



Original Work

Effect of levothyroxine therapy on dyslipidemia in hypothyroid patients

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ABSTRACT: The aims of the present study are to observe the prevalence of hypothyroidism (both subclinical and overt hypothyroidism), its association with dyslipidemia and whether replacement therapy with thyroid hormone has an effect on plasma lipid profile of hypothyroid patients. This prospective study of one-year duration recruited 232 clinically suspected patients belonging to both sexes and age group between 20-70 years attending OPD of endocrinology department of MLN Medical College, Allahabad. Patients were screened for T3, T4 and TSH and those who were euthyroid (52 cases) were excluded from the study. Thus, the present study included only 180 newly diagnosed cases of hypothyroidism. Levothyroxine replacement therapy was administered and patients were assessed every 3-4 months for an effect on lipid profile and body mass index during the study period. In both subclinical and overt hypothyroidism associated with dyslipidemia, replacement therapy with levothyroxine resulted in reversal to normal in significant number of cases. Although majority of hypothyroid cases were overweight yet therapy with levothyroxine caused no significant changes in BMI in all grades of obesity.

KEY WORDS: *Levothyroxine therapy; Dyslipidemia; Hypothyroidism*

INTRODUCTION

Dyslipidemia means abnormalities of plasma lipids and lipoprotein concentration. Disorders of the metabolism of lipoproteins, including lipoprotein overproduction and deficiency are classified as dyslipidemia. These may manifest in one or more of the following ways, a raised total cholesterol (CH) levels, a raised low density lipoprotein (LDL) cholesterol levels, a raised triglyceride (TG) levels and a decreased high density lipoprotein (HDL) cholesterol levels. Lipoproteins are a family of lipid carrying, water soluble proteins including chylomicrons (CM), high, intermediate, low and very low density lipoproteins (HDL, IDL, LDL, VLDL) which are responsible for the transport of cholesterol (CH), cholesterol esters (CE),

phospholipids and triglycerides throughout the circulation.¹ Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body functions.² Hypothyroidism can occur due to many causes of which iodine deficiency remains the most common cause world wide. In areas of iodine sufficiency, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic cause (treatment of hyperthyroidism) are most common.³ Hypothyroidism accounts for about 2% of all cases of hyperlipidemia, and is second only to diabetes mellitus as a cause of secondary hyperlipidemia.⁴ Various other studies^{5,6} have also reported that dyslipidemia is commonly associated with hypothyroidism. Jung et al⁷ and Duntas⁸ have also observed higher levels of total cholesterol and LDL-cholesterol in both subclinical and overt hypothyroidism. The effect of hypothyroidism in lipid metabolism is more marked in patients with higher serum TSH levels i.e. patient with overt hypothyroidism and observed significant

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correlation between raised TSH levels and serum total cholesterol and LDL cholesterol.⁹

Dyslipidemias, including hyperlipidemia (hypercholesterolemia) and low levels of high density lipoprotein cholesterol (HDL-C), are major causes of increased atherogenic risk. Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis induced conditions, such as coronary heart disease (CHD), ischaemic cerebrovascular disease and peripheral vascular disease.¹⁰ A number of studies reported that subclinical hypothyroidism (SCH) did not appear to be associated with abnormalities in serum cholesterol or triglycerides levels when adjusted for confounding variables.^{11,12} Caparevic et al¹³ observed that most patients with subclinical hypothyroidism should be treated with thyroxine to prevent progression to overt hypothyroidism, and thyroid hormone replacement therapy may slow the progression of coronary heart disease, because of its beneficial effects on lipids. Furthermore, a number of studies have reported that hypothyroidism is an important but overlooked cause of secondary hypertension, particularly diastolic mainly due to an increase in peripheral resistance, and restoration of euthyroidism with thyroxine therapy resulted in substantial reduction in both systolic and/or diastolic blood pressure.¹⁴⁻¹⁷ Besides, thyroxine therapy also exerts a beneficial effect on dyslipidemia.^{5,18,19}

The present study has been undertaken to study the prevalence of hypothyroidism and of dyslipidemia in patients of hypothyroidism, and to observe the effects of levothyroxine replacement therapy on lipid profile of hypothyroid patients in our tertiary care hospital.

METHODOLOGY

This prospective study of one year duration (Oct 2006-Sep 2007) was conducted in the departments of pharmacology and endocrinology at Motilal Nehru Medical College, Allahabad, UP. Patients belonging to both sexes and of age group between 20 to 70 years attending the outpatient department of endocrinology and having one or more clinical manifestations of hypothyroidism e.g. fatigue, weakness, loss of strength, loss of stamina, weight gain, coarse dry hair, dry, rough and pale skin, hair loss, cold intolerance, muscle cramps, frequent muscle aches, constipation, depression, irritability, memory loss, decreased libido and in women abnormal menstrual cycle were recruited for the study. Ethical clearance had been granted as it was an MD thesis topic and informed consent from the patients was also taken. Patients were screened for T3, T4 and TSH. Based on these values, patients were either classified as cases of overt hypothyroidism (high TSH and low T3 and T4 than normal) or as subclinical hypothyroidism (high

TSH but normal T3 and T4). The patients having normal thyroid profile (euthyroid) were excluded from the study. Cases which showed a deranged T3, T4 and /or TSH levels were further evaluated and blood samples of these patients were drawn aseptically after 12 hours overnight fasting for lipid profile pertaining to total cholesterol, triglycerides, HDL-C (High density lipoprotein cholesterol), LDL-C (Low density lipoprotein-cholesterol) and VLDL (Very low density lipoprotein).

Serum T3 and T4 were measured by immuno-chemiluminiscence microparticle assay. Serum TSH was measured by ultrasensitive sandwich chemiluminiscent immuno-assay. Total cholesterol was measured by CHOD/PAP (Cholesterol oxidase/peroxidase aminoantipyrine) method in serum or plasma, whereas for the determination of triglycerides in serum or plasma G PO/PAP (Glycerol phosphate oxidase/peroxidase aminoantipyrine) method was used,²⁰ HDL cholesterol was estimated by PEG/CHOD-PAP (Polyethylene glycol/Cholesterol oxidase-peroxidase amino antipyrine) method.²⁰ LDL-cholesterol was calculated indirectly by Freidewald's formula in individuals with triglyceride levels <4.5 mmol/L (<400mg/dl). In persons with triglyceride levels >4.5 mmol/L (>400mg/dL), direct measurement of LDL-cholesterol was undertaken in ultra centrifuged plasma. VLDL cholesterol was estimated to be the plasma triglyceride level divided by five.²⁰

Hypothyroid patients were classed as overt hypothyroidism (OH), and subclinical hypothyroidism (SCH) cases. Further, those patients who have borderline or undesirable plasma concentration of total cholesterol and/or triglycerides were considered as dyslipidemias and subgrouped into cases of hypercholesterolemia only, hypertriglyceridemia only, and as both hypercholesterolemia and hypertriglyceridemia.

Patients with overt hypothyroidism (OH) were given 50 to 100µg levothyroxine daily on empty stomach in the morning, dose was adjusted to achieve normal TSH values. In cases of subclinical hypothyroidism (SCH) levothyroxine was administered 25-50 µg/day with the goal of normalizing TSH.

Body mass index was calculated as weight in kilogram divided by the height in meter squared (Kg/m²). Blood pressure was measured twice, with a 3-min. interval, after 30 minutes of rest and the mean value of the two measurements was used.

The patients were reassessed at 3-4 months (First follow-up) and then at 6-7 months (Second follow-up) and 9-10 months (Third follow-up) for T3, T4, TSH and lipid profile, and for blood pressure reversal or regression. Dyslipidemic patients who had more than one lipid parameter deranged were also observed for partial reversal.

Statistical analysis was carried out using a paired student's t-test for lipid parameters. The lipid parameters were compared before and after levothyroxine therapy.

RESULT

A total 4697 patients who attended the endocrinology department during the study period, 232 were clinically suspected cases of hypothyroidism. Amongst these, 52 cases showed a normal thyroid profile and were not evaluated further. Thus, the present study included only 180 newly diagnosed cases of hypothyroidism consisting of 92 SCH and 88 OH cases.

The prevalence of hypothyroidism was found to be 3.83% (180 out of 4697). The prevalence of subclinical hypothyroidism (SCH) was 1.96 (92/4697) and that of overt hypothyroidism (OH) was 1.87 (88/4697). Of 92 SCH cases 7 were males and 85 females, and of 88 OH cases, there were 17 males and 71 females. M: F ratio was 1: 6.5 (**Table 1**). Maximum 67 cases belonged to the age group of 21-30 years (6 males and 61 females) and minimum number of patients was in the 61-70 years with 3 females only (**Table 1**). 147 hypothyroid patients belonged to urban population and 33 to rural population. The urban-rural ratio was 4.45:1.

Mean values of T3 and T4 were lower in patients of overt hypothyroidism, (OH) while values of TSH higher as compared to that of subclinical hypothyroid (SCH) cases (**Table 2**).

Out of 180 cases of hypothyroidism, 17(9.44%) cases had only hypertension, 49(27.22%) only dyslipidemia while 34(18.88%) cases had both dyslipidemia and hypertension (**Table 3**).

Out of 180 patients of hypothyroidism, dyslipidemia was found in 83 (46.11%) cases. Amongst 92 SCH cases, 29 had associated dyslipidemia, while amongst 88 OH cases, 54 cases were dyslipidemics. Majority of cases 39 (46.99%) had only increased total cholesterol; only triglycerides were increased in 14 (16.87%) cases whereas combined hypercholesterolemia and hypertriglyceridemia was observed in 30 (36.14%) cases (**Table 4**). The detailed breakup of 29 dyslipidemic SCH cases included 15 (18.07%) cases had hypercholesterolemia, 6 (7.23%) were hypertriglyceridemia and 8 (9.64%) had both hypercholesterolemia and hypertriglyceridemia. The detailed breakup of 54 dyslipidemic OH cases included 24 (28.92%) had only hypercholesterolemia, 8 (9.64%) had only hypertriglyceridemia and 22 (26.50%) had both hypercholesterolemia and hypertriglyceridemia. Out of 92 SCH cases, 18 (19.57%) had associated hypertension, while amongst 88 OH cases 33 (37.5%) were hypertensive. Hypertension, whether

systolic, diastolic or both was observed in both SCH and OH cases though the incidence of hypertension was more common in OH cases.

Table 5 shows follow-up of dyslipidemia in SCH cases following levothyroxine replacement therapy. It was observed that out of total 15 cases having only hypercholesterolemia 3 cases dropped out during follow up of 12 cases who completed the study 10 (83.33%) reverted to normal. In only hypertriglyceridemia cases, of total 6 cases, one case dropped out and reversal was observed in 2 out of 5 remaining cases (40%). In 8 SCH cases where both total cholesterol and triglycerides were raised, reversal was seen in only 1 (14.29%) case, 2 (28.57%) cases showed partial reversal, no reversal was seen in 4 cases and 1 case dropped out. In short, out of 29 SCH cases with dyslipidemia, 5 cases did not complete the study (drop-out), and of the remaining 24 cases, 13 cases showed reversal, 2 cases showed partial reversal and in 9 cases no reversal was noted.

Table 6 exhibits lipid parameters before and after levothyroxine replacement therapy in SCH patients with dyslipidemia. It was observed that there was a statistically significant decrease in mean values of total cholesterol, triglycerides, and LDL-cholesterol levels and a statistically significant increase in mean HDL-cholesterol level following replacement therapy with levothyroxine.

Table 7 shows follow-up of levothyroxine treatment in OH cases having dyslipidemia. It was observed that out of 19 cases having only hypercholesterolemia, only 12 (63.16%) cases showed reversal to normal. Whereas in 7 OH cases having only hypertriglyceridemia only 4(57.14%) showed reversal, while in 17 cases that had raised total cholesterol as well as triglycerides levels, 3 (17.65%) cases showed complete while 8 (47.06%) cases had partial reversal. Overall, of total 54 dyslipidemic OH cases, 11 dropped out, and 43 OH cases who completed the study, complete reversal of dyslipidemia was noted in 19(44.19%), partial reversal in 8 OH cases and no reversal in 16 cases.

Table 8 shows lipid parameters before and after levothyroxine replacement therapy in OH patients with dyslipidemia. A significant decrease in mean values of total cholesterol, triglycerides and LDL-cholesterol levels along with a significant increase in mean HDL-cholesterol levels was observed following replacement therapy with levothyroxine.

The risks associated with increasing BMI begin at BMI above 25 kg/m², and these subjects were classified as overweight. Among 180 hypothyroid cases, 133 (73.88%) were overweight, 71 SCH and 62 OH cases. Mean BMI of SCH cases was 28.1±3.7kg/m² and that of OH was 27.4±3.5 kg/m². Following replacement therapy with levothyroxine, there were no significant changes in BMI in all grades of obesity. Comparatively BMI of SCH was reduced more than OH cases.

Table 1: Distribution of hypothyroid patients according to age and gender (n=180)

Age Group (Years)	Subclinical Hypothyroidism		Overt Hypothyroidism		Total	
	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)
21-30	3 (1.67)	37 (20.56)	3 (1.67)	24 (13.33)	6 (3.33)	61 (33.89)
31-40	1 (0.56)	32 (17.78)	4 (2.22)	25 (13.89)	5 (2.78)	57 (31.67)
41-50	3 (1.67)	13 (7.22)	8 (4.44)	18 (10.00)	11 (6.11)	31 (17.22)
51-60	0	2 (1.11)	2 (1.11)	2 (1.11)	2 (1.11)	4 (2.22)
61-70	0	1 (0.56)	0	2 (1.11)	0	3 (1.67)
Total	92 (51.11)		88 (48.89)		180 (100)	

Table 2: Mean values and standard deviation of thyroid parameters in SCH & OH (n=180)

Thyroid Parameter	SCH (n=92) Mean ± SD	OH (n=88) Mean ± SD
T ₃ (ng/dL)	95.5 ± 23.9	47.5 ± 14.9
T ₄ (µg/dL)	6.5 ± 1.4	3.2 ± 1.5
TSH (µU/mL)	14.3 ± 6.1	79.2 ± 56.6

Table 3: Distribution of hypertension and dyslipidemia in hypothyroid patients (n=180)

	Hypertension only No (%)	Dyslipidemia only No. (%)	Both Hypertension & Dyslipidemia No. (%)
SCH	10 (5.55)	21 (11.67)	8 (4.44)
OH	7 (3.89)	28 (15.55)	26 (14.44)
Total	17 (9.44)	49 (27.22)	34 (18.88)

Table 4: Incidence of dyslipidemia in hypothyroid patients

	Hyper-cholesterolemia No. (%)	Hyper-triglyceridemia No. (%)	Both Hyper-cholesterolemia & Hypertriglyceridemia No. (%)	Total cases of Dyslipidemia No. (%)
SCH	15(18.07)	6(7.23)	8(9.64)	29(34.94)
OH	24(28.92)	8(9.64)	22(26.50)	54(65.06)
Total	39(46.99)	14(16.87)	30(36.14)	83(100)

Table 5: Effect of replacement therapy with levothyroxine on follow-up of dyslipidemia in subclinical hypothyroid patients (n=29)

	Hyper-cholesterolemia	Hyper-triglyceridemia	Both Hyper-cholesterolemia & Hypertriglyceridemia	Total Cases
Patients at 1 st visit	15	6	8	29
Reversal at 1 st follow-up	4	1	0	5
Reversal at 2 nd follow-up	4	1	1	6
Reversal at 3 rd follow-up	2	0	0	2
Partial reversal	0	0	2	2
No reversal	2	3	4	9
Dropout	3	1	1	5

Table 6: Lipid parameters before and after levothyroxine replacement therapy in subclinical hypothyroid patients with dyslipidemia (n=24)

Lipid Parameters (mg/dL)	Before Therapy Mean ± S.D.	After Therapy Mean ± S.D.	P-value
Total Cholesterol	211.3 ± 30.5	194.9 ± 25.1	< 0.001
Triglycerides	145.7 ± 38.6	133.9 ± 28.6	< 0.01
HDL-cholesterol	46.7 ± 9.1	52.4 ± 8.4	< 0.001
LDL-cholesterol	129.1 ± 22.9	123.6 ± 19.1	<0.001

Table 7: Effect of replacement therapy with levothyroxine on follow-up of dyslipidemia in overt hypothyroid patients (n=54)

	Hyper-cholesterolemia	Hyper-triglyceridemia	Both Hyper-cholesterolemia & Hypertriglyceridemia	Total Cases
Patients at 1 st visit	24	8	22	54
Reversal at 1 st follow-up	6	1	2	9
Reversal at 2 nd follow-up	4	2	1	7
Reversal at 3 rd follow-up	2	1	0	3
Partial reversal	0	0	8	8
No reversal	7	3	6	16
Dropout	5	1	5	11

Table 8: Lipid parameters before and after levothyroxine replacement therapy in overt hypothyroid patients with dyslipidemia (n=43)

Lipid Parameters (mg/dL)	Before Therapy Mean \pm S.D.	After Therapy Mean \pm S.D.	P-value
Total Cholesterol	219 \pm 32.6	194.4 \pm 27	< 0.001
Triglycerides	149.4 \pm 32.1	137.3 \pm 22.5	< 0.001
HDL-cholesterol	40.2 \pm 8	48.2 \pm 7.3	< 0.001
LDL-cholesterol	139.6 \pm 27.5	125.8 \pm 23.5	<0.001

DISCUSSION

Thyroid disorders are among the most common endocrine disorders and these usually alter lipid metabolism. Hypothyroidism is the second most common ailment affecting patients attending endocrinology outpatient departments. Increase in serum TSH level is the key laboratory finding for early detection of thyroid failure. Of 232 clinically suspected cases of hypothyroidism, only 180 cases were diagnosed as hypothyroid. The prevalence of hypothyroidism was found to be 3.83% (180 out of 4697), the prevalence incidence of SCH was 1.96% (92/4697) and that of OH was 1.87% (88/4697). Pirich et al²¹ reported an incidence of 1.1% for newly diagnosed subclinical hypothyroidism and no case of overt hypothyroidism. Jung et al⁷ observed the prevalence of overt hypothyroidism and subclinical hypothyroidism as 0.16% and 0.64% respectively. Ravishekhar et al²² reported the prevalence of SCH as 8.29%, whereas Tehrani et al²³ observed a prevalence of 21.2% of SCH cases in reproductive aged women. It is estimated that about 2-20% of people in the world are suffering from SCH and its prevalence is influenced by geographic location, sex, diet and race. However, our prevalence is fairly low as compared to 21.9% reported by Shantha²⁴ in India. The prevalence of SH cases was more common compared to OH cases. Our findings are in concurrence with other workers.⁷

In the present study, a predominance of females was noted in cases of hypothyroidism with M:F ratio 1:6.5. Other studies also reported that hypothyroidism was more prevalent among females than males^{7,22,25}. Maximum number of hypothyroid females belonged to the age group of 21-30 years 33.89%, followed by 31-40 years age group 31.67%. Among males maximum incidence was found in the age group of 41-50 years 6.11%. This suggested involvement of younger age group in females and middle age group in males. Ravishekhar et al²² reported that mean age was 50.20 years for male SCH, and mean age of 48.02 years in female SCH. Further, greater number of hypothyroid

patients belonged to urban population (81.67%) as compared to rural population (18.33%).

The mean values of T3, T4 and TSH among SCH patient were 95.5 \pm 23.9 ng/dl, 6.5 \pm 1.4 μ g/dl and 14.3 \pm 6.1 μ u/ml. Arem et al²⁶ reported mean TSH value to be 9.1 \pm 1 μ u/ml in variance with our findings. Among OH patients, the mean values of T3, T4 and TSH were found to be 47.5 \pm 14.9 ng/dl, 3.2 \pm 5 μ g/dl and 79.2 \pm 56.6 μ u/ml. Satio et al¹⁶ reported mean T4 as 2.9 \pm 0.1 μ g/dl and mean TSH as 105 \pm 6.8 μ u/ml. Arem et al²⁶ reported mean TSH values to be 42 \pm 6.5 μ u/ml. This shows wide fluctuations in TSH values by different authors in their study group.

Hypothyroidism leads to many effects on the cardiovascular system including hypertension as well as dyslipidemia which are major causes of atherosclerosis and coronary heart disease. Workers in the field also observed that restoration of euthyroid state by levothyroxine replacement therapy usually resulted in substantial reduction of the above parameters and improvements in the cardiovascular profile.¹⁵⁻¹⁷

In the present study, cases of hypothyroidism, had only hypertension, or only dyslipidemia or had both hypertension and dyslipidemia. We observed systolic, diastolic or combined systolic and diastolic hypertension in both SCH and OH cases, though the prevalence of hypertension was more in OH cases. Tehrani et al²³ observed a positive significant correlation between serum level of TSH and diastolic blood pressure, a correlation that remained after further adjustment for age, BMI and HOMA-IR. Diastolic hypertension was more commonly seen than systolic hypertension because of increased peripheral resistance^{14,16}. Saito et al¹⁶ found 15% of myxoedema patients to be hypertensive in a series of 477 patients. Duntas⁸ observed that hypothyroidism was often accompanied by hypertension and in conjunction with dyslipidemia, may promote atherosclerosis. Other authors also noted that subclinical hypothyroidism (SCH) was associated with increased prevalence of hypertension, elevated serum lipid levels, atherosclerosis, and ischaemic heart disease^{27,28}. On the contrary, Akbar et al¹²

observed in SCH elderly women no increased risk of hypertension, hyperlipidemia or ischaemic heart disease despite high prevalence of SCH in their sample. The Rotterdam study reported that total cholesterol was not elevated in SCH²⁹. Pirich et al²¹ also observed that mild subclinical hypothyroidism was not associated with any adverse cardiovascular risk profile.

Thyroid hormones influence nearly all major metabolic pathways and lipid metabolism is more influenced by thyroid hormones.³⁰ In this study, dyslipidemia was present in 83(46.11%) cases. Various other studies^{5,6,22} supported our findings that hypothyroidism was commonly associated with dyslipidemia. Of 88 OH cases, 54 (65.06%) were dyslipidemic. Amongst 92 SH, 29 (34.94%) had associated dyslipidemia. Jung et al⁷ and Duntas⁸ also documented higher levels of total cholesterol and LDL-cholesterol in both SCH and OH cases in agreement with those of our findings. Ravisekhar et al²² observed higher levels of serum total cholesterol and LDL cholesterol in SCH group and that TSH levels were significantly correlated with total cholesterol and LDL-cholesterol, however triglycerides and HDL cholesterol did not correlate with TSH levels and that the triglyceride levels were not raised in the study. In contrast Tehrani et al²³ observed that there was no significant correlation between TSH levels in SCH subjects (reproductive aged women) and other metabolic syndrome components although hypothyroid SCH women exhibited metabolic syndrome in varying percentage. The authors observed that after adjustment for BMI, there was no statistically significant association between TSH and total cholesterol, LDL or FBS but a negatively significant association between TSH and HDL-C. Contrary to our observations, Hueston and Pearson¹¹ observed that SCH cases did not appear to be associated with abnormalities in serum cholesterol or triglyceride levels when adjusted for confounding variables. Furthermore, correlation between SCH and metabolic syndrome (MetS) and its components (dyslipidemia being one of the components) varies in different studies and seems to be influenced by age, gender and race of study participants.

A positive correlation between OH and hypercholesterolemia is well recognized³¹. A similar correlation was also arrived at in our study as well wherein 65.06% cases of OH cases were dyslipidemics. Prakash and Lal⁹ observed that the effect of hypothyroidism over lipid metabolism was more marked in patients with higher serum TSH levels ie in OH patients. The authors noted a significant correlation between raised TSH levels and serum total cholesterol and LDL-cholesterol ($p < 0.05$, $P < 0.01$ respectively).

In the present study lipid profile of the hypothyroid patients showed that maximum number of 46.99%

cases had only raised cholesterol, 16.84% cases had only raised triglycerides, and both hypercholesterolemia and hypertriglyceridemia was seen in 36.14% cases. Hypothyroidism results in a rise in circulating total cholesterol and LDL cholesterol. Pearce¹⁸ observed an increase in serum total cholesterol, low-density lipoprotein (LDL) cholesterol and possibly triglyceride levels in both OH and SCH cases. Their findings supported those of our observations. It may be mentioned that elevation in LDL cholesterol levels may be accompanied by increased formation of oxidized LDL cholesterol contributing to enhanced risk of atherosclerosis³². Kotsis et al³³ observed that fasting serum cholesterol tended to be higher in hypothyroid patients compared with volunteers though it was not significant, while fasting serum triglycerides were significantly higher. These observations in reference to triglycerides were supporting those of our observations. Carantoni et al⁶ also observed higher mean triglyceride levels and lower HDL-cholesterol in hypothyroid patients, but total cholesterol concentrations did not change with impaired thyroid function in variance to our observations. In short, in hypothyroid cases (both SCH and OH) lipid profile particularly total cholesterol and LDL-cholesterol were adversely affected. Alterations in these parameters are implicated in atherosclerosis and are important risk factors for cardiovascular diseases.

Replacement therapy with levothyroxine in dyslipidemic SCH cases showed that 83.33% cases having only hypercholesterolemia and 40% cases having only hypertriglyceridemia reverted to normal values. In 7 cases where both total cholesterol and triglycerides were raised 14.29% case showed complete while 28.57% showed partial reversal. Overall, complete reversal of dyslipidemia was seen in 13 out of 24(54.17%) SCH cases following replacement therapy with levothyroxine.

In patients with SCH and elevated total cholesterol level, levothyroxine treatment may reduce serum cholesterol and thereby decrease the incidence of CAD, stroke and peripheral vascular diseases³⁴. Various other workers also reported significant reduction in the levels of total cholesterol and LDL-cholesterol following levothyroxine replacement therapy thus supporting our observations^{12,35,36}. Monzani et al³⁵ also found a reduction in the triglyceride levels in agreement with those of our observations. Contrary findings with regard to triglycerides levels have also been reported by a few of these authors. Ineck et al³⁶ and Meier et al³⁷ did not observe any change in triglyceride levels following levothyroxine replacement therapy contrary to our findings.

In the present study, in SCH patients there was a statistically significant decrease in mean values of total cholesterol ($p < 0.001$), triglycerides ($p < 0.01$)

and LDL cholesterol levels ($p < 0.001$), and a significant increase in mean HDL cholesterol ($p < 0.001$) following replacement therapy with levothyroxine. Thus, levothyroxine therapy definitely caused a beneficial effect on altered lipid profile parameters in SCH. Monzani et al³⁵ reported that replacement with levothyroxine in SCH patients significantly reduced both total cholesterol (214.2 ± 37.5 mg/dL Vs 191.6 ± 2.5 mg/dL), and LDL cholesterol (138.9 ± 32.3 mg/dL Vs 119.2 ± 27.8 mg/dL). There was a reduction in the levels of triglycerides (94.0 ± 31.9 mg/dL Vs 88.1 ± 30 mg/dL) as well. These findings supported our observations. However, in contrast to our observations, these authors reported a decline in HDL cholesterol levels (56.5 ± 11.7 mg/dL Vs 54.7 ± 7.4 mg/dL). Other workers in the field^{25,37,38} similarly observed a reduction in total cholesterol and LDL cholesterol levels following levothyroxine therapy, however, effect on HDL cholesterol were found to be variable in these studies^{37,38}. In contrast to our findings, Efstathiou et al³⁹ observed no significant changes in serum lipid profiles after levothyroxine therapy except for a decrease in HDL-cholesterol (59 ± 15 to 55 ± 14 mg/dL, $p < 0.05$).

In this study replacement therapy with levothyroxine in OH showed that 63.16% cases having only hypercholesterolemia and 57.14 cases having only hypertriglyceridemia reverted to normal. In 17 cases who had both a raised total cholesterol as well as triglycerides, levels 17.65% cases showed complete while 47.06% cases had partial reversal. Thus, overall complete reversal of dyslipidemia was noted in 19 out of 43 cases of hypothyroidism who completed levothyroxine replacement therapy while 8 cases showed partial reversal. Other workers in the field^{5,8,18,26} also reported a reduction in levels of total cholesterol, LDL cholesterol and triglycerides after levothyroxine therapy thus supporting our observations.

Besides, a significant increase in mean HDL-cholesterol (40.2 ± 8 mg/dL Vs 48.2 ± 7 mg/dL, $p < 0.001$) was observed in OH cases following replacement therapy with levothyroxine. In short, replacement therapy with levothyroxine in OH cases too produced definite beneficial effects in cases of hypercholesterolemia and hypertriglyceridemia, besides an increase in HDL levels. In contrast, Tanis et al¹⁹ reported that HDL – cholesterol levels decreased in OH cases and that levothyroxine substitution in OH cases was highly dependent on the pretreatment levels of total cholesterol. Thus, in OH patients when plasma levels of total cholesterol were elevated upto 310 mg/dL there was a decrease by 46.5 mg/dL and when plasma levels were higher than 310 mg/dL, the decrease was by 131.5 mg/dL.

In the present study an evaluation was also undertaken regarding BMI. An increased BMI was observed in 133 (73.88%) cases belonging to both SCH and OH cases. Mean BMI of SCH cases was slightly more than those of OH cases (28.1 ± 3.7 kg/m² Vs 27.4 ± 3.5 kg/m²) Efstathiou et al³⁹ reported mean BMI of SCH cases as 28.2 ± 5.6 kg/m². Kotsis et al³³ also observed mean BMI to be significantly higher in patients with hypothyroidism. Tehrani et al²³ observed that prevalence of obesity/overweight in women with SCH was higher than those of euthyroid women. These authors reported a BMI of 26.3% kg/m² amongst SCH Iranian women of reproductive age group. Jung et al⁷ also observed that patients with hypothyroidism exhibited higher waist to hip ratios, an index of obesity. In contrast, Manji et al⁴⁰ reported that there was no significant association between BMI and serum TSH levels in subjects with no apparent impairment of thyroid function. Additionally Poyrazoglu et al⁴¹ observed no significant differences in any clinical parameter (age, gender, BMI) between patients with SCH and control group, though in patients receiving levothyroxine therapy, LDL, high sensitive CRP, TSH and BMI were significantly decreased after levothyroxine therapy whereas TC, HDL and TG showed no significant changes. A positive correlation between OH and hypercholesterolemia as well as BMI is well recognized³¹.

In the present study, replacement therapy with levothyroxine caused statistically no significant changes in BMI in hypothyroid cases (both SCH and OH). This intriguing finding cannot be reasonably explained but is probably due to the fact that patients were not advised to drastically reduce their dietary intake habits or else to do extra physical exercise or change their lifestyles. Moreover, thyroid hormone levels have been reported to be normal, increased or decreased in obese patients. A longitudinal multicentric study will throw more light on this aspect. Lomenic et al⁴² did not support the notion of hypothyroidism as a cause of obesity (in children) and the authors suggested that practitioners should not expect significant changes in weight after treatment in most children with hypothyroidism, thus supporting our contention. Yet, it is reasonable to expect a weight reduction in SCH patients through a favourable effect of levothyroxine upon metabolism. Moreover, even small variations in serum TSH caused by minimal changes in levothyroxine dosage during replacement therapy were associated with significantly altered resting energy expenditure in hypothyroid patients.⁴³

A possible correlation between levothyroxine, and lipid profile as well as BMI could be explained as:

- Fat cells produce leptin which physiologically regulates energy homeostasis. Leptin is also an important neuro-endocrine regulator of

hypothalamic-pituitary-thyroid axis by regulating TRH gene expression in the paraventricular nucleus, and TSH in turn will stimulate leptin secretion by human adipose tissue^{44,45}. Leptin also effects thyroid deiodinase activities with activation of T4 to T3 conversion⁴⁶.

- TSH seems to be positively related to the degree of obesity and a positive correlation has been identified between serum leptin and serum TSH levels in obese individuals⁴⁷. This could reflect a positive association between TSH and BMI reported in some individuals. Additionally leptin increases susceptibility to autoimmune thyroid dysfunction which is the main cause of hypothyroidism in adults, by regulating immune processes in obese men and premenopausal obese women⁴⁸.
- Association between TSH and serum lipid in women with normal thyroid function is regulated via insulin sensitivity and that insulin sensitivity can be affected by thyroid function and a positive association between overt hypothyroidism and BMI has been well recognized^{43,49}.
- A decline in number of hepatocytes cell surface receptors for LDL resulted in reduced LDL catabolism in women with overt hypothyroidism leading to increased level of cholesterol and LDL-C and reductions in HDL-C^{7,50}.
- Another mechanism which may explain the correlation between TSH levels and obesity is in adipocytes and preadipocytes expressed receptors, TSH binds with its receptors and induces preadipocytes to produce and release adipokines⁵¹.

In conclusion, our study demonstrated that dyslipidemia is a definite entity in hypothyroidism (both SCH and OH) and that replacement therapy with levothyroxine in both SCH and OH patients causes various beneficial effects on lipid parameters. In SCH cases associated with hypercholesterolemia, levothyroxine therapy resulted in reversal to normal in more than 80% of cases, similarly reversal is also observed in hypertriglyceridemia though in lesser number of cases. However, levothyroxine replacement therapy did not produce statistically significant changes in BMI in both SCH and OH patients.

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