Running title: *Hypothyroidism and its systemic complications*

Hypothyroidism as a Multisystem Disorder: Pathophysiological Basis and Contemporary Evidence - A Comprehensive Review of Anemia, Dyslipidemia, and Systemic Inflammation

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ABSTRACT

Background:

Hypothyroidism, characterized by reduced serum triiodothyronine (T3) and thyroxine (T4) with elevated thyroid-stimulating hormone (TSH), significantly influences basal metabolic rate and systemic metabolism. Increasing evidence suggests its association with anemia, dyslipidemia, inflammation, and oxidative stress.

Objective:

This narrative review aims to synthesize current evidence on the interrelationship between hypothyroidism, anemia, inflammation, and oxidative stress, highlighting shared pathophysiological mechanisms and clinical implications.

Methods:

A comprehensive literature search was conducted in Scopus, PubMed, and Google Scholar for articles published between January 2022 and September 2024. Keywords included hypothyroidism, anemia, inflammation, dyslipidemia, lipid profile, cardiovascular risk, iron parameters, smoking, and alcohol consumption. Only full-text English-language studies were included.

Results:

Hypothyroidism is frequently associated with anemia (prevalence 5–26%), dyslipidemia, and systemic inflammation. Elevated oxidative stress markers, particularly malondialdehyde (MDA), along with increased inflammatory markers such as TNF-α and C-reactive protein (CRP), are consistently reported. Smoking, alcohol consumption, iodine deficiency, and iron deficiency may further exacerbate thyroid dysfunction and oxidative imbalance.

Conclusion:

Current evidence supports a strong association between hypothyroidism and adverse hematological and inflammatory outcomes. However, robust randomized clinical trials are required to clarify the long-term benefits of thyroid hormone replacement therapy on these systemic complications.

Keywords: Hypothyroidism; Anemia; Dyslipidemia; Inflammation; C-reactive protein; Tnf-α.

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Introduction

Thyroid disorders represent a significant category of endocrinological conditions, both in India and globally, impacting over 200 million individuals. According to numerous research studies in India, around forty-two million people are affected by thyroid diseases[1]. Compared to the male population, the incidence of thyroid gland problems is 10–15% higher in females. The prevalence of thyroid diseases is around 15 - 25% in various regions of India, while in developed countries, it has a prevalence of about 4-9% only. [2]

Thyroid Dysfunction

In humans, Hyperthyroidism & Hypothyroidism are the two main categories of Thyroid Dysfunction that have been characterised.

Hyperthyroidism - Decreased serum levels of Thyroid Stimulating Hormone (TSH) and increased thyroid hormone concentrations (T3 and T4) are characteristic features of thyrotoxicosis or hyperthyroidism. High dietary iodine intake remains the most common cause of thyrotoxicosis in iodine-rich regions. In contrast, Graves' disease remains common in autoimmune disorders. The most common clinical manifestations are weight loss, increased appetite, heat intolerance, insomnia, tremors, diplopia, and sometimes dyspnoea.[3]

Hypothyroidism: This is the most prevalent form of thyroid disease, which can be diagnosed by decreased serum (T3, T4) levels and a high concentration of serum TSH. Although low serum iodine levels or low iodine dietary intake deficiency contribute to the development of overt hypothyroidism, Hashimoto's thyroiditis remains the leading cause of an autoimmune disorder in which antibodies develop against the TSHr receptor, which works as an antagonist against TSHr-Ab (thyrotropin-stimulating hormone receptor antibody). Common symptoms present in hypothyroid individuals are weight gain, Bradycardia, fatigue, tiredness, & slow speech [4]. The functions of the thyroid hormones are depicted in **Figure:1.**

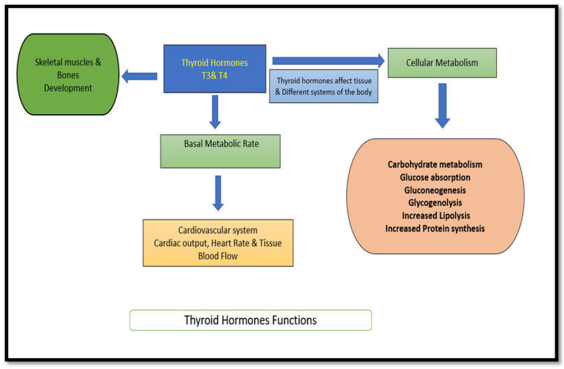

Figure 1: Functions of Thyroid Hormones on Different Metabolism (Abbreviations**:** T3-triiodothyronine; T4-thyroxine).

Types of hypothyroidism

Congenital hypothyroidism: This occurs frequently, and it presents no symptoms at birth. Biochemical investigations are done only on clinical symptoms that appear in the child after birth, such as jaundice, low muscle tone, delay in bone development, or an umbilical hernia. Delay in congenital hypothyroidism diagnosis can result in severe brain impairment damage, or, left undiagnosed, can turn into adult hypothyroidism symptoms. Latest clinical evidence shows that, in most cases, it occurs due to thyroid dysgenesis, but the dysfunction of the central hypothalamic pituitary axis also contributes [5]**.**

Primary hypothyroidism: This type of hypothyroidism can be accompanied by goitre (Goitrous thyroiditis or Hashimoto's) or, in later stages, by atrophic thyroiditis. In autoimmune hypothyroidism, there is a reduction of Free T4 levels with an elevation in TSH levels. Clinically, it is denoted as subclinical hypothyroidism with mild or no symptoms. Longitudinal cohort data suggest that enduring subclinical hypothyroidism, particularly when accompanied by thyroid autoantibodies, correlates with an elevated chance of advancing to overt hypothyroidism.[6]

Secondary hypothyroidism: results from impaired TSH secretion due to pituitary or hypothalamic dysfunction. The release of an immunoreactive but physiologically inactive hormone might cause TSH levels to appear normal or slightly elevated. Low

free T4 levels in the context of established pituitary disease provide the basis for diagnosis. The goal of management is to maintain free T4 concentrations within the upper part of the reference range.[7]

Hypothyroidism & Anemia

Anemia is the most typical symptom of hypothyroidism, which primarily affects the hematopoietic system. Numerous anemia illnesses can be brought on by hypothyroidism. Numerous processes, including microcytic, macrocytic, & normocytic, are implicated in the pathophysiology of this anemia **Figure:2.**

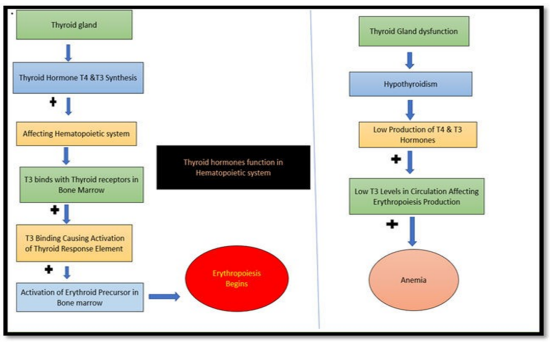

Figure 2: Thyroid hormone role in the hemopoietic system (Abbreviations**:** T3-triiodothyronine; T4-thyroxine).

Microcytic anemia is frequently observed in hypothyroidism, mostly attributed to iron deficiency, which is often linked to menorrhagia resulting from various hormonal imbalances and reduced gastrointestinal absorption**.** Iron is an essential component required by the enzyme Thyroid Peroxidase (TPO) in the synthesis of T3 & T4 hormones. Evidence from experimental and clinical studies shows that low iron levels can impair the peripheral conversion of T4 to T3 and lower circulating thyroid hormone concentration.[8] Increased free iron in the body increases toxicity in the cells. So, to prevent the effect of free iron, the human body has generated a protective mechanism to bind free iron in tissues. Hemosiderin and ferritin are the iron storage forms. The control of ferritin production at the post-transcriptional level requires the engagement of the cytoplasmic iron regulatory protein (IRP) with the iron-responsive element (IRE) found in the 5′ untranslated region of ferritin mRNA**.** Ferritin is a protein that stores iron inside cells.[9] Thyroid problems have been linked to altered ferritin levels, indicating that ferritin may be an indirect indicator of thyroid function. [10]**.** A summary of the studies related to hypothyroidism and the hemopoietic system is depicted in **Table:1**

Sno	**Authors/year**	**Study design**	**Age Group Years**	**Population size**	**Results**
1	Neeta Dhabhai/2023	Observational study	18-30	2317	Anemia and obesity are high-risk factors for hypothyroidism [11]
2	Shalini Dutt / 2023	Cross-sectional study	Above 18 years	160	70% of the population was suffering from anemia in the hypothyroid population [12]
3	Wisal Abbas/ 2023	Cross-sectional study	18-45	127	32% of the Population had High TSH levels and 37% had iron deficiency, found [13]
4	Sardar Jawad Gul / 2023	Cross-sectional study	15-60	297	A prevalence of 27% for anemia was

					noted within the thyroid group, with normocytic anemia being the most frequently observed type.[14]
5	Swapnika / 2024	Case-controlled study	14-55	100	Subclinical hypothyroidism shows a positive correlation with iron deficiency anemia [15]

Table1: Summary of the Studies related to hypothyroidism and anemia

Hypothyroidism & Dyslipidemia

Increased levels of triglycerides (TG) or low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C) in the blood are the hallmarks of dyslipidemia. Age, dietary habits, decreased physical activity, increased stress, genetic or inherited variables, and thyroid function are probable factors for causing hyperlipidemia **Figure:3**

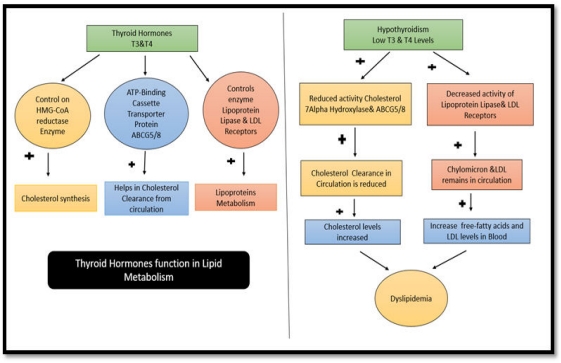

Figure 3: Thyroid hormone role in lipid metabolism **(**Abbreviations**:** HMG-CoA-3-hydroxy-3-methylglutaryl-coenzyme A; LDL- low density lipoprotein, T3-triiodothyronine; T4-thyroxine; ABCG5/8 - ATP-binding cassette subfamily G members 5 and 8).

Evidence reveals that newly diagnosed hypothyroid people have significant variations in lipid profiles and adipokine levels, supporting a direct metabolic consequence of thyroid hormone insufficiency**.**[16] The liver organ helps in the metabolism of T3 &T4 by regulating their systemic endocrine impacts. Additionally, the hormones T3 and T4 influence hepatic function by modulating the liver's basal metabolic rate, which encompasses the activity of liver cells. Lipid levels can be impacted by thyroid disease, which can also impair liver function [17]**.** By regulating the activity of the LDL receptor gene, free T3 can upregulate LDL receptors, thus LDL can be shielded from oxidation. Deficiency of FreeT3 can enhance lipid peroxidation, causing an increase in LDL levels in circulation[18]**.** Clinical investigations further demonstrate that lipid problems in hypo- and hyperthyroidism correspond largely with variations in free T4 levels rather than genetic variants in LDL-related pathways.[19] Summary of the studies related to hypothyroidism and dyslipidemia depicted in **Table:2**

Sno	**Authors/year**	**Study design**	**Age Group Years**	**Population size**	**Results**
1	Moeber M Mahzari / 2022	Cross-sectional study	18-75	412	Total cholesterol, LDL, HDL & Triglycerides levels were elevated in hypothyroid people with p< 0.001[20]

2	Hye In Kim, /2023	Cohort study	18-60	1665	Dyslipidemia was found to be positive in hypothyroidism with p=0.014 [21]
3	Richa Bhattarai/ 2023	Cross-sectional study	18-75	222	A statistically significant association between the thyroid and the control group in terms of dyslipidemia was not observed .[22]
4	Xueran wang /2024	Cohort study	18-50	952	A positive association was found between LDL, Total cholesterol, Hypothyroidism & increased risk of pregnancy outcomes [23]
5	A.O. Dada,/ 2024	Cross-sectional study	19-82	132	32% of the study population have Hypothyroidism with dyslipidemia (69%), most observed in the thyroid population [24]

Table 2: Summary of the Studies related to hypothyroidism and dyslipidemia

Hypothyroidism & smoking

The effects of smoking on thyroid function are often influenced by age, smoking history, daily cigarette intake, and iodine levels in the body. Cigarettes include chemical components such as nicotine, thiocyanate, and benzopyrene, which impede thyroid hormone synthesis. These chemical components act as enzyme inhibitors, reducing iodine uptake in the body. Because benzopyrene stimulates the neurological system, it may impact thyroid gland function and cause TSH levels to decline. In the smoking population in iodine-deficient areas, Goitre prevalence is higher, and reduced TSH levels are commonly observed[25]. Multiple studies found a positive association between smoking and TSH levels, leading to increased CVD disorders[26]. However, studies have Contradictory data showing that smoking functions as an independent variable and discovered no correlation between smoking status and thyroid dysfunction[27].

Inflammatory markers

Previously, hypothyroidism was believed to be an inflammatory disorder characterized by elevated amounts of inflammatory interleukin like *Tumour Necrosis factor alpha* (TNF- α) & *Interleukin six* (IL- 6). High levels of these inflammatory indicators in the system may contribute to the issues associated with hypothyroidism. This occurs through mechanisms such as inducing endothelial dysfunction, promoting the proliferation and migration of smooth muscle cells, and recruiting and activating inflammatory cells. In addition, they stimulate cells to produce interferon-gamma and facilitate cellular death[28]

The heart and lungs are cognizant of the effects of hormones produced by the thyroid, and even small deviations from the usual level of T3 & T4 can lead to noticeable fluctuations in heart function. Increased levels of thyroid hormones, as observed in hyperthyroidism, can encompass heightened resting heart rate, increased myocardial contractility, augmented left ventricular strength, and susceptibility to atrial arrhythmias. Individuals with hyperthyroidism may experience cardiac issues such as chest pain, a condition called angina pectoris, and irregular heartbeats, while dyslipidemia, which occurs in hypothyroidism, is characterised by elevated levels of hypercholesterolemia, which then results in the formation of ischemic heart diseases[29].

TNF- α (Tumor Necrosis Factor)

TNF-alpha is a monokine that is predominantly generated by monocytes and macrophages. It may also be secreted by lymphocytes, fibroblasts, and thyroid epithelial cells. The excessive synthesis of TNF-α has been associated with the aetiology of several immune-related inflammatory disorders. TNF-alpha exerts its biological effects through interaction with two different types of transmembrane receptors. Research has demonstrated the presence of these receptors in the thyrocytes of humans and fauna[30]. TNF-α has several effects on the circulatory system, such as influencing endothelial function, interacting with inflammatory cells, causing vasodilation, affecting visceral muscles' cellular physiology, impacting cardiac myocyte function, &influencing blood glucose homeostasis [31]. Multiple studies have indicated that persons with hypothyroidism, including its many subtypes, have considerably higher levels of tumour necrosis factor-alpha (TNF-α) compared with euthyroid individuals, with a positive association between hypothyroidism and TNF-α levels [32].

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CRP (C-Reactive Protein)

C-reactive protein (CRP) is a plasma acute-phase protein made up of five analogous polypeptide subunits, with each subunit containing 206 amino acids. High plasma CRP levels result from the body's reaction to cytokines present in the plasma, namely Interleukin-1b & Interleukin-six. These cytokines are mostly generated by macrophages and adipocytes [33].CRP levels may increase by up to 50,000 times the usual amount. The levels of CRP begin to rise after 6 hours following irritation in the human body and reach their highest point within two days, depending on the extent of damage to tissues [34]. CRP serves as a highly responsive indicator of inflammation. Various studies have consistently shown a positive association between high CRP levels and Cardiac disease and mortality [35]. Vuda et al. show in their study that elevated levels of CRP in the hypothyroid Population compared with the Control Group [36] Another study was done by. Demirkol et al confirm a Positive association between Thyroiditis and CRP [37].

This report critically reviewed the literature that describes the current situation and challenges. According to the literature, limited studies related to hypothyroidism, anemia, and cardiovascular diseases in iodine-deficient populations have been reported. Only a few studies reported the smoking and alcohol effects on inflammation in correlation with hypothyroidism, but the sample population size was the major limitation of the available data. Few studies have found that thyroid dysfunction is prevalent in people with mild to moderate anemia and dyslipidemia and but failed to address the issues of chronic inflammation and nutritional status. Further, limited data are available in comparative studies on the association of oxidative stress and lipid profile with cardiac complications in hypothyroid patients.

Material & Methods

A thorough literature review was conducted using the Scopus, PubMed, and Google Scholar databases. The search strategy incorporated keywords, Boolean operators, and field-specific filters. The inclusion criteria were based on the following keywords: hypothyroidism and its effects on anemia, inflammation, dyslipidemia, smoking, alcohol consumption, lipid profile, cardiovascular system, and iron parameters. Only original research articles, review papers, and abstracts published in full English text between January 2022 and December 2024 were considered. Studies published in languages other than English were excluded. Following a thorough screening and critical appraisal process, 90 articles were selected for inclusion. Comprehensive data were extracted from these studies, encompassing the year of investigation, geographical location, sample demographics, clinical presentations, and bibliographic references.

Discussion

The narrative review explored the effects of hypothyroidism leading to anemia, dyslipidemia, and inflammation, highlighting their coexistence and pathophysiological mechanisms. The evidence suggests that hypothyroidism and its types can lead to anemia, especially microcytic anemia and iron deficiency anemia most commonly observed. Recent studies have further clarified the relationship. For instance, Huang et al[38]. confirm in their two-sample Mendelian randomization study that thyroid-related gene disorders increase the risk of iron deficiency anemia. Low levels of thyroid hormone affect the liver, leading to alterations in lipid metabolism that result in changes in cholesterol and lipoprotein levels, ultimately causing dyslipidemia, the most common finding in hypothyroidism. Dyslipidemia causes lipid peroxidation, leading to the generation of free radicals, causing high levels of oxidative stress marker MDA, and a rise in inflammatory markers like CRP and TNF-alpha levels, while decreasing antioxidant levels in the body. Multiple studies have confirmed that high levels of BMI, smoking, and cytokine levels are positively correlated with hypothyroidism and thus further increase the risk of cardiovascular disorders.[39] Recent research confirms that higher CRP, TNF-alpha, and TSH levels, more than 10mIU/L, can lead to changes in the cardiac system, causing to increase in systemic inflammation, the generation of foam cells, low cardiac output, and a higher risk of carotid intima thickness, leading to a higher risk of cardiovascular disease in the future [40]. Therefore, the clinician needs to have early diagnosis and treatment of hypothyroidism, thus limiting the impact of hypothyroidism on different systems and possibly reducing the long-term risk of cardiovascular disorders in individuals.

Recommendations: According to the available data, there is a need to enhance the diagnostic and treatment approaches to lessen the global health impact of thyroid disease. As a first step, early detection has the potential to greatly benefit patients undergoing treatment while at the same time alleviating the demand placed on the global distribution of thyroid disease. Treating low iron levels earlier can prevent the risk of thyroid disorders in individuals. In iodine-deficient areas, knowledge and awareness among the tribal and illiterate people about the importance and function of iodine and its prevention of thyroid diseases become essential.

Conclusion

Based on clinical data and the magnitude of its worldwide burden, thyroid disorders are among the most prevalent endocrine disorders, particularly in India, where they are more common in women. Both hyperthyroidism and hypothyroidism are significant global health issues with varying clinical approaches and unique pathophysiology. Hyperthyroidism is known to be part of the autoimmune spectrum, such as Graves' disease, while hypothyroidism is mainly found because of iodine deficiency & autoimmune conditions such as Hashimoto's thyroiditis. The different classes of hypothyroidism, congenital, autoimmune, secondary, and subclinical, only complicate the nature of their disorders further. The association of hypothyroidism with anemia, dyslipidemia, and inflammatory markers demonstrates that thyroid dysfunction is involved in the diagnosis of diseases other than primary thyroid disorders. Numerous research investigations have demonstrated that hypothyroidism is associated with the development of anemia, and a significant proportion of individuals suffering from anemia also exhibit dyslipidemia, a condition recognized as a risk factor for cardiovascular disease. In addition, inflammatory mediators such as TNF-α and CRP strongly relate to the complications of hypothyroidism and, indeed, temper the possible mechanisms that link thyroid disease to cardiovascular inflammation. This is an important message for those living in regions characterized by iodine deficiency, as increased vigilance and pre-emptive measures would aid in detecting and managing these disorders.

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