Review Article

Hypothyroidism and obesity: An intriguing link

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ABSTRACT

According to common perception, hypothyroidism is held responsible for obesity. However, linking them causally is controversial. Overt hypothyroidism is associated with modest weight gain, but there is a lack of clarity regarding subclinical hypothyroidism. Novel view indicates that changes in thyroid-stimulating hormone (TSH) could well be secondary to obesity. The increasing prevalence of obesity further confounds definition of normal TSH range in population studies. Thyroid autoantibody status may help in establishing the diagnosis of subclinical hypothyroidism in obesity. High leptin levels may play a role in the hyperthyrotropinemia of obesity and also increase susceptibility to thyroid autoimmunity and subsequent hypothyroidism. There is at most a modest effect of L-T4 treatment in overt hypothyroidism in inducing weight loss; benefit in subclinical hypothyroidism is not established with no data supporting thyroid hormone use in euthyroid obese patients.

Key words: Hyperthyrotropinemia, hypothyroidism, leptin, obesity, thyroid autoimmunity

Introduction

Obesity and hypothyroidism are two common clinical conditions that have been linked together closely. The link has become more relevant in the context of an unprecedented rise in the prevalence of obesity worldwide. Obesity is generally regarded by patients as being secondary to thyroid dysfunction. Novel view indicates that changes in thyroid-stimulating hormone (TSH) could well be secondary to obesity. Recent data have also disclosed a relation between obesity and thyroid autoimmunity with the adipocyte hormone leptin appearing to be the key factor linking these two conditions. In this article, we will review the intriguing relationship between obesity and hypothyroidism and the consequent clinical implications.

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Thyroid Dysfunction and Body Weight

Body composition and thyroid hormones appear to be closely related. Thyroid hormones regulate basal metabolism, thermogenesis and play an important role in lipid and glucose metabolism, food intake and fat oxidation.[1] Thyroid dysfunction is associated with changes in body weight and composition, body temperature and total and resting energy expenditure (REE) independent of physical activity.

Hypothyroidism is associated with decreased thermogenesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity.[2] There is clinical evidence suggesting that even mild thyroid dysfunction in the form of subclinical hypothyroidism is linked to significant changes in body weight and represents a risk factor for overweight and obesity;[2] however, this remains a gray area. It has been further noted that small

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variations in serum TSH caused by minimal changes in L-T4 dosage during replacement therapy are associated with significantly altered REE in hypothyroid patients.[3] However, there is a paucity of data regarding the actual extent of weight gain and weight loss with L-T4 treatment in hypothyroidism.

Thyroid-stimulating Hormone and Body Weight Among Euthyroid Individuals

Evidence suggests that slight variations in thyroid function that are within laboratory reference ranges, also contribute to the tendency to gain weight,[4] although this has not been confirmed by all studies. An inverse correlation between free T4 (fT4) and BMI, even when fT4 remains in the normal range has been reported;[3] fat accumulation has been associated with lower fT4 and higher TSH levels among slightly overweight euthyroid individuals, thereby resulting in a positive correlation between TSH and the progressive increase in weight with time.[5] Altered thyroid function with normal feedback regulation may be the primary event that induces alterations in energy expenditure with subsequent increases in BMI and weight.[4]

Thyroid Function in Obese Subjects

TSH levels are at the upper limit of the normal range or slightly increased in obese children, adolescents, and adults and are positively correlated with BMI.[4] Low fT4 with a moderate increase in T3 or free T3 (fT3) levels has been reported in obese subjects.[6] Progressive fat accumulation was associated with a parallel increase in TSH, and fT3 levels irrespective of insulin sensitivity and metabolic parameters and a positive association has been reported between the fT3 to fT4 ratio and both waist circumference and BMI in obese patients.[7] Although the typical picture of high TSH, low fT4, and high fT3 is the most common, various studies on adult obese individuals report thyroid hormone and TSH concentrations as normal, elevated, or reduced.

In obese children, the most common abnormality clearly is hyperthyrotropinemia. Recently, it has also been shown that obese pediatric patients frequently have an ultrasound pattern of the thyroid which is highly suggestive of Hashimoto's thyroiditis.[8] These findings are not associated, however, with production of thyroid autoantibodies.

The causes underlying these alterations in thyroid functions are not known. One theory suggests an increased deiodinase activity leading to a high conversion rate of T4 to T3. This is interpreted as a defense mechanism in obese subjects capable of counteracting the accumulation of fat by increasing energy expenditure.[8] Another probable mechanism is the compensatory increase in secretion of TSH and fT3 in an attempt to overcome decreased tissue responsiveness to circulating thyroid hormones due to the reduced expressions of both TSH and thyroid hormones in adipocytes of obese subjects.[9] High levels of leptin, found in obese subjects, is another potential cause. The main action of leptin is to report centrally the amount of fat, leading to a decrease in appetite and food intake. Leptin has also been shown to stimulate centrally the transcription of pro-thyrotropin-releasing hormone (TRH) and consequently also that of TRH and TSH. Leptin also enhances the activity of deiodinases. Further explanation is that inflammatory cytokines secreted from adipose tissue such as tumor necrosis factor alpha, interleukin (IL)-1 and IL-6, inhibit sodium/iodide symporter mRNA expression and iodide uptake activity.

Normalization of Thyroid Function After Weight Loss

The hyperthyrotropinemia of obese patients was found to revert after weight loss induced either by bariatric surgery or by hypocaloric diet.[5] Weight loss induces a significant decrease in serum fT3 and TSH levels.[4] It seems that even simple changes of lifestyle, characterized by increased physical activity and improvement in body composition without concomitant changes of BMI lead to a decrease of TSH and fT3.[10] Modification in body composition reduces the state of inflammation, decreases the secretion of cytokines, and consequent worsening of thyroid function This phenomenon further implies that autoimmune destruction of thyrocytes is not responsible for the raised serum TSH, and the changes in thyroid function tests are largely functional.

Role of Autoimmunity

The link between obesity and the risk of autoimmune thyroid dysfunction (AITD), which is the main cause of hypothyroidism in adults, is a gray area. The prevalence of AITD in obesity has been reported to be 12.4% in children and between 10% and 60% in adults.[11] Marzullo *et al*. addressed the intriguing hypothesis of a link between obesity, leptin, autoimmunity, and hypothyroidism. This study suggested that obesity is a risk factor for thyroid autoimmunity, thus establishing a link between the main cause of acquired thyroid failure and obesity.[12] This investigation as well as other studies supports a role for autoimmune subclinical hypothyroidism in the pathogenesis of obesity.[13]

Thyroid Hormone and Brown Adipose Tissue in Energy Homoeostasis

Thermogenically active brown adipose tissue (BAT) is found in adults. Hence, the presence of thermogenically active D2 BAT in an adult is clinically important. In the recent years, the presence of BAT has been recognized as an important target for treating obesity. The energy homeostasis in the BAT has been found to be affected by a great extent by thyroid hormone signaling. Thyroid hormone signaling, particularly by inducing type II deiodinases, has a cardinal function in brown tissue adipogenesis. The BAT gets activated by local D2 (type II deiodinase) mediated action. D2 increases expression of the gene Ppargc1a by enhancing thyroid hormone signaling, which coactivates thyroid hormone receptors, leading to increased expression of the gene Ucp1. Dio2 is also upregulated by increased (triiodothyronine) T3 signaling. These (type II deiodinase) D2-dependent pathways provide the mature brown adipocyte with its full thermogenic identity. D2 dependent T3 is necessary for BAT to be functional and also for brown adipogenesis as demonstrated by preclinical trials and cell line studies. Thereby, activation of BAT in adults, specifically through thyroid hormone-mediated pathways, has a potential role in treating obesity.[14]

Clinical implications

From a clinical perspective, obesity and mild thyroid failure are common diseases and frequently coexist. An Indian study showed that among the obese, 33% had overt, and 11% had subclinical hypothyroidism. It further showed that obesity was more common (46% vs. 34%) in overt than in subclinical hypothyroidism.[13]

Clinicians should be particularly alert to the possibility of thyroid dysfunction in obese patients. The problem lies in identifying obese subjects who are affected by mild thyroid hormone deficiency On one hand, raised TSH may be a just a functional consequence of obesity. On the other hand, thyroid failure, especially the subclinical form, may go undiagnosed in obese patients. These patients will continue to increase in weight and will develop a deranged lipid profile, thereby bringing the thyroid/obesity association to a full circle.

The question that emerges is whether an obese patient should be diagnosed as having subclinical hypothyroidism based on an elevated serum TSH level alone. Data suggest that just an elevated serum TSH might not be enough for diagnosing subclinical hypothyroidism in patients with morbid obesity. Thus, it would seem reasonable to measure circulating plasma levels of thyroid hormones and thyroid autoantibodies in these patients to support a diagnosis of autoimmune thyroid failure.[11]

Obese children may show different degrees of alterations pertaining to thyroid function and thyroid ultrasound. Caution is recommended when diagnosing Hashimoto's thyroiditis in these patients. The diagnosis should not be based just upon a pathological ultrasound, without establishing the presence of antithyroid antibodies.

The other important issue is to be unbiased and not attribute all the weight gain to hypothyroidism. We must remember that there is a significant subset of patients who are overtly hypothyroid, yet lean. All said and done there is paucity of data regarding the extent of actual weight gain in hypothyroidism and the amount of weight loss after restoration to euthyroidism with L-T4 treatment. Limited data available show that contrary to popular belief, treatment of overt hypothyroidism results in only modest weight loss and that too not necessarily in all patients.

It is also very important to note that although thyroid hormones have been frequently used in attempts to induce weight loss in obese euthyroid subjects, there is no indication for their administration to control body weight except in obese hypothyroid subjects.

Conclusion

In the near future, the increasing prevalence of obesity may confound the definition of normal TSH range in population studies. Mild hyperthyrotropinemia could well be secondary to obesity, so thyroid autoantibody status may help in establishing a diagnosis of subclinical hypothyroidism in obesity. There is at the most a modest effect of L-T4 treatment in inducing weight loss in overt hypothyroidism and benefit in subclinical hypothyroidism is not established. There is no indication for L-T4 administration to control body weight except in obese hypothyroid subjects. Further research is necessary to determine whether subclinical hypothyroidism is causally involved in the development of obesity. The link between leptin, thyroid autoimmunity, and development of subsequent hypothyroidism needs to be studied. It is conceivable that selected thyroid analogs might be a means to improve weight loss by increasing energy expenditure in obese patients with low T3 during continued caloric deprivation.[15]

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Conflicts of interest

There are no conflicts of interest.

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