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SUBCLINICAL HYPOTHYROIDISM AND INTERLEUKIN 6 (IL-6): - A SHORT REVIEW

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Abstract

The most common thyroid disorder among Indian population is Subclinical Hypothyroidism (SCH). Inflammatory markers can assist to identify consequences of Subclinical Hypothyroidism. In this review we discuss the impact of interleukin-6, an inflammatory marker, on individuals with SCH. In Subclinical Hypothyroidism, TSH levels are slightly higher (4.5-10 mIU/L) but Triiodothyronine (T3) and Thyroxine (T4) levels remain normal, indicating that increased TSH is related with increased interleukin-6. Evaluating the factors that may decrease the risk of prognosis of patients with SCH to overt hypothyroidism is needful. Further studies required to identify the risk factors including inflammatory markers like IL-6 and other cytokines and their effect on SCH.

INTRODUCTION

Subclinical Hypothyroidism (SCH) is a prevalent disorder characterized by minimal or no signs and symptoms resembling hypothyroidism. In this condition, the levels of blood triiodothyronine (T3) and thyroxine (T4) are within the normal range, but there is a slight increase in the serum concentration of Thyroid Stimulating Hormone (TSH), ranging from 4.5-10 mIU/L [1]. The global prevalence of SCH exhibited variations based on factors such as gender, age, race/ethnicity, and geographic region, ranging from 0.4% to 16.9%. In India it is found to be between 9-11.4%, whereas in the adult population of northern India, it is around 10.25% [2,3,4]. The incidence of SCH is more in women [5].

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Interleukin-6 (IL-6) is an early inflammatory marker of inflammation and belongs to the Th2 class of cytokines, playing a crucial role in humoral immune response. IL-6 has diverse effects on different types of cells, including promoting the differentiation of B cells, stimulating the growth of myeloma, hybridoma, and plasmacytoma, activating T cells and thymocytes, inducing the production of acute phase proteins, promoting the growth and differentiation of precursor cells involved in blood cell formation, and inducing the differentiation of myelomonocytic cells [6]. IL-6 serves as a prominent and dependable indicator for quantifying the inflammatory reaction, leading to synthesis of C-reactive protein in the liver. Consequently, it indirectly stimulates the development of atherosclerosis. Thyroid Stimulating Hormone stimulates adipocytes to generate IL-6. TSH induces the release of IL-6 from mature 3T3-L1 adipocytes. This is achieved via TSH signalling through the cAMP-PKA pathway, which leads to the activation of IL-6 gene transcription [7].

Disorders of Thyroid Hormones

The thyroid gland is responsible for synthesising thyroid hormones, mostly Thyroxine (T4) and a smaller amount of Triiodothyronine (T3), which are then released into the bloodstream [8]. The hypothalamic-pituitary-thyroid axis has a conventional endocrine feedback loop mechanism to regulate thyroid function. The anterior pituitary gland releases TSH in response to the release of Thyrotropin-Releasing Hormone (TRH), which leads to the secretion of Thyroid Hormone (TH) by the thyroid gland. TH levels govern the creation and release of TRH and TSH. The link between TSH and thyroxine (T4) levels is log-linear, meaning that even small changes in TH concentrations result in significant changes in TSH. Therefore, serum TSH is a reliable indicator of the overall thyroid hormone levels in the body. Given the fact that TSH is highly responsive to even little fluctuations in thyroid hormone levels, and with the introduction of advanced TSH tests, medical professionals may now detect small alterations in thyroid function. This has led to the emergence of the notion of subclinical thyroid illness [9].

Hyperthyroidism refers to the condition of having an excessive production or release of thyroid hormones. Thyrotoxicosis causes systemic symptoms by affecting tissues with an excess of thyroid hormone [10]. The primary causes of hyperthyroidism include toxic multinodular goitres, toxic adenomas and Graves' disease. GD is an autoimmune disorder characterized by reduced immunotolerance and the formation of thyrotropin receptor antibodies (TRAb), which attach to and stimulate TSH receptors. The secretion and production of thyroid hormones are enhanced. Nodular goitres are non-toxic, but they have the potential to become autonomous and induce hyperthyroidism [11].

Hypothyroidism refers to a condition when there is a total or partial deficiency in the activity of thyroid hormones. This deficiency can manifest as Overt Hypothyroidism (OH) or Subclinical Hypothyroidism (SCH). SCH can be diagnosed when blood serum levels of FT3 and FT4 are normal and TSH increases above normal limits. In contrast, increased TSH levels combined with below-normal FT4 levels are indications of Overt Hypothyroidism (OH). The global prevalence of hypothyroidism continues to be

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significantly influenced by iodine shortage. The most prevalent causes of autoimmune illness (namely Hashimoto's thyroiditis) and iatrogenic factors (such as the therapy of hyperthyroidism) are observed in regions where there is an adequate supply of iodine. The main characteristics of Hashimoto's thyroiditis are the large-scale, sensitized T lymphocyte infiltration of the gland, the progressive fibrous material replacement and destruction of thyroid tissue, elevated antithyroid antibody levels, and the presence of goitre or variable degrees of thyroid glandular atrophy and dysfunction [12]. Hypothyroidism can lead to various complications in humans, encompassing mental health issues like depression and impaired cognitive function. Additionally, it can contribute to cardiac problems by elevating levels of low-density lipoprotein (LDL) cholesterol. In some cases, hypothyroidism may result in cardiac failure and enlargement of the heart. Furthermore, the condition can disrupt the ovulation process in women, potentially leading to infertility [13]. Hypothyroidism is characterized by increases in inflammatory cytokines, such as CRP, IL-6, and other similar substances. TNF and IL-6, as inflammatory markers, may cause several types of hypothyroidism-related issues by affecting endothelium cells, encouraging the growth of smooth muscle cells, and stimulating immune cells [14].

Chronic inflammation may be linked to endothelial dysfunction. The aetiology of AIT involves the involvement of several cytokines and adhesion molecules that have a role in both the thyroid gland and immune system. T cells and other immune cells have been seen to infiltrate the thyroid and disrupt the integrity of the epithelium. IL-6 has been identified as one of the markers of systemic inflammation with increased concentrations of IL-6 in the blood serum following the treatment of Hashimoto's thyroiditis [15]. Prior research has yielded inconsistent findings about the correlation between hypothyroidism and abnormal inflammatory markers. A study conducted by Shilpi Goyal et al. found that hypothyroid individuals had significantly elevated levels of IL-6 and TNF-α in their serum compared to euthyroid controls. In agreement with the research done by Taddei S et al., it was found that those diagnosed with hypothyroidism displayed a mild and chronic inflammatory state, as indicated by a significant rise in high sensitivity CRP and IL-6 levels [16].

Subclinical Hypothyroidism is a condition characterized by an increase in blood TSH, although the levels of total or free T3 and T4 remain within the normal range [1]. Multiple studies conducted on SCH have reported varying ranges for serum TSH levels, with a lower limit of 4.5 mIU/L and a upper limit of 10 mIU/L. A study conducted in Brazil, has classified SCH (Subclinical Hypothyroidism) into two grades. TSH levels between 4.5 and 9.9 mIU/L characterize grade 1, while levels above 10 mIU/L characterize grade 2 [17]. Research conducted in Korea indicated that SCH levels were found to be greater than 6.68 mIU/L [18]. A study conducted in the United States has classified Subclinical Hypothyroidism (SCH) into three groups based on the level of elevation in Thyroid-Stimulating Hormone (TSH). The first category is slightly increased, with TSH levels ranging from 4.50 to 6.9 mIU/L. The second category is moderately high, with TSH levels ranging from 7 to 9.9 mIU/L. The third category is significantly elevated, with TSH levels

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ranging from 10.0 to 19.9 mIU/L [19]. A study conducted in Europe classifies Subclinical Hypothyroidism (SCH) into two groups based on the extent of elevation in Thyroid-Stimulating Hormone (TSH) levels. The first category includes individuals with a modestly raised serum TSH level ranging from 4.5 to 10 mIU/L, while the second category includes patients with serum TSH values beyond 10 mIU/L [20].Similarly, a research conducted in India by the Indian Thyroid Society found that patients with Subclinical Hypothyroidism (SCH) may be divided into two groups: those with a slightly raised Thyroid Stimulating Hormone (TSH) level ranging from 4.5 to 10 mIU/L, and those with a much higher TSH level beyond 10 mIU/L [21].

In SCH, symptoms may or may not be seen, similar to Overt Hypothyroidism. Thyroid function testing is the method used to diagnose SCH because it yields biochemical proof of the disorder. SCH affects up to 10% of the general population, particularly women and older individuals, in populations with sufficient iodine level [5]. The effects of SCH on serum lipid fractions remain uncertain. Several studies have demonstrated that individuals with SCH experience impaired lipid digestion, resulting in higher levels of LDL-C and TC in the bloodstream. In most instances, changes are considered to be risk factors due to their association with coronary heart disease and atherosclerosis. Furthermore, individuals in their middle years who have SCH may encounter cognitive dysfunction, non-specific symptoms such as fatigue, and fluctuations in mood [22]. SCH is linked with higher risk of coronary artery disease, cardiovascular disease, and coronary disease-related death. In addition, persons with middle-aged SCH may have bouts of emotional disturbances, mental abnormalities, and vague symptoms such as weariness. SCH has been associated with atherosclerosis and other cardiovascular risk factors, including alterations in pulse. SCH also causes alterations in the lipid profile (LP). Thyroid hormone governs the regulation of lipid metabolism. Furthermore, several studies have observed a positive correlation between increasing TSH levels and elevated lipid levels [23].

Various mechanisms might account for the association between SCH and mortality linked to CVD. Thyroid hormone levels impact the relaxation of vascular smooth muscle cells and the contractility of heart due to their involvement in controlling calcium absorption and the expression of proteins responsible for heart muscle contraction [24].

A study done by Vierhapper et al. in patients with Overt Hypothyroidism, SCH, and Euthyroidism. They found that LDL-C values were higher in patients with Overt Hypothyroidism and SCH, but not in euthyroid patients. Additionally, Hueston et al. reported that anomalies in blood cholesterol or TG levels are not linked to SCH. On the other hand, comparable findings from an Indian study indicated that elevated TSH levels are correlated with elevated LDL, TG, and TC levels. Hyperlipidaemia is therefore more prevalent in SCH patients [22].

Role of Interleukin-6 (IL-6) in Subclinical Hypothyroidism

IL-6 serves as an initial indicator of inflammation and belongs to the Th2 category of cytokines, playing a crucial role in humoral immune response [6]. Interleukins exert a

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potent influence on hepatocytes, prompting them to generate a group of proteins referred to as acute-phase proteins. The basal amounts of acute phase proteins in serum were observed in normal and healthy individuals. Nevertheless, their concentrations are elevated during hepatic stimulation. Thyroid Stimulating Hormone induces the secretion of IL-6 in adipocytes. IL-6 has a crucial function in the first phases of inflammation and also acts as a regulator.

Gaurav G et al. in their research that found a connection between dyslipidemia and increased inflammatory markers in individuals with SCH. According to their, the TSH level in the SCH group (mean ± SD: 11.12±4.17) was significantly greater compared to the control group (mean ± SD: 2.73±0.80). Although the T3 concentration showed a significant difference compared to the control group (Mean±SD: 0.96±0.17 vs 1.08±0.26), the FT4 level in the SCH group (Mean ± SD: 1.16±0.25 vs 1.15±0.22) did not exhibit any meaningful difference. The IL-6 level of the SCH group was significantly elevated compared to that of the control group, indicating increased inflammatory activity. The mean ± standard deviation for IL-6 levels were 9.30±2.54 in one group and 4.04±0.70 in another group. As per the research conducted by Taddai S et al., individuals with Subclinical Hypothyroidism (SCH) had increased levels of Interleukin-6 and C-reactive protein, which are both markers of inflammation [5].

Similarly, Sandeep Kumar et al, found that individuals with SCH may exhibit elevated levels of IL-6. Based on their research, the study found that TSH levels were significantly elevated in the SCH group (9.57 ± 6.84 vs 2.97 ± 0.91) compared to the control. The FT4 levels in the SCH group showed no significant difference, ranging from 13.55 ± 2.52 to 13.81 ± 18.5. When comparing patients with Subclinical Hypothyroidism (SCH) to the people with normal, there was no significant difference in the concentration of FT3 (4.27 ± 0.82 vs. 4.51 ± 1.2). However, the serum IL-6 levels in SCH patients were significantly higher (397.24±66.78 vs. 84.42±35.02) [23].

Conclusion: Patient with Subclinical Hypothyroidism show raised levels of inflammatory markers. IL-6 is elevated in SCH patients. If SCH left untreated, SCH will progress into overt hypothyroidism. Further studies are required to highlight the factors which may help to prevent SCH from developing into overt hypothyroidism.

Summary of the Studies

Study	Conclusion
Abdulsalam A.A.Al-Azazi T, et al, 2022	The study found that blood Zn2+ levels were reduced in patients with SCH, suggesting an aberrant metabolism of Zn2+ in these individuals.
Goyal S, et al, 2022	The study found that levothyroxine medication had a notable impact in normalizing elevated levels of inflammatory markers in individuals with hypothyroidism. The observed reduction in low-grade chronic inflammation following therapy holds therapeutic significance, as chronic inflammation is known to be linked with atherosclerosis and heart illness.
Sgarbi JA, et al,2021	SCH is a condition that is quite common the general population and is becoming more prevalent in medical practice. If it is not identified and treated, it can lead to significant long-term consequences.

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Ejaz M, et al, 2021	This study concluded a higher occurrence of dyslipidaemia in people with SCH. It is linked to increased TC and low-density lipoprotein LDL levels, which are known to be risk factors for cardiovascular disease and death
Kumar S,2020	The research found adult population had a prevalence rate of 10.25% for SCH. Women had a greater frequency compared to males.
Hongyan L, et al, 2019	The findings indicate that IL-2, IL-6, and IL-8 have a role in the onset and progression of hyperthyroidism and subclinical hyperthyroidism. Furthermore, these cytokines interact with one other, therefore influencing and controlling one another. This interaction partially reflects alterations in thyroid function. Studying the pathophysiology of thyroid illness is highly valuable for understanding the prognosis of thyroid function and assessing the clinical status of thyroid disease.
Gupta G, et al,2018	The study indicated Patients with SCH who have elevated levels of TSH exhibit an atherogenic lipid profile. Elevated levels of IL-6, in conjunction with increased levels of C reactive protein, may indicate an early risk of development towards atherogenic risk
Bhagwat N, et al,2017	Primary autoimmune hypothyroidism is a condition where inflammation occurs due to the immune system targeting the thyroid gland. Increased cytokine levels indicate this inflammation, which decrease with LT4 therapy. It is linked to depression and a low quality of life. The administration of treatment for hypothyroidism leads to the relief of depression in the majority of patients.
Gupta G, et al,2015	According to this study, dyslipidemia and increased levels of inflammatory markers are present in people with SCH. As so, there is an increased probability of developing cardiovascular disorders in the future. The levels of inflammatory markers in patients grow as the disease progresses if it is not treated.

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