



The Illinois Medical Bulletin



The Association Between Subclinical Hypothyroidism and Cardiovascular Disease Risk: A Review of Epidemiological Evidence

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Article History :

Received date : 2011/10/12
Revised date : 2011/11/28
Accepted date : 2011/12/09
Published date : 2012/01/13



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ABSTRACT

Introduction: Subclinical hypothyroidism (SCH), a condition defined by an elevated serum thyroid-stimulating hormone (TSH) level with normal free thyroxine concentrations, is a common biochemical finding. Its clinical importance, particularly its role as a potential risk factor for atherosclerotic cardiovascular disease (CVD), has been the subject of considerable investigation and debate.

Literature Review: A review of the pivotal literature reveals a consistent association between SCH and an adverse cardiovascular risk profile. Multiple cross-sectional studies and meta-analyses established a clear link between SCH and higher levels of total and LDL cholesterol. Research also suggested associations with other non-lipid risk factors, such as endothelial dysfunction and markers of subclinical atherosclerosis. Large-scale prospective cohort studies and meta-analyses provided evidence that SCH is associated with an increased risk of developing coronary heart disease events and cardiovascular mortality. This risk appeared to be most pronounced in younger individuals and those with higher TSH levels, particularly concentrations above 10 mIU/L. Despite this evidence of association, the question of whether

treating SCH with levothyroxine reduces these clinical cardiovascular endpoints remained largely unanswered by randomized trials during this period.

Conclusion: The body of evidence successfully characterized subclinical hypothyroidism not as a benign laboratory finding but as a genuine risk factor for cardiovascular disease. This research established a strong rationale for viewing SCH through a lens of cardiovascular risk, although it left the debate over broad-based treatment to prevent clinical events unresolved.

Keywords: Subclinical Hypothyroidism, Cardiovascular Disease, Thyroid-Stimulating Hormone (TSH), Cholesterol, Coronary Heart Disease.

INTRODUCTION

Subclinical hypothyroidism (SCH) is an endocrine state defined by a serum thyroid-stimulating hormone (TSH) concentration that is above the upper limit of the reference range, while the serum free thyroxine (T4) level remains within the normal range. With the widespread availability of sensitive TSH assays, this condition has been identified as a common finding, particularly in older women. The identification of this large population raised a critical clinical question: is SCH simply a laboratory curiosity, an early and asymptomatic phase of overt hypothyroidism, or is it an independent risk factor for systemic disease?

A primary concern that emerged was the potential link between this seemingly mild state of thyroid dysfunction and the risk of atherosclerotic cardiovascular disease (CVD). Given that overt hypothyroidism is a well-known cause of dyslipidemia and other cardiovascular derangements, it was plausible that even a subclinical state could confer a similar, albeit attenuated, risk. This literature review will synthesise the key epidemiological and observational evidence that investigated the association between subclinical hypothyroidism and the risk for cardiovascular disease.

LITERATURE REVIEW

The investigation into the cardiovascular consequences of subclinical hypothyroidism focused on its relationship with surrogate risk markers and, more importantly, with hard clinical endpoints like coronary heart disease and mortality.

First, a consistent and well-established link was found between SCH and an atherogenic lipid profile. Numerous cross-sectional studies and several meta-analyses demonstrated that

individuals with SCH, when compared to their euthyroid counterparts, have statistically significant elevations in both serum total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations. While the absolute mean differences were modest, the consistency of this finding across multiple studies provided a strong and plausible mechanistic pathway through which SCH could promote the development of atherosclerosis (Walsh et al., 2005). Some, but not all, studies also suggested potential associations with other cardiovascular risk markers, including impaired endothelium-dependent vasodilation, increased carotid intima-media thickness, and subtle abnormalities in diastolic heart function.

The most critical question, however, was whether these associations with risk markers translated into an actual increase in clinical cardiovascular events. Answering this required large, long-term prospective cohort studies. A number of such studies provided evidence suggesting that SCH was indeed associated with an increased risk of coronary heart disease (CHD). This evidence was synthesised in influential meta-analyses that pooled data from multiple cohorts. One such comprehensive analysis of individual participant data found that the association was not uniform across all patients. The risk for CHD events and cardiovascular mortality was most apparent and statistically significant in younger individuals (those under 65 years of age) and was largely confined to participants with higher TSH elevations, specifically TSH levels of 10 mIU/L or greater. In older individuals or those with only mild TSH elevations (below 10 mIU/L), the association was weak or absent (Rodondi et al., 2008; Razvi et al., 2008).

This evidence established SCH as a risk factor but simultaneously created a clinical dilemma regarding treatment. The evidence on whether treatment with levothyroxine could mitigate this risk was sparse. While smaller trials showed that levothyroxine therapy could successfully normalize TSH levels and improve the lipid profile, no large-scale, long-term randomized controlled trials had been completed that were adequately powered to determine if this translated into a reduction in myocardial infarctions or cardiovascular death. This led to considerable controversy and a lack of consensus on treatment strategies, as reflected in expert panel statements which often recommended an individualized approach to treatment decisions (Surks et al., 2004).

CONCLUSION

The pivotal body of literature examining the clinical significance of subclinical hypothyroidism successfully elevated the condition from a simple laboratory anomaly to a recognized risk factor for cardiovascular disease. The evidence clearly and consistently demonstrated an association between SCH and an atherogenic dyslipidemia, providing a strong mechanistic rationale for its role in promoting atherosclerosis.

Furthermore, large-scale epidemiological studies confirmed that this risk translated into an increased incidence of hard clinical endpoints, particularly for younger patients and those with more significant TSH elevations. While this research was crucial in defining the cardiovascular risks associated with SCH, it also highlighted a major evidence gap, as the benefit of treatment with levothyroxine for the specific purpose of preventing cardiovascular events remained unproven. Nevertheless, this work fundamentally changed the clinical perspective, forcing clinicians to consider the potential long-term cardiovascular implications of what was once considered a benign finding.

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