SCOPE OF INFLAMMATORY MARKERS IN SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Subclinical hypothyroidism (SCH) and inflammatory diseases are now a day’s one of the most popular topics of research. Previous studies have shown that the patients with SCH have increased levels of triglycerides and signs of low-grade inflammation (raised C-reactive protein levels). Disorder might be a risk factor for the development of cardiovascular and other inflammatory diseases. However, there is still some controversy concerning the inflammatory impact of SCH. Treating patients with thyroid stimulating hormone one value of <10 mIU/L is not compelling, except in pregnant women. Fortifying the association between SCH and inflammation and a better understanding of research data may provide a more compelling argument for future treatment.

Keywords: Thyroid stimulating hormone, C reactive protein, interleukin-6, inflammation

INTRODUCTION

Subclinical hypothyroidism (SCH) is a common endocrine disorder, which affects worldwide population [1]. Around 3-8% prevalence of general population is affected by this disorder [2,3]. The Colorado study has observed that 9% of the US population were presented with SH having elevated thyroid stimulating hormone (TSH) level [4]. In India, not an exception, its prevalence varies from 9% to 12% approximately [5]. Although it is not gender specific disease; however, it is quite common in female compared to male population and grows with age [6,7]. 13.5% female population from North India is affected by SCH during the first trimester of pregnancy [8]. SCH is an oscillated state between euthyroidism to overt hypothyroidism without previous history of thyroid disorder. It is an asymptomatic disorder or present few to various well-defined symptoms of overt hypothyroidism [9,10]. The biochemical presentation of thyroid profile confirms the presence of SCH with mildly elevated TSH above the upper limit of normal concentration while free thyroxine (FT₄) and tri iodothyronine (FT₃) within the reference range [11]. Thyroid hormones are quite known to affect the various metabolic process of the body which can create various diseases in future [12]. The irregular concentration of thyroid hormones produces adverse effects on different metabolic systems, which can give rise to various inflammatory diseases, e.g. myocardial infarction [13], rheumatoid arthritis [14], atherosclerosis [15], or ischemic heart disease, etc., as disease progress. Inflammatory disease is initiated by inflammation, a biological complex protective response in which leukocytes migrate from the vasculature into damaged tissues to destroy the agents that potentially can cause tissue injury [16]. It mediates tissue effects including vasodilation, edema, and cell proliferation through complex immunologic pathways [17]. Weight gain, a characteristic feature of hypothyroidism, can leads to the obesity [18], one of the factors for low-grade chronic inflammation by increasing the expression of some cytokines [19]. Various other signs or symptoms of hypothyroidism might be responsible for the development of inflammatory disorder [20,21] due to which, investigating the role of inflammatory markers could be useful to predict the risk of disease. SCH presents mimics reactions to overt hypothyroidism which might suggest a possibility of inflammatory disorder in coming future [22]. The reason behind presenting this review was not to revisit what has already been done or has been investigated. Instead of that the purpose is to give the researchers to considerate their focus to investigating the role of inflammatory markers in SCH, which is not clearly defined and the physiology or mechanism behind this is still unclear.

ASSOCIATION BETWEEN INFLAMMATORY MARKERS AND SCH

SCH is associated with increased prevalence of atherosclerosis, a disease of lipid accumulation, may be initiated or promoted by chronic inflammation by adverse effects on vascular endothelium and may be one of the reasons for increased endothelium dysfunction which leads to cardiovascular risk [23-27]. A variety of inflammatory markers are found to be increased in SCH which could play a crucial role in insulin resistance disorder [28], supporting the mechanism that TSH is responsible to induce tumor necrosis factor-α (TNF-α) in bone marrow cells [29]. TNF-α, mediating the downstream anti-resorptive effects of TSH on the skeleton [30] can impair nitric oxide (NO) activity in endothelial cells by promoting endothelial dysfunction. Yang et al. concluded that TNF-α and interleukin 6 (IL-6) expression in serum were increased in SCH rats [31]. TNF-α related apoptosis inducing ligand (TRAIL) is associated with atherosclerosis. The circulating TRAIL level was decreased in SCH and positively associated with endothelial function [32]. In a clinical study, Taddei et al. concluded that low-grade chronic inflammation causes not only lipid alteration but can also triggers a endothelial dysfunction in patient with SHT by observing elevated C-reactive protein (CRP) and IL-6 levels and suggested that endothelial dysfunction, being an independent promoter of cardiovascular events, dependent vasodilation could be one of the early mechanism promoting atherosclerosis and cardiovascular disease [33]. Likewise Türemsen et al proposed that inflammatory markers including IL-6, CRP, and TNF-α were elevated in SCH patients along with the positive correlation of flow-mediated dilatation (FMD) with inflammation markers suggesting that low-grade chronic inflammation could be one of the factors to leads endothelial dysfunction in SCH patients [34]. Thyroid peroxidase Abs, positively correlated with TSH, may promote the release the variety of cytokines, e.g. IL-6, TNF-α, and interferon γ [35,36].

Eshenawy et al. concluded that SCH is characterized by elevated concentration of IL-6; a pro-inflammatory cytokine [37], over produced in obesity [38], found to be detrimental to endothelium, and atherosclerosis [39] is also induced by TSH in adipocytes [40]. Furthermore, CRP an acute phase reactant produced by liver under inflammatory response later discovered as one of the important markers for cardiovascular risk is observed to be increased in SCH [41,42] CRP, indirectly promoted by IL-6, plays an important role in the progression of atherosclerosis [43]. Elevated concentration of CRP, observed in SCH [44,45] was associated with vascular alteration, characterized by increased carotid arterial stiffness values [46] positively correlated...
with TSH [47,48] and in Taiwanese population [49]. CRP stimulates the production of IL-6 and endothelin 1 (ET-1) and quenches an unidentified inhibitory factor; such as NO, known to decrease IL-6 and ET-1 secretion [50]. Feutin A, an indicator of inflammation which induces low-grade chronic inflammation and represses adiponectin production in humans [51] positively correlated with high-sensitivity [52] found to be low as a negative acute phase reactant in patients with SCH [53]. Reduced level of Feutin A was considered to make worsening the cardiovascular events via vascular calcification and inflammatory process in atherosclerosis [54]. In recent years level of homocystein, considered as marker of inflammation which is found to be associated with cardiovascular risk [55] was increased with patients with SCH [56] inflammation increases the synthesis of NO which is responsible to increases the level of homocystein through the binding to B12 by inhibiting enzymatic activity of methionine synthase in the remethylation reaction [57].

![Image](image-url)

Subclinical Hypothyroidism

Low Grade chronic inflammation

Elevated Nitric Oxide

Endothelial Dysfunction

Atherosclerotic lesion formation

Cardiovascular disease events

It has been discovered TSH is able to produce various effects binding through different receptors. TSH is able to bind hepatocyte TSH receptors to promote cholesterol synthesis [50] bind adipocyte TSH receptor (TSHR) to induce IL-6 synthesis and bind bone marrow cell TSHR to increase TNF-α secretion [59]. These actions are promising to associate with endothelial dysfunction, and this underlying mechanism promotes the correlation of SCH and endothelial function [60].

L-thyroxine treatment in SCH

Achievement of euthyroidism in SCH patients by treating the levothyroxine seems to be beneficial in various studies. Proper amount of L-thyroxine (LT4) aids to the increase in serum FT4 and FT3 which lowers the concentration of TSH by negative feedback mechanism on the pituitary [61,62]. There are insufficient evidences to support the hypothesis that increased inflammation can be reduced by the addition of LT4 in SCH patients. In the study carried out by Bilgir et al. concluded that LT4 therapy exerts anti-inflammatory and anti-apoptotic effects in the 3 months follow-up of levothyroxine treatment [63]. Similar to this in another study Sengil et al. observed there was a remarkable significant reduction in homocystein concentration in SCH after the treatment with L-thyroxine LT4 [64]. Similarly in 12 weeks, double blind, randomized crossover study concluded that all the cardiovascular events, e.g. total cholesterol, low-density lipoprotein cholesterol, waist-to-hip ratio were improved in SCH patients by the treatment of LT4 [65].

All these studies support that LT4 treatment could be beneficial in the achievement of euthyroidism as well as to reduce the cardiovascular risk in SCH patients.

However, contradictory result was also observed in SCH patients when treated with LT4 [66]. A replacement study showed that the improvement of 12 months LT4 treatment on PMD and mean carotid intima-media thickness were significantly different between SCH and control group [67]. In another study, where 6 months treatment with LT4 in SCH does not effective as thyroid substitution therapy does not affect lipidemic profile and systemic inflammation in patients with SCH [68]. Similar to this Aksoy et al. did not find any improvement in any parameters after the treatment with LT4 in SCH patients [69].

CONCLUSION

SCH was found to be associated with endothelial dysfunction due to increased level of inflammatory markers through various mechanisms. As the earliest sign of atherosclerosis, endothelial dysfunction is most frequently observed in SCH patients. These studies support the future occurrence of cardiovascular risk in SCH patients. LT4 therapy found to be beneficial in most of these studies, specially [TSH >10 µIU/ml], in the achievement of euthyroidism and improvement in the early stage of endothelial dysfunction, prevent from future risk of cardiovascular diseases. A controversial opinion exists due to LT4 therapy may increase the risk of osteopenia and arterial fibrillation in elderly. More studies with large sample size should be conducted to establishing the fact.

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