Editorial

Thyroid and Obesity: An Intriguing Relationship

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Obesity is one of the most important health risks of our time. The prevalence of obesity has increased worldwide since the mid 1970s. According to the National Health and Nutrition Examination Survey, obesity affected 32.2% of adults in 2003–2004 and reached a peak in subjects in the fifth decade of life (1). Obesity is associated with an increased risk of diabetes, dyslipidemia, kidney disease, cardiovascular disease, all-cause mortality, and cancer (1). Thus, severe obesity is an important cause of premature mortality among middle-aged adults (2). Moreover, obesity, especially central obesity, is linked to many endocrine abnormalities (3), including thyroid dysfunction (4). This is not surprising because T_3 regulates energy metabolism and thermogenesis and plays a critical role in glucose and lipid metabolism, food intake, and the oxidation of fatty acids (4).

Thyroid Dysfunction and Body Weight

Thyroid dysfunction is associated with changes in body weight and composition, body temperature, and total and resting energy expenditure independently of physical activity. Moreover, weight gain often develops after treatment of thyroid dysfunction (5). Both subclinical and overt hypothyroidism are frequently associated with weight gain, decreased thermogenesis, and metabolic rate (5, 6). In a recent cross-sectional, population-based study of 27,097 individuals above 40 yr of age with body mass index (BMI) of at least 30.0 kg/m^2, subclinical and overt hypothyroidism correlated with a higher BMI and a higher prevalence of obesity in both smokers and nonsmokers (6). It has been noted that small variations in serum TSH caused by minimal changes in L-T_4 dosage during replacement therapy are associated with significantly altered resting energy expenditure in hypothyroid patients (7). These studies support the clinical evidence that mild thyroid dysfunction is linked to significant changes in body weight and likely represents a risk factor for overweight and obesity.

Relationship between TSH and Body Weight among Euthyroid Individuals

Evidence suggests that slight variations in thyroid function, even as indicated by tests that are within laboratory reference ranges, contribute to the development of regional obesity and the tendency to gain weight (8, 9), although this has not been confirmed by all studies (10). Furthermore, BMI has been negatively associated with serum free T_4 (FT4) (8), and fat accumulation has been associated with lower FT4 (8, 11) and higher TSH levels among slightly overweight euthyroid individuals (4, 8, 9, 11), thereby resulting in a positive correlation between TSH and the progressive increase in weight with time (9).

Fat cells produce leptin and are thus considered an active endocrine organ (4, 12). The correlation between TSH and BMI could be mediated by leptin produced by adipose tissue. Leptin physiologically regulates energy homeostasis by informing the central nervous system about adipose tissue reserves (4). It modulates the neuroendocrine and behavior responses to overfeeding, thereby regulating food intake and energy expenditure. Leptin is also an important neuroendocrine regulator of the hypothalamic-pituitary-thyroid axis (12, 13) by regulation of TRH gene expression in the paraventricular nucleus, and TSH in turn will stimulate leptin secretion by human adipose tissue (13–15). Leptin also affects thyroid deiodinase activities with activation of T_4 to T_3 conversion (4, 16). All the

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Abbreviations: AITD, Autoimmune thyroid dysfunction; BMI, body mass index; FT3, free T_3; FT4, free T_4; TPOAb, antithyroid peroxidase antibody.

foregoing data support the concept of an inverse relationship between thyroid hormone and leptin.

In subclinical hypothyroidism, for example, altered thyroid function with normal feedback regulation (FT4 at the lower limit of normal range and increased TSH albeit within normal range) may be the primary event that induces alterations in energy expenditure with subsequent increases in BMI and weight (4, 8). The consequent increase in fat mass and in TSH values might increase serum leptin levels.

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 (17–23). TSH seems to be positively related to the degree of obesity (17). A positive correlation has been identified between serum leptin and serum TSH levels in obese individuals (17), which could reflect the positive association between TSH and BMI reported in some individuals (4, 8, 9, 11). Leptin, adjusted for BMI, was found to correlate with TSH (17), which suggests that the increase in TSH and leptin levels in severe obesity could result from the increased amount of fat. Thyroid hormone levels have been reported to be normal, increased, and decreased in obese patients (4); this discrepancy among studies probably reflects the fact that patients were examined at different times (during overeating or a hypocaloric diet) and may differ in degree and type of obesity and in plasma insulin sensitivity.

Interestingly, a moderate increase in total T_3 or free T_3 (FT3) levels has been reported in obese subjects (19–21). Progressive fat accumulation was associated with a parallel increase in TSH and FT3 levels irrespective of insulin sensitivity and metabolic parameters (20), and a positive association has been reported between the FT3 to FT4 ratio and both waist circumference and BMI in obese patients (20). This finding suggests a high conversion of T_4 to T_3 in patients with central fat obesity due to increased deiodinase activity as a compensatory mechanism for fat accumulation to improve energy expenditure (20).

Despite the higher plasma TSH levels, TSH receptors are less expressed on adipocytes of obese *vs.* lean individuals (21). This reduced TSH receptor expression might induce down-regulation of thyroid hormone receptors and thyroid hormone action, thereby further increasing plasma TSH and FT3 concentrations and constituting a condition of peripheral thyroid hormone resistance (21). This sequence of events would be reversed by weight loss, which restores the size and function of mature adipocytes (21). Aberrant thyroid function and TSH level usually normalize after weight loss whether consequent to diet or to bariatric surgery (19–23). Weight loss induces a significant reduction in both TSH and FT3 (19–23), thereby increasing rT_3 due to reduced 5′-deiodination. The decrease in T_3 levels during weight loss with continued caloric deprivation reduces energy expenditure. Therefore, decreased T_3 levels may be responsible for difficulties in maintaining or further decreasing weight loss (23). The finding that TSH, FT3, and leptin levels are increased in obese subjects and that weight loss leads to decreased serum TSH, FT3, and leptin levels supports the hypothesis that the alteration in thyroid function observed in obese subjects is reversible by losing weight (24).

Whatever the mechanism underlying elevated TSH in obesity, it is difficult to identify obese subjects who are affected by mild thyroid hormone deficiency. It seems reasonable to suggest that hypothyroidism should be suspected in obese subjects with slightly increased TSH levels only after measuring plasma levels of thyroid hormones and thyroid autoantibodies, and after having detected evidence of impaired thyroid hormone activity at a tissue level. Thyroid hormone deficiency can be excluded in obese subjects with high serum TSH in the case of FT3 levels that are at the upper limit of the normal range or slightly higher, especially in the presence of normal peripheral parameters of thyroid hormone action (*e.g.* lipid profile that would be expected to be particularly deranged in obese patients with thyroid hormone deficiency) (19, 25). Furthermore, in this condition, the association with normal thyroid autoantibodies may help exclude even further the presence of mild thyroid dysfunction and its potential progression to overt disease.

The evaluation of the thyroid structure by ultrasound does not help to diagnose hypothyroidism in obese patients (18, 26). In fact, in obese children and adults, the moderate increase in TSH is frequently associated with an increase in thyroid volume and hypoechogeneity with an ultrasound pattern suggestive of Hashimoto thyroiditis, even in the absence of thyroid autoantibodies (18, 26). The increased hypoechogenicity in obese subjects has been linked to cytokines and other inflammatory markers produced by adipose tissue. These cytokines can increase TSH levels (thereby increasing thyroid size) and can induce vasodilatation and increase permeability of thyroid vessels with increased parenchymal inhibition (via imbibition) of the thyroid gland that might be responsible for the hypoechogenicity at ultrasound (18). Interestingly, median TSH was reported to be higher in overweight/obese patients with hypoechogenicity than in those with a normal ultrasound pattern (26). In this regard, it is important to recall that an ultrasound pattern suggestive of Hashimoto thyroiditis may precede antithyroid peroxidase antibody (TPOAb) positivity in autoimmune thyroid disease (27),

and TPOAb may not be detected in more than 20% of individuals with ultrasound evidence of thyroid autoimmunity (27).

There is some debate about the link between obesity and the risk of autoimmune thyroid dysfunction (AITD), which is the main cause of hypothyroidism in adults. The prevalence of AITD in obesity has been reported to be 12.4% in children and between 10 and 60% in adults (25, 28). This discrepancy may be due to such factors as sex, age, menopausal status, smoking habit, environmental factors, iodine intake, and degree of obesity.

In this issue of *JCEM*, Marzullo *et al.* (28) address the intriguing hypothesis of a link between obesity, leptin, autoimmunity, and hypothyroidism. They estimated the prevalence and characteristics of thyroid autoimmunity in a population of obese men and premenopausal obese women and found that leptin increases susceptibility to AITD by regulating immune processes. As much as 69% of their patients had severe obesity (BMI > 40 kg/m^2), and the prevalence of hypothyroidism was higher in obese patients than in a control group of age- and sex-matched subjects with normal BMI ($P < 0.05$), as documented by lower FT3 and FT4 plasma levels ($P < 0.01$) and a deranged lipid profile.

AITD patients (*i.e.* positive TPOAb) were mostly severely obese (BMI > 40 kg/m^2) (68%; $\chi^2 = 5.04$; $P < 0.05$), with nonsignificantly higher TSH levels than AITD-negative patients. Leptin levels were higher in AITD-positive obese patients than in AITD-negative patients, and the prevalence of AITD was higher in patients with leptin levels above a median of 33.8 μg/liter (24 *vs.* 8.6%; $P < 0.01$). Logistic regression analysis revealed an association between AITD and leptin ($r = 0.26$; $P < 0.001$) that was unrelated to either fat body mass or BMI ($P < 0.001$). Multiple logistic regression analysis in pooled groups identified female sex and leptin as significant predictors of AITD (28).

Based on these data, one may envisage a link between obesity, TSH increase, leptin increase, autoimmunity, alterations in thyroid morphology and structure, and development of subclinical and overt hypothyroidism. The onset of thyroid hormone deficiency, especially the subclinical form, may go undiagnosed in obese patients. Consequently, 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.

Recent studies suggest that a higher BMI is associated with an increased risk of thyroid cancer (29). Moreover, a serum TSH in the upper half of the normal range is considered as an independent predictor for the presence of thyroid cancer in thyroid nodules (30, 31). Both of these findings together suggest that the higher serum TSH levels could be responsible for the development of thyroid malignancy in obese patients.

Conclusions

It is important to note that the increased prevalence of obesity worldwide may further confound the definition of the normal TSH range in population studies. More research is necessary to determine whether mild thyroid hormone deficiency and the consequent mild TSH increase, *i.e.* to the upper limit of the reference range, are involved in the development of obesity. Moreover, studies are required to establish the potential role of high leptin levels in increasing susceptibility to thyroid autoimmunity, which in turn entails a high risk of developing subclinical or overt hypothyroidism.

Obesity and thyroid dysfunction are common diseases, and consequently clinicians should be particularly alert to the possibility of thyroid dysfunction in obese patients. On the other hand, although thyroid hormones have been inappropriately and 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. In fact, long-term treatment with thyroid hormones does not significantly improve weight loss in obese subjects without thyroid dysfunction and, on the contrary, will entail a risk of adverse effects (32). It is conceivable that selected thyroid analogs might be a means by which to improve weight loss by increasing energy expenditure (as well as improving lipid profiles) in obese patients with low T_3 during continued caloric deprivation (33).

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