Original article

Hypothyroidism causing dyslipidemia in both subclinical & overt hypothyroidism

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ABSTRACT:

Introduction: Thyroid hormones play an essential role in regulating energy balance, metabolism of glucose, and lipids. Clinical Hypothyroidism leads to altered lipid profile according to previous studies. We have examined this relationship in subclinical hypothyroidism.

Material & methods: Estimation of lipid profile (Cholesterol, Triglyceride and HDL) was done in overt & subclinical hypothyroidism and compared with the healthy control group.

Observation & Results: In the present study the mean Total Cholesterol values were 131.0±22.38mg/dl, 172.06±27.51mg/dl, 204.46±26.43mg/dl, Serum Triglyceride values were 113.83± 20.45 mg/dl, 169.67±31.24 mg/dl, 178.67±28.86 mg/dl, LDL Cholesterol values were 66.06±23.29mg/dl, 99.10±27.43mg/dl, 134.56±25.77mg/dl, Serum HDL Cholesterol values were 42.36±4.17mg/dl, 38.56±4.14mg/dl, 34.13±2.58mg/dl respectively in the healthy control, subclinical hypothyroidism and overt hypothyroidism.

Conclusion: In Overt hypothyroid group, TSH showed statistically significant positive correlation with total Cholesterol ($r = 0.434$, $p < 0.0164$), Triglyceride ($r = 0.339$, $p < 0.05$), LDL Cholesterol ($r = 0.409$, $p < 0.05$). TSH had negative correlation with HDL Cholesterol ($r = -0.394$, $p < 0.05$).

In Subclinical hypothyroid group, TSH showed statistically significant correlation with total Cholesterol ($r = 0.387$, $p < 0.05$), LDL-C ($r = 0.404$, $p < 0.05$). The correlation between TSH was statistically not significant for Triglyceride, VLDL, HDL-C. The study has demonstrated and has further proved that hypothyroidism also causes dyslipidemia both in overt and subclinical hypothyroidism.

Keywords: Hypothyroidism, Lipid Profile, Dyslipidemia

INTRODUCTION:

Thyroid hormone plays an important role on various aspects of metabolism, development and differentiation of cells[1]. The thyroid gland secretes the thyroid hormones, thyroxine (T4) and the more biologically active form triiodothyronine (T3).[2]The World Health Organization (WHO) estimates that about 2 billion people are iodine- deficient, based on urinary excretion data. [3]Thyroid disease is being increasingly diagnosed with greater awareness and is one of the chronic non-communicable disease affecting women more though male population is not spared of the ailment. It is estimated that about 200 million people are at the risk of Iodine Deficiency Disease in our country. [4]

It is known that overt hypothyroidism leads to an increase in plasma cholesterol levels [5] . Most studies in sub clinical hypothyroidism show comparable but less pronounced associations [6, 7]. There remains a debate regarding extent to which cardio vascular events and lipid profile are affected by various degrees of thyroid dysfunction. This study was proposed to understand the hypothyroid population from north eastern part of India and to find out if dyslipidemia occurs in these patients from population. With this background in consideration present study was planned todetermine the level of fasting blood glucose, fasting lipid profile in patients diagnosed with hypothyroidism & to determine the relationship between lipid profile and thyroid function.

MATERIAL & METHODS:

Cases selected in the present study for the test group were amongst those who were newly diagnosed with hypothyroidism not on treatment. These were further divided into two groups. 30 cases of Sub-clinical hypothyroidism and 30 cases of Overt hypothyroidism. 30 Healthy control group contained age and sex matched healthy population Normal range for TSH was (0.4–4.0) µIU/ml and for FT4 was (0.89–1.76) ng/dl. Subclinical Hypothyroidism (SCH) was defined as serum free T4 levels within their respective reference ranges in the presence of abnormal high serum TSH levels. Patients with high TSH and low FT4 levels (< 0.89 ng/dl) were classified as being overt hypothyroid. Patients with normal TSH and FT4 were considered euthyroid.

The inclusion criteria adopted were newly diagnosed and untreated cases for sub clinical and overt hypothyroidism.To avoid confounding factors following exclusion criteria were applied: Patients suffering from diabetes, Polycystic ovarian disease, Tuberculosis, other systemic illness, liver disorders, renal disorders, congestive cardiac failure, intake of oral contraceptive pills, statins and other medications that alter thyroid functions and lipid levels led to exclusion from the study. Pregnancy also accounted for exclusion from the study.

All individuals of the control group co-operated voluntarily and informed consent was taken. The individuals selected for this group were of either sex and of different age groups. A thorough history (personnel, occupational etc.) and physical examination were done to exclude the exclusion criterion. Taking all aseptic and antiseptic precautions 5ml of blood is drawn from the median cubital vein. The blood is collected 12 to 14 hours after the last meal i.e. fasting blood sample is used for all the investigations.

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Estimation of lipid profile (Cholesterol, Triglyceride and HDL) and serum fasting blood sugar was done using Spectrophotometer (Spectra scan UV 2600,chemito). For lipid profile kits marketed by Coral clinical system are used. For Fasting Blood sugar kit from Merck Specialities were used. LDL was calculated using Friedwald's formula.Estimation of thyroid levels were measured by Immulite 1000 Immunoassay system, SIEMENS. For TSH and FT4 determination Immulite Test units & Reagents by Siemens Healthcare Diagnostics were used. All the chemicals used in the study are of analytical grade and deionized (Milipore) water is used.

The association between the various parameters in different groups was evaluated using Pearson's correlation coefficient. P<0.05 was considered statistically significant. Statistical analysis was performed using GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California USA, www.graphpad.com". All the statistical graphs were prepared using Microsoft Excel 2007.

RESULTS AND OBSERVATION:

Table 1: Mean Age in different groups.

	No of Cases	Mean Age in years.	Std. Deviation	Std. Error	Minimum	Maximum
Control	30	38.76	11.82	2.15	23	67
Subclinical	30	39.43	9.72	1.77	20	61
Overt	30	38.16	10.32	1.88	20	66

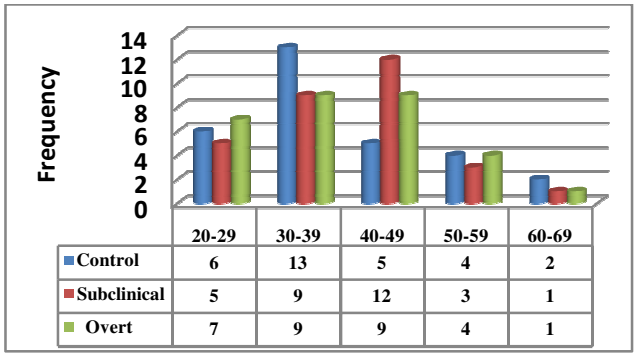

Figure 1: The frequency distribution of subjects with age (in years) in all the study groups is shown above.

Table 2: The Frequency distribution of sex in various groups.

	Control	Subclinical	Overt	Total
Female	17 (57%)	18 (60%)	21 (70%)	56
Male	13 (43%)	12 (40%)	9 (30%)	34
Total	30	30	30	90

	Control	Subclinical	Overt	One-Way Analysis Of Variance (ANOVA) F Value P Value
Mean Fasting Blood Sugar**(Mg/dl)**	80.07 ± 5.278	88.43 ± 9.940*	84.93 ± 9.059$	F=7.613, P<0.001.
Mean Total Cholesterol (Mg/dl)	131.00 ± 22.38	172.06 ± 27.5*	204.46 ± 26.43$	F=62.340, P <0.001.
Mean Triglyceride (Mg/dl)	113.83 ± 20.45	169.67 ± 31.2*	178.67 ± 28.86$	F=41.162, P<0.001.
Mean VLDL C (Mg/dl)	22.56 ± 4.61	34.40 ± 7.17*	35.76 ± 5.81$	F=37.587, P<0.001.
Mean LDL C (Mg/dl)	66.06 ± 23.29	99.10 ± 27.43 *	134.56 ± 25.77$	F=56.270, P<0.001.
Mean HDL C (Mg/Dl)	42.36 ± 4.17	38.56 ± 4.14*	34.20 ± 2.59$	F=23.382, P<0.001.
Mean TSH (Miu/Ml)	2.35 ± .87	9.03 ± 3.02 *	46.95 ± 31.51 $	F=51.918, P<0.001.
Mean FREE T4 (Ng/Dl)	1.161 ± .1071	1.114 ± .1037	.698 ± .0725 $	F=213.076, P<0.001

(*statistically significant between Control & Subclinical Hypothyroidism $ statistically significant between Control & Overt Hypothyroidism)

Table 3: Biochemical Parameters observed in Control, Subclinical, Overt hypothyroid Groups.

	Control		Subclinical		Overt	
	Female	Male	Female	Male	Female	Male
Mean Cholesterol (mg/dl)	135.41	125.23	171.05	173.58	202.42	209.22
Mean Triglyceride (mg/dl)	119.41	106.53	176.72	159.08	179.90	175.77
Mean VLDL (mg/dl)	23.88	20.84	36.27	31.58	36.04	35.11
Mean LDL(mg/dl).	69.76	61.23	95.55	104.41	132.42	139.55
Mean HDL(mg/dl).	41.76	43.15	39.22	37.58	33.95	34.55
Mean TSH(µIU/ml)	2.54	2.10	8.42	9.94	44.66	52.3
Mean FT4 (ng/dl)	1.13	1.19	1.09	1.15	0.68	0.72

Table 4: Biochemical Parameters observed in Control, Subclinical, Overt hypothyroid Groups in males & females.

		20-29 years	30-39 years	40-49 years	50-59 years	60-69 years
Mean Cholesterol(mg/dl) age groups	**Control**	125.66	133.07	146.4	117.5	122
	Subclinical	143.8	178.55	175.16	180	194
	Overt	187.42	214.55	208.66	209.33	206
Mean Triglyceride (mg/dl)	**Control**	107.83	116.61	114.6	122.75	94
	Subclinical	151.4	168.4	172.91	184	190
	Overt	163.85	178.77	189.66	191.33	180
Mean LDL(mg/dl).	**Control**	59.66	68.15	84.8	51	55
	Subclinical	71.6	104.22	104.16	102.33	120
	Overt	120.28	145.66	137.55	135	131
Mean HDL (mg/dl)	**Control**	44.5	41.53	39.8	42	48.5
	Subclinical	42.2	38.55	36.66	41	36
	Overt	34.28	33.22	33.11	36	39
Mean TSH (µIU/ml)	**Control**	2.68	2.41	1.86	2.41	2.01
	Subclinical	7.31	9.44	9.16	8.34	14.5
	Overt	34.87	58.32	54.56	35.5	25.1
Mean FT4 (ng/dl)	**Control**	1.20	1.13	1.224	1.075	1.21
	Subclinical	1.082	1.13	1.11	1.07	1.28
	Overt	0.67	0.71	0.67	0.77	0.72

Table 5: Biochemical Parameters observed in Control, Subclinical, and Overt hypothyroid Groups in different age groups.

Table 6: Correlation of TSH & lipid profile						
Parameters	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
	control group		**Subclinical group**		**Overt**	
TSH vs. Cholesterol	-0.04438	0.8159 not significant	0.3872.	0.0345 significant	0.4345	0.0164 significant
TSH vs. Triglyceride	-0.1921	0.3091 not significant	0.1060	0.5773 not significant	0.3339	0.0414 significant
TSH vs. HDL Cholesterol	0.1965	0.2979 not significant	-0.07917	0.6775 not significant	-0.3948	0.0308 significant
TSH vs. LDL Cholesterol	-0.05772	0.7619 not significant	0.4044	0.0266 Significant.	0.4097	0.0266 Significant.

DISCUSSION:

The present study is done among the hypothyroid patients attending a tertiary care Hospital. The possible Correlation among TSH, FT4 and serum concentrations of lipids was evaluated. Hypothyroidism is one of the most common functional disorder of the thyroid gland.

Age and Sex :

In the present study the mean age of patients in control, subclinical & overt hypothyroid groups are 38.76±11.82years, 39.43±9.72 years, 38.16 ±10.32 years respectively, suggesting that mean age of patients of hypothyroidism seeking healthcare is around 40 years. These persons are more prone to cardiovascular complications and other problems. If treatment and other lifestyle interventions are initiated at a proper time these complications can be delayed, if not fully corrected.

In the present study majority of the subjects i.e. 57%, 60%, 70% respectively in control, subclinical and overt hypothyroid groups were females. These findings suggest that hypothyroidism is much more prevalent in the female population. According to Reaven[8], Vanderpump et al[9], Agarwal [10]et al thyroid disease is much more prevalent in women than in men.

Fasting Blood Sugar :

The mean fasting blood sugar was 80.07±5.27 mg/dl, 88.43±9.94 mg/dl, 84.93±9.05 mg/dl in the normal control, subclinical hypothyroidism and overt hypothyroidism. The difference between Control and Subclinical group, Control and Overt groups were statistically significant. Singh et al[11] ,Al Sayed A et al[12] ,Tuzcu et al[13] have found in their studies mean fasting blood sugar is slightly higher in Subclinical & Overt hypothyroid groups than the control group. This is in consistence with our study findings.

Lipid profile:

In the present study the mean Total Cholesterol values were 131.0±22.38mg/dl, 172.06±27.51mg/dl, 204.46±26.43mg/dl respectively in the healthy control, subclinical & overt hypothyroidism. The difference between Control and Subclinical group, Control and Overt groups were statistically significant. Singh et al[11] have found 128±23.9 mg/dl, 178±35.3 mg/dl, 219±50.1 mg/dl in the control, subclinical, overt hypothyroid groups. Al Sayed A et al[12] have found 186.87±32.81 mg/dl, 210±31.27 mg/dl, Tuzcu et al[13] have found 167±39 mg/dl, 181±40 mg/dl in control & subclinical hypothyroidism. The level of Cholesterol is rising with age in all the groups. This demonstrates that with higher grades of hypothyroidism and increasing age there is increase in Total Cholesterol levels.

In the present study the mean Serum Triglyceride values were 113.83± 20.45 mg/dl, 169.67±31.24 mg/dl, 178.67±28.86 mg/dl respectively in the normal control, subclinical hypothyroidism and overt hypothyroidism. The difference between Control and Subclinical group, Control and Overt groups were statistically significant. . Al Sayed A et al[12] have found 140.70±61.94 mg/dl, 152.21±50.44 mg/dl, Tuzcu et al[13] have found 125±96 mg/dl, 120±65 mg/dl in control & subclinical hypothyroidism. Singh et al[11] have found 115.7±19.3 mg/dl, 193.2±91.19 mg/dl, 242.6±52.5 mg/dl in the control, subclinical, overt hypothyroid groups. The level of Triglyceride is rising with age in all the groups. This suggests that increasing grades of hypothyroidism and increasing age leads to increase in Triglyceride levels.

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In the present study the mean LDL Cholesterol values were 66.06±23.29mg/dl, 99.10±27.43mg/dl, 134.56±25.77mg/dl respectively in the normal control, subclinical hypothyroidism and overt hypothyroidism. The difference between Control and Subclinical group, Control and Overt groups were statistically significant. Singh et al[11] have found 64.0±20 mg/dl, 106.2±33.97 mg/dl, 126.2±40.9 mg/dl in the healthy control, subclinical, overt hypothyroid groups. Al Sayed A et al[12] have found 120.46±27.41mg/dl, 138±23.93 mg/dl, Tuzcu et al[13] have found 99.9±36 mg/dl, 116±36 mg/dl in control & subclinical hypothyroidism. In all the studies the mean values were higher in Overt & Subclinical hypothyroid groups than the control group as found in our study. The level of LDL Cholesterol is also rising with age in all the groups till 50 years.

In the present study the mean Serum HDL Cholesterol values were 42.36±4.17mg/dl, 38.56±4.14mg/dl, 34.13±2.58mg/dl respectively in the healthy control, subclinical hypothyroidism and overt hypothyroidism. The difference between Control and Subclinical group, Control and Overt groups were statistically significant. Tuzcu et al[13] have found mean HDL-C values of 42.4±12.1 mg/dl, 44.6±10.6 mg/dl, Al Sayed A et al[12] have found 42.08±6.94mg/dl, 37.83±7.33 mg/dl in the control & subclinical hypothyroid population. Singh et al[11] have found mean HDL-C values of 40.7±4.8 mg/dl, 33.9±11.1 mg/dl, 31.3±7.6 mg/dl in the control, subclinical, overt hypothyroid groups respectively. This demonstrates that with increasing grades of hypothyroidism there is decrease in serum HDL values. The level of HDL Cholesterol is decreasing with age in all the groups till 50 years.

TSH and Lipid Profile :

The correlation of TSH values with Serum Cholesterol, Serum Triglyceride, Serum LDL Cholesterol, in the normal control population is statistically not significant but in and subclinical hypothyroidism and overt hypothyroidism these are statistically significant.

In the present study the correlation of TSH values with Serum HDL Cholesterol in the normal control population & subclinical hypothyroidism is statistically not significant. In overt hypothyroidism it is statistically significant.

Lu et al found that in euthyroid population there were no significant correlations between TSH and serum Total Cholesterol, Triglyceride, HDL-C and LDLC.[14] Singh et al[11] have found Cholesterol, Triglyceride, LDL were significantly raised in Overt Hypothyroidism as compared to control where as HDL level was significantly lower. In Subclinical Hypothyroid group Triglyceride and LDL showed significantly higher levels. TSH showed significant correlation with total cholesterol. Al Sayed A et al[12] have found that patients with subclinical hypothyroidism exhibited elevated LDL-C. Althaus et al[15] reported that in subjects with Subclinical Hypothyroidism LDL-C levels were significant increased and HDL-C levels were decreased when compared to euthyroid subjects, after adjustment for age, sex, and BMI. Patients with subclinical hypothyroidism had significantly lower HDL-C levels than the euthyroid[14]. The Colorado thyroid disease prevalence study showed that Total Cholesterol and LDL-C in SCH were significantly higher than in euthyroidism but Triglyceride and HDL-C were not significantly different.[7]

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Most of the studies there is similar findings to our study suggesting positive correlation between TSH and T Cholesterol, LDL-C and Triglyceride. There is negative correlation between TSH and HDL-C. This finding further suggests that increasing grades of hypothyroidism causes dyslipidemia.

Thyroid hormone role in glucose and lipid metabolism:

Lipid and glucose metabolism are among the many physiological processes that are regulated by thyroid hormone. In fact, there is a strong link between thyroid hormone disorders and number of widespread metabolic diseases including diabetes[16], obesity[17] and cardiovascular disease [18]. Along with heart and muscle, the liver is one of the main organs affected by T3[19]. In liver, T3 increases the abundance of a number of genes potentially involved in hepatic triglyceride production, including spot 14 and fatty acid transporter protein as well as a range of genes involved in hepatic lipogenesis and low density lipoprotein receptor expression[20]. Paradoxically, T3 simultaneously induces genes involved in lipolysis including lipoprotein lipase [21].

In hypothyroidism there is decrease in energy metabolism and heat production. It is reflected by low basal metabolic rate, decreased appetite, cold intolerance, and slightly low basal body temperature.[22]

In hypothyroidism biosynthesis of fatty acids and lipolysis are reduced[23]. The lipid changes bear in general a reciprocal relationship to the level of thyroid activity. The increased serum cholesterol may represent an alteration in a substrate steady state level caused by a transient proportionally greater retardation in degradation than in synthesis [24]. The increase of serum cholesterol is largely accounted for by an increase of LDL-cholesterol, which is cleared less efficiently from the circulation due to a decreased T3-dependent gene expressing of the hepatic LDL-receptor [25].

Interestingly, the LDL particles of hypothyroid patients are also susceptible to increased oxidizability [26]. The changes in plasma LDL and HDL-cholesterol are related to changes in free thyroxine, not to polymorphisms in LDL receptor or cholesteryl ester transfer protein genes [27]. The increase of serum triglycerides has been related to a decreased lipoprotein lipase activity in post-heparin plasma. Lipoprotein (a) is increased in hypothyroidism in some but not all studies. Remnant particles in serum (reflecting chylomicron and VLDL remnants) are less effectively cleared in hypothyroidism [28]. Thus, the changes in plasma lipids in hypothyroidism result in an atherogenic lipid profile.

CONCLUSION :

The study has demonstrated and has further proved that hypothyroidism also causes dyslipidemia. Thus, it may be a good practice to screen patients with hypothyroidism for evidence of metabolic syndrome and in preventing various other complications. The screening and treatment for subclinical hypothyroidism should be done to prevent its adverse effects on lipid metabolism.

Thyroid hormones regulate the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of lipids, in thyroid disease. Dyslipidemia coexists with other metabolic abnormalities, including, hypertension, insulin resistance, and oxidative stress, all of them being risk

factors for other diseases. In addition, dyslipidemia induces insulin resistance and oxidative stress, via a vicious cycle. However, more studies need to be done, especially prospective, to elucidate the real significance of dyslipidemia or other metabolic changes in clinical and, even more, in subclinical hypothyroidism.

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