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STUDY OF CRP AND LIPID PROFILE IN PATIENTS OF SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Background: Subclinical Hypothyroidism (SCH) is a prevalent condition globally, more common than overt Hypothyroidism. It is characterized by elevated thyroid-stimulating hormone (TSH) levels with normal peripheral thyroid hormone levels. Recent findings indicate that inflammation and disturbances in lipid metabolism play a role in the development of SCH. Low grade inflammation is indicated by increase in levels of a marker C reactive protein (CRP) produced by hepatocytes. CRP has been linked to cardiovascular disease (CVD). Dyslipidemia, which refers to abnormal lipid levels, has been commonly linked to Overt Hypothyroidism. However, its significance in subclinical hypothyroidism (SCH) is still a topic of debate.

Aims and objectives: The objective of the study is to assess the levels of CRP and lipid profile in patients with subclinical hypothyroidism and compare these values with normal standard values. Additionally, the study aims to investigate the relationship between CRP and lipid profile with subclinical hypothyroidism and evaluate the potential risk of developing cardiovascular disease in patients with subclinical hypothyroidism.

Materials and Methods: In a cross-sectional study, 63 patients over the age of 18 with subclinical hypothyroidism were newly diagnosed through the measurement of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). These patients were also examined for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, serum triglycerides, and C-reactive protein (CRP). The levels of TSH were then compared with the lipid parameters and CRP levels.

Results: This study demonstrates a significant association between subclinical hypothyroidism, dyslipidemia and elevated CRP levels. These findings show lipid metabolism disturbances and inflammation play a crucial role in SCH's pathophysiology, potentially increasing cardiovascular risk. Total cholesterol, TG, LDL, and VLDL were significantly higher in patients with SCH ($P < 0.05$). No association was found between HDL and SCH.

Conclusion: The analysis revealed that TSH is significantly correlated with elevated levels of total cholesterol, LDL, VLDL, TG, and CRP. This suggests that subclinical hypothyroidism

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(SCH) can lead to dyslipidemia, which in turn can cause inflammation and become an independent risk factor for developing cardiovascular disease (CVD) in the future.

Keywords: Subclinical hypothyroidism (SCH), TSH, Lipid Profile, CRP.

INTRODUCTION

Subclinical hypothyroidism (SCH) is a common public health issue. In subclinical hypothyroidism due to thyroid dysfunction, serum thyroid-stimulating hormone (TSH) levels are appropriately elevated while the peripheral thyroid hormone levels are within the normal range [1,2]. The prevalence of subclinical hypothyroidism is 9% [3]. Thyroid hormones have a significant impact on metabolic processes, particularly the metabolism of proteins, carbohydrates, and lipids. They change lipid metabolism by making more lipid substrates available, creating and moving around triglycerides stored in adipose tissue, increasing the amount of non-esterified fatty acids (NEFA), and making lipoprotein-lipase work better. In hypothyroid patients, the most frequent lipid abnormality is high cholesterol, mainly due to increased low-density lipoproteins (LDL) cholesterol. Very low-density lipoproteins (VLDL) and high-density lipoproteins (HDL) cholesterol can also be elevated. Plasma triglycerides increase due to enhanced fatty acid esterification at the hepatic level. Additionally, plasma concentrations of lipoprotein (a) increase in hypothyroidism, which has been shown to have thrombogenic and atherogenic effects. Subclinical hypothyroidism is also linked to mild hyperlipidemia, potentially increasing the risk of atherogenesis [4]. Thyroid hormones play a significant role in regulating cholesterol levels in the body. They increase the activity of HMG-COA reductase in the liver, leading to a reduction in cholesterol. Additionally, thyroid hormones boost the number of LDL receptors in various tissues, including the liver, which aids in the absorption of cholesterol from the intestine. These hormones also impact the levels of HDL cholesterol and hepatic lipase activity, as well as influence the excretion of cholesterol from the intestine through bile acids [5]. Patients with subclinical hypothyroidism may be at risk of developing heart disease due to changes in their lipid profile. The buildup of cholesterol in the body may lead to the development of atherosclerosis, an inflammatory condition associated with myocardial infarction [6].

C-reactive protein (CRP) is an acute-phase inflammatory protein, which has been used as a clinical marker of inflammation, infection, and tissue damage [7]. Generally, CRP is elevated during inflammatory disorders, such as CVD, rheumatoid arthritis, and some acute or chronic infections [8]. CRP plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide release, and the production of cytokines. CRP production is part of the nonspecific acute-phase response to most forms of inflammation, infection, and tissue damage [9]. Recently, research outputs showed that minor CRP elevation could contribute to an increased future risk of major cardiovascular events [10]. Hence, CRP measurements have potential utility as a clinical tool in assessing disease status and progression, including CVD, some infections, and cancer. Existing literature demonstrated that subclinical hypothyroidism may be associated with elevated CRP, although the clinical implications were uncertain [11, 12, 13]. Some researchers found that there was a significant positive correlation between TSH and CRP [13, 14]. Thyroid hormones play an important role in the cardiovascular system's normal functioning [15] and maintaining cardiovascular homeostasis [16]. Changes in the thyroid status can affect ventricular functions, serum lipids, heart rate, and rhythm, leading to an increased risk of CVD theoretically with

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heightened morbidity and mortality [17]. However, thyroid dysfunction has not been labeled a coronary risk factor.

METHODOLOGY

A cross-sectional study was conducted at Government Medical College, Chhatrapati Sambhaji Nagar, Maharashtra, from March to October 2024, involving 63 cases of subclinical hypothyroidism, defined as elevated TSH levels (3.10 to 6.80 pmol/L) with normal FT3 and FT4. Patients with overt hypothyroidism, end-stage renal disease, known cardiac disease, diabetes (types 1 & 2), severe systemic illness, hypertension, those on thyroxine/anti-thyroid, anti-hypertensive drugs or anti-lipidemic drugs, pregnant women, oral contraceptive users, and those without consent were excluded.

Ethical clearance was granted by the Institutional Ethics Committee (IEC-GMCA), and informed consent was obtained (No: Pharma/IEC-GMCA/179/2024).

FT3, FT4, and TSH were estimated using a chemiluminescence immunoassay (CLIA). The lipid parameters were estimated colorimetrically after overnight fasting, and CRP was estimated using immunoturbidimetry. VLDL was estimated using the Friedewald equation (TG/5).

We used Pearson's correlation test for statistical analysis by SPSS software. The correlation coefficient, r value, that ranged from -1 to 0 showed a negative correlation, whereas the r value from 0 to 1 showed a positive correlation, and the r value towards -1 or +1 showed a stronger negative or stronger positive correlation, respectively. Statistical significance was set at $p < 0.05$.

RESULTS

In the present study, 63 patients with subclinical hypothyroidism were enrolled. Table 1 shows the demographic profile of patients; table 2 shows the correlation of TSH with lipid parameters using Pearson’s coefficient. Table 3 shows the correlation of TSH with CRP.

Table 1: Demographic profile of patients

		Number of patients	Percentage (%)
Age-Group (In years)	≤30 years	21	33.3
	31-40	24	38.1
	>40	18	28.6
	Mean±SD (for age)	35.76±6.50	
Gender	Male	33	52.4
	Female	30	47.6

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Out of 63 patients with subclinical hypothyroidism, the majority of 24 (38.1%) were from the age group of 31–40 years, and 18 (28.6%) were from the age more than 40 years. The mean age of patients was 35.76±6.50 years. Maximum 33 (52.4%) patients were male and 30 (47.6%) patients were female.

Table 2: Correlation between TSH and lipid values

Parameters	r- value	p- value
TSH and Total Cholesterol (mg/dl)	0.321	P=0.010 S
TSH and HDL (mg/dl)	-0.203	P=0.121 NS
TSH and LDL (mg/dl)	0.302	P=0.016 S
TSH and VLDL (mg/dl)	0.300	P=0.017 S
TSH and TG (mg/dl)	0.297	P=0.021 S

r- pearson's coefficient, S- statistically significant, NS- statistically nonsignificant

1. There was a positive correlation between TSH and total cholesterol. This correlation was found to be statistically significant (p = 0.010).
2. There was a negative correlation between TSH and HDL, which was not found to be statistically significant (p = 0.121).
3. There was also a positive correlation between TSH and LDL, VLDL, and TG (p values less than 0.016, 0.017, and 0.021, respectively). These correlations were found to be statistically significant.

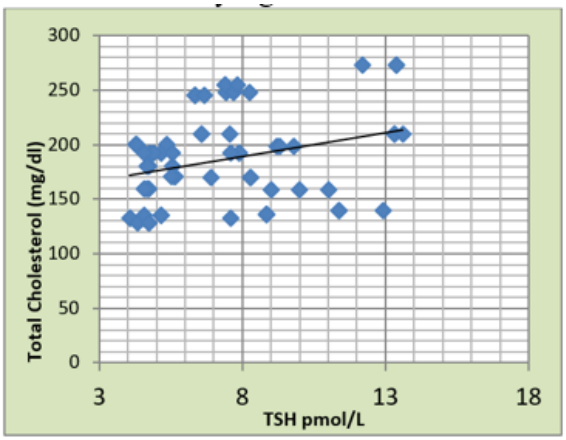

Figure 1a

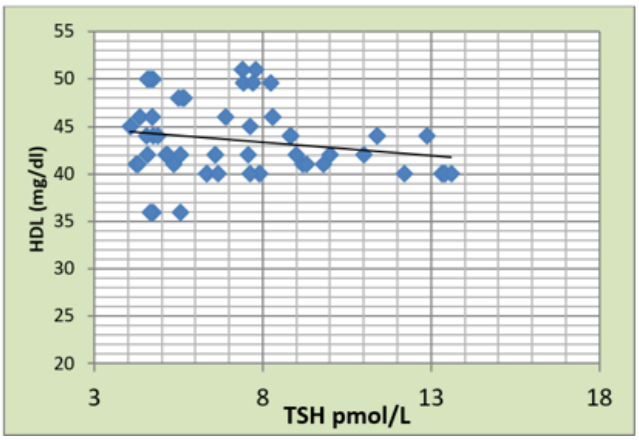

Figure 1b

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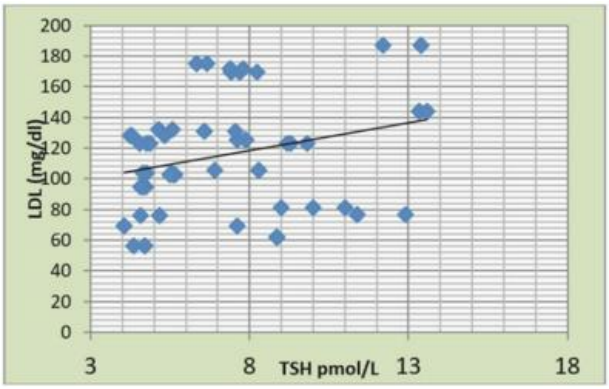

Figure 1c

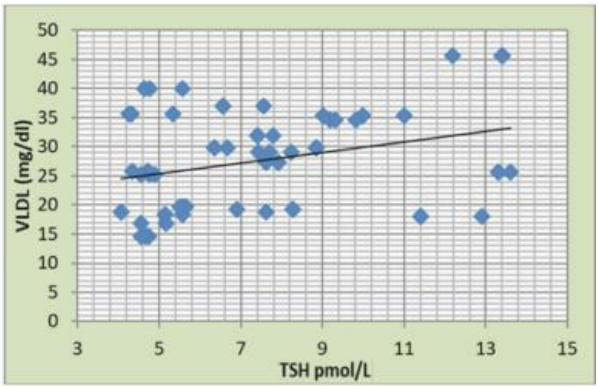

Figure 1d

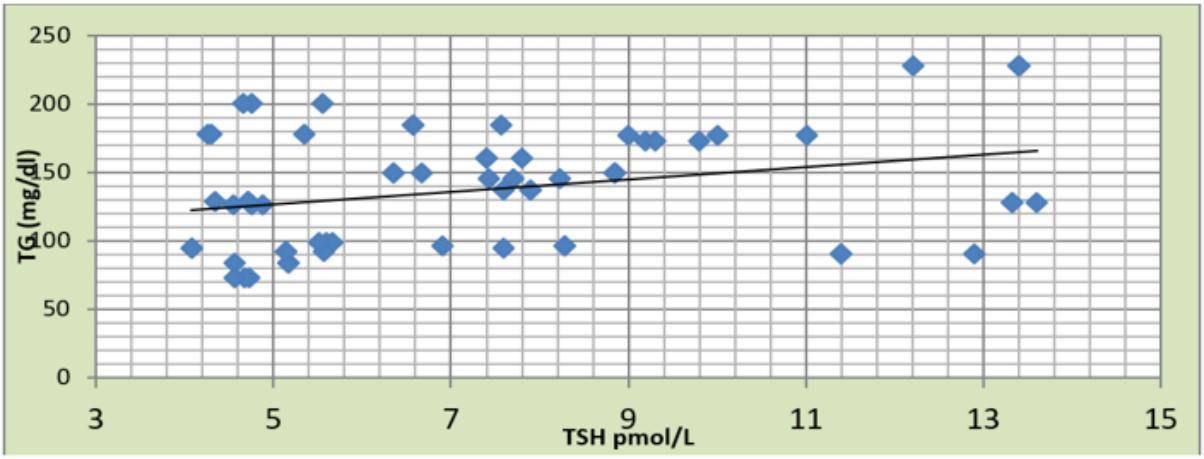

Figure 1e

Figure 1a: Relation between TSH and TC; Figure 1b: Relation between TSH and HDL; Figure 1c: Relation between TSH and LDL; Figure 1d: Relation between TSH and VLDL; Figure 1e: Relation between TSH and TG.

Table 3: Correlation between TSH and CRP

Correlation	r-value	p-value
TSH and CRP	0.329	P=0.008 S

There was a positive correlation between TSH and CRP; this correlation was found to be statistically significant (p = 0.008).

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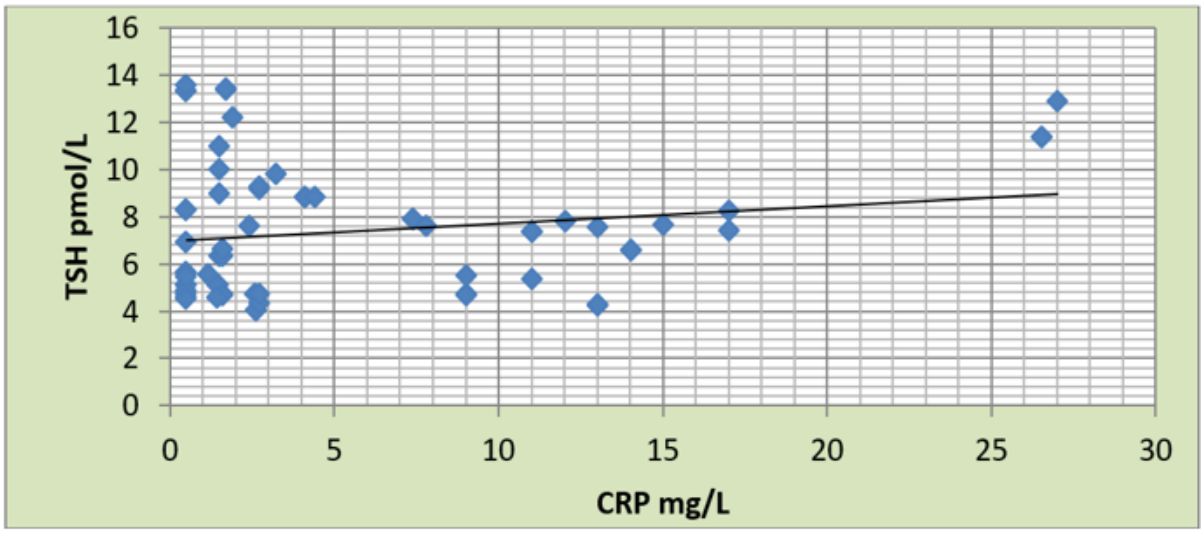

Figure 2: Relationship between TSH and CRP

DISCUSSION

Thyroid hormones have several physiological effects on the body. They increase the basal metabolic rate, influence the metabolism of carbohydrates and lipids, and have an impact on protein anabolism and catabolism. Additionally, they have a permissive effect on catecholamines and play a role in bone growth, particularly in children. Thyroid hormones are also essential for the maturation of the brain during the prenatal period and can affect mood and cognitive function in adults. Furthermore, they have an influence on fertility, ovulation, and menstruation [18].

Thyroid hormone plays a key role in regulating lipid metabolism. It stimulates the breakdown of fats in white adipose tissue and dietary fat sources, leading to the production of free fatty acids (FFAs). These FFAs enter hepatic cells through various protein transporters such as FATP, L-FABP, and CD36. Additionally, thyroid hormone triggers de novo lipogenesis (DNL) by activating the transcription of important lipogenic genes, including Acc1, Fasn, Me, and Thrsp. Furthermore, thyroid hormone indirectly influences the transcriptional regulation of hepatic DNL by controlling the expression and activities of other transcription factors such as SREBP1C, LXRs, and ChREBP. The influx of high levels of carbohydrates or glucose from high-carbohydrate diets, facilitated by glucose transporters (GLUTs), also contributes to DNL by promoting FFA generation. The FFAs are then either converted to triglycerides and packaged into VLDL for export or stored as intracellular lipid droplets. The stored triglycerides can be hydrolyzed back to FFAs through lipases and lipophagy, undergo mitochondrial β-oxidation, or target the transcription of specific genes through the activity of various co-activators or nuclear receptors such as PPARα, ERRα, FGF21, and PGC1α [19].

In hypothyroidism, the decreased levels of thyroid hormone (TH) lead to various effects on lipid metabolism. Thyroid hormone reduction results in a decrease in de novo lipogenesis (DNL) and the activity of HMG-COA reductase (HMGCR), leading to reduced cholesterol production. Additionally, the decrease in TH reduces the activity of cholesterol 7α-hydroxylase (CYP7A1) and ATP-binding cassette transporter G5/8 (ABCG5/8), resulting in reduced cholesterol clearance. As a result, triglyceride (TG)-rich very low-density lipoprotein (VLDL) levels increase, and the concentration of Niemann-Pick C1-like 1 protein (NPC1L1) leads to an increase in TG-rich chylomicron (CM). On the other hand, the increase in thyroid-

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stimulating hormone (TSH) leads to the elevation of proprotein convertase subtilisin/kexin type 9 (PCSK9), HMGCR, and hormone-sensitive lipase (HSL) levels and the decrease of CYP7A1. These changes have various effects on lipid metabolism, including the clearance of LDL and remnant lipoprotein (RLP) by LDL receptor (LDLR) and LDL receptor-related protein 1 (LRP1) [20]. Overall, the altered functions in subclinical hypothyroidism have significant impacts on lipid metabolism, and understanding these effects is crucial for managing the condition effectively.

Thyroid dysfunction has been associated with cardiovascular disease. Hypothyroidism and subclinical hypothyroidism (SH), which is characterized by elevated thyroid stimulating hormone (TSH) levels and normal circulating free thyroid hormones, are independent risk factors for the pathogenesis of atherosclerosis and cardiovascular disease, affecting adversely the endothelial function [21,22,23].

C-reactive protein (CRP) is a type of pentraxin primarily produced in the liver in response to inflammatory cytokines. It has two distinct isoforms: the highly pro-inflammatory monomeric isoform (mCRP) and the circulating pentameric CRP (pCRP), which can also convert to mCRP. Elevated levels of CRP are associated with increased risk of cardiovascular disease [24].

Patients with altered lipid profiles may be at risk for developing cardiac disease due to the accumulation of cholesterol associated with atherosclerosis, an inflammatory disorder. In subclinical hypothyroidism, there is a potential for future development of atherosclerosis [25]. Inflammatory markers such as CRP can serve as effective predictors of cardiovascular risk and are important for assessing inflammation. CRP, induced by IL-6, is particularly useful for diagnosing cardiac risk [26].

Our study has demonstrated that TSH had a positive and statistically significant correlation with total cholesterol, LDL, VLDL, TG, and CRP levels. However, the negative correlation observed between TSH and HDL was not statistically significant. Additionally, the positive correlation between TSH and CRP was also statistically significant. The observed association between SCH, lipid profile abnormalities and elevated CRP levels supports the hypothesis that dyslipidemia and inflammation contribute to SCH's pathophysiology. The study's limitations include its cross-sectional design and relatively small sample size.

Further, considering clinical implications of low thyroid hormone levels, we suggest

1. Regular monitoring of CRP and lipid profiles in SCH patients.
2. Consideration of lipid-lowering therapies and anti-inflammatories in SCH management.
3. Further research is needed on the potential benefits of thyroid hormone replacement therapy on lipid metabolism and inflammation.

CONCLUSION

Recent analysis indicates a significant correlation between TSH levels and heightened concentrations of total cholesterol, LDL, VLDL, triglycerides (TG), and C-reactive protein (CRP). This finding suggests that subclinical hypothyroidism (SCH) may contribute to dyslipidemia, which could, in turn, lead to inflammation. The accumulation of cholesterol is linked to the development of atherosclerosis, which poses an independent risk for future cardiovascular disease (CVD). Consequently, CRP emerges as a valuable marker for inflammation and holds promise as a clinical tool for evaluating both the status and progression of CVD in patients with SCH.

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