REVIEW ARTICLE

Cardiovascular Risk in Hashimoto's Thyroiditis: Role of Thyroid Autoimmunity

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Abstract

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease synonymous with hypothyroidism. The link between hypothyroidism and the risk of cardiovascular diseases is of contemporary interest. Studies have indicated the prevalence of metabolic syndrome and endothelial dysfunction in HT patients. HT *per se* might possess a role in atherosclerosis. Association of HT with dyslipidemia and chronic inflammation leading to endothelial dysfunction has been documented. However, the role of thyroid autoimmunity in promoting cardiovascular diseases remains unclear. Further studies unraveling the causal relationship between HT and cardiovascular disease would provide greater insight into the management of atherogenic complications observed in HT patients.

Keywords: Chronic inflammation, Dyslipidemia, Endothelial dysfunction, Hashimoto's thyroiditis.

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Introduction

Hashimoto's thyroiditis (HT) is an autoimmune disease characterized by the destruction of thyroid cells by both cell- and antibody-mediated immune responses[1] and is regarded as the commonest cause of hypothyroidism. HT has a prevalence rate of 1–4%. HT is more common in women and increases with age.[2,3] Several studies have shown the association of hypothyroidism with dyslipidemia and chronic inflammation, which in turn enhances the risk for cardiovascular diseases.[4] A marked increase in low-density lipoprotein (LDL) is seen in hypothyroidism, attributed to decreased LDL receptors in the liver culminating in reduced LDL clearance.[5,6] Hyperlipidemia and chronic inflammation are implicated in atherosclerotic lesion formation. The levels of major inflammatory markers, such as interleukin (IL) 6, tumor necrosis factor-alpha (TNF-α), and high sensitive C-reactive protein (hs-CRP), were found to be elevated in HT patients.[7] Though cardiovascular risk seen in overt hypothyroidism is a well-established fact, the influence of thyroid autoimmunity in increasing the cardiovascular events independent of thyroid dysfunction still remains a conundrum. Few studies suggest a putative role of thyroid autoimmunity in atherosclerosis development independent of thyroid dysfunction. Chronic inflammation and endothelial dysfunction could be the link. Cytokines are believed to modify epithelium thereby allowing infiltration of the thyroid by immune cells: a mechanism underlying HT.[8] Thus, the purpose of this review is to primarily provide the discerning researchers an overall picture of cardiovascular risk seen in HT patients, which might be a great source of help in the management.

Dyslipidemia and Hashimoto's Thyroiditis: the Nexus

Dyslipidemia as observed in thyroid abnormalities is a potent risk factor of cardiovascular events among patients with abnormal thyroid function.[9] Studies have shown a positive association of extracellular thyroid stimulating hormone (TSH) with lipid levels in hypothyroid subjects. In a prominent study referred to as the HUNT study, the association of hypothyroidism with high blood lipids was observed as a linear function across the entire reference range of TSH.[10] Tagami et al. determined an association between serum TSH and lipid levels.[11] A pronounced atherosclerotic lesion has been demonstrated in children and adolescents with hypothyroidism, with an accompanying elevation in total cholesterol (TC) and LDL levels and decreased high-density lipoprotein (HDL) level.[12]

Endothelial Dysfunction—An Important Point for Consideration

Whickham's study showed no association between elevated TSH and dyslipidemia.[13] A study by Tamer et al. also showed no discernible correlation of TSH levels with serum lipids. However, an interesting point had emerged, viz., anti-thyroperoxidase antibodies (TPOAb) have correlated positively and pronouncedly with serum triglyceride (TG).[14] Increased carotid intima-media thickness in HT women, independent of thyroid function has also been reported.[15] Subclinical hypothyroid patients are more prone to

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developing atherosclerotic cardiovascular disease, in spite of having lower TC levels when compared to healthy controls.[16] As per another study, no pronounced difference in serum lipid levels between the hypothyroid and healthy controls was observed.[17,18] According to Volpe's hypothesis,[19] due to defective suppressor T cells, T cells are not suppressed and produce a lot of cytokines such IFN-γ, IL-2, and TNF-α. These cytokines might cause hyperlipidemia as suggested by another study.[20] Hyperlipidemia diminishes the expression of endothelial nitric oxide synthase (eNOS) and increases asymmetric dimethylarginine levels, an eNOS endogenous inhibitor, ultimately leading to endothelial dysfunction.[21,22]

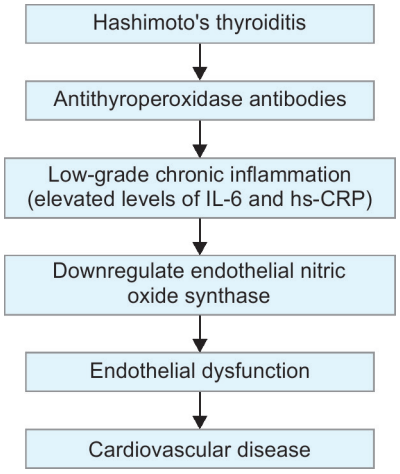
Inflammatory Markers and Hashimoto's Thyroiditis

Inflammation is another probable factor that could cause endothelial dysfunction. Acute and chronic inflammations are strongly related to endothelial dysfunction.[23-25] A study done by Türemen et al. has shown an increase in inflammatory factors, such as IL-6, hs-CRP, and TNF-α, in HT patients. Furthermore, these are positively correlated with flow-mediated dilation. This event points to the contribution of low-grade chronic inflammation in promoting atherosclerosis in HT subjects.[7] IL-6 plays a pivotal role in vascular inflammation by promoting endothelial dysfunction, smooth muscle cell proliferation, and migration.[25] Few studies documenting an increase in serum IL-6 levels in HT are available.[26,27]

hs-CRP, a marker of systemic inflammation, is used as a biomarker for cardiovascular risk assessment. A point of significance is that endothelial dysfunction attributed to dyslipidemia and low-grade chronic inflammation is purported to be the contributing factors for cardiovascular disorders visualized in HT.[7] However, the role of thyroid autoimmunity is unclear. According to another study, no correlation between anti-TPO and IL-6 or anti-TPO and IL-15 in HT subjects irrespective of thyroid function status was observed.[28] The exact role of antibodies against thyroid peroxidase remains a mystery and it is suggested that they may promote the release of cytokines, including IL-6, TNF-α, and INF-γ.[29] Few studies describe a correlation between TSH and TPOAb that might promote the release of cytokines, including IL-6, TNF-α, and INF-γ.[29,30] TSH may promote endothelial dysfunction by increasing IL-6 and TNF-α secretion by binding to adipocyte TSH receptor and bone marrow cell TSH receptor, respectively.[4] Higher levels of TSH could be proinflammatory stimuli of adipocytes.[31] In a study done by Sieminska et al., thyroid autoimmunity was found to be associated with elevated IL-6 concentration, regardless of thyroid function. However, no association was found between TSH and IL-6 levels.[8] However, in the analysis done by LeGrys et al., there was no connection between the presence of thyroid antibodies and the risk of myocardial infarction (Flowchart 1).[32]

Taddei et al. observed an increase in IL-6 and hs-CRP levels in HT subjects, which could trigger endothelial dysfunction, one of the early mechanisms promoting atherosclerosis and cardiovascular disease. IL-6 promotes atherosclerosis either directly by endothelial-dependent mechanisms or indirectly by stimulating hepatic production of hs-CRP.[27] CRP may interfere with endothelial function by downregulating eNOS and by upregulation of endothelin-1, a potent vasoconstrictor that antagonizes nitric oxide action.[33] Though the clear association of elevated CRP with HT subjects is shown in certain studies,[27] Pearce et al. could not find any difference in CRP levels among HT patients and controls.[34]

Flowchart 1: Role of thyroid autoimmunity in cardiovascular disease manifestation in Hashimoto's thyroiditis



Conclusion

Thyroid autoimmunity is found to be associated with dyslipidemia and low-grade chronic inflammation, which might result in future cardiovascular morbidities. However, there is significant heterogeneity of results among the studies included. Further studies are needed to address the causality of cardiovascular diseases in HT patients, which may have implications in understanding the disease mechanisms and future treatment strategies.

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