

Is Subclinical Hypothyroidism a Risk Factor for Coronary Artery Disease?

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Subclinical hypothyroidism is defined as serum TSH levels above the upper limit of normal (4.0 or 5.0 mIU/L depending on the laboratory) despite normal serum free thyroxine.^{1,2} For diagnosis of subclinical hypothyroidism, other causes of elevated TSH, such as recovery from non-thyroidal illness, assay variability, heterophile antibodies, and certain cases of central hypothyroidism with biologically inactive TSH, should be excluded.²

Subclinical hypothyroidism, or mild thyroid failure, is a very common problem, with a prevalence of 4–8.5% in the United States adult population, in patients without known thyroid disease.^{1–4} The prevalence increases with increasing age and is higher in the female population.¹ Some studies, including our own, show that the prevalence in men approaches that of women, with a combined prevalence over 10%, after the sixth decade of life.⁵ In mild thyroid failure, 75% have TSH values less than 10 mIU/L.¹

Adverse effects of subclinical hypothyroidism are the subject of heated debate.^{6,7} Therapy of mild elevation of TSH and the

upper limit of normal for serum TSH are also controversial.^{6,9} Some scientific societies have suggested lowering the upper limit of normal serum TSH to 3 mIU/L.⁸ Some suggest therapy for all cases of mildly elevated TSH⁷ and some argue for selective therapy and individualization.^{10,11} The most important argument in favor of therapy is possibility of adverse cardiac effects and likelihood of increased cardiovascular end points associated with mild thyroid failure.^{12,13} If it is proven that elevated serum TSH has adverse cardiac effects, then therapy of all cases of subclinical hypothyroidism will make sense. Evidence for both association and for lack of association with cardiac events and cardiovascular mortality has been published.^{12,14} However, the published data are insufficient and the subject remain controversial.¹⁰

Adverse effects of subclinical hypothyroidism on cardiovascular function have been extensively studied by Italian investigators.¹⁵ There is evidence for slowed left ventricular (LV) relaxation time, increased vascular tone at rest and LV systolic dysfunction with exercise. Some studies have shown improvement of cardiac contractibility and systolic time interval with thyroxine therapy.¹⁶ Although studies were not categorized for various levels of TSH, there is more evidence for

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adverse effects for serum TSH levels above 10 mIU/L.¹⁰

Does subclinical hypothyroidism increase the risk factors for cardiovascular disease? Overt hypothyroidism is a risk factor for coronary heart disease because of associated metabolic abnormalities. The atherogenic aspects of subclinical hypothyroidism are less clear. Possible atherogenic factors other than hyperlipidemia,^{16,17} such as increased homocysteine and lipoprotein (a) [Lp(a)] levels, have been suggested in mild thyroid failure.¹⁸⁻²⁴ It is now clear that although homocysteine levels are elevated in overt hypothyroidism, they are not elevated in subclinical hypothyroid patients.²⁵ Evidence for increased Lp(a) is also insufficient.²⁰ Recent reports indicate elevated CRP (C-reactive protein) in mild thyroid failure, raising the possibility of association of an inflammatory process contributing to atherosclerosis.^{18,19,21}

In the population-based Whickham cohort study, in a 20-year follow up, the mortality from cardiovascular causes was not higher in the group who had subclinical hypothyroidism at baseline, as compared with normal counterparts.¹⁴ In a study from United Kingdom, an association of abnormally low TSH with cardiovascular mortality in a 10-year follow up was noted, but there was no association with elevated serum TSH.²⁶ However, in a recent case-control study from Rotterdam, Holland,¹² subclinical hypothyroidism in women, with a mean age of 69 years, was associated with a greater age-adjusted prevalence of aortic atherosclerosis (odds ratio 1.7) and myocardial infarction (odds ratio 2.3). The difference persisted after adjustment for body mass index, systolic and diastolic blood pressure, tobacco abuse, and total cholesterol and high-density lipoprotein levels. Surprisingly, a more recent study in individuals aged over 80 showed increased survival benefit for mildly elevated TSH.²⁷ This report raises the possibility that, at least in older individuals, normalization of TSH may not have survival benefits, and the opposite may be the case. Because of these conflicting reports and the

large numbers of populations afflicted by this condition, there is an urgent need for settling the controversy. Carefully designed randomized trials are required since the results will impact management of millions of patients who have subclinical hypothyroidism.

In this issue of the *International Journal of Endocrinology*, Shams and colleagues supply new information on the subject.²⁸ The message of the Shams and colleague study is that elevated serum TSH level does not predict presence of CAD in patients undergoing coronary angiography. They measured serum TSH levels in 390 persons (239 men and 151 women) who were referred for coronary angiography. They found no correlation between TSH levels or subclinical hypothyroidism and presence or severity of angiographically demonstrated coronary artery disease. There were only 25 patients who had abnormally elevated serum TSH levels. Nine of 119 persons with normal coronaries and 16 of 271 patients with CAD had subclinical hypothyroidism. Although this is useful information, the authors correctly cite several limitations of their study. The number of patients with subclinical hypothyroidism was small. The study was confounded because of selection bias and the study subjects were all patients with possible coronary symptoms and did not represent a cross section of general population. Thus, the conclusion that subclinical hypothyroidism is not associated with coronary artery disease cannot be generalized from this small selected group of patients with subclinical hypothyroidism. Although the authors indicate that non-thyroidal illness did not play a role, it is likely that patients with CAD were sicker, and TSH levels might have been lower in that group. Furthermore, if the assumption of Parle and colleagues is correct that low levels of TSH below 0.5 mIU/L are associated with cardiovascular mortality,²⁶ the data might have been confounded by lower levels of TSH in the CAD group. In other words, if both elevated and lower serum TSH levels are associated with CAD, then correlation of TSH level with

coronary atherosclerosis may not be detected. The authors do not give data for abnormally low TSH in their study group. Studies of larger groups of subclinical hypothyroid patients after exclusion of other baseline con-

foundings factors in a longitudinal, prospective study are needed.

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