Low Thyroid Function and Metabolic Syndrome: The "Chicken-And-Egg" Dilemma.

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Abstract

Low thyroid function and metabolic syndrome are very common conditions in clinical practice. Worldwide, it is estimated that 0.2 to 5.3% of the population has overt hypothyroidism and 2 to 10% subclinical hypothyroidism. In Brazil, recent studies have found a 7.4% (5.8-9%) prevalence of overt hypothyroidism and 5.4% (3.8-7%) of subclinical hypothyroidism. As for the metabolic syndrome, the prevalence ranges from 22 to more than 30% of the population and, in Brazil, it seems to be higher in women. This high frequency of both diseases sharing some of the same signs and symptoms has suggested that this is not merely a casual association, but a conspicuous relationship. However, the question remains as to who would be the egg and who would be the chicken: could low thyroid function be a risk factor for metabolic syndrome or, on the contrary, would the latter in fact be responsible for the thyroid condition? We have reviewed the subject looking for clues and answers that may lead us to a better approach for our patients.

Introduction

Low thyroid function and metabolic syndrome are very common diseases in clinical practice [1–6]. Worldwide, it is estimated that 0.37 to 0.4% of the population present overt hypothyroidism and 3.8 to 9% subclinical hypothyroidism [1]. In Brazil, recent studies have found 7.4% (5.8-9%) prevalence of overt hypothyroidism and 5.4% (3.8-7%) of subclinical hypothyroidism [3,7,8]. Like other thyroid disorders, this dysfunction is more frequent in women. Regarding metabolic syndrome, the prevalence ranges from 22 to more than 30% of the population, and in Brazil, it also seems to be higher in women [9,10]. This high frequency of both diseases sharing some of the same signs and symptoms has evoked some hypothesis that low thyroid function could be a risk factor for metabolic syndrome and vice-versa. In fact, the frequent concomitance of the two conditions and the similarity of the involved mechanisms suggest a vicious cycle in which, inevitably, a question arises: which came first, the egg or the chicken?

Defining Hypothyroidism and Metabolic Syndrome

Hypothyroidism represents the set of clinical and laboratory manifestations resulting from absolute or relative deficiency of thyroid hormones.

Metabolic syndrome, in turn, has traditionally been described as a set of characteristics that follow increased adiposity, which is usually measured by waist circumference. There are 2 main definitions that are currently used: that of the International Diabetes Federation (IDF), which is narrower [11], and that of the National Cholesterol Education Program - Adult Treatment Panel II (NCEPT-ATPIII) [12], as shown in Table 1. A new definition proposed by a Polish group defined the basic diagnostic criteria as abdominal obesity, measured by waist circumference greater than 88cm in women or 102cm in men, or body mass index greater than 30kg/m22. As additional criteria, they consider: (i) prediabetes or diabetes (fasting glucose > 100mg/dL or >140mg/dL after 120min in oral glucose tolerance test; or HbA1c > 5.7%; or on glucose-lowering drugs); (ii) elevated non-HDL cholesterol level (non-HDL cholesterol level > 130mg/dL or on lipid-lowering drugs); and (iii) normal high blood pressure or hypertension (SBP > 130 and/or DBP > 85mmHg in-office measurement; or SBP > 130 and DBP > 80mmHg on measurement at home or on antihypertensive treatment). Metabolic syndrome is then diagnosed in patients with excess adiposity and 2 of the 3 additional criteria [2]. Thus, the presence of excess adipose tissue represents the cornerstone for the existence of the syndrome.

Both conditions have been associated with poor outcomes. The presence of diabetes, one of the criteria used for the diagnosis of the syndrome, for example, is associated with greater risks of congestive heart failure, chronic kidney disease, blindness, and neuropathy, with increased mortality, mainly due to cardiovascular disease. Hypothyroidism, in turn, has also been associated with increased cardiovascular risk and mortality. In this thyroid dysfunction, the greater risk of death would be associated with factors such as increased insulin resistance, arterial hypertension, increased systemic vascular resistance and arterial stiffness, endothelial dysfunction, and altered coagulability [13].

"THE EGG": low thyroid function as an important driver to metabolic syndrome

 Important evidence indicate that the low thyroid function may be the cause of metabolic syndrome. Hypothyroidism affects all components of the syndrome [14].

TSH and thyroid hormones (T3 and T4) are strong regulators of metabolic rate. The gain or loss of adiposity depends on the energy balance, which includes satiety, sympathetic activity of the neural system and endocrine systems [5]. Thyroid hormones, especially T3, have direct effects on ATP utilization with chronotropic and inotropic effects, regulate body temperature, appetite, and control sympathetic activity [15–18]. Thyroid hormone metabolites (T2) are known to prevent hyperlipidemic diet-induced adiposity gain by increasing the energy expenditure of white adipose tissue [19,20]. In addition, thyroid hormones accelerate the anabolic and catabolic pathways of macronutrient

metabolism, such as lipolysis, fatty acid oxidation, and protein turnover [21–25]. They also play a role in mitochondrial biogenesis in the brown adipose tissue, through type 1 UCP protein [26–29]. The "beige" adipose tissue is also influenced by thyroid hormones, since they have a direct and indirect (via irisin) role in "darkening" white adipose tissue [26,28,30]. In fact, type 2 deiodinase plays a crucial role in thermogenesis [23,30]. Thyroid hormones influence other modulators of energy expenditure such as FGF [21], fetuin A and neuroregulin [31,32].

TSH is becoming another important factor in increasing adiposity, as it has been shown that TSH receptors on mesenchymal stem cells can influence lineage differentiation into muexpenditure suchne cells [33]. Especially in adipose cells, activation of TSH receptors stimulates early adipogenesis, lipolysis and may favor the formation of brown adipose tissue [26,28,30,31,34]. Together, reduced energy expenditure at rest associated with decreased thermogenesis and hypothalamic control of body temperature and energy partition due to low thyroid function contribute to increased waist circumference [18,26].

Regarding lipid metabolism, hypothyroidism decreases hepatic LDL receptors, cholesterylester transfer protein (CEPT), hepatic lipase and lipoprotein lipase [35–37]. It is also associated with increased PCSK9 (Proprotein convertase subtilisin/kexin type 9), which plays an essential role in lipid metabolism through degradation of the LDL receptors [35,38,39]. New insights into lipoprotein subfractions are suggesting that low thyroid function is associated with a more atherogenic lipoprotein profile, even when total levels are within the reference range [40–43]. For example, LDL subfractions have been shown to become smaller and denser as TSH levels increased [41]. Very small and very large triglyceride-rich lipoproteins, thought to be more atherogenic, are also elevated in individuals with low thyroid function [42,44]. Likewise, there are lower levels of the small subfraction of HDL, which is thought to be protective for cardiovascular disease [40].

Hypothyroidism can cause increased diastolic and systolic blood pressure due to increased peripheral vascular resistance [5,45–47]. Thyroid hormones act in vasculature and heart through nuclear genic regulation and also through non-classical pathways [5]. The chronotropic and inotropic effects on the heart cause systemic vasodilation that reduces peripheric vascular resistance. The action on central nervous system leads to autonomic blood pression regulation48. Recently, it has been shown that parvalbuminergic neurons on the anterior hypothalamus reduce blood pressure and are dependent of TRa signaling [49].

Concerning glycemic metabolism, there is a positive association between high TSH levels and insulin resistance, even within the reference range [50]. This peripheric resistance to insulin leads to reduced

glucose uptake. Thyroid hormone T3 also acts directly on the liver through TRb, inducing hepatic gluconeogenesis, affecting glycogen metabolism and insulin signaling [51,52]. The central action on the hypothalamus increases the sympathetic flow to the liver, enhancing gluconeogenesis and glucogenolysis and reducing glycogen synthesis [52]. On the other hand, excessive T3 levels cause B-cells apoptosis and death, so it is necessary that T3 levels to be lower in the pancreas53. Therefore, it appears that the correlation between thyroid function and the incidence of diabetes must follow a U-shaped curve, where low and high T3 levels are not adequate for optimal pancreatic function. However, most studies to date have primarily found an association between low thyroid function and type 2 diabetes risk [54–56]. A recent Brazilian study showed that higher levels of FT4 are protective for diabetes and a higher conversion rate (T3/T4) is associated with a higher risk of diabetes while, on the contrary, lower levels of FT4 are associated with a higher incidence of diabetes and lower conversion rates are protective for diabetes in overweight and obese individuals[57].

Some groups are even considering high TSH as a new cardiometabolic marker [58].

"THE CHICKEN": the metabolic syndrome affecting thyroid function

There are several key points of metabolic syndrome that could connect it to hypothyroidism: increase of adipose tissue, insulin resistance and chronic inflammation [6,59,60]. It seems that the main factor linking metabolic syndrome to hypothyroidism is leptine61. Leptine is a hormone produced by adipose tissue that acts at the hypothalamus inducing society and increased energy expenditure [62]. Most patients with obesity have hyperleptinemia but are central-resistant to its actions [52,62]. The relationship between leptin and the thyroid axis is complex [63–66]. In general, leptin increases TRH (thyroid releasing hormone), which increases TSH and thyroid hormone production [62]. However, this mechanism is different between species and nutritional state. In fasting, leptin production is reduced leading to thyroid function suppression. In fact, in these cases, when exogenous leptin is administrated, thyroid hormones are normalized [65,67,68]. High or normal levels of leptin may have inhibitory actions on TSH, NIS and thyroglobulin. Leptin administration increases D1 activity in the liver and pituitary and decreases D2 activity in hypothalamus and brown adipose tissue [52].

Another factor that might be a causative linker between metabolic syndrome and hypothyroidism are inflammatory cytokines [69,70]. The chronic inflammation of the adipose tissue leads to increased cytokine levels that alters thyroid function through decreased NIS expression and decreased activity of D1 which reduces T3 levels [22,65]. In addition, inflammatory cytokines can affect thyroglobulin and thyroperoxidase production/function and impair T3 release [68].

Finally, insulin resistance, especially when tied to leptin disturbances, seems to be related to obesity and leads to increased levels of serum TSH [71]. Recent studies have indeed showed that the use of metformin, a drug to reduce insulin resistance, may reduce serum TSH levels [72]. Other mechanisms have been proposed to harness both entities (metabolic syndrome and hypothyroidism) and the activation of the AMP activated protein kinase (AMPK) pathway may be involved [73].

The relationship between obesity and hypothyroidism has been observed in other studies, such as one from a Brazilian group that analyzed TSH levels before and periodically after Roux-en-Y gastric bypass [74]. They concluded that weight loss after bariatric surgery led to normalization of TSH levels in 89,5% of obese patients that had previous subclinical hypothyroidism. Another Brazilian study has shown that BMI had a positive relationship with TSH levels. However, after bariatric surgery, TSH levels fell, suggesting that excessive weight led to TSH increase.

Despite there is evidence that metabolic syndrome could cause hypothyroidism, thyroid dysfunction could in turn worsen the consequences of the syndrome such as chronic and acute complications of diabetes - increased risk for cardiovascular disease, stroke, heart failure, chronic kidney disease, retinopathy, and neuropathy [75–78]. A meta-analysis that evaluated the relationship between diabetic retinopathy and subclinical hypothyroidism found that the latter could increase 2.13 times the risk for diabetic neuropathy [76]. Another study found similar results for nephropathy and cardiovascular disease [78]. Carotid intima-media thickness is also higher in patients with metabolic syndrome that had subclinical hypothyroidism than euthyroid individuals [79].

Which Came First? The Egg or the Chicken?

Excess adiposity represented by abdominal obesity is only the tip of the iceberg that involves many complications for the body[2,80]. It leads to hypertension, diabetes and atherogenic dyslipidaemia, which results, in the long-term, in impaired kidney function, non-alcoholic fatty liver disease, heart failure, obstructive sleep apnea, polycystic ovary syndrome, sympathetic activation and tachycardia, hyperuricemia and chronic inflammation.

On the other hand, hypothyroidism also interferes in many systems and organs. From central nervous system impairment (mood disorders, depression, confusion, memory loss) to altered skin and nails, low thyroid function has multi-organ effects that lead to decreased basal metabolic rate, decreased exercise intolerance, weight gain, increased body mass index, decreased thermogenesis in brown adipose tissue and decreased lipolysis in white adipose tissue, impaired cholesterol regulation in the

liver and cardiac dysfunction [5,22,81]. The consequences of hypothyroidism and the metabolic syndrome are very similar and may share the same etiopathogenesis. Actually, it seems to be a bidirectional pathway between hypothyroidism and metabolic syndrome, as there is evidence for both sides being responsible. From the evidence presented, it is clear that the question persists: which came first, the egg or the chicken?.

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