Association of Thyroid-stimulating Hormone and Cardiovascular Risk Factors

Xianglan Sun1, Ying Sun2, Wan-Chun Li3,4, Chang-Yi Chen3, Yen-Hui Chiu4, Hung-Yu Chien5 and Yao Wang6

Abstract

Thyroid hormone plays an important role in regulating the lipid and glucose metabolism. Previously, much attention has been drawn to define the pathophysiological relationship between thyroid dysfunction and the incidence of cardiovascular diseases (CVDs). While the conditions of overt hypothyroidism and subclinical hypothyroidism were both emphasized, the association between CVD risks and the deregulated circulating thyroid-stimulating hormone (TSH) level remains to be elucidated. Nevertheless, multiple TSH-mediated physiological adaptations, including alteration of the serum lipids, body mass index, blood pressure and insulin sensitivity, have led to the difficulty of clearly examining the association between the TSH level and CVD prevalence. The current review aims to 1) summarize the evidence for the role of thyroid dysfunction and TSH abnormality in CVD pathogenesis and 2) explore the possible underlying molecular mechanisms of TSH-mediated cardiovascular pathology in hopes of providing better therapeutic strategies for the patients with deregulated TSH.

Key words: thyroid-stimulating hormone, hypothyroidism, cardiovascular disease, lipid metabolism, thyroxine


Introduction

Subclinical hypothyroidism (SH), the mildest form of hypothyroidism, is characterized by an increased level of thyroid-stimulating hormone (TSH) with normal thyroid hormone concentrations. The prevalence of SH has been previously reported to be 4-10% in the general population and the incidence is increased to 15-20% in women older than 60 years of age and men older than 74 years of age (1-3). Moreover, Lindeman et al. found that a greater proportion of non-Hispanic white women were diagnosed with SH compared with Hispanic women, suggesting that the SH rate varies with ethnicity (4). The clinical significance of SH is not only due to its high prevalence, but also because SH may serve as a potential predictor of overt hypothyroidism (OH), which may subsequently result in cardiac and lipid abnormalities (5, 6). The etiology of SH, which is similar to that of OH (7), is often caused by chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis) and systemic impacts of impaired thyroid function have been reported (8). For example, it is recognized that SH/OH may be one of the confounding factors for cardiovascular diseases (CVDs) and metabolic syndrome, as the association between hypothyroidism and CVD/metabolic syndrome-related physiological cues (including obesity, atherogenic dyslipidemia, and hypertension) have also been described (9). However, the underlying mechanism(s) of SH/OH-mediated regulation for the progression of CVD has not yet been fully elucidated, especially for the cases of SH. While an elevated TSH level is routinely detected in the SH patients, the TSH-mediated regulation for CVD-associated pathology will also be em-
phosphorylated. The current article seeks to reveal the possible underlying mechanisms of TSH-induced CVD in the subjects with thyroid dysfunction at the molecular level.

**TSH and Cardiovascular Risk Factors**

OH is commonly considered to be a risk factor for atherosclerosis, possibly due to lipid abnormalities (10, 11). While SH has been shown to be an independent factor for atherosclerosis and myocardial infarction in elderly women (12), whether the correlation between atherosclerosis and thyroid dysfunction also exists in other SH subjects, however, is still highly debated (11-14).

Numerous studies have demonstrated the serum TSH levels to positively correlate with atherogenic lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), apoB, Lp(a) levels, non-high-density lipoprotein cholesterol (non-HDL-C) and the LDL-C/HDL-C (L/H) ratio (1, 15-21), thus suggesting that TSH may control lipid homeostasis, which potentially modulates the cardiovascular conditions, although the relationship between hypothyroidism and the HDL-C level have been inconsistent in SH subjects (1, 18, 22-24). Additionally, the TSH level appears to be closely correlated with the carotid intima-media thickness (CIMT), a marker of early atherosclerotic change, in both the OH and euthyroid subjects (25-27). Nevertheless, several previous studies did not find a prevalence of lipid abnormalities in the individuals with SH compared with those with euthyroidism (12, 15, 28-34). In addition, a 20-year follow-up study found no significant association between SH and an increased risk of ischemic heart disease (35), while Lindeman et al. additionally showed that the SH physiology did not correlate with cardiovascular disease in elderly patients, thus indicating that the TSH-mediated regulation of the lipid profile may not be the primary factor leading to a high prevalence of CVD in the SH patients (36). Furthermore, several potential factors, including age (37), sex (38), an increase of lipoprotein, an upregulation in oxidation (39, 40), a deregulation of angiotensin-mediated vascular remodeling (41, 42) and impaired endothelial-dependent arteriole dilatation (43), were suggested to be underlying mechanisms for thyroid hormone control of atherogenesis. However, a better understanding of the orchestration of these molecular regulations for controlling cardiovascular physiology is still required.

**TSH and Hypertension**

The association between the TSH level and hypertension has also been emphasized. It has been previously shown that the diastolic blood pressure was higher in women with SH than in the euthyroid controls (44), whereas normotensive patients with a history of total thyroidectomy surgery exhibited reversibly elevated diastolic blood pressure in response to the iatrogenic induction of short-term hypothyroidism (45). A cross-sectional, population-based study investigating more than 30,000 individuals without a history of thyroid disease additionally concluded that within the reference range, namely 0.50-3.5 mIU/L, a linear positive association between TSH and systolic and diastolic blood pressure was detected, suggesting that the TSH concentration may have a long-term influence on the cardiovascular condition (46). Other epidemiological reports have further demonstrated positive associations between the systolic blood pressure and TSH values (20, 31, 47-49), and negative correlations between the HDL-C and TSH levels (27, 31, 47, 48) further confirmed that TSH may play an important role in regulating blood pressure, partly by the modulation of the lipid profile. Larger perspective cohorts are essential to further define the correlation between TSH and blood pressure, while *in vivo* animal studies are necessary to elucidate the underlying cellular and molecular mechanisms of how the TSH level affects the blood pressure.

**Thyroid Hormone-mediated Regulation for Vascular Conditions**

**I. Thyroid hormone-regulated endothelial function**

Endothelial dysfunction, a common pre-atherosclerosis condition (46), has been detected in both the SH and OH patients, thus suggesting that hypothyroidism may play a role in this disease (50, 51). Multiple hypothyroidism-mediated mechanisms, including the induction of hypercholesterolemia, increased oxidized LDL-C, upregulation of insulin resistance (52), stimulation of hypercoagulation (53) and an elevation of peripheral vascular resistance (52, 54), have been shown to accelerate atherosclerosis. In addition, thyroid hormone itself may also induce vasodilation, activate T3-mediated vasodilatation on vascular smooth muscle, increase the circulating noradrenaline level, and decrease vascular β-adrenergic receptors in the skeletal muscle (49, 52, 54, 55). Moreover, increased peripheral vascular resistance and the upregulation of arterial stiffness (56) may additionally play essential roles in modulating the cardiovascular condition in subjects with hypothyroidism. Additionally, at the molecular level, there is evidence demonstrating that the expression of type II iodothyronine deiodinase in cultured human coronary artery and aortic smooth muscle cells implicated the importance of the T3 level for maintaining the normal physiology of vascular smooth muscle cells (57). Interestingly, recent studies have found that TSH stimulated the production of cyclic 3,5-adenosine monophosphate (cAMP) in human coronary artery smooth muscle cells, implying that TSH may trigger the cAMP signaling pathway to regulate vascular homeostasis (58, 59).

**II. Thyroid modulated lipid metabolism**

In addition to the impact on endothelial cells, hypothyroidism may regulate the vascular condition via modulation of lipid metabolism. It was previously reported that thyroid hormone increased the conversion of cholesterol ester from
HDL-C to LDL-C and VLDL in exchange for triglyceride (60). Another study showed that thyroid hormone could upregulate the hepatic lipoprotein lipase activity resulting in an altered HDL-C sub-fraction (61), possibly via the increased expression of HDL-C receptor scavenger receptor class-B, type I (SR-BI) to initiate HDL production (62). In contrast, thyroid hormone stimulated the LDL degradation via the activation of the LDL receptor while the effect of T3 on the LDL receptor was abolished in the receptor-null human fibroblasts (63). Moreover, an epidemiological analysis showed that post-menopausal women with lower thyroid levels exhibited higher CVD-associated mortality, potentially due to lack of estrogen to compensate for the elevated circulating TG and TC, further implying the potential association of thyroid hormone and lipid-mediated CVD pathology (64). Taken together, it may therefore be feasible to attenuate lipid abnormality via thyroid hormone therapy in CVD patients.

In the condition of hypothyroidism, hypercholesterolemia was detected, potentially due to increased cholesterol synthesis and a decreased activity of hepatic lipoprotein lipases (65) or LDL clearance in the liver (13, 66) in OH subjects. Recent studies further demonstrated that thyroid hormone could directly regulate sterol regulatory element-binding protein-2 (SREBP-2), a major transcriptional activator for LDL receptor synthesis (67), and increased plasma TG levels caused by a reduction of the removal rate (13) further provided an alternative thyroid hormone-mediated regulatory signal for lipid homeostasis.

Nevertheless, the results from other investigations of the elevation of the serum cholesterol levels in SH individuals, in which only TSH is elevated, but the thyroid hormone levels are normal, raised the argument as to whether elevated TSH levels play a direct role in the development of hypercholesterolemia in hypothyroidism. To address this issue, clarifying the distribution of the TSH receptor (TSHR)-mediated signaling activity may be a link. It is well known that TSH acts on thyroid follicular cells as well as many non-thyroidal tissues, such as lymphocytes, the pituitary, thymus, testes, kidney, brain, adipose tissue, and fibroblasts via TSHR-mediated signaling machinery (68-74). Active TSHR signaling could be transduced via the cAMP - phospholipase C (PLC) - protein kinase A cascade (60). The downstream effectors, including the cAMP response element-binding protein (CREB), a member of a large family of basic leucine zipper proteins, could be stimulated and translocated into the cell nucleus to activate the cAMP target genes (75, 76). Our previous finding demonstrated that TSHR mRNA and protein are present in human and rat liver tissues, as well as in human hepatic L-02 cells, while the cAMP production could be activated by TSH treatment in dose-, time- and TSHR-dependent manners (77). Moreover, the results suggested that TSH induced the transcriptional activity of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCRC), the rate-limiting enzyme in cholesterol synthesis, through the cAMP/PKA/CREB pathway in vitro (78) because the TSH administration was capable of increasing the serum TC using surgically thyroidectomized rats in vivo (78). Other studies demonstrating increased hepatic HMGCRC gene expression and elevated cholesterol levels during thyroid hormone deficiency further confirmed that the TSH signaling activity could regulate the lipid physiology in liver cells (79). Taken together, these findings are of great interest since they may help us to obtain a better understanding of how TSH clinically controls the development of hypercholesterolemia.

**TSH and Insulin Resistance**

Insulin resistance is one of the major pathophysiological conditions in the patients with metabolic syndrome (80) and is associated with an increased cardiovascular risk (81). Although the TSH and LDL-C levels showed a promising correlation with insulin resistance (30), the relationship between hypothyroidism and insulin resistance remains controversial (82-86). Recent studies have suggested that TSH may regulate glycemic metabolism, thereby leading to a metabolic imbalance, through a thyroid hormone-independent mechanism. Indeed, it was reported that a higher TSH level was associated with an increased risk of metabolic syndrome in euthyroid postmenopausal women (20), while other studies demonstrated that the circulating TSH level was positively correlated with the BMI (84, 87, 88) and HbA1c (27). Interestingly, Bakker et al. reported that insulin-resistant subjects with higher TSH levels have elevated LDL-C concentrations compared with insulin-sensitive individuals, indicating that the thyroid-mediated regulation for lipid metabolism may become more dominant under conditions with imbalanced glucose metabolism (30). In addition, Miyauuchi et al. found that IL-18 maybe an important factor for inducing insulin resistance in hyperthyroidism (89). However, the evidence for insulin resistance and the mechanisms during hyperthyroid states remains unclear.

**Effects of Thyroxine Therapy**

Overall, the correlation between the thyroid hormone level with the risk for CVD in the SH subjects may result from various factors, such as hyperlipidemia, endothelial dysfunction, enhanced LDL oxidation, inflammation and hyperhomocysteinemia (36, 90-93). Furthermore, whether long-term thyroxine therapy can improve dyslipidemia, thereby leading to a reduction of the cardiovascular risk, is still questionable. The effect of thyroid hormone on lowering TC through an accelerated LDL-C clearance rate has been demonstrated in previous studies (64, 94), although evident side effects, such as an increasing metabolic rate, have hindered the progress of utilizing high-dose thyroid hormone for the treatment of coronary artery disease (95). A significant reduction in the mean TC, LDL, VLDL and TG levels, but not the HDL level, after treatment with thyroxine (96) was found, whereas no significant changes in the
lipid profile in response to L-thyroxine treatment during SH was detected in various trial studies. Therefore, these studies did not indicate any benefit of L-thyroxine treatment during SH (97).

The development of thyroid hormone analogs to treat hypercholesterolemia was emphasized due to their potential effect on lipid homeostasis in the liver and heart. These potential analogs should exhibit lipid-lowering actions without unexpected cardiac side effects. Several effective T3 analogs, including Triac, 3,5-diiodothyropropionic acid (DITPA) and 3,5-dichloro-4 [(4-hydroxy-3-isopropylphenoxy)phenyl]acetic acid (KB-141), have been demonstrated to lower TC with minimal side effects, while an alternative advantageous impact of these compounds for increasing the HDL-C level was additionally found (98-101). Furthermore, it was found that DITPA treatment for heart failure could lead to significant metabolic changes, including lower TC, LDL and TG levels, however, no effect on the HDL level was observed (101, 102). More recently, a novel functional analog of iodothyronines, TRC150094, was shown to down regulate the serum TC and TG levels and accelerate fatty acid oxidation in rats on a high-fat diet, thereby revealing a potential strategy for counteracting the metabolic dysfunction associated with visceral fat accumulation (103).

Several trials demonstrated that thyroxine administration did not change the TC (97, 104, 105), LDL-C (105), HDL-C (105-109) or apo A1 levels (19, 33, 105, 108, 109). More recently, a large randomized, double-blind, controlled cohort revealed that physiologic thyroxine replacement lowered the LDL-C level, decreased the TC level and accelerated fatty acid oxidation in rats on a high-fat diet, thereby revealing a potential strategy for counteracting the metabolic dysfunction associated with visceral fat accumulation (103).

Figure. The association between thyroid-stimulating hormone and cardiovascular risk factors.

Conclusion and Future Perspectives

Thyroid hormone has a significant cardiovascular impact and lower thyroid hormone levels may serve as an important predictor for the mortality of cardiac patients. SH has been found to be associated with many early cardiovascular abnormalities, while accumulating evidence suggested that TSH-mediated lipid metabolism regulation may play a key role for this pathophysiological condition (Figure). Although no large cohort studies have so far shown promising clinical
outcomes, thyroid hormone replacement therapy in SH patients may nevertheless provide beneficial effects in controlling the risks of cardiovascular diseases. In addition, although hemodynamic improvements have been reported following thyroid analog therapy, the side effects of high-dose treatment remain a concern for safely applying this therapeutic intervention clinically. Further investigations, including large-scale multicenter trials, are essential before the routine use of thyroid hormone replacement treatment in SH individuals. Future work to develop a tissue-specific thyroid analog to avoid unexpected, harmful effects and possible alterations in the thyroid hormone signaling pathways are also necessary.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We thank the members of our respective laboratories and many colleagues for their helpful discussions.

The work of the authors is supported by grants from the National Science Foundation of Shandong Province (Z2003C02 and 2008GG2NS02004) and the Taipei City Hospital/Department of Health, Taipei City Government, Taiwan (100TPECH06 to W-C Li).

References


36. Litman DM, Romero LJ, Schade DS, Wayne S, Baumgartner RN, Garry PJ. Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey. Thyroid 13: 595-600, 2003.


© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html