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Relationship between thyroid hormone with obesity

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بسمِ اللَّه الرحمٰن الرَحيم

﴿ وَنُنَزِّلُ مِنَ الْقُرْآنِ مَا هُوَ شِفَاءٌ وَرَحْمَةٌ لِّلْمُؤْمِنِينَ وَلَا يَزِيدُ الظَّالِمِينَ إِلَّا خَسَارًا

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صدق الله العلي العظيم

سورة الاسراء آية (82)

الاهداء

للقلم حلم يعتنق حبره وللورق وجه يحمل في طياته اثر السعي وبعد....

هنيئا لنا ولكل زميل وزميله لم يقف او يستسلم بل قاوم بصبره وسعيه واثقاً بربه ونفسه، وها نحن اليوم نتوج لحظاتنا الأخيرة في ذلك الطريق الذي كان يحلم في باطنه العثرات والشوك ورغما عنها ظلت اقدامنا تخطو بكل صبر وطموح، وكم من ايام مرت شعرنا بثقلها ومرارتها ولكن لم تعيقنا بل كان الذكرى تمر لتنير احلامنا بقلوبنا .

شكرا اولا لوالدي ، تلك الايدي الخفية التي تربت على اكتافنا وتدعو في اوان الليل،،شكرا لكل اعضاء هيئه التدريسية....

وشكرا لمن كان يؤثر بنا بطموحه العالي وبصمته وليس بأخلاقه ودروسه فقط فهنيئا لك حقا يا استاذتي وعسى الله ان يجعل حياتك محفوظه بالتوفيق ومليئة بالسعادة اينما كنتي....

واخيرا تتمنى محادثتكم ان ترى قلوبكم الطموحة على مناصب العليا من العلم والطموح....

ولا تكن احلامكم رفيقه دربكم دوما....

الشكر و التقدير

الحمد لله حمدا كثيرا حتى يبلغ الحمد وهو منتهى والصلاة والسلام على اشرف مخلوق اناره الله بنوره واصطفاه ...

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List of Contant

Abstract

Obesity remains a pressing global health concern, with multifaceted etiological factors contributing to its prevalence. Among these factors, the intricate interplay between thyroid hormones and obesity has garnered significant attention in both clinical and scientific realms. This review aims to elucidate the nuanced relationship between thyroid function and obesity, encompassing the bidirectional influences and underlying mechanisms involved.

Thyroid hormones, primarily thyroxine (T4) and triiodothyronine (T3), play pivotal roles in regulating metabolic rate, energy expenditure, and lipid metabolism. Perturbations in thyroid function, characterized by hypo- or hyperthyroidism, often coincide with alterations in body weight and composition. Hypothyroidism is commonly associated with weight gain, fluid retention, and adiposity, whereas hyperthyroidism may lead to weight loss, increased metabolic rate, and muscle wasting.

Beyond the conventional view of thyroid dysfunction impacting obesity, emerging evidence suggests a complex bidirectional relationship. Adipose tissue expresses thyroid hormone receptors and deiodinases, indicating a potential regulatory role of thyroid hormones in adipogenesis, lipolysis, and adipokine secretion. Conversely, adiposity, particularly visceral adiposity, can disrupt thyroid hormone metabolism through various mechanisms, including altered hypothalamic-pituitary-thyroid axis function, adipokine-mediated inflammation, and adipocyte dysfunction.

Moreover, genetic predispositions, environmental factors, and lifestyle behaviors further modulate the interaction between thyroid hormones and obesity. Understanding these intricate relationships is paramount for optimizing clinical

management strategies for obesity and thyroid disorders, highlighting the importance of comprehensive assessment and tailored interventions.

In conclusion, the relationship between thyroid hormones and obesity extends beyond a simple cause-effect paradigm, encompassing intricate molecular mechanisms and bidirectional influences. Further research endeavors are warranted to delineate the precise pathways linking thyroid function with adiposity and metabolic health, ultimately paving the way for innovative therapeutic approaches and personalized interventions in the management of obesity and thyroid disorders.

Keywords: Thyroid hormones, Obesity, relationship.

1. Introduction

1.1. Obesity has emerged as a global epidemic.

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) with its prevalence reaching alarming levels in recent decades. It poses significant health risks, including cardiovascular disease, type 2 diabetes, and certain cancers, thereby imposing a substantial burden on healthcare systems worldwide. While numerous factors contribute to the development and progression of obesity, the role of thyroid hormones in modulating metabolic homeostasis and body composition has garnered considerable attention. (2). Obesity is associated with an increased risk of diabetes, dyslipidemia, kidney disease, cardiovascular disease, all-cause mortality, and

cancer. Thus, severe obesity is an important cause of premature mortality among middle-aged adults (3). Moreover, obesity, especially central obesity, is linked to many endocrine abnormalities including thyroid dysfunction (3). This is not surprising because T3 regulates energy metabolism and thermogenesis and plays a critical role in glucose and lipid metabolism, food intake, and the oxidation of fatty acids (4).

1.2. 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/m2 , 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-T4 dosage during replacement therapy are associated with significantly altered rest ing 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.

1.3. 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 T4 (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 T4 to T3 conversion (4, 16). All the 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.

1.4. 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 (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 T3 or free T3 (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 T4 to T3 in patients with central fat obesity due to increased deiodinase activity as a compensatory mechanism for fat accumulation to improve energy expenditure (20)

Aim of study

In this review, we aim to comprehensively explore the relationship between thyroid hormones and obesity, encompassing the latest research findings, underlying molecular mechanisms, clinical implications, and future directions. By elucidating the intricate connections between thyroid function and adiposity, we endeavor to provide insights that may inform personalized approaches to obesity management and thyroid disorder treatment, ultimately improving patient outcomes and public health.

2. literature review

2.1. The metabolic consequences of hypothyroidism

A seminal study by Bray and colleagues (1976) demonstrated the metabolic consequences of hypothyroidism, highlighting its propensity for weight gain, decreased basal metabolic rate, and altered lipid metabolism. Subsequent research endeavors corroborated these findings, revealing the role of thyroid hormones in regulating energy expenditure, thermogenesis, and adipose tissue metabolism. (21)

2.2. The molecular mechanisms underlying these metabolic alterations.

Conversely, investigations into hyperthyroidism elucidated its catabolic effects, characterized by weight loss, increased metabolic rate, and muscle wasting. Studies by Salvatore and colleagues (2014) and Brent and colleagues (2012) further elucidated the molecular mechanisms underlying these metabolic alterations, emphasizing the central role of thyroid hormone signaling pathways in modulating adipocyte differentiation, lipolysis, and lipid oxidation. (22)

2.3. The bidirectional relationship between thyroid hormones and adiposity.

Beyond the conventional view of thyroid dysfunction impacting obesity, emerging studies have shed light on the bidirectional relationship between thyroid hormones and adiposity. For instance, research by Rosenbaum and Leibel (2010) revealed that weight loss interventions, such as calorie restriction, can induce adaptive changes in thyroid function, leading to reductions in circulating T3 levels and metabolic rate. (23)

2.4. The influence of adipose-derived hormones

Furthermore, investigations into the role of adipose tissue in thyroid hormone metabolism have uncovered novel insights into the regulation of thyroid function by adipokines and cytokines. Studies by Mullur and colleagues (2014) and Mantzoros and colleagues (2011) highlighted the influence of adipose-derived hormones, such as leptin and adiponectin, on hypothalamic-pituitary-thyroid axis function, thereby implicating adiposity in the pathogenesis of thyroid disorders. (24)

2.5. Genetic Studies:

Genome-wide association studies (GWAS) and candidate gene approaches have identified genetic variants associated with both thyroid function and obesity. For instance, studies by Day and colleagues (2015) and Yang and colleagues (2012) identified genetic loci associated with thyroid hormone levels and body mass index (BMI), providing insights into the genetic basis of the relationship between thyroid function and obesity. (25)

2.6. Animal Models:

Animal studies, particularly in rodent models, have elucidated the physiological and molecular mechanisms linking thyroid hormones with adiposity. For example, research by López and colleagues (2016) using rodent models demonstrated the role of thyroid hormone signaling in brown adipose tissue thermogenesis and energy expenditure, highlighting its potential therapeutic implications for obesity. (26)

2.7. Clinical Trials:

Clinical trials investigating the effects of thyroid hormone replacement therapy on body weight and metabolism have yielded mixed results. While some studies reported modest reductions in body weight and improvements in metabolic

parameters with thyroid hormone supplementation (Jonklaas et al., 2014), others found no significant effects on weight loss or metabolic rate (Biondi, 2013). These findings underscore the complexity of thyroid hormone metabolism and the need for individualized treatment approaches. (27)

2.8. Mechanistic Studies:

Mechanistic studies have elucidated the molecular pathways through which thyroid hormones influence adipocyte function and metabolism. Research by Lanni and colleagues (2016) demonstrated the role of thyroid hormone receptors in regulating adipose tissue lipolysis and insulin sensitivity, providing mechanistic insights into the metabolic effects of thyroid hormones. (28)

Recommendations:

Based on the current understanding of the relationship between thyroid hormones and obesity, as well as the findings from previous studies, here are some recommendations for future research and clinical practice:

1. **Longitudinal Studies:** Conduct longitudinal studies to elucidate the temporal relationship between thyroid dysfunction and obesity, including the impact of thyroid hormone levels on changes in body weight and composition over time. This would help clarify the causal relationship between thyroid function and obesity and identify individuals at higher risk for developing obesity-related complications.

2. **Mechanistic Investigations:** Further explore the molecular mechanisms underlying the bidirectional relationship between thyroid hormones and adiposity, including the role of adipose tissue metabolism, adipokines, and cytokines in modulating thyroid function. This could lead to the identification of novel therapeutic targets for obesity and thyroid disorders.

3. **Clinical Trials:** Design and implement well-controlled clinical trials to evaluate the efficacy and safety of thyroid hormone replacement therapy in individuals with obesity and thyroid dysfunction. Assess the impact of thyroid hormone supplementation on body weight, metabolic parameters, and cardiovascular outcomes to inform evidence-based treatment guidelines.

4. **Individualized Treatment Approaches:** Develop personalized treatment approaches for individuals with obesity and thyroid disorders, taking into account genetic predispositions, environmental factors, and lifestyle

behaviors. Tailor treatment strategies to optimize thyroid function, promote weight loss, and mitigate the risk of obesity-related complications.

5. **Lifestyle Interventions:** Emphasize the importance of lifestyle interventions, including dietary modifications, regular physical activity, and behavioral therapy, in the management of obesity and thyroid disorders. Encourage patients to adopt healthy lifestyle habits to support thyroid function, promote weight loss, and improve overall metabolic health.

6. **Health Education and Awareness:** Increase public awareness and health literacy regarding the relationship between thyroid hormones and obesity, emphasizing the importance of early detection, diagnosis, and management of thyroid disorders. Educate healthcare providers and patients about the potential impact of thyroid dysfunction on body weight and metabolic health.

By implementing these recommendations, we can advance our understanding of the complex interplay between thyroid hormones and obesity and improve clinical outcomes for individuals affected by these conditions. Additionally, fostering collaboration among researchers, clinicians, and policymakers will facilitate the translation of research findings into effective interventions and public health strategies for combating obesity and thyroid disorders.

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. 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 T3 during continued caloric deprivation.

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