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Assessment of serum lipid profile in patients with thyroid disorders in a rural backdrop of central India

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ABSTRACT

Introduction: Thyroid diseases are among the commonest endocrine disorders worldwide. Thyroid dysfunction can result in lipid abnormalities which increase the risk of endothelial dysfunction, hypertension and cardiovascular disease. *Aim:* This cross-sectional

study was conducted to determine changes in serum lipid profiles in patients with thyroid disorders in a rural backdrop of central India and to compare this with normal rural population. *Methods:* Participants were divided into two subgroups: study group with hypothyreosis (n = 49) and control group with euthyreosis (n = 42). Fasting of venous blood sample was collected, and lipid profile was estimated. *Results:* We found a negative association between thyroid levels and body mass index. Mean serum TG, TC, LDL-C and VLDL-C levels were higher in hypothyroid subjects as compared to euthyroid and hyperthyroid subjects. HDL-C levels were higher in hyperthyroid subjects as compared to hypothyroid subjects but lower than the euthyroid subjects. TC/HDL-C was higher in hypothyroid subjects than hyperthyroid and euthyroid subjects. Thyroid levels were correlated positively with serum HDL-C and negatively correlated with TG, TC, LDL-C, VLDL-C and TG/HDL-C ratio. *Conclusion:* Findings of this study shows that hypothyrodism is associated with altered lipid disorders. Thus; hypothyroid state has a role in increased cholesterol levels which in turn can be responsible for cardiovascular complications. Therefore biochemical screening for lipid profile is of paramount importance in all patients with thyroid dysfunction and underlying lipid abnormalities should be recognized and treated. Also; thyroid dysfunction should be taken into account when evaluating and treating dyslipidemic patients.

Keywords: Thyroid dysfunction, altered lipid disorders, rural population

1. INTRODUCTION

Thyroid diseases are among the commonest endocrine disorders worldwide (Unnikrishnan and Menon, 2011). In India too, there is a significant burden of thyroid diseases. It has been estimated that about 42 million people in India suffer from thyroid diseases (Unnikrishnan and Menon, 2011). Subclinical and overt hypothyroidism are relatively common disorders in the general population especially in females (Neves et al., 2008; Pearce, 2004; Maryam Fatemi Tekieh et al. 2019). Populaces at particular risk appear to live in remote and mountainous areas in South-East Asia, Latin America and Central Africa (Vanderpump, 2011). In spite of the wide coverage of National iodine deficiency diseases control Programme (NIDDCP), iodine deficiency is still predominant in many parts of India (Dhok AJ et al., 2015). A cross-sectional population survey conducted in urban coastal area of central Kerala revealed that thyroid function abnormalities were present in 19.6% of subjects with subclinical hypothyroidism in 9.4% (Usha Menon et al., 2009). A survey of 1905 subjects attending a tertiary care hospital in Wardha district in central India revealed that 35.7% of subjects in the age range of 10 to 80 years had thyroid dysfunction (Dhok AJ et al., 2015). Hypothyroid status was noted in 21.7% subjects while hyperthyroid status was noted in 2.3% subjects (Dhok AJ et al., 2015).

Hypothyroidism is a condition in which thyroid hormones are produced in lesser amount by thyroid gland and the subjects eventually will have lower metabolic rate and clinical symptom such as fatigue, hypotension, overweight, depression; etc. Regulation of metabolism is one of the most important functions of thyroid hormones. Thyroid hormones affects numerous metabolic parameters; including the metabolism of lipoproteins and has multiple effects on regulation of synthesis, absorption, and metabolism of lipids (Knudsen et al., 2005a; Pearce, 2012). Thyroid dysfunction can result in lipid abnormalities which increase the risk of endothelial dysfunction, hypertension and cardiovascular disease (Neves et al., 2008). The composition and the transport of lipoproteins are seriously disturbed in thyroid diseases (Duntas, 2002). However; the action of thyroid hormone on lipoprotein is still a matter of debate, because both decrease and no changes have been reported. The discrepancies are mostly because of genetic polymorphism of apo(a) and to the differences between the various study groups (Duntas, 2002).

Even within the normal range of thyroid-stimulating hormone (TSH) values; a linear increase in triglycerides (TGs), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and a linear decrease in high-density lipoprotein cholesterol (HDL-C) levels has been observed with increasing TSH (Asvold et al., 2007). TC and LDL levels have been shown to be are higher (Jung et al., 2003; Yetkin and Dogantekin, 2015) and high-density lipoprotein (HDL) levels to be normal or even elevated in severe hypothyroidism (Duntas, 2002). However; some studies have shown no significant differences between hypothyroid patients and healthy controls regarding LDL levels (Kim et al., 2009). Hyperthyroidism; on the other hand; exhibits a decrease of total and LDL cholesterol; whereas HDL are decreased or not affected (Duntas, 2002; Liberopoulos and Elisaf, 2002). These variations in the lipid profile are elucidated by the regulatory effect of thyroid hormones on the activity of enzymes involved in the metabolism of lipoproteins.

Although some studies have estimated that 1 to 11% of all patients with dyslipidemia have subclinical hypothyroidism; the effects of hypothyroidism on serum lipid values are less clear and inconclusive at present; especially in a rural setting (Pearce, 2012). There is a paucity of data regarding an association between variations in thyroid function and lipid levels (Budnevsky et al., 2015). It

remains poorly elucidated whether thyroid function has impact on the lipid profile. The action of thyroid hormone on lipids is still debated, because both decrease and no changes have been reported.

Indian studies on dyslipidemia in thyroid disorders are currently lacking. Because of this inconsistency and paucity in data pertaining to serum lipid profile in patients with thyroid disorders; especially in a rural set-up; this cross-sectional study was planned to explore the association of dyslipidemia in patients with thyroid disorders in a rural-based Indian setting. This study can be of help to physicians to decide whether dyslipidemic patients should be screened for thyroid diseases or whether patients diagnosed with thyroid disorders should be monitored for the possible occurrence of dyslipidemia in future which may increase the risk of accelerated atherosclerosis and premature coronary artery disease in some patients.

Aims and Objectives

Hypothesis

We hypothesise that lipid profile is deranged in patients with thyroid disorders.

Aim

The aim of the study is to determine the changes in serum lipid profiles in patients with thyroid disorders in a rural backdrop of central India.

Objectives

The objectives of the study are:

1. To determine the changes in serum lipid profiles in patients with thyroid disorders in a rural backdrop of central India.
2. To compare this with normal (euthyroid) rural population of in a rural backdrop of central India.

2. MATERIAL AND METHODS

This Cross-sectional study was conducted in a tertiary care Rural Hospital in central India, between May 2016 to September 2016 after seeking the approval from Insitutional Ethical Committee (IEC).

We included patients with hypothroidism/ hyperthyroidism, attending/ followed-up/ being treated in medicine and surgery out-patient department (OPD) and wards of a tertiary-care fully equipped rural hospital. A control group of healthy volunteers with normal thyroid-stimulating hormone (TSH) and free thyroxin (FT_4) concentration were also enrolled.

Selection criteria

Inclusion criteria

- Any adult subject between 18 and 60 years irrespective of gender
- All types of thyroid disorders; irrespective of duration and etiology
- Patients willing to participate in the study.

Exclusion criteria

- Patients and controls with diabetes mellitus
- Current and ex-smokers
- Obesity (body mass index (BMI) > 30 kg/m^2)
- Liver disease and systemic illness
- Excessive alcohol consumption
- Subjects receiving treatment with diuretics, ß blockers or lipid lowering drugs, or other medications that might alter serum lipid parameters and thyroid functions
- History of heart surgery or other cardiovascular interventions
- Pregnancy
- Chronic kidney disease
- Not willing to participate in the study

Data collection procedures

The participants were recruited from the Medicine and Surgery departments of a rural hospital. Participants were divided into two subgroups: the study group with hypothyreosis or hyperthyreosis (n = 45) and control group with euthyreosis (n = 22). The participants were explained about the purpose and nature of the study. The patients were assured that the confidentiality will be maintained. After taking informed and written consent; we entered the details of the subject in the data collection forms. If the participant fulfilled the inclusion criteria; he/she was called on the next morning in fasting state for collection of venous blood samples.

Anthropometric measurements

Anthropometric measurements (height, weight) were measured in all subjects and body mass index (BMI) was calculated from the formula: BMI= Weight in Kg/ Height in metres^2(WHO, 2000). Hence; depending on their height and weight, a person was categorised as (WHO, 2000):

- Underweight: BMI less than 18.5 Kg/m^2
- Normal weight: BMI between 18.5 & 24.9 Kg/m^2
- Overweight: BMI between 25.0 & 29.9 Kg/m^2
- Obese: BMI 30.0 Kg/m^2 and above

Thyroid Profile

Serum Thyrotrophin (TSH), free triiodothyronine (FT_3), and free tetraiodothyronine (FT_4) in our laboratory is done by mini VIDAS® which is a compact automated immunoassay system based on the Enzyme Linked Fluorescent Assay (ELFA) principles.

Reference values for thyroid profile of our Laboratory were:

- Normal: TSH (0.4-4.5 µIU/ml), FT_4 (0.8-2.0 ng/dL), FT_3 (1.5-4.1 pg/ml). A TSH concentration of 0.1-0.4 µIU/ml was considered as mildly suppressed.
- Hypothyroidism was classified as clinical if TSH was ≥4.5 µIU/ml and FT_4 was ≤0.620 ng/dL and subclinical if TSH was ≥4.5 µIU/ml and FT_4 ≥0.620 ng/dL.
- Hyperthyroidism was classified as clinical if TSH was ≤0.1µIU/ml and FT_4 was ≥1.705 ng/dL and subclinical if TSH was ≤ 0.1µIU/ml and FT_4 ≤1.705 ng/dL.

Lipid Profile

Fasting plasma triglycerides (TG), total cholesterol (TC), high-density-lipoprotein cholesterol levels (HDL-C) were determined in all the participants by Randox kits. TC was determined by Cholesterol oxidase method, TG by Lipase/ GPO-PAP method and HDL by Direct HDL method. VLDL was calculated using the formula: TG/5 and LDL-C was calculated using the formula: TC-(HDL+VLDL).

Normal values for thyroid profile of our Laboratory were:

- TG (65-160mg/ dl)
- TC (160-200 mg/dl)
- HDL-C (35-75 mg/dl)
- LDL-C (50-165 mg/ dl)
- VLDL-C (13-32mg/dl)
- TC/ HDL-C ratio (4.0)

Quality control: Following quality control measures were undertaken:

- The study tried to adhere to the protocol
- The confidentiality of all the participants was strictly maintained.
- Study and control groups were concealed from the statistician
- Quality control of data management was maintained throughout the study.
- Early involvement of the local research support unit.

Plan of analysis/ statistical tools

Statistical analysis was conducted using SPSS 14 (SPSS Inc., Chicago, IL, USA) software.

3. OBSERVATIONS AND RESULTS

The study assessed a total of 67 participants including 22 (32.84%) euthyroid, 30(44.78%) hypothyroid and 15(22.39%) hyperthyroid subjects. 34(50.75%) males and 33(49.25%) females with a mean age of 39.1 years in hypothyroid and 49.8 years in hyperthyroid participants participated in the study (Table 1, Figure 1).

Table 1 Demographic profile of the study population

	Number (%)	Male (%)	Female (%)	Mean Age (in years)
Euthyroid	22 (32.84%)	13 (59.09%)	9 (40.91%)	43.6
Hypothyroid	30 (44.78%)	12 (40%)	18 (60%)	39.1
Hyperthroid	15 (22.39%)	9 (60%)	6 (40%)	49.8
Total	67 (100%)	34 (50.75%)	33 (49.25%)	44.17

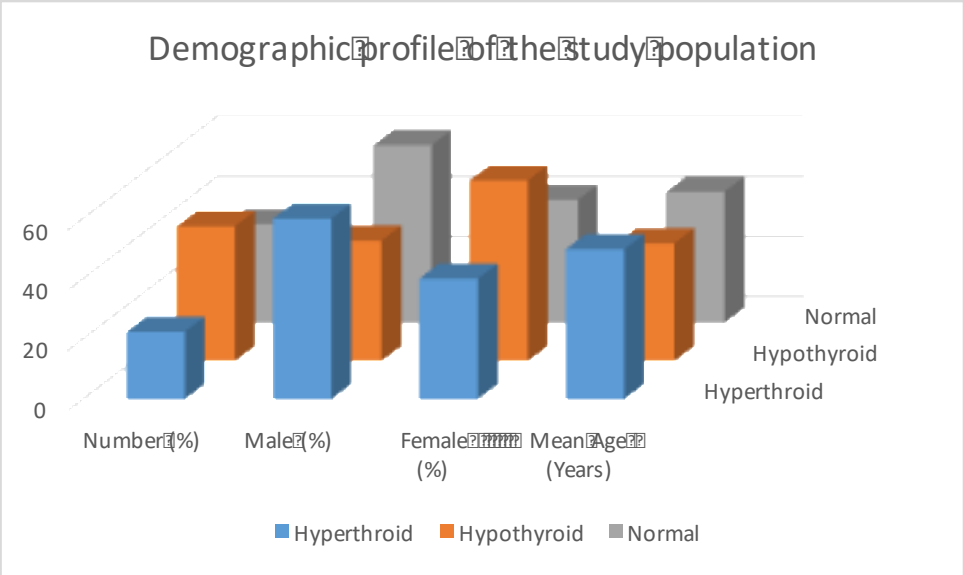

Figure 1 Demographic profile of the study population

BMI and thyroid status

As can be seen in Table 2 and Figure 2; nine (30%) hypothyroid subjects and only one (6.67%) subject was overweight while two (6.67%) hypothyroid and two (13.33%) and hyperthyroid subjects were underweight. Obesity was more prominent in hypothyroid subjects (13.33%) while least in hyperthyroid subjects (6.67%). Overall; we found a negative association between thyroid levels and body mass index (Table 2 and Figure 2).

Lipid profile and thyroid status

Mean serum TG, TC, LDL-C and VLDL-C levels were higher in hypothyroid subjects as compared to euthyroid and hyperthyroid subjects. HDL-C levels were higher in hyperthyroid subjects as compared to hypothyroid subjects but lower than the euthyroid subjects. TC/HDL-C was higher in hypothyroid subjects than hyperthyroid and euthyroid subjects. In euthyroid subjects; thyroid levels were correlated positively with serum HDL-C and negatively correlated with TG, TC, LDL-C, VLDL-C and TG/HDL-C ratio and TSH levels were associated negatively with HDL-C.

Table 2 The BMI status of the study population

	Underweight	Normal	Overweight	Obese	Total
Euthyroid (n=22)	2(9.09%)	15(68.18%)	3(13.64%)	2(9.09%)	22(100%)
Hypothyroid (n=30)	2(6.67%)	15(50%)	9(30%)	4(13.33%)	30(100%)
Hyperthroid (n=15)	2 (13.33%)	11(73.33%)	1(6.67%)	1(6.67%)	15(100%)
Total (n=67)	6(8.96%)	41(61.19%)	13(19.4%)	7(10.45%)	67(100%)

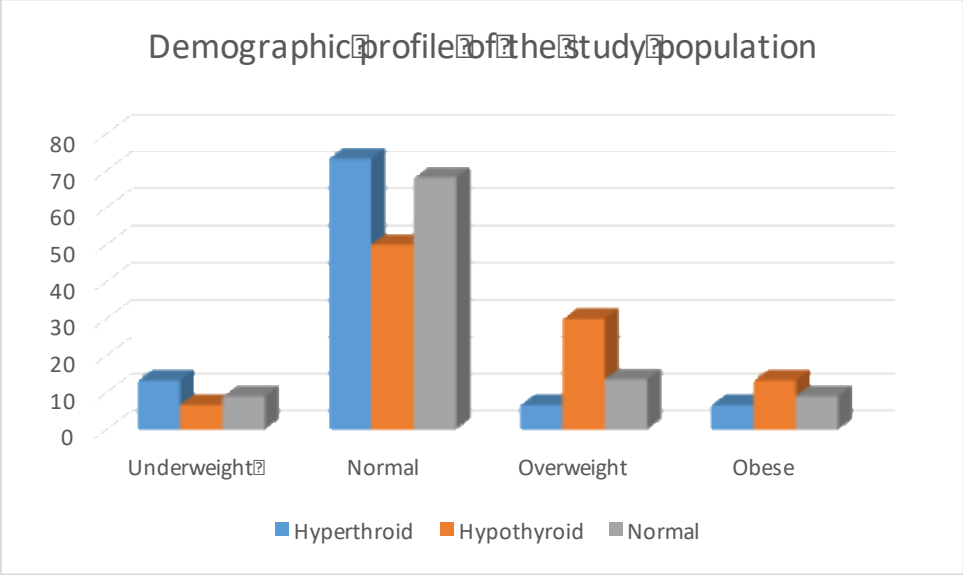

Figure 2 The BMI status of the study population

4. DISCUSSION

This study conducted on 67 participants from central India to determine the changes in serum lipid profiles in patients with thyroid disorders in a rural backdrop of central India and to compare this with euthyroid rural population of central India.

We found a negative association between thyroid levels and body mass index (Table 2, Figure 2). Our findings are similar to the findings of other studies by Knudsen et al., De pergola et al. and Jung et al. (De Pergola et al., 2007; Jung et al., 2003; Knudsen et al., 2005b). Knudsen et al. (Knudsen et al., 2005b) held that small differences in thyroid function may be important for BMI and the occurrence of obesity in the population while De pergola et al. (De Pergola et al., 2007) found that free T_3 and TSH are directly associated with waist circumference, independently of metabolic parameters in overweight and obese women.

Our study shows that in hyperthyroid participants; TG, TC and LDL-C levels were decreased as compared to euthyroid and hypothyroid subjects (Table 3, Figure 3). HDL-C levels were higher in hyperthyroid subjects as compared to hypothyroid subjects but lower than the euthyroid subjects (Table 3, Figure 3). Our data appear to confirm the results of some other studies of Duntas et al and Liberopoulos et.al (Duntas, 2002; Liberopoulos and Elisaf, 2002); where they found negative correlation between thyroid hormones and TG, TC and LDL-C.

Table 3 Mean lipid profile status of the study population

	TG (mg/ dl)	TC (mg/ dl)	LDL-C (mg/ dl)	VLDL-C (mg/ dl)	HDL-C (mg/ dl)	TC/HDL-C ratio
Euthyroid (n=22)	103.8	183.4	106.34	20.76	56.3	3.25
Hypothyroid (n=30)	181.3	233.9	166.84	36.26	30.8	7.59

Hyperthyroid (n=15)	97.9	171.2	101.95	20.15	49.1	3.48

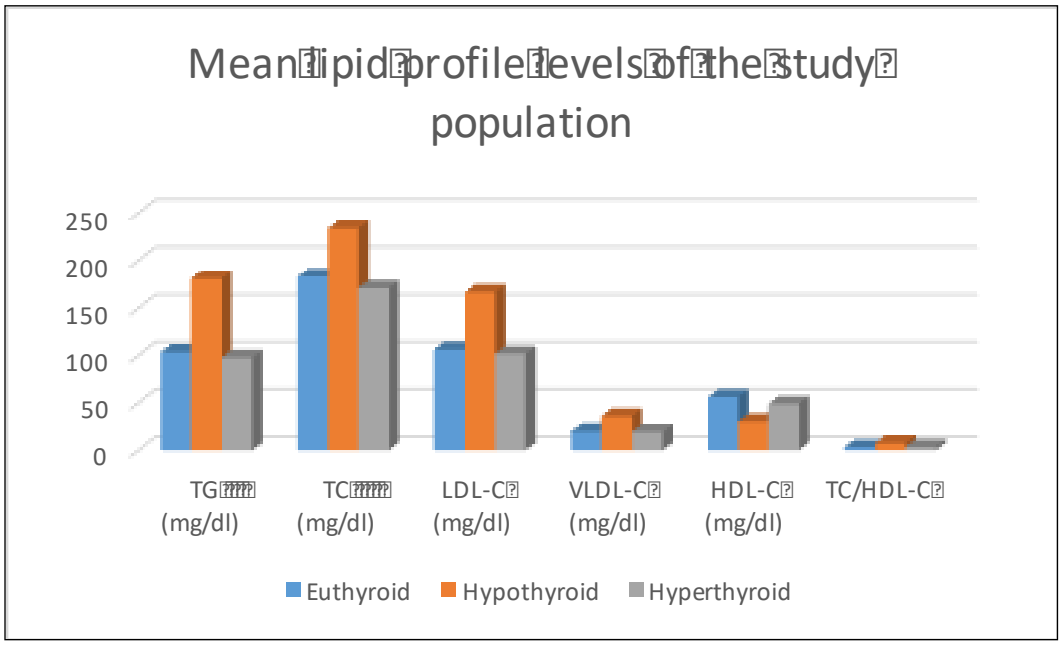

Figure 3 Mean lipid profile levels of the study population

The data from our study reveals that the participants with hypothyroid status have high TG, TC, LDL-C VLDL-C and TC/HDL-C ratio, and lower HDL-C which goes in favour with other studies which show that subclinical hypothyroidism is associated with dyslipidemia (Bansal et al., 2014; Efstathiadou et al., 2001; Farah Aziz Khan et al., 2014; Kibria et al., 2016; Luboshitzky et al., 2002; O'Brien et al., 1993; Pallas et al., 1991; Pearce, 2004; Prakash and Lal, 2006). Decrease in HDL-C level in our study might be due to increased activity of cholesteryl-ester transfer protein (CETP) and lipoprotein lipase in hypothyroid patients.

There is some controversy regarding the presence or severity of thyroid induced altered lipid profile. In contrast to our study; there have been studies indicating no significant difference in lipid profile between subclinical hypothyroid patients and controls (Alamdari et al., 2015; Langer et al., 2003; Velkoska Nakova et al., 2009, 2009). However; individual analysis in Velkoska Nakova et al. and (Luboshitzky et al., 2002) revealed that the percentages of patients with SCH hypertriglyceridaemia, elevated LDL-C, TC/HDL-C ratios were higher than the percentages in controls. Alamdari (Alamdari et al., 2015) found correlations between serum FT_4 and TSH and lipid profiles but Velkoska et al (Velkoska Nakova et al., 2009) found no significant correlation between TSH and lipid profile parameters.

Studies of lipid metabolism related to thyroid dysfunction may provide some understanding of mechanisms that could underlie the associations in our study. Triiodothyronine (T_3) up regulates LDL receptors by controlling the LDL receptor gene activation (Rizos et al., 2011). High serum TC and LDL-C in hypothyroid subjects may be caused by fewer cell-surface receptors for LDL; resulting in reduced LDL catabolism and decreased fractional clearance of LDL (Cappola and Ladenson, 2003; Duntas, 2002). Hyperthyroidism; on the other hand shows an increased excretion of cholesterol and an increased turnover of LDL causing a decrease of TC and LDL-C; whereas HDL may decrease or may not be affected (Duntas, 2002).

T_3 has also been associated with protecting LDL from oxidation (Faure et al., 2004). Hypothyroidism increases the oxidation of plasma cholesterol mainly because of an altered pattern of binding and to the increased levels of cholesterol, which presents a substrate for the oxidative stress (Duntas, 2002). Reduced activity of lipoprotein lipase(Lithell et al., 1981; Pykälistö et al., 1976), or impaired clearance of lipoproteins dependent on LDL receptor function (Liu et al., 1998), may result in higher levels of TG in hypothyroid subjects.

Costantini et al. (Costantini et al., 1998) investigated the effect of different levels of thyroid hormone and metabolic activity on low density lipoprotein (LDL) oxidation. Hypothyroidism was also characterized by high β-carotene LDL content. In hyperthyroidism; LDL oxidation was strongly influenced by free thyroxine blood content. The study concluded that both hypothyroidism and hyperthyroidism are characterized by higher levels of LDL oxidation compared with normolipidemic control subjects. LDL oxidation was markedly higher in hyperthyroidism than in hypothyroidism or control subjects.Hyperthyroidism hastens mitochondrial

oxidative metabolism; resulting in increased free radical production and lipid peroxidation (Asayama et al., 1987b; Pereira et al., 1994). Moreover, hyperthyroid patients have also been shown to have higher arachidonic acid content which are easily oxidized and contribute to increased lipid peroxidation (Bonanome et al., 1992). In hyperthyroid patients; the increased lipid peroxidation was strictly related to free thyroxine levels, whereas; in hypothyroidism it was strongly influenced by serum lipids (Costantini et al., 1998). However; another study by Faure et al. held that T_3 was associated with protecting LDL from oxidation (Faure et al., 2004).

Thyroid hormone stimulates the synthesis of cholesterol by inducing the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which is the first step in the biosynthesis of cholesterol which results in an higher cholesterol concentration in hyperthyroidism (Rizos et al., 2011). Moreover; thyroid hormones stimulates the lipoprotein lipase (LPL), which catabolizes hepatic lipase (HL) and triglyceride-rich lipoproteins and contributes to the formation of LDL (Santamarina-Fojo et al., 2004).

Thyroid hormones can influence HDL metabolism by increasing the activity of cholesteryl ester transfer protein, which exchanges cholesteryl esters from HDL to VLDL and TG to the opposite direction (Farah Aziz Khan et al., 2014; Lagrost, 1994). Another effect of T_3 is the up-regulation of apolipoprotein AV, which plays a major role in TG regulation (Prieur et al., 2005).

Despite the increased activity of the HMG-CoA reductase; levels of TC, LDL -C tend to decrease in patients with clinical or subclinical hyperthyroidism due to increased bile excretion of cholesterol and mainly to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles (Liberopoulos and Elisaf, 2002). Therapy of hyperthyroidism results in restoration of the above mentioned alterations of lipid metabolism. Furthermore, hyperthyroidism results in enhanced LDL oxidability, which is strictly related to FT_4 levels (Costantini et al., 1998).

The incidence of hyperthyroidism is lower than that of hypothyroidism in the general population (Canaris et al., 2000). However, hyperthyroidism can also be the underlying cause of unexpected improvement of the lipid profile of hyperlipidemic patients (Liberopoulos et al., 2001). In the latter case, therapy of thyrotoxicosis restores the lipid parameters to the previously elevated levels (Liberopoulos et al., 2001). On the other hand thyroid hormone replacement therapy, has been shown to lead to some improvement of the lipid abnormalities in hypothyroid patients (Duntas, 2002; Pearce, 2004). Some studies have found that treatment of subclinically hypothyroid individuals with thyroxine may reduce serum TC and LDL-C (Danese et al., 2000; Iqbal et al., 2006; Meier et al., 2001). Another review has concluded that thyroxine replacement therapy can reduce TC and LDL-C, with no effect on TG (Ineck and Ng, 2003). However; in contrast to this; some studies have suggested that thyroid substitution therapy does not seem to significantly improve dyslipidemia in the hypothyroid patients. Larger prospective studies are needed to clarify these issues. Development of specifically targeted thyroid hormone analogues that could potentially treat hyperlipidemia without causing systemic thyrotoxicosis is currently ongoing.

An analysis of the soil characteristics of Wardha district indicates that one-fifth of the soil is classified as bardi, while four-fifths is accounted for by kanhar and madhyam that have relatively better levels of productive potential (Dhok AJ et al., 2015). However, kanhar and madhyamcategory soils have several inherent problems and deficiencies such as low level of availability of macro and micronutrients, which aggravates the iodine deficiency and hence can br accountable for high prevalence of hypothyroidism in the region (Dhok AJ et al., 2015). The people are not much aware of nutrient intake and consume goiterogenic food, which can induce antibodies that cross react with thyroid gland and interfere thyroid peroxidasewhich further aggravates the problem.

5. CONCLUSION AND RECOMMENDATIONS

Findings of this study show that; hypothyrodism is associated with altered lipid disorders that are characterized by elevated TG, TC, LDL-C, VLDL-C and lower HDL-C. From this findings; we can conclude that hypothyroid state has a role in increased cholesterol levels which in turn can be responsible for complications of high blood cholesterol like hypertension, cardiovascular disease etc. Therefore biochemical screening for lipid profile is of paramount importance in all patients with thyroid dysfunction and underlying lipid abnormalities should be recognized and treated. Also; thyroid dysfunction should be taken into account when evaluating and treating dyslipidemic patients. There is an absolute need for larger studies designed to answer the question as to why thyroid abnormalities are associated with altered lipid profile levels and whether therapy of these disorders might influence cardiovascular risks associated with dyslipidemias.

Implications

This study can enhance knowledge in regards to understanding the effects of hypothyroidism and hyperthyroidism on serum lipid values.

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Conflicts of Interest:

The authors declare no conflict of interest.

Ethical Approval

Institutional Ethical Committee Datta Meghe Institute of Medical Sciences.

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