

“High normal” thyroid stimulating hormone: does it matter?

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Metabolic syndrome characterized by central obesity, glucose intolerance, hypertension, and atherogenic dyslipidemia is associated with an increased risk of cardiovascular disease (CVD). It is estimated that approximately 20% to 25% of the world's adult population have the metabolic syndrome and they are two times as likely to die from and three times as likely to have CVD compared with those without the syndrome. Insulin resistance and central obesity are considered to be the underlying causes of the metabolic syndrome [1].

Since thyroid hormone regulates metabolism, its dysfunction has adverse effects on various organs in our body. Especially, hypothyroidism can alter normal metabolism of glucose and lipid, and body composition, which could lead to the appearance of the metabolic syndrome.

Insulin resistance occurs when cells in the body such as liver, muscle, and fat tissue become less sensitive to insulin, which is produced by pancreatic β cells to facilitate glucose utilization. As a result, glucose is not absorbed well by the cells but remains in the blood, triggering the need for more insulin to be produced (leading to hyperinsulinemia) to overcome

insulin resistance. The presence of insulin resistance is well known in hypothyroidism. It is due to defects in the ability of insulin to increase glucose utilization in muscle and fat tissue [2]. Weight gain is common in hypothyroidism. Hypothyroidism is also a common cause of secondary dyslipidemia. The synthesis and the degradation of lipid are impaired in hypothyroidism, but degradation is reduced to a greater extent, with a net effect of accumulation of low density lipoprotein cholesterol and triglycerides [3]. Hypothyroidism from overt hypothyroidism to subclinical hypothyroidism has been shown to be a risk factor for CVD in several studies, although others have not shown this association [4].

Recently, there were studies suggesting that even euthyroidism with “high normal” thyroid stimulating hormone (TSH) levels is also associated with the metabolic syndrome. Ruhla et al. [5] reported that euthyroid subjects with a TSH in the upper normal range (2.5 to 4.5 mU/L) were more obese, had higher triglyceride levels, and had an increased likelihood for the metabolic syndrome. Also, in Korea, Lee et al. [6] reported in a population-based study that subjects with high normal TSH levels had an almost 2-fold higher risk of the metabolic syndrome compared to those

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within reference group.

In concert with these studies, Oh et al. [7] in this issue of *The Korean Journal of Internal Medicine* reported interesting findings in 2,760 young Korean women aged < 40 years old. They found a significant association between elevated TSH levels within normal range and the metabolic syndrome. Waist circumference, systolic and diastolic blood pressure, and triglycerides were significantly associated with TSH levels, though fasting hyperglycemia and low high density lipoprotein cholesterol levels were not significantly associated with TSH levels. Subjects with TSH levels greater than 2.5 mU/L had approximately a 2-fold greater risk of the metabolic syndrome than those with TSH levels less than 2.5 mU/L. In addition, the degree of insulin sensitivity was associated with TSH levels. Therefore, they concluded that healthy young women with TSH levels greater than 2.5 mU/L should be assessed for the presence of the metabolic syndrome even TSH levels are in the normal range.

The main strength of the current study is that it limited study subjects to young (therefore, premenopausal) women. So, it could minimize the confounding effects of aging and menopause on the presence of the metabolic syndrome. Next, they measured insulin sensitivity more accurately using oral glucose tolerance-based metabolic clearance rate of glucose [8]. However, the relationship between TSH levels and insulin resistance in these euthyroid subjects is still unclear because the authors failed to demonstrate significant hyperinsulinemia and correlation between a homeostasis model analysis of insulin resistance and TSH levels. Another notable point of this study is that their data support the lowering of the upper limit of the normal range to 2.5 mU/L as proposed in Caucasians by the National Academy of Clinical Biochemistry [9]. Lastly, this study's results seem to be meaningful in clinical practice as early detection of those individuals with the metabolic syndrome is important. Once a diagnosis of the metabolic syndrome is made, the future management of the condition should aim to reduce the risk of CVD and type 2 diabetes through lifestyle interventions, including low calorie diet and exercise.

However, there are some limits and unanswered questions in the current study. First, they did not analyze the association of thyroid hormone levels (i.e.,

free T₄ levels) and components of the metabolic syndrome. Though TSH levels are more sensitive than free T₄ levels in assessing the thyroid hormone status, thyroid hormones, not TSH, are likely to determine the metabolic process. Also, the cause of high normal TSH levels was not clear because they did not measure thyroid autoantibodies. Second, the association this study revealed was very weak, though statistically significant, as reflected by correlation coefficients (r) < 0.1. It is therefore doubtful that high normal TSH levels alone will contribute to the presence of the metabolic syndrome. Third, they included only women in study subjects. Lastly, the lowering of the upper limit of the normal range to 2.5 mU/L is still problematic because fluctuation of TSH levels is not uncommon in clinical setting, especially in patients with autoimmune thyroiditis. To address these issues and avoid unnecessary burdens on otherwise "healthy" population, we need more clinical studies, including a longitudinal one, in the future.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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