Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 7
Open Access

Effect of Oxidative Stress Markers and Lipid Profile in Patients with Hypothyroidism

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Cite this paper as: Bushra, Pothu Ushakiran, Sangeeta Kapoor ,Jigar Haria (2024). Effect of Oxidative Stress Markers and Lipid Profile in Patients with Hypothyroidism. *Frontiers in Health Informatics*, *13 (7) 1063-1073*

Abstract

Background: *Oxidative damage is one of the effects of abnormal thyroid hormone levels. Owing to their diverse effects on lipid synthesis, mobilization and breakdown, thyroid hormones may impact the initiation of dyslipidemia.*

Objective: *This research sought to evaluate the lipid profile and indicators of oxidative stress (MDA and Ox-LDL) in individuals with hypothyroidism.*

Material and methods: *A cross-sectional study was carried out in the Biochemistry Department at TMMC&RC, involving 160 participants with hypothyroidism and 40 euthyroid individuals, comprising 106 subclinical hypothyroid patients and 54 overt hypothyroid patients, aged between 18 and 65 years. Serum levels of markers for oxidative stress were measured using the Enzyme-linked Immunosorbent Assay (ELISA), while the thyroid profile was analyzed with the Enzyme-Linked Fluorescent Immunoassay (ELFA). Statistical analysis was performed using the one-way ANOVA to compare oxidative stress marker levels among different groups. The data was analyzed using SPSS software version 28.1 for Windows.*

Results: *Levels of TSH, total cholesterol, LDL, MDA and Ox-LDL showed strong significant differences while the levels of T3, T4, and TG exhibited statistically significant differences among the 3 groups. Additionally, overt hypothyroidism displays higher values for these markers compared to subclinical hypothyroidism. In hypothyroid patients, TSH levels have a significantly positive association with TC, TG, LDL, MDA, and Ox-LDL, while HDL levels reveal a negative correlation. Conversely, T4 levels demonstrate a notable negative correlation with TC, TG, LDL, MDA, and Ox-LDL.*

Conclusion: *This research emphasizes the notable changes in oxidative stress and lipid metabolism that are linked with hypothyroidism. Elevated levels of total cholesterol, TG and LDL raise the likelihood of cardiovascular disease and are linked to hypothyroidism. Monitoring lipid profiles and oxidative stress, in addition to aiding in the overall management of hypothyroidism, can assist in preventing vascular disorders.*

INTRODUCTION

In addition to regulating healthy growth and development, thyroid hormones are essential for controlling metabolism. It also speeds up metabolism by influencing the metabolism of fat, protein and carbohydrates. Thyroid hormone impacts the synthesis, mobilization and breakdown of lipids. The thyroid hormone has a greater effect on the breakdown than the production (1).

The inability of the thyroid to produce enough thyroid hormones through synthesis and secretion is known as hypothyroidism and causes the pituitary to release more thyroid-stimulating hormone (TSH) (2).

Reactive oxygen species (ROS) are molecules with an unpaired electron and an oxygen atom, possibly contributing to their existence. The main cause of ROS production in mitochondrial respiratory chains is a variety of bioenergetic ATP-generating processes (3). Cellular damage is mostly caused by oxidative stress. The body's weakened defence mechanism

is unable to offset the increased production of ROS, which results in an imbalance between ROS and their defence, dominating the state of oxidative stress. (4) (Halliwell B et al., 2007).

The thyroid gland's endocrine activity is synthesizing thyroid hormones (T3 and T4). Thyrocytes, which are follicular thyroid cells, generate a large quantity of H_2O_2 during this process in the follicular lumen, also known as colloid, found in the apical membrane of thyroid cells. (5) As a result, the thyroid gland remains one of the organs most vulnerable to the harmful impacts of oxidative stress, given that the production of thyroid hormones involves oxidative processes. Consequently, the challenging task of closely controlling the balance between ROS generation and scavenging falls on thyrocytes (6).

Oxidative stress may result from a deficit or depletion of antioxidants. Antioxidants modify inflammatory processes that are crucial to the etiology of diseases linked to oxidative stress in addition to shielding against the direct harmful effects of oxidants (7).

Lipoprotein metabolism is regulated by thyroid hormones. Numerous molecular and metabolic changes are linked to thyroid dysfunction. The transport and composition of LP are significantly disrupted in hypothyroidism. Hypercholesterolemia brought on by hypothyroidism is indicated by elevated low-density lipoprotein (LDL) levels (8).

Thyroid function, in addition to lipoprotein metabolism, has a major impact on CVD risk factors, which subsequently affects the overall likelihood of coronary artery disease (CAD) (9). One prevalent cause of secondary dyslipidemia is hypothyroidism (10). As a result of a shift towards greater synthesis over degradation rate, in hypothyroidism dyslipidemia mainly arises due to raised levels of TC, primarily LDL-C, which serves as a substrate for lipid peroxidation affected by ROS and oxidative stress. (11).

Consequently, this study sought to assess oxidative stress indicators and relate them to lipid levels in patients with hypothyroidism.

SUBJECTS AND METHODS

This cross-sectional study was conducted at Teerthankar Mahaveer Hospital in Moradabad, India. 160 participants were included in this study, who ranged in age from 20 to 60 (12), 54 of the 160 hypothyroid cases were being overt, while the remaining 106 were subclinical and 40 were euthyroid. Subclinical hypothyroid individuals were those with increased TSH (>4.5 μIU/ml) levels and normal T3 and T4 levels. Overt hypothyroid individuals were defined as those having an increased TSH level and either a drop in T3 or T4 levels, or both. Informed consent was obtained from all the study subjects.

Exclusion criteria: Patients who were on antioxidant vitamin supplements, those exposed to high-iodine environments, smokers, alcohol users, pregnant individuals, those undergoing hormone replacement therapy, people with diabetes mellitus and those suffering from acute, chronic, or malignant illnesses were excluded from the study (13) (14).

Sample Collection

8ml of venous blood was collected from the antecubital vein of the patients who were on overnight fasting (following aseptic techniques) and was stored in a plain vial. The collected samples were subsequently centrifuged at 3000RPM for 5 minutes and aliquots of serum were stored at −80°C for up to 4 weeks, the separated serum was utilized for the estimation of analytes:

Thyroid Profile: Blood levels of TSH, T3, and T4 were assessed using Enzyme-Linked Fluorescent Immunoassay (ELFA) for the evaluation of the thyroid profile. (15).

Lipid Profile: The serum triglycerides and total cholesterol levels were assessed using the enzymatic colorimetric method of the fully automated analyzer. For measuring high-density lipoprotein cholesterol, the homogeneous enzymatic colorimetric method for cholesterol was employed (16)(17).

Oxidative stress markers: The concentrations of Malondialdehyde (MDA) and Oxidized LDL (Ox-LDL) were assessed using enzyme-linked immunosorbent assay (ELISA), which utilizes the principle of biotin double antibody sandwich technology(18) (19).

Statistical Analysis

For data analysis, SPSS software version 28.1 for Windows was employed. Statistical data was depicted using mean ± standard deviations. Three groups were compared using the one-way ANOVA. Pearson correlation was conducted to explore the relationship between oxidative stress markers, thyroid hormones and lipid parameters. A statistically significant P value was defined as less than 0.05.

RESULTS:

Table 1: Comparison of different biochemical parameters among different groups (euthyroid, subclinical and overt hypothyroidism) by using one-way ANOVA

Parameters	Euthyroid	Subclinical	Overt hypothyroid	p-value
T3	0.85± 0.56	1.09 ± 0.40	0.74 ± 0.49	0.04*
T4	7.33 ± 1.21	6.44 ± 1.48	2.16 ± 1.78	0.02*
TSH	2.40 ± 1.36	12.80 ± 6.21	33.84 ± 16.16	0.00**
TC	170.46 ± 10.28	216.13 ± 23.89	274.30 ± 30.98	0.00**
TG	95.22 ± 19.36	180.23 ± 26.06	192.72 ± 43.34	0.04*
HDL	40.14 ± 7.78	34.38 ± 6.25	27.09 ± 5.26	0.06
LDL	102.58 ±12.04	145.70 ± 26.08	208.66 ± 27.65	0.00**
VLDL	19.04 ± 3.87	26.04 ± 5.21	28.54 ± 10.45	0.10
MDA	6.89 ± 0.63	10.50 ± 4.24	18.11 ± 5.70	0.00**
Ox-LDL	420.77 ± 52.24	497.23 ± 47.28	537.32 ± 47.29	0.00**

All values are expressed in Mean ± SD

Table 1 shows the statistical comparison of all parameters among different groups (euthyroid, subclinical and overt hypothyroid patients). In this research, the concentrations of TSH, total cholesterol, LDL, MDA, and Ox-LDL showed strong significant differences ($p<0.001$) among the groups. At the same time, the levels of T3, T4, and TG exhibited statistically significant differences among the 3 group patients. While, the remaining parameters like HDL and VLDL were statistically not significant.

Table 2: Relationship between thyroid function and lipid levels in patients with hypothyroidism

Thyroid Profile	T. Chol	TG	HDL	LDL	VLDL
T3	r = -0.238*	r = -0.019	r = 0.183	r = -0.256	r = -0.019
T4	r = -0.611*	r = -0.307*	r = 0.220	r = -0.616*	r = -0.307
TSH	r = 0.663**	r = 0.341*	r = -0.430**	r = 0.650**	r = 0.341

**** The correlation is extremely significant at the p<0.001 level**

*** The correlation is significant at the p<0.05 level**

Table 2 illustrates the relationship between the thyroid profile and the lipid profile in hypothyroid patients through Pearson's Correlation coefficient. The statistically significant correlations are discussed below:

- T4 levels showed a significant negative correlation with TC (r=-0.611), TG (r=-0.307) and LDL (r=-0.616) in hypothyroid patients.
- In hypothyroid patients, TSH levels showed a strong positive correlation with TC (r=0.663), TG (r=0.341), and LDL (r=0.650). Conversely, TSH levels exhibited a negative correlation (r=-0.430) with HDL in these patients.

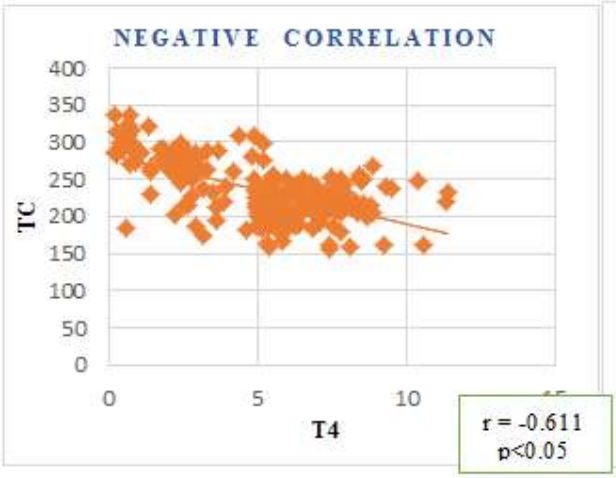

Fig 1: Correlation between T4 and TC

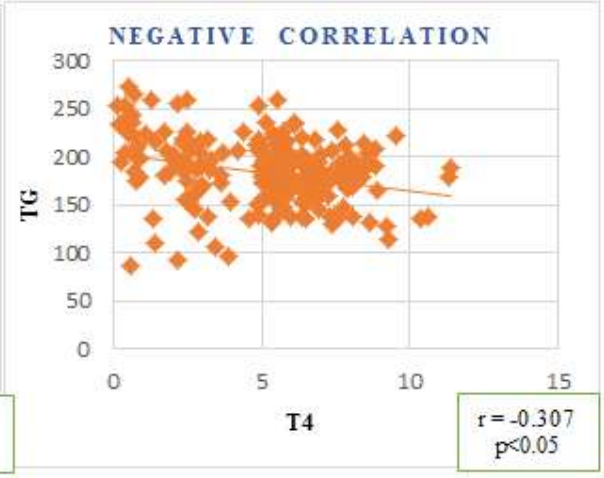

Fig 2: Correlation between T4 and TG

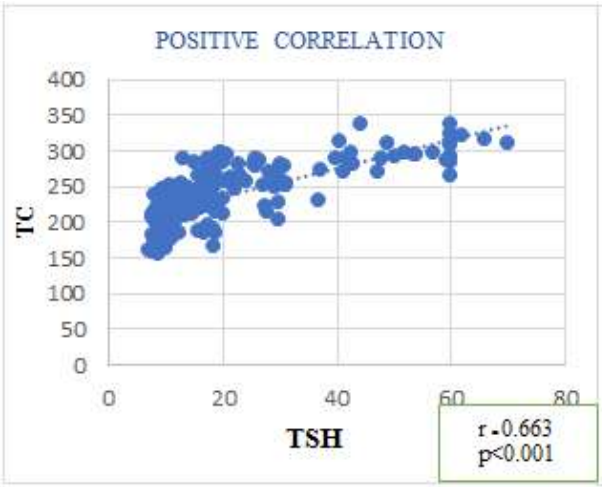

Fig 3: Correlation between TSH and TC

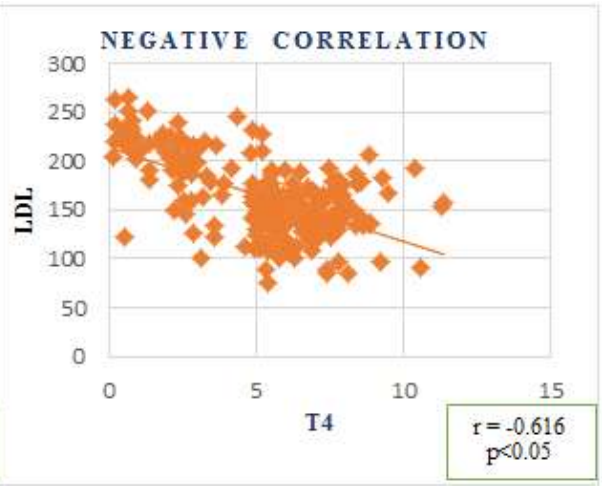

Fig 4: Correlation between T4 and LDL

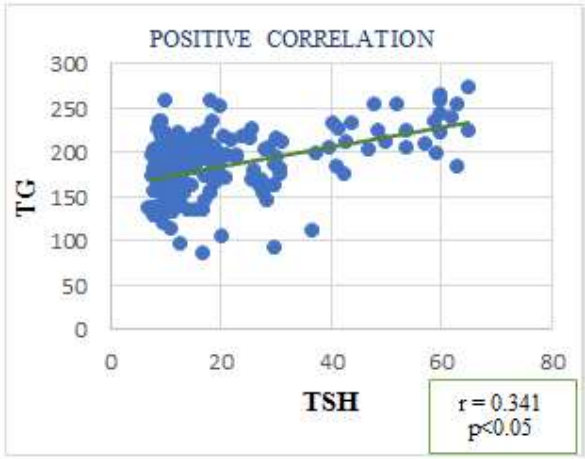

Fig 5: Correlation between TSH and TG

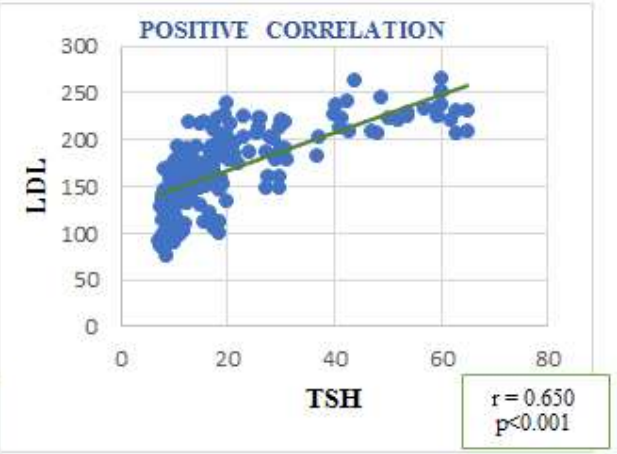

Fig 6: Correlation between TSH and LDL

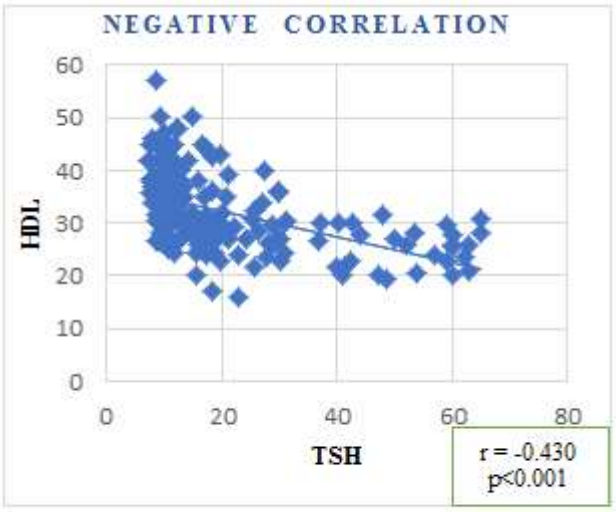

Fig 7: Correlation between TSH and HDL

Table 3: Association between thyroid profile and oxidative stress markers in hypothyroid patients

Parameters	MDA	Ox-LDL
T3	r = -0.244	r = -0.049
T4	r = -0.511*	r = -0.477*
TSH	r = 0.749**	r = 0.660**

Table 3 presents the relationship between thyroid hormones and markers of oxidative stress in hypothyroid patients through Pearson's Correlation coefficient. The statistically significant correlations are discussed below:

- In hypothyroid patients, T4 levels showed a significant negative correlation with MDA (r=-0.511) and Ox-LDL (r=-0.477).
- In hypothyroid patients, TSH levels exhibited a strong positive correlation with MDA (r=0.749) and with Ox-LDL (r=0.660).

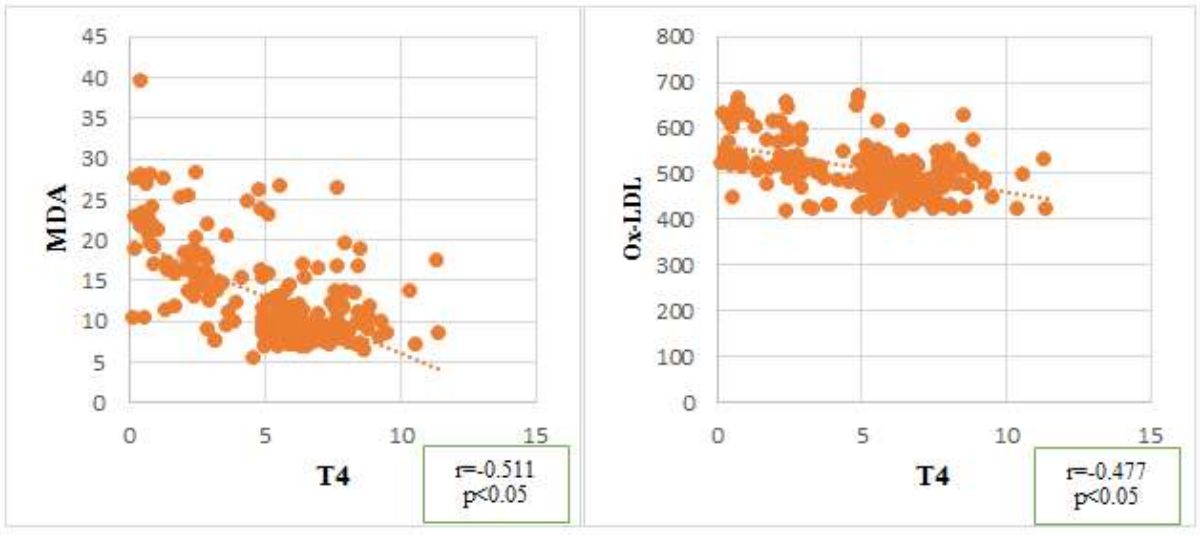

Fig 10: Correlation between T4 and MDA **Fig 11: Correlation between T4 and Ox-LDL**

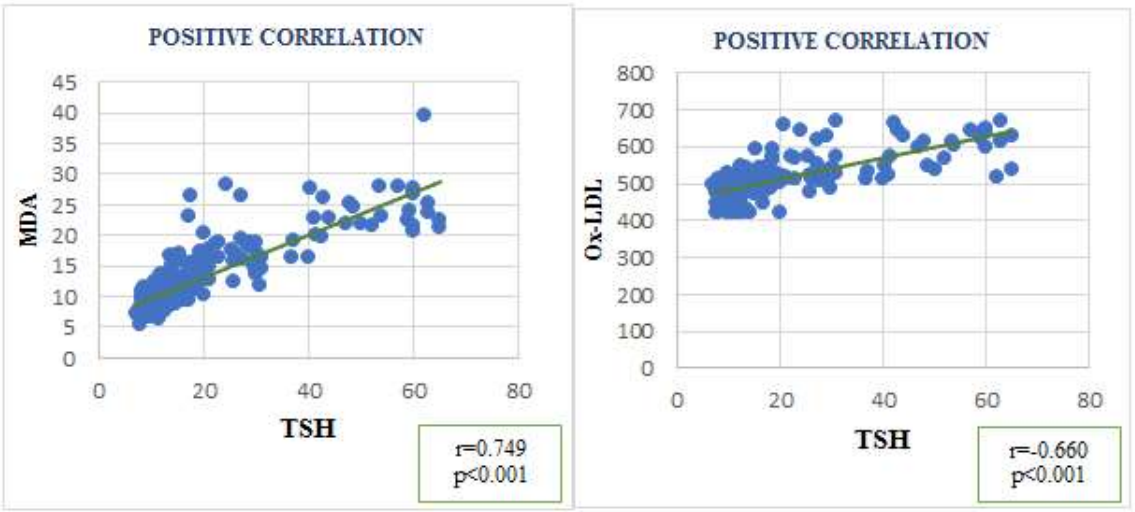

Fig12: Correlation between TSH and MDA Fig 13: Correlation between TSH and Ox-LDL

DISCUSSION

Among the 160 hypothyroid patients examined in this study, 106 were diagnosed with subclinical hypothyroidism and 54 with overt hypothyroidism. The statistical analysis comparing various parameters among euthyroid, subclinical hypothyroid and overt hypothyroid patients, is presented in **Table 1**. Between 4.3% and 9% of people have SCH, a condition significantly more prevalent than overt hypothyroidism that has the potential to become overt (20) (9) (21). Hypothyroid patients have a frequency of 1.4% to 13% of hyperlipidemia suggesting that hyperlipidemia is frequent and may go undiagnosed in these people (22) (23).

The lipid profiles (TC, TG, and LDL) of the three groups (euthyroid, overt and subclinical hypothyroidism) in our study showed notable differences. Additionally, it was revealed that the highest levels of TC, TG, and LDL were present in individuals with overt hypothyroidism. Although these parameters were elevated in participants with subclinical hypothyroidism compared to euthyroid individuals, the elevation was more pronounced in those with overt hypothyroidism when compared to both subclinical hypothyroidism and euthyroid subjects. As the severity of thyroid dysfunction increased, so too did the levels of these measurements. However, there was no significant difference in HDL and VLDL among different groups. Vierhapper et al. (24) found comparable outcomes, suggesting that overt hypothyroidism correlated with increased levels of total cholesterol and LDL compared to subclinical hypothyroidism. The group with SCH exhibited elevated levels of TC, LDL and TG, however, Xiao-Li et al.'s meta-analysis of 16 studies (25) revealed no significant variations in HDL. Muls E et al. and Agdeppa et al. previously reported that blood HDL concentrations were more complex, as various studies showed high, normal and low levels (26)(27). Still, there is a lack of consensus regarding the presence and extent of dyslipidaemia induced by SH. Because some of the studies such as those done by Al-Tonsi et al., Teixeira et al., Lee WY et al. and Brenta et al. have shown that there is no significant difference in the lipid profiles between patients with SCH and those who are euthyroid (28–30) (31). Research by Tian et al. found that liver cells can express TSH receptors and that TSH may stimulate these receptors to enhance the production of hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, an enzyme that controls the cholesterol synthesis rate (32).

Insufficient management of possible confounding variables, including sex, age, race, insulin resistance, smoking, and alcohol consumption, might explain the inconsistent findings in these cross-sectional studies. All of these factors could be associated with cholesterol levels (33–35). A National Health and Nutrition Examination Survey (NHANES III) research claims that, SCH patients had greater serum TC and TG levels than euthyroid individuals. However, when factors like sex, age and race were considered, this difference disappeared (36). The sex-age match approach was used in numerous research to adjust for potential confounding variables. According to those investigations, SCH patients had greater levels of TC and LDL than those of euthyroid participants (37–40). Although lower HMG-CoA reductase activity

is associated with reduced thyroid function, individuals with overt hypothyroidism exhibited elevated levels of TC and LDL-C. This occurs because of diminished activation of LDL receptors, leading to a reduction in the breakdown of LDL and IDL (39). Our study also had not followed this sex-age match approach so the result may be biased because of these confounding factors.

The connection between thyroid function and lipid profiles in individuals with hypothyroidism is illustrated in **Table 2**. A moderate association was discovered between the lipid profile and T3 levels. In individuals with hypothyroidism, T4 levels displayed a negative correlation with total cholesterol (r=-0.611), TG (r=-0.307) and LDL (r=-0.616). Conversely, in this same group, TSH levels showed a strong positive correlation with TC (r=0.663), TG (r=0.341) and LDL (r=0.650). However, within hypothyroid individuals, a negative association (r=-0.430) was observed between TSH and HDL levels.

Implies correlation study gives a better picture of the effect of thyroid hormones in case of bias due to confounding factors as we had considered for this study. In a cross-sectional analysis by Santos-Palacios S et al. found a positive correlation between TSH and the levels of LDL, TG and total cholesterol which is giving a similar picture as of our study. This significance persisted even after accounting for factors such as age, gender, BMI and smoking status (41). A different study discovered no noteworthy connection between blood TSH levels and TG, LDL, HDL, or total cholesterol. Furthermore, the research by Alamdari et al. indicated that there were no relationships between TSH and lipid profiles in people with SCH. However, a minor inverse correlation was noted between T4 levels and LDL, TG, total cholesterol and HDL (42).

The current study indicates that patients with OHT and SCH exhibited markedly elevated levels of MDA, suggesting increased lipid peroxidation. There were significant differences in the MDA and ox-LDL levels between individuals with overt and subclinical hypothyroidism. Several studies (43,44) showed higher MDA levels in OHT patients which was consistent with our findings. Few studies on SCH provide conflicting results about no change in the levels of MDA (45,46) and few studies showed a higher MDA concentration when compared to controls (47). In individuals with both overt and subclinical hypothyroidism, increased LDL levels may enhance the production of ox-LDL (48), thereby contributing to the development of coronary heart disease and atherosclerosis (49). Elevation in ROS induced by thyroid hormone may lead to oxidative stress in specific tissues, potentially causing a lipid peroxidative response. Increased generation of radical oxygen species, particularly from lipid peroxidation processes, and most likely weakened antioxidant defence mechanisms are potential causes of higher free radicals in hypothyroid individuals (50).

The association between the thyroid profile and markers of oxidative stress in individuals with hypothyroidism is presented in **Table 3**. In this study, TSH concentration exhibited a significant positive correlation with both MDA and Ox-LDL in hypothyroid subjects, whereas T4 levels displayed a negative correlation with these two markers. Research conducted by Fuleshwar Mandal et al. supports that TSH and MDA levels are positively correlated. Mitochondria operate less efficiently when levels of TSH are elevated and thyroid hormones (T3 and T4) are diminished. This inefficiency leads to the escape of electrons from the mitochondrial electron transport chain, which interferes with ATP synthesis. The escaping electrons generate reactive oxygen species (ROS), when these ROS target lipids in cell membranes, lipid peroxidation occurs. One consequence of this damage is the increase of malondialdehyde (MDA), a marker of oxidative stress, which rises as a result of these processes. (51). In a different study conducted by Sandeep Kumar et al., it was found that elevated TSH concentration corresponded to increased ox-LDL levels (52). These results highlight how thyroid hormone abnormalities contribute to oxidative damage and lipid peroxidation, which may impact managing cardiovascular risk.

CONCLUSION

This research emphasizes the important changes in oxidative stress and lipid metabolism that are associated with hypothyroidism. There is a connection between a heightened risk of cardiovascular disease and hypothyroidism, characterized by increased concentration of TC, TG and LDL. Lipid profile and oxidative stress screening can help avoid cardiovascular accidents and other problems, as well as aid in the overall treatment of hypothyroidism. To reduce long-term health effects, this study highlights the significance of routine monitoring and possible treatment options targeted at both thyroid function and related metabolic disorders.

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