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Lipoproteins and Lipid Peroxidation in Thyroid disorders

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Abstract: *Alteration in thyroid function results in changes in composition and transport of lipoproteins. Abnormalities of lipid metabolism associated with hypothyroidism may predispose to the development of atherosclerotic coronary artery disease. The aim of our study is to evaluate lipids and the oxidative stress due to thyroid dysfunction. Serum T3, T4, TSH, total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides were measured using standardized assays. In a total of 80 patients with thyroid dysfunction, 53 patients are hypothyroid and 27 patients are hyperthyroid as compared with 40 healthy controls. In hypothyroid cases, T_3 (2.741 ng/dl), T_4 (7.3 µg/dl) are significantly decreased where as TSH (10.16 µ IU/ml) levels were elevated. In hyperthyroid patients T_3 (6.071 ng/dl) and T_4 (7.36 µg/dl) were increased but TSH values are low (2.042 µ IU/ml) but statistically not significant compared to controls. In hypothyroid cases total cholesterol (5.87mg/dl), triglycerides (3.233mg/dl), LDL (5.48mg/dl), VLDL (3.142mg/dl) were significantly increased, but there was no significant change in HDL cholesterol. In hyperthyroid cases, total cholesterol (2.51mg/dl), HDL (3.066mg/dl) significantly high, whereas triglycerides (0.633mg/dl), LDL (2.149mg/dl) and VLDL (0.532mg/dl) are within normal. MDA is higher in both hypothyroid (7.88mg/dl) and hyperthyroid (6.829mg/dl) cases. In conclusion, thyroid disorders are related to oxidative damage in tissues.*

Keywords: *atherosclerotic cardiovascular disease, dyslipidemia, malondialdehyde, oxidative stress, thyroid dysfunction*

I. Introduction

1.1. Nature of the Problem

Iodine deficiency is a major nutrition problem in India.Functional studies of the goitrous subjects showed overall prevalence of 5.4% in hypothyroidism, 1.9% in hyperthyroidism and of 7.5% in autoimmune thyroiditis. [3, 4]

1.1.2. Purpose of Present Study

1.1.3. Lipid Metabolism and Peroxidation

Much of the energy utilized by a cell is for driving the Na- K ATPase activity. Thyroid hormones enhance the function of this pump by increasing the number of pump units and associated increase of oxygen consumption leads to the production of free oxygen radicals. On the other hand, Iodine oxidation is catalysed by thyroperoxidase which requires H_2O_2 as an oxidizing agent. [5] H_2O_2 production is believed to be NADPH – dependant enzyme resembling cytochrome c reductase. TSH stimulates iodine incorporation into thyroglobulin primarily by increasing H_2O_2 generation. [5, 6]In hyperthyroidism TSH receptor antibodies stimulate the TSH receptor to induce excessive and sustained thyroid hormones. [7] Hence in hyperthyroidism there will be both increase in hormone biosynthesis and free radical production. Several liver enzymes such as NADPH – cytochrome P -450 reductase are regulated by the thyroid hormones and this enhanced activity of cytochrome p 450 reductase is responsible for the superoxide anion production and hydroperoxide in hyperthyroid state in rats. [8, 9]Hence hyperthyroid state is a pro oxidant state which is reflected as an oxidative stress at the cellular level which is well documented in myopathy and cardiomyopathy.

The alternations in thyroid function results in changes in the composition and transport of lipoproteins. [13, 14] In general overt and subclinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of LDL cholesterol levels, whereas high density lipoprotein (HDL) cholesterol concentration is usually normal or even elevated [15, 16, 17] and may predispose to the development of atherosclerotic coronary artery disease. [23] This is due to arterial constriction produced by angiotensin with its resultant intimal damage where cholesterol is deposited.

Hyperthyroidism (both overt and subclinical) is accompanied by increased activity of HMG Co A reductase, decreased levels of total cholesterol, LDL cholesterol, HDL Cholesterol, apolipoprotein B and

Lipoprotein A. These changes in lipid profile are explained by regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism one of which is the stimulation of denovo synthesis of cholesterol. Furthermore, HDL cholesterol levels are also decreased due to increased CETP mediated transfer of cholesteryl esters from HDL to VLDL and increased hepatic lipase mediated catabolism of HDL_2. Triglyceride levels remain unchanged. Hyperthyroidism results in enhanced LDL oxidability, which is strictly related to free T4 levels. Also hyperthyroidism constitutes not only a significant cause of acquired hyper β lipoproteinemia but also the unexplained improvement of the lipid profile. [25]

Hence Cholesterol levels are directly related to thyroid function. With normal thyroid function, there is greater rate of cellular replacement with its attendant increased utilization of cholesterol. However, hypothyroidism may result in decreased cholesterol production by the liver, which in turn may translate into normal or low cholesterol levels. Thus a normal cholesterol level is not always an accurate indicator of normal thyroid function but an elevated cholesterol level is an absolute indicator for hormone deficiency.

1.1.4. Previous work

The relation between hyperthyroidism and lipid peroxides determined by Kumar et al., found out that lipid peroxide levels were significantly increased and the Ascorbic acid, GSH levels were decreased in hyperthyroid patients. [26]

Komosinska et al., found out that there is increased incidence of lipid peroxidation in hyperthyroid patients and is associated with increase in intracellular antioxidant enzymes. Extracellular anti free radical scavenging systems potential, measured by glutathione reductase activity and total antioxidant status level, was found to be significantly decreased in untreated Grave's patients. Treatment with thiamazole resulted in normalisation of free radical and antioxidant activity indices. [27]

In a study by Bianchi et al., they found out that plasma levels of ThioBarbituric Acid Reactive substances (TBARS) which are by-products of lipid peroxidation were increased whereas Vitamin E and coenzyme Q 10 were reduced.[28]

Constatini et al., studied the effect of different levels of thyroid hormone and metabolic activity on LDL oxidation and found out that both hypothyroidism and hyperthyroidism are characterised by higher levels of LDL oxidation when compared to normolipidemic control subjects. In hyperthyroidism the lipid peroxidation is strictly related to free thyroxine levels, where as in hypothyroidism it was strongly related to serum lipids.[29]

In a study to examine the relationship between hyperthyroid state and the oxidative state by Kader et al., Malondialdehyde (MDA) and Thiol (SH) levels were determined and found that MDA levels were raised in hyperthyroid patients and SH levels were lower.[30]

No single study determined the effect of thyroid dysfunction (both hypothyroidism and hyperthyroidism) and lipid peroxidation. Many studies point to that hyperthyroidism causes lipid peroxidation. Hence the present study is aimed to evaluate the lipids and the oxidative stress due to thyroid dysfunction.

II. Materials

After institutional ethics committee approval 80 patients with thyroid dysfunction and 40 healthy controls were taken for study. After 12 hours overnight fasting, 6ml blood was withdrawn by standard venipuncture, serum was separated and T3, T4, TSH were estimated according to the protocol mentioned in the test kits from ERBA. The estimation of triglycerides is with dynamic extended stability with lipid clearing agent (Glycerol Phosphate Oxidase – Trinder method). [31, 32, 33] The estimation of Cholesterol is by Dynamic extended stability with lipid clearing agent (CHOD – PAP method or Modified Roeschalau's method) [34, 35] HDL Cholesterol estimation is done by Phosphotungstic Acid method. [36] Estimation of Malondialdehyde (MDA) is by Thiobarbituric Acid (TBA) reaction.

III. Results

Table 1: Demographic Data

Age(Yrs)	Controls	Hypothyroid	Hyperthyroid

	Male	Female	Male	Female	Male	Female
1 – 10	2	-	-	2	-	-
11 – 20	-	7	1	6	-	6
21 – 30	2	11	1	17	1	5
31 – 40	1	11	3	10	-	7
41 – 50	2	2	2	7	1	5
51 – 60	-	2	2	1	-	2
61 – 70	-	-	1	-	-	-
Total	07	33	10	43	2	25

44 patients are from the age group of 21 – 40 yrs and out of 53 hypothyroid patients 31 are in this age group; 13 out of 27 hyperthyroid patients are in this group.

Table 2: Comparison of T_3, T_4, TSH, Triglycerides, T.Cholesterol, HDL, LDL, VLDL and MDA in control, Hypothyroid and Hyperthyroid cases.

S.No	Parameter	Control	Hypothyroid	Hyperthyroid
1	T3 (ng/dl)	137. 6± 45.3	108 ± 55.6	411 ± 280
2	T4 (µg/dl)	7.7 ± 2.5	4.05 ± 2.3	15.2 ± 5.7
3	TSH (µ IU/ml)	2.7 ± 1.3	15.4 ± 7.8	1.8 ± 2.3
4	T. Cholesterol (mg/dl)	193 ± 23	250 ± 58	172 ± 45
5	HDL Cholesterol (mg/dl)	43 ± 7.4	44 ± 6.6	38 ± 5
6	LDL Cholesterol (mg/dl)	127 ± 24	174 ± 50	111 ± 37
7	VLDL Cholesterol (mg/dl)	23 ± 5.3	32 ± 17.5	24 ± 10
8	Triglycerides (mg/dl)	115 ± 26	161 ± 87	121 ± 51
9	MDA (n.mol/dl)	221 ± 54	638 ± 331	582 ± 329

Table 3: Comparison of statistical values of T_3, T_4, TSH, Triglycerides, T.Cholesterol, HDL, LDL, VLDL and MDA in control and Hypothyroid cases.

S.No	Parameter	"t"	"p" value
1	T3 (ng/dl)	2.741	< 0.001
2	T4 (µg/dl)	7.3	> 0.001
3	TSH (µ IU/ml)	10.16	> 0.001
4	T. Cholesterol (mg/dl)	5.87	> 0.001
5	HDL Cholesterol (mg/dl)	0.685	< 0.20
6	LDL Cholesterol (mg/dl)	5.48	> 0.001
7	VLDL Cholesterol (mg/dl)	3.142	< 0.002
8	Triglycerides (mg/dl)	3.233	< 0.002
9	MDA (n.mol/dl)	7.88	> 0.001

Table 4: Comparison of statistical values of T_3, T_4, TSH, Triglycerides, T.Cholesterol, HDL, LDL, VLDL and MDA in control and Hyperthyroid cases.

S.No	Parameter	"t"	"p" value
1	T3 (ng/dl)	6.071	>0.001
2	T4 (µg/dl)	7.36	> 0.001
3	TSH (µ IU/ml)	2.042	< 0.02 (NS)
4	T. Cholesterol (mg/dl)	2.51	< 0.01
5	HDL Cholesterol (mg/dl)	3.066	< 0.002
6	LDL Cholesterol (mg/dl)	2.149	> 0.02 (NS)
7	VLDL Cholesterol (mg/dl)	0.532	< 0.5 (NS)
8	Triglycerides (mg/dl)	0.633	< 0.5 (NS)
9	MDA (n.mol/dl)	6.829	> 0.001

In our study, a total number of 80 patients with thyroid dysfunction were included. Out of them, 53 patients are hypothyroid and 27 patients are hyperthyroid. The values are compared with 40 healthy controls. 44 patients out of 80 study group are from the age group of 21 to 40 years. In hypothyroidism 31 out of 53 belongs to the same age group. 13 out of 27 hyperthyroidism are also in the same age group.

Plasma T_3, T_4 and TSH levels were determined by ELISA method in all the groups. In hypothyroid cases hormone levels are significantly decreased T_3 (2.741 ng/dl) and T_4 (7.3 µg/dl) where as TSH (10.16 µ

IU/ml) levels were elevated compared to controls. (Table 2.) In hyperthyroid patients T_3 (6.071 ng/dl) and T_4 (7.36 µg/dl) were increased but the TSH values are low (2.042 µ IU/ml) but statistically not significant compared to controls. Basing on this, lipoprotein fractions were analyzed in both hypothyroid and hyperthyroid cases. In hypothyroid cases total cholesterol (5.87mg/dl), triglycerides (3.233mg/dl), LDL cholesterol (5.48mg/dl), VLDL cholesterol (3.142mg/dl) were significantly increased, but there was no significant change in HDL cholesterol. (Table 3.) In hyperthyroid cases, total cholesterol (2.51mg/dl) and HDL Cholesterol (3.066mg/dl) significantly high, whereas triglycerides (0.633mg/dl) LDL cholesterol (2.149mg/dl) and VLDL cholesterol (0.532mg/dl) (Table 4.) has no significant change compared to controls.

IV. Discussion

In thyroid patients, despite the reduced activity of the HMG - Co A reductase; there is often an increase in the total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol and intermediate density lipoprotein (IDL) cholesterol. [17, 37] Also, decreased activity of LDL receptors resulting in decreased receptors' mediated catabolism of LDL and IDL is the main cause of the cholesterolemia observed in hypothyroidism. [31, 36]

Hypertriglyceridemia associated with increased levels of VLDL and occasionally fasting chylomicronemia are found less commonly in this population. These changes are attributable to the decreased activity of LPL, which results in a decreased clearance of triglyceride rich lipoproteins. [39]

The VLDL and IDL particles in hypothyroidism are rich in cholesterol and apolipoprotein E, thus resembling β - VLDL particles of type III hyperlipoproteinemia. [40]

Hence these lipid abnormalities predispose to the development of atherosclerotic coronary artery disease. Furthermore, hypothyroidism may contribute to the development of atherosclerosis by other mechanisms as outlined below:

1) Decreased thyroid function not only increases number of LDL particles but also promotes LDL oxidability. An obvious reason being that T_4 has three binding sites on apolipoprotein B and inhibit LDL oxidation in vitro. [10]
2) Thyroid failure is accompanied by an increase in plasma homocysteine levels with its known adverse effect on the cardiovascular system. [41]
3) Hypothyroidism is strongly associated with arterial hypertension via sympathetic and adrenal activation and increased aortic stiffness. [42]
4) The insufficient concentrations of thyroid hormones induces a hypercoaguable state. [23]

Despite the increased activity of the HMG Co A reductase, levels of total cholesterol, LDL Cholesterol, apolipoprotein B and Lp (a) 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. [24]

Hypothyroid patients usually exhibit elevated levels of high density lipoprotein (HDL) cholesterol mainly due to increased concentration of HDL_2 particle. Decreased activity of the cholesteryl ester transfer protein (CETP) results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL cholesterol levels. Furthermore decreased activity of hepatic lipase leads to decreased catabolism of HDL_2. [23]

Furthermore, HDL cholesterol levels are also decreased in hyperthyroidism due to increased CETP mediated transfer of cholesteryl esters from HDL to VLDL and increased hepatic lipase mediated catabolism of HDL_2. Triglyceride levels remain unchanged. Hyperthyroidism results in enhanced LDL oxidability, which is related to free T_4 levels. However, hypothyroidism constitutes not only a significant cause of acquired hypobetalipoproteinemia but can also the underlying cause of unexpected improvements of the lipid profile of hyperlipidemic patients. [25]

Videla et al., have reported that the rate of lipid peroxidation induced by free oxygen radicals increases in hyperthyroidism but is suppressed in hypothyroidism. [43, 44, 45, 46] Contrary to this Mano et al., suggested that lipid peroxidation decreases in hyperthyroidism and increases in hypothyroidism. [47] On the other hand, Dumitriu et al., defended that lipid peroxidation increases in both states by different mechanisms. [12]

The free oxygen radicals produced in excess may cause toxic effects which is described as oxidative damage on biological membranes. The oxidation of membrane lipids has been implicated as one of the preliminary events in the oxidative cellular damage. [48]

Due to the increased activity of HMG Co A reductase, levels of total cholesterol, LDL cholesterol tend to decrease in patients with hyperthyroidism due to increased bile excretion of cholesterol and mainly due to increased LDL receptor gene expression resulting in enhanced LDL receptor mediated catabolism of LDL particles. HDL cholesterol levels are also decreased even though not significant due to increased CETP mediated transfer of cholesteryl esters from HDL to VLDL and increased hepatic lipase mediated catabolism of HDL_2. Triglyceride levels remain unchanged in hyperthyroidism (TABLE 5.)

In our study, Malondialdehyde (MDA), a breakdown product of lipid peroxidation estimated to assess the extent of oxidative damage due to the thyroid dysfunction. MDA was found to be higher in both hypothyroid (7.88mg/dl) and hypothyroid cases (6.829mg/dl) compared to controls (TABLE 2.); which is comparable other studies by Videla et al., [45, 49]

In conclusion, Hyperthyroidism or hypothyroidism is associated with pro-oxidant state which will be reflected as an oxidative stress at cellular level to the tissues which are subjected to the action thyroid hormones.

V. Conclusion

Thyroid disorders are known to influence lipid metabolism and are common in dyslipidemic patients. Hypothyroidism have an adverse effect on the serum lipid profile that may predispose to the development of atherosclerotic disease. Hyperthyroidism is also a pro oxidant state and decreased HDL cholesterol. MDA levels are increased in both hypothyroidism and hyperthyroidism which is an indirect marker for lipid peroxidation. Hence we conclude that lipid peroxidation is present in both states of thyroid dysfunction.

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