Circulating Thyroxine
A Major New Risk Marker for Atherosclerosis?

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Background: Thyroid Function and Atherosclerotic Cardiovascular Disease Risk
Thyroid dysfunction has long been known to affect certain cardiovascular conditions. Measuring thyroid function to discover occult hyperthyroidism is recommended to evaluate causal factors for new-onset atrial fibrillation. Similarly, thyroid function testing is advocated to exclude hypothyroidism as a secondary cause of dyslipidemia before initiating lipid-lowering therapy. However, the effect of thyroid hormone on atherothrombosis, the major cause of cardiovascular morbidity and mortality, remains controversial, with various studies showing no effect on cardiovascular risk, increased risk associated with low thyroid function, and greater risk associated with high thyroid function in some cases within the reference range. Thus, whether variations in thyroid function both without and within the normal reference range can impact atherosclerotic cardiovascular disease (ASCVD) risk is unresolved.

Summary of the Current Study
In this issue of Circulation Research, Bano et al10 examine the relationship of 3 metrics of thyroid function to 3 measures of atherosclerosis, spanning its spectrum from preclinical disease (defined by coronary artery calcification), to clinical ASCVD events, to ASCVD-related mortality. To examine this association, they turned to the well-known prospective population-based Rotterdam Cohort Study—an ongoing investigation of the determinants of chronic disease occurrence and progression in middle-aged and older adults. The Rotterdam Study enrolled its first cohort in 1989 and added a second cohort in 2000 and a third in 2006, with clinical follow-up for health outcomes every 3 to 5 years.

The present study included 9420 subjects, including those seen at the third visit for cohort 1 and the first visits for cohorts 2 and 3, who had complete baseline thyroid function measurements for thyroid-stimulating hormone (TSH), free thyroxine (FT4), and thyroid peroxidase antibodies, and who also had complete information on ASCVD. Over a mean follow-up of 8.8 years, 912 incident ASCVD events occurred, 612 of them fatal. FT4 levels were found to be associated with coronary artery calcification and positively and linearly associated with both ASCVD events and mortality, including within the currently recognized normal reference range for FT4. Associations with TSH were much weaker and were significant only for ASCVD mortality, whereas no associations were found with thyroid peroxidase antibodies. Results for FT4 were robust, persisting in the face of multivariable adjustments and through several sensitivity analyses.

These associations were not only of statistical but also of clinical significance. Strikingly, results were at least as strong or stronger within the euthyroid range, where a 2.70× higher risk of incident ASCVD events and a 4.15× greater risk of ASCVD mortality were noted for participants with an FT4 at the upper reference range (1.94 ng/mL) compared with those at the lower reference limit (0.86 ng/mL). A lesser magnitude of association was noted with non-ASCVD mortality, indicating atherosclerosis as a major target of thyroid hormone on the risk of mortality. Interactions with mortality were significant for sex (association stronger in men) and prevalent ASCVD (stronger if ASCVD was present at baseline) in the overall population but not in the 7575 euthyroid participants.

Based on these findings, the authors suggest that FT4, even within the euthyroid range, be considered a novel predictor of ASCVD risk. Further, they conclude that the reference range of FT4 and TSH should be reevaluated.

Current Study Perspectives
The current study has many advantages, including the use of the large population-based Rotterdam Study with its long and nearly complete follow-up. Further, the major finding of a linear relationship between FT4 throughout its measured population range, from below, to (remarkably) within, to above the reference range, and risk across preclinical disease, clinical ASCVD, and cardiovascular mortality, independent of traditional risk factors, is a striking and potentially actionable observation. This finding was robustly persistent through multivariable adjustments and multiple sensitivity analyses. Further, the diminished association with non-ASCVD mortality argues for an element of cardiovascular specificity. The study also points to less promising thyroid function tests: no association between ASCVD risk and thyroid peroxidase antibodies and a weak and variable association with TSH.

The study does experience limitations inherent to all observational studies, as the authors acknowledge. These include residual confounding, applicability limited strictly to the
population studied (white/Northern Europeans), and the inability to elucidate mechanisms or prove causality. However, arguing against simply marker status for the association of FT4 and ASCVD risk, the authors noted that nonthyroidal illness typically causes lower (rather than higher) FT4 levels in association with normal serum TSH levels. They also explored the question of reverse causality by analyzing outcomes after excluding events occurring within the first 2 years after baseline thyroid function testing and found results to be unchanged. Another limitation is that thyroid function was measured only at baseline; nevertheless, lack of serial measurement would be expected to underestimate rather than overestimate effects. Finally, the study lacks information on serum-free triiodothyronine—the most potent thyroid hormone\(^\text{11}\)—and the impact of this omission on study conclusions is uncertain.

Although several limitations of the study are inherent in its observational design and the restrictions of its database, additional observations of interest should be possible and could be the topics for future communications. For example, the study assessed only the first ASCVD event, although, given the long follow-up, many additional (nonfatal and fatal) events would be expected, and the rate of these recurrent events is of interest. Also, several subsets excluded in sensitivity analyses, are of themselves of interest. These include those on thyroid medications, those with specific ASCVD subtypes (coronary artery disease versus cerebrovascular disease versus peripheral vascular disease), those with prevalent ASCVD at baseline, and those with prevalent and incident arrhythmias (eg, atrial fibrillation). Also of interest is the extent to which traditional ASCVD risk factors known to be affected by thyroid function (eg, lipids, body mass index, and age) correlated with FT4 and TSH in the Rotterdam Study, and to what extent their association with normal serum TSH levels. They also explored the mechanisms typically causing lower (rather than higher) FT4 levels in association with normal serum TSH, the authors note that set points for circulating FT4 are tightly regulated by the hypothalamic–pituitary–thyroid axis but differ between individuals, whereas TSH, which generally has been used to define the euthyroid range, reflects these differences and so complicates a universal definition of its range of normal.

So, what are reasonable first steps in applying these results to clinical medicine at the present? They may include the reevaluation of the reference ranges for FT4 and TSH, as the authors suggest. Although ASCVD risk seems to continue to decrease down through the lower reference range of FT4, it is clear that thyroid hormones in appropriate concentrations are essential to normal human physiology. Hence, a careful balance of overall benefit and risk will be essential in this process. Once redefined, these new reference ranges may be used in more appropriately selecting patients for treatment, choosing thyroid hormone doses, and setting thyroid function test targets for replacement therapy.

Beyond these steps, the Rotterdam Study findings call for an aggressive approach in future research to discover the mechanisms and pathways responsible for the risk associations observed and then to develop safe and effective therapies to moderate this risk.

**Study Implications and Future Needs**

Despite remarkable progress in the prevention and treatment of ASCVD in the Western world during the past 3 decades, there remains a high residual burden of disease.\(^\text{12}\) This reality highlights the pressing need to discover additional, and especially modifiable, risk factors. The results of this carefully executed study suggest that circulating thyroxine should be considered as a new and potentially modifiable risk factor for atherosclerosis. Indeed, the hazard ratios for ASCVD risk associated with a doubling of FT4 (2.7 for ASCVD events; 4.2 for ASCVD mortality) compare well with those for the presence versus absence, or for comparable incremental increases, in traditional risk factors or in coronary artery calcification (ie, hazard ratios of 1.5–3.0).\(^\text{2,13}\)

However, before thyroid function can be actualized as a modifiable factor, confirmation of findings in independent populations and reconciliation with disparate literature reports will be required. Mechanisms will need to be elucidated, causality proven, and specific treatments discovered. Adding external support to potential causality is a separate recent communication from the Rotterdam Study, which reported an association between FT4 levels within the euthyroid range and incident atrial fibrillation, for which excessive thyroid hormone is accepted as an etiologic factor.\(^\text{14}\)

Mechanisms to be explored linking thyroid function to ASCVD include hemodynamic effects, endothelial injury (eg, by reactive oxygen species, causing expression of adhesion molecules), and increased thrombogenesis (via increased levels of procoagulant factors), as referenced by the authors. Some prior evidence also indicates that these effects may extend into the upper reference range of thyroid function.\(^\text{8}\) However, large gaps in knowledge of pathways and mechanisms remain, many of which likely await discovery.

Implications for TSH are less clear than for FT4. In attempting to explain the weaker association of outcomes with TSH, the authors note that set points for circulating FT4 are tightly regulated by the hypothalamic–pituitary–thyroid axis but differ between individuals, whereas TSH, which generally has been used to define the euthyroid range, reflects these differences and so complicates a universal definition of its range of normal.

References


Disclosures

None.


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