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REVIEW ARTICLE

Thyroid hormone deficiency and coronary artery disease

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ABSTRACT

The heart is sensitive to thyroid hormone action and thyroid dysfunctions. Thyroid hormone deficiency (hypothyroidism) either overt or subclinical has adverse cardiovascular consequences. They results from direct influences of hypothyroidism on heart function as well as due to secondary effects like atherogenic lipid profile, diastolic hypertension and impaired endothelial function leading to atherosclerosis. This review summarizes the basic and clinical studies on the role of hypothyroidism in development of atherosclerosis and traditional risk factors for coronary artery disease.

Key words: Thyroid hormone; Hypothyroidism; Coronary artery disease; Thyroid stimulating hormone; Hyperhomocysteinemia

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INTRODUCTION

Thyroid hormones (TH; thyroxine, T_4 & tri-iodothyronine T_3) and thyroid stimulating hormone (TSH) have a number of profound effects on the cardiovascular system.[1] Normal thyroid hormone level is essential for maintaining normal structure and function of heart. This is because of their important role in metabolism through alterations in oxygen consumption and changes in protein, lipid, carbohydrate, and vitamin metabolism.[2] Thyroid hormone affects several genes encoding the expression of important structural and regulatory and proteins in the myocardium.[3] Moreover, thyroid hormones play important role in maintaining cardiovascular homeostasis.

Hypothyroidism or thyroid hormone deficiency is a graded phenomenon characterized by low TH and high TSH in overt and only TSH elevation in subclinical hypothyroidism. Worldwide most

common reason of hypothyroidism is iodine deficiency in areas where iodine intake is low and chronic autoimmune thyroiditis in iodine sufficient countries.[4,5] The prevalence of overt hypothyroidism is in the range of 1–2% and that of subclinical hypothyroidism is 4.0-20% of general population. Its incidence is more common in female than male gender and increases with increasing age.[5] Thyroxine supplementation is the only treatment of choice in overt hypothyroidism. However, thyroxine supplementation in subclinical hypothyroidism is controversial and is recommended only when TSH level is > 10 IU/L or TSH level above population normal range is accompanied by high titer of thyroid antibodies and/or presence of goiter.[4,6]

Hypothyroidism produces major derangements of human physiology.[5] It causes a hypodynamic cardiovascular state like decreased left ventricular contraction and relaxation and decrease in cardiac output. Hypothyroidism is, either overt or subclinical may cause or accelerate heart diseases.[1] It is because receptors for thyroid hormones are present in myocardial and vascular endothelial tissues and are responsive to changes in circulating thyroid hormone concentration.[1,2] Although a relationship between overt hypothyroidism and cardiovascular diseases was appreciated about one and half century ago, but role of subclinical hypothyroidism in coronary heart disease was first suggested by Bastenie et al (1971).[7] Over the past two decades, accumulating evidence supports the role of hypothyroidism in atherosclerosis development and derangement of traditional risk factors for coronary artery disease (CAD). A plethora of clinical and experimental data had consistently showed an association of hypothyroidism- overt, subclinical and low triiodothyronine syndrome with increased risk of atherosclerosis as well as ischemic heart disease.[8-10] Recently expansion of this relationship is being extended to normal healthy population with slightly increased TSH level within normal population range.[11-12] Some emerging risk factors for atherosclerosis like thyroid autoimmunity, increased C-reactive protein (CRP) level and hyperhomocysteinemia are also under intensive investigation to seek explanation of the relationship between hypothyroidism and heart disease.[13,14] In addition, some recent studies have suggested an anti-atherosclerotic effect of thyroid hormone.[15] The results of recent clinical trials elucidating effect of thyroid hormone supplementation to cardiovascular diseases are promising but results of all studies are not uniform.[17] Moreover, a causal association per se of low TH, high TSH, thyroid autoimmunity or additive effect of all components of hypothyroidism on coronary artery disease is still elusive.[8,16] In this brief review role and effect of both overt and subclinical hypothyroidism on atherosclerosis and traditional risk factors for CAD is summarized.

HYPOTHYROIDISM AND DEVELOPMENT OF ATHEROSCLEROSIS

Atherosclerosis is the central event in CAD. It is a process of intimal deposition of lipid in coronary arteries and its progression into atherosclerotic plaques. Carotid intima-media thickness (CIMT) is a good marker of early atherosclerotic change and future cardiovascular event.[18] CIMT is evaluated using high-resolution ultrasound technique and is a low cost non-invasive method. Nagasaki et al. found that in patients with overt hypothyroidism CIMT was larger as compared to euthyroid control (0.635 ± 0.08 mm vs. 0.559 ± 0.021 mm, $p < 0.005$) and it decreased (0.552 ± 0.015 mm) after one year levothyroxine replacement.[19] The presence of atherosclerosis in overt hypothyroidism is probably secondary to associated hypertension, hypercholesterolemia and hyperhomocysteinemia. An alternative mechanism is proposed by Zhang et al.[20] according to which enhanced CIMT in patients with hypothyroidism is because of increased serum level of a microRNA (miRNA) called miRNA21-5. This miRNA is already reported to enhance proliferation and migration of vascular smooth muscle cells.[21]

A number of epidemiological studies supported the direct association between subclinical hypothyroidism and atherosclerosis. In Rotterdam study cross-sectional analysis showed that women with subclinical hypothyroidism had a significantly more incidence of atherosclerosis than euthyroid women after adjustment for age, body mass index, high density lipoprotein (HDL), blood pressure and smoking status.[22] Mya et al.[23] and Monzani et al.[24] reported the same findings which were confirmed by later studies.[25,26] Valentina et al. reported that increased CIMT and presence of carotid plaques in subclinical hypothyroid patients was independent of classical risk factors for atherosclerosis.[26] However, studies of Rodondi et al.[27] and Cappola et al.[28] reported contradictory results. First meta-analysis of such studies[29] published in 2008 and reported significant association between subclinical hypothyroidism and coronary heart disease with relative risk (RR) of 1.533. Another meta-analysis[30] reported the same conclusion with RR of 1.20. Moreover, in a reanalysis of the Wickham study, Ravzi et al. demonstrated a

strong association between ischemic heart disease and subclinical hypothyroidism.[31]

Recently, association of TSH with cardiovascular diseases have been investigated among healthy subjects with normal thyroid status.[32-35] Although findings of these studies are not same but majority of them showed that higher levels of serum TSH within reference range were positively associated with coronary artery disease.[32,33,35] Thus even mild thyroid dysfunction may affect atherogenesis. The clinical utility of such findings remain to be determined. Only large prospective studies can prove whether reducing of TSH by thyroxine replacement therapy in such healthy subjects reduces the potential risk of coronary heart disease.

It has been suggested that patient age had significant impact on relationship between subclinical hypothyroidism and atherosclerosis. The positive association between TSH and atherosclerosis risk was increased in younger patients but not older subjects.[35,36] So far two meta-analyses of such studies had reported that relationship between subclinical hypothyroidism and coronary artery disease only existed[37] or stronger[30] in subjects younger than 65 year old. In older patients higher TSH level is physiological and suggested to have protective effect on cardiac health.[38]

HYPOTHYROIDISM AND CARDIOVASCULAR RISK FACTORS

Hypothyroidism, overt or subclinical is associated with an increased prevalence of cardiovascular heart disease through its effect on each individual risk factor like hyperlipidemia, hypertension, endothelial dysfunction etc. for cardiovascular diseases. If these risk factors are not accounted for then hypothyroidism per se is not associated with an increased risk for carotid atherosclerosis as reported for example by Chiche et al in hyperlipidemic patients.[39] In the past two decades a growing body of research about TH regulation of lipid metabolism, effects on blood pressure and modulation of atherosclerotic factors like endothelial function, oxidative stress, homocysteine and C-reactive protein (CRP) level had widen our understanding of how hypothyroidism predisposes patients to cardiovascular disease. A brief account of each derangement associated with hypothyroidism is provided below:

Lipid Profile

Thyroid hormone effects absorption, synthesis and degradation of lipids and thus regulates the intravascular metabolism of lipoproteins. In hypothyroidism lipid metabolism is impaired. Staub et al. reported that total cholesterol, low density lipoprotein (LDL) cholesterol and apo B levels are elevated in overt hypothyroidism.40 Among hypercholesterolemic patients about 14% are reported to have hypothyroidism.[41] TH regulates LDL receptor in liver as promoter region of the gene coding for LDL receptor contains functional thyroid response elements. Animal studies have shown that expression of mRNA in liver is directly related to peripheral concentration of thyroid hormones. Induction of hypothyroidism decreases 50% expression of LDL receptor mRNA in rat liver.[42] This reduced expression of LDL receptor results decreased LDL clearance and hence its increase concentration in blood. In a clinical study receptor-mediated LDL metabolism was significantly improved in a hypothyroid woman after T4 supplementation.[43] The increased LDL cholesterol in hypothyroid patients is more prone to oxidation that enhances its atherogenicity.[43,44] The HDL cholesterol is antiatherosclerotic but its profile is variable in hypothyroid patients. However, low levels of proteins related to HDL metabolism are reported in hypothyroidism.[43] Another reason for dyslipidemia in overt hypothyroidism is its association with insulin resistance that worsens the atherogenic lipid profile and makes the LDL subfraction more prone to oxidation.[45] In subclinical hypothyroidism inconsistent effects on lipid profile were reported in different studies. Vierhapper et al. reported no effect of subclinical hypothyroidism on serum total cholesterol, LDL and HDL cholesterol levels.46 Similarly, HUNT study revealed a positive association of serum TSH in euthyroid range (0.2 – 4.5 mIU/L) with LDL cholesterol and triglyceride levels.47 A meta-analysis of 16 observational studies in 2014 reported that in subclinical hypothyroid patients LDL cholesterol and triglyceride levels were significantly elevated but HDL cholesterol levels were unaffected.[48] A number of clinical studies and trials have reported effect of thyroxine replacement therapy on serum lipid profile of subclinical patients.[24,33] A meta-analysis of such studies revealed modest reduction in LDL but no change in HDL cholesterol after thyroid hormone replacement in such patients.[49] Thus relationship of thyroid deficiency and atherogenic lipid profile is confirmed. However, in interpretation of this association patient age, gender and thyroid autoimmune status should be necessarily considered.[12,35,37,50]

Hypertension

Hypertension is one the major risk factor for cardiovascular diseases.[51] Euthyroid state is important

for the maintenance of appropriate blood pressure (BP). Both hyperthyroidism and hypothyroidism are associated with hypertension.[15] In Japan, Saito et al. reported a higher prevalence of hypertension in overt hypothyroid patients as compared to euthyroid subjects (14.8% vs 5.5%).[52] In an Indian study 44% hypothyroid patients were reported to have hypertension.[45] In most hypothyroid patients only increase in diastolic blood pressure is reported but it may also affect systolic blood pressure.[15] A plausible mechanism for hypertension in hypothyroidism is the enhanced systemic vascular resistance and arterial stiffness[53,54] or altered lipid profile. However, Purohit and Mathur showed that hypertension in hypothyroid patients is also associated with insulin resistance and C-peptide.[45] A few studies also suggested subclinical hypothyroidism as a risk factor for hypertension but this association is still a matter of debate.[55] Recently Canbolat et al showed that patients with subclinical hypothyroidism had significantly higher diastolic hypertension, though within normal BP limits, than the controls but had significantly higher prevalence of diastolic non-dipping.[56] Among healthy subjects association of high levels of TSH within the reference range with hypertension was reported in children and adolescents[57] as well as adults[58] but a latest study did not confirm this relationship.[55] However, influence of family history of blood pressure on serum TSH levels in healthy individuals is reported that points to existence of possible genetic variants affecting both hypertension and serum TSH levels.[59]

The effect of replacement with thyroxine in both overt and subclinical hypothyroid patient was evaluated in a number of studies.[60-62] The beneficial response was significant in overt than subclinical hypothyroidism and in later group was limited to improvement in systolic component only.[60] Another study reported improvement only in arterial stiffness with L-thyroxine in subclinical hypothyroidism without alteration in myocardial functional reserve.[61] However, in these studies subclinical hypothyroid patients were not stratified on the basis of presence or absence of autoimmune thyroiditis, a leading cause of this subclinical hypothyroidism. Only a small study by Traub-Weidinger et al reported improvement in coronary microvascular function after supplementation with LT4 in asymptomatic subjects with subclinical hypothyroidism due to thyroid autoimmunity.[62] Further large studies are warranted to evaluate and confirm this effect.

Endothelial Function

The endothelium plays an important role in vascular function by production of vasodilator and vasoconstrictor substances. The most important vasodilator is nitric oxide (NO).[63] Endothelial dysfunction is characterized by low production of NO from endothelial cells and is one of the initial steps in atherosclerosis development.[64] In both overt and subclinical hypothyroidism endothelium-dependent flow-mediated vasodilation is impaired.[65,66] Association of high levels of TSH with impaired endothelial function[67] and arterial stiffness[68] is also reported. However, it is not clear whether this effect is because of thyroid hormone deficiency or hypothyroidism-associated hypercholesterolemia and hypertension that also cause endothelial dysfunction.[64] The role of thyroid hormone deficiency is evident from the improvement of endothelial function after L-T4 therapy in hypothyroidism.[69,70] However, some studies have suggested that hypothyroidism-mediated endothelial dysfunction is because of chronic inflammation caused by autoimmune thyroiditis.[63] This low-grade inflammation also causes increased oxidative stress in hypothyroidism.[63] This assertion is verified by an increase in serum levels of CRP in patients with overt and subclinical hypothyroidism.[71] However, replacement of thyroid hormone in patients with subclinical hypothyroidism did not affect CRP levels.[72] Moreover, molecular mechanism for the thyroid hormone regulation of CRP is still not elucidated. Therefore, further studies are required to clarify this mechanism.

Homocysteine

Serum homocysteine level in human is affected by genetic, nutritional and acquired factors. Vitamin B6, B12 and folate are important nutritional factors while smoking and renal function also affect homocysteine level.[15] Presence of high concentration of serum homocysteine is an established and known cardiovascular risk factor promoting premature atherosclerosis.[73] Presence of high level of serum homocysteine is suggested to increase oxidative stress, enhance endothelial dysfunction and induce thrombosis in atherosclerosis.[74] An elevation in serum homocysteine concentration in overt hypothyroidism as compared to healthy subjects is reported,[75,76] that was successfully reduced after thyroxin supplementation.[71,77] In mild or subclinical hypothyroidism serum homocysteine levels is not significantly affected.[77,78] Moreover, no association between euthyroid chronic autoimmune thyroiditis and homocysteine levels was found in women. However, decrease in homocysteine level after L-T4 replacement as compared with healthy controls is intriguing.[79] A recent meta-analysis by Zhou et al.,

reported a significant association between degree of hypothyroidism and levels of serum homocysteine.[80] The plausible mechanism may be the role of thyroid hormone in modulating the expression of genes involved in the homocysteine metabolism.[81] An alternative explanation is the change in folate levels in hypothyroidism that increased serum homocysteine level.[81,82] Another suggested mechanism for increased homocysteine in hypothyroidism is the renal function impairment that reduce renal clearance of homocysteine.[15,83]

CONCLUSION AND FUTURE DIRECTION

Overt hypothyroidism is strongly associated with all components of coronary artery disease but relation of subclinical hypothyroidism is partially proved in different studies. The favorable effect of thyroxine supplementation on cardiac health in subclinical hypothyroid patients points to some missing confounder. In this regard thyroid autoimmunity is the best candidate. A few studies have elucidated the contribution of autoimmune thyroiditis in context of hypothyroidism and CAD. Recently involvement of euthyroid autoimmune thyroiditis in early atherosclerosis is reported in postmenopausal women and adolescent girls.[14,84] As thyroid autoimmunity is associated with chronic inflammation which may cause endothelial dysfunction it is expected that it might have greater role in cardiovascular diseases. Thus role of thyroid autoimmunity still need further exploration. A second point is the consideration of patient age and gender. Both hypothyroidism and heart diseases have different profile in male and female with increasing age.[12] Cross-sectional and longitudinal studies recruiting exclusively male or female subjects may elucidate relation of subclinical hypothyroidism with heart more clearly. Third consideration is the lack of oxidized low density lipid (ox-LDL) determination in most studies pertaining to lipid profile and cardiovascular risk in hypothyroidism.[85] Ox-LDL is the chief culprit in atherosclerosis and its determination should be included in future studies.

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Author contribution:

SS - conceived idea, Literature search

SA - Literature study, review

NS - Editing, literature study, writing

NBR – Manuscript writing

SE - Manuscript writing, reviewing

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