tissue and that this mechanism is mediated through central effects of these hormones on energy balance [58]. This beneficial effect of LT4 treatment in childhood obesity also needs exploration in future studies.

## CONCLUSIONS

Thyroid dysfunction occurs commonly in children with simple overweight and obesity. However, the underlying mechanisms of thyroid dysfunction are poorly understood at present. Several metabolic alterations such as increased leptin concentrations, lipid concentrations, and IR may have a link with thyroid dysfunction. The thyroid dysfunction usually reverses after weight loss, and hence, specific therapy with LT4 is considered inappropriate. However, the data on the effects of specific LT4 therapy in childhood obesity, other than on weight and body mass index, are scarce. Further research should focus on the effects of normalization of thyroid function either by weight loss or specific LT4 treatment on the various metabolic abnormalities commonly occurring with thyroid dysfunction in childhood obesity.

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