Thyroid dysfunction and obesity - what comes first? A complex relationship between hypothyroidism and weight gain.

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Summary.
This study explores the complex relationship between thyroid dysfunction and obesity, emphasizing the bidirectional influences between these conditions. It highlights that Hashimoto's thyroiditis (HT), a prevalent autoimmune thyroid disorder, involves progressive thyroid gland damage due to circulating thyroid antibodies. Obesity is associated with altered thyroid function, where higher BMI correlates with increased TSH and lower FT4 levels. Leptin, elevated in obesity, influences thyroid regulation by increasing TRH receptors and TSH secretion. Hypothyroidism leads to metabolic disturbances, including dyslipidemia and
insulin resistance, contributing to metabolic syndrome risk. The study concludes that obesity-induced thyroid changes are often reversible with weight loss and that hormone replacement therapy should be carefully considered in obese patients with subclinical hypothyroidism, with attention to thyroid antibodies for accurate diagnosis.

Keywords: Hashimoto’s thyroiditis; Hypothyroidism; Obesity; Leptin.

Highlights.
- Although many genetic and environmental factors that could trigger an autoimmune response have been identified, the exact pathogenic mechanisms of HT are still unknown.
- Hashimoto’s disease is considered one of the most common autoimmune diseases and is characterized by progressive damage to the gland associated with circulating thyroid antibodies.
- A higher BMI is positively correlated with an increased TSH level and a lower FT4 level.
- Leptin plays a crucial role in regulating the hypothalamic-pituitary-thyroid axis by increased expression of TRH receptors, which results in elevated TSH secretion. Excessive obesity is linked to hyperleptinemia.
- Hypothyroidism is characterized by increased triglycerides and LDL cholesterol levels and decreased HDL cholesterol measure, which is a risk factor in the development of metabolic syndrome.
- In the diagnosis of thyroid diseases in obese patients, besides TSH, it is worth considering measuring the levels of thyroid antibodies.

Abstract
Introduction: Obesity and mild thyroid failure are common diseases, and the complex relationship between thyroid function and excess weight gain is still being researched. This study analyzes and summarizes the current scientific reports on the intricate correlation between thyroid dysfunction and obesity.
Material and methods: We have gathered the available materials and scientific reports, analyzing and summarizing them in a single study.

Aim of study: We aimed to summarize the studies conducted so far by analyzing the available scientific reports to answer the question of ‘what comes first’ and to understand the correlation between thyroid dysfunction and excessive weight gain.

Discussion: Thyroid dysfunction in the form of hypothyroidism is associated with metabolic abnormalities, which may play a crucial role in the development of metabolic syndrome. On the other hand, excess level of leptin associated with excess adipose tissue is a potential cause of disruptions in the hypothalamic-pituitary-thyroid axis, manifested as elevated TSH levels. Therefore, it is worth considering certain aspects regarding the inclusion of hormone replacement therapy in obese patients presenting laboratory features of subclinical hypothyroidism.

Conclusion. Obesity-induced thyroid dysfunction is typically reversible with weight loss and hormone replacement therapy should be considered for obese patients with subclinical hypothyroidism only if thyroid antibodies are present to confirm an autoimmune thyroid disorder.

Etiology of autoimmune thyroid diseases.

Autoimmune thyroid diseases (AITD) have a complex etiology and are due to the development of autoimmunity against the thyroid, which is more frequently targeted than any other organ by autoimmune responses. It is a polygenic disorder resulting from a combination of genetic predisposition in conjunction with environmental factors and gender [1]. There were identified many SNPs in gene loci that are strongly associated with AITD, such as cytotoxic T lymphocyte antigen 4, CD40, protein tyrosine phosphatase N22, thyroglobulin (TG) and TSH receptor (TSH-R) genes, even though the precise cause and effect connection between specific gene function and the disease has not been found [1,2]. The critical role of AITD development is also determined by environmental factors, among which infection, diet, iodine, medications, stress and smoking appear to be most important [1]. At last, AITD is much more common among women than men. According to the study, the prevalence of
Hashimoto’s thyroiditis in both females and males was 16.626% and 2.651%, respectively. In the case of Graves’ disease, the prevalence was 1.92% in males and 5.54% in females [3].

Hashimoto Thyroiditis.

Hashimoto thyroiditis (HT) is considered the most common autoimmune disease and consequently the most common disease among autoimmune thyroid disorders. The infiltration of the thyroid by lymphocytes, driven by an autoimmune response involving antibodies against thyroid peroxidase (TPO Abs), results in the destruction of thyroid cells (thyrocytes). [4]. The clinical manifestations of Hashimoto's Thyroiditis (HT) include: (A) thyrotoxicosis, which occurs when stored thyroid hormones are released into the bloodstream from damaged thyroid follicles; (B) euthyroidism, which happens when the remaining healthy thyroid tissue compensates for the loss of thyroid cells; and (C) hypothyroidism, which arises when the thyroid gland is unable to produce adequate amounts of thyroid hormones. [4].

The clinical symptoms of HT are dependent on its evolution into hypothyroidism. Signs and symptoms of hypothyroidism are consequences of thyroid hormone deficiency in target tissues and exhibit a wide spectrum of severity that include, but are not limited to, falling hair, dry and thickened skin, muscle cramps, decreased memory, poor concentration, depression, constipation, anemia, increased levels of total and LDL cholesterol, bradycardia, menstrual irregularities and anovulatory cycles [4,5]. The most extreme, but rare presentation of decompensated hypothyroidism is myxedema coma, which is an endocrine emergency with high risk of mortality [6].

Histopathological features of Hashimoto's Thyroiditis (HT) include infiltration by lymphocytes and plasma cells, the presence of fibrotic tissue, formation of lymphatic follicles, atrophy of the thyroid parenchyma, and the presence of large lymphoid follicles with eosinophilic granules in their cytoplasm [6].

The diagnosis of HT is based on clinical symptoms, anti-thyroid antibodies and histological features. Serum anti-TPO antibodies are considered the most important feature of HT and are present in about 95% of patients. Instead, anti-thyroglobulin antibodies are present in a lower (60–80%) percentage of cases and therefore are less reliable for diagnosis [6]. The ultrasound appearance of the thyroid gland may be helpful with differential diagnosis, especially when anti-TPO is negative. The ultrasound features of HT include decreased echogenicity, heterogeneity, hypervascularity, and the presence of small cysts [7]. The main method and
The purpose of HT treatment is the control of hypothyroidism, which consists of taking a synthetic hormone, levothyroxine (LT-4) [8], at a dose of 1.6-1.8mg per kg to achieve the correct level of thyrotropin [9].

Association between thyroid function 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 [10]. Thyroid hormones (T3, T4) control food intake by regulating appetite, thermogenesis and influencing glucose, lipid metabolism and adipogenesis [11], but their secretion remains under the control of thyroid-stimulating hormone (TSH) produced in the anterior pituitary gland, which itself is under the influence of thyrotropin-releasing hormone (TRH) produced in the hypothalamus [13]. Even slightly elevated serum TSH levels are associated with the occurrence of obesity [11]. BMI has been negatively associated with serum free T₄ (FT4) and fat accumulation has been associated with lower FT4 [11]. On the other hand, study shows a positive correlation between higher TSH levels and the progressive increase in weight [11,12,14]. A moderate increase [22] or no association at all was found between BMI and serum free T₃ levels [12]. Longitudinal studies have suggested that obesity impacts thyroid function and leads to an increased level of TSH, indicating that changes in thyroid hormones are a consequence of rising body weight rather than a cause of obesity [11]. A weight gain of 0.6 kg in women and 0.7 kg in men was associated with a 1 mIU/L increase in TSH, suggesting that a slight rise in serum TSH may be a secondary effect rather than a primary factor in obesity [11,19]. This hypothesis is further supported by the observation that thyroid function modifications typically return to normal following weight loss achieved through bariatric surgery or low-calorie diets [10,11,20].

The role of leptin.

Leptin, produced by adipocytes, is considered an active endocrine organ, because of its ability to modulate the responses to overfeeding, thereby regulating food intake and energy expenditure [10]. Leptin plays a crucial role in regulating the hypothalamic-pituitary-thyroid axis by controlling the expression of the TRH gene in the paraventricular nucleus [10,17]. In turn, TSH stimulates the secretion of leptin from human fat tissue [10,17,18]. It also activates T₄ to T₃ conversation by influencing thyroid deiodinase [17,18], however, the local effects of T₃ may be different according to the expression of thyroid receptors in adipocytes [11].
The prospective studies show that after bariatric surgery of patients with morbid obesity levels of TSH and expression of TSH receptor were lower compared to before surgery [21]. This discovery shows that adipocytes have a major influence on the control of TSH and thyroid hormones and that obesity can lead to the development of central and peripheral thyroid hormone resistance, which manifests in increased TSH and T3 levels and can be reversed with weight loss [11,21]. All the above data support the idea of an inverse correlation between thyroid hormones and leptin and lead to hypothesis that obese patients often present an elevated serum level of TSH, which is not indicative of hypothyroidism- this hyperthyrotropinemia being the consequence, rather than the cause, of weight excess [10,11,16].

Thyroid function and body composition.

Hypothyroidism is typically linked to a slight weight gain, primarily due to alterations in body composition. [11], which include four molecular-level components: water, fat, proteins and minerals, usually in that order of decreasing amounts [25]. BMI is very useful in large epidemiological studies [24], but despite of its widespread use, BMI does not accurately reflect body composition and is simply a representative for measuring body fatness [23]. Body composition is usually evaluated by using BIA (bioelectric impedance analysis), which calculates total body water (TBW) and fat-free body mass (FFM) without causing any fluid or electrolyte abnormalities [26,27]. Hypothyroidism is characterized by an increase in body fat, besides a relatively unaffected lean body mass component [28]. The studies show that higher TSH is associated with higher triglycerides and a lower HDL level [29,30]. Furthermore, lowered thyroid hormone levels are the cause of increased triglyceride synthesis and decreased reverse cholesterol transport, which is associated with lower HDL cholesterol activity [29, 31]. Increased insulin resistance has also been documented in both overt and subclinical hypothyroidism, however, no association was found between thyroid function and insulin resistance [29]. Considering metabolic abnormalities, subclinical hypothyroidism and TSH >10mIU/L may be a risk factor in the development of metabolic syndrome, which appears to be driven primarily by higher triglycerides and lower HDL [29,32].

Treatment of subclinical hypothyroidism in obese Patients.

In the past, thyroid hormone preparations were widely used as anti-obesity drugs, and they continue to be inappropriately prescribed today. [11]. Analogs of thyroid hormone due to
iatrogenic thyrotoxicosis may cause unfavorable loss of fat-free tissue and have harmful effects on the cardiovascular system, such as cardiac arrhythmia, heart failure, or ischemic events [11,33]. It is debatable whether an obese patient should be diagnosed as having subclinical hypothyroidism based only on an elevated serum TSH level [16]. Obese patients have an increased prevalence of raised serum TSH, which in most cases is not accompanied by circulating thyroid antibodies; the finding of a thyroid hormone profile suggestive of SH may not indicate true hypothyroidism in patients with morbid obesity [11,16,34].

According to the guidelines of the European Society of Endocrinology and the American Thyroid Association, LT4 treatment is not advised for obese patients who have isolated hyperthyrotropinemia [11,16,34,35,36]. It would seem reasonable to take into consideration routine circulating thyroid antibodies testing in obese patients to further support a diagnosis of autoimmune thyroid disorder [11,16].

Conclusions.
Thyroid dysfunction can be responsible for modest changes in body weight, mostly based on changes in body composition, and in the past, thyroid hormone deficiency was considered responsible for obesity. According to the studies, severe obesity is usually not secondary to hypothyroidism, because when treated, only less than 10% weight loss is observed. The role of leptin produced by fat cells and its influence on TSH level should be taken into consideration and further explored. It is worth considering expanding diagnostics in obese patients to include thyroid antibodies and not relying solely on elevated TSH levels.

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