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Editorial Comment
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Nocturnal Non-Dipping: An Overlooked Clinical Manifestation of Subclinical Hypothyroidism Linking to Increased Cardiovascular Risk

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Subclinical hypothyroidism is characterized by levels of thyroid-stimulating hormone (TSH) above the conventional upper limit of 4 mIU/L, normal serum free T4 levels, along with inexplicit and nonspecific clinical manifestations. Given that TSH levels increase with advancing age and the presence of anti-thyroid peroxidase (anti-TPO) antibody, the prevalence of subclinical hypothyroidism ranges between 4-10% in general populations.[1,2] The common causes of subclinical hypothyroidism include iatrogenic and autoimmune thyroid diseases, of which most are Hashimoto's thyroiditis.[3] Elevated TSH levels could, however, be transient. While about 1/3 of individuals with subclinical hypothyroidism might recover spontaneously years later, those with higher levels of TSH (often referred to as above 10-12 mIU/L) or the presence of anti-TPO antibody are more likely to develop overt hypothyroidism afterwards.[4]

Growing evidence has indicated that subclinical hypothyroidism is associated with increased cardiovascular risk, though consensus remains elusive regarding the management of subclinical hypothyroidism because of its indeterminate natural course. The association is more substantial if the TSH level is above 10 mIU/L. In a meta-analysis exploring individual data from 55,287 participants with 542,494 person-years of follow-up in eleven prospective cohorts, the risk of coronary heart disease and the relevant mortality were raised by 89% and 58%, respectively, in subclinical hypothyroidism with TSH level of 10.0 to 19.9 mIU/L, relative to euthyroidism with TSH of below 5 mIU/L.[5] As for the association between subclinical hypothyroidism and the risk of heart failure, a study combined individual participant data from six prospective cohort studies enrolling 25,390 participants with 216,428 person-years of follow-up. The results of the pooled analysis demonstrated that the presence of TSH level of 10 to 19.9 mIU/L predisposed those with subclinical hypothyroidism to an 86% increase in the risk of heart failure events.[6] Besides, another study also found that individuals with subclinical hypothyroidism tended to have a modest, albeit insignificant, trend of increased risk for stroke events and fatal stroke in the pooled analysis of 47,573 individuals with 489,192 person-year of follow-up from 17 cohort studies.[7]

Endothelial dysfunction induced by high TSH levels is one of the plausible pathophysiologic links between subclinical hypothyroidism and cardiovascular diseases.[8] It has been shown that TSH could induce endothelia to upregulate atherogenic expression of inflammatory adhesion molecules, and also to attenuate the atheroprotective expression of endothelial nitric oxide (NO) synthase.[9] As a result, the endothelial dysfunction not only could increase the risk of atherosclerosis and subsequent cardiovascular events,[8] but might alter the circadian patterns of blood pressure, evidenced by the relationship between the presence of NO-associated endothelial dysfunction and the increased occurrence of nocturnal non-dipping in hypertensive patients.[10,11]

Nocturnal non-dipping is defined as, relative to awakening blood pressure, sleep-time blood pressure decline of less than 10 percent, and has been recognized as a cardiovascular risk marker in both hypertensive and normotensive individuals.[12] However, it has remained unclear whether individuals with subclinical hypothyroidism are predisposed to nocturnal non-dipping, considering the evidence supporting high TSH

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level-mediated endothelial dysfunction.[8,13] Therefore, Canbolat IP et al. conducted a study enrolling 49 normotensive participants with subclinical hypothyroidism, and 50 sex- and age-matched normotensive controls, to compare the differences in circadian alteration of blood pressure using 24-hour ambulatory blood pressure monitoring.[14] In this issue of the Journal, the authors reported that the presence of subclinical hypothyroidism significantly correlated with the occurrence of nocturnal non-dipping.

From a clinical perspective, the results of the study implied that nocturnal non-dipping could be identified as a cardiovascular manifestation of subclinical hypothyroidism, and a feature pertaining to individuals who might benefit from correction of high TSH levels. However, evidence is thus far conflicting on whether cardiovascular health would improve with thyroid hormone treatment for subclinical hypothyroidism. A study analyzing the United Kingdom General Practitioner Research Database explored the association between levothyroxine treatment of subclinical hypothyroidism and cardiovascular events in 4735 patients followed for a median of 7.6 years. The authors found that, relative to untreated patients of subclinical hypothyroidism with TSH level of 5 to 10 mIU/L, supplement of levothyroxine could reduce the risk of fatal and non-fatal cardiovascular risk by 39 percent in patients aged between 40 and 70 years, but not in those beyond 70 years of age.[15] Nevertheless, the analysis of a Denmark registry including 12,212 patients with a median follow-up period of 5.0 years did not support the beneficial effect of levothyroxine substitution in patients with subclinical hypothyroidism on reducing the risk of myocardial infarction and mortality.[16] In the Thyroid hormone Replacement for Untreated older adult with Subclinical Hypothyroidism (TRUST) study, the double-blinded randomized placebo-controlled trial enrolled 737 adults who had a mean age of 74.4 years and diagnosed as subclinical hypothyroidism with a mean TSH level of 6.4 mIU/L.[17] However, the authors concluded that, even with TSH levels restored to normal range, those in the levothyroxine-treated group did not have the quality-of-life improvement measured by the questionnaires of the Hypothyroid Symptoms score and Tiredness score.[17] The results remained pending about fatal and non-fatal cardiovascular events. More evidence would be available in near future, from a randomized controlled trial investigating whether use of levothyroxine for subclinical hypothyroidism could confer beneficial effects on ventricular function, endothelial function and blood coagulability and rheology in the setting of post-acute myocardial infarction.[18]

Taken together, using ambulatory blood pressure monitoring could be justifiable for supplementing global assessment of cardiovascular risks in individuals with subclinical hypothyroidism, even whose baseline blood pressures are within normal range. Considering that endothelial dysfunction could be improved with levothyroxine treatment of subclinical hypothyroidism,[19,20] further research would be worthwhile to clarify the effects of thyroid hormone replacement on restoring circadian pattern of blood pressures, and reducing the risk of cardiovascular diseases in individuals with subclinical hypothyroidism.

DISCLOSURES

All authors have nothing to disclose.

CONFLICT OF INTEREST

None declared.

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