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RESEARCH ARTICLE

TO STUDY GLYCEMIC STATUS AND LIPID FRACTIONS IN SUBCLINICAL HYPOTHYROID, OVERT HYPOTHYROID AND HYPERTHYROID SUBJECTS

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Background: Thyroid function disorders lead to changes in the lipoprotein metabolism. Glycation is the process of non enzymatic addition or insertion of sugar to protein.

Aims & Objective: The aim of this study was to find out relationship of glycemic status and lipid fractions with subclinical hypothyroid, overt hypothyroid and hyperthyroid subjects.

Methodology: The present study was conducted on 100 overt hypothyroid, subclinical hypothyroid and hyperthyroid patients attending the Medical OPD and Radio Immuno Assay (RIA) Laboratory of the Biochemistry Department of JawaharLal Nehru Medical College & Hospital, Ajmer. The results of patients were compared with 50 healthy control subjects of either sex of similar age group.

Results: All the lipid fraction were comparable to those of studied groups and they were significantly deranged, as compared to those of Group-I. The mean serum fructosamine (FA) level was observed statistically highly significant ($p<0.001$) in Group-II and Group-III and vice versa in the Group –IV subjects.

Conclusion: This study indicates that monitoring of lipid in patients with thyroid dysfunction would be helpful in preventing cardiovascular diseases. The fructosamine values which are largely in excess of the fasting plasma glucose (FPG) and glycatedhaemoglobin (HbA1c) values, indicate a higher propensity to glycation and a decrease turnover of the proteins in the overt hypothyroid and the subclinical hypothyroid subjects,vice versa is true of the hyperthyroid subjects.

INTRODUCTION

Thyroid hormones play a key role in the regulation of synthesis and in the metabolism and the mobilization of lipids. Subclinical and overt hypothyroidisms are relatively common disorders in general population. Subclinical hypothyroidism (SCH) is characterized by elevated serum TSH concentrations in association with normal serum thyroid hormones. By affecting the metabolism of the lipids, hypothyroidism accelerates the process of atherogenesis and it increases the cardiovascular risk. Hyprethyroidism exhibits an enhanced excretion of cholesterol and an increased turnover of low density of lipoprotein-cholesterol (LDL-C), resulting in a decrease in the total cholesterol and LDL-C levels and in raised high density of lipoprotein-cholesterol (HDL-C) levels (19). Fructosamine (FA) is glycated protein, the generic name for plasma proteins ketoamines. It is formed by a spontaneous non-enzymatic reaction between a carbonyl group of a glucose molecule and an amino group of a protein with elimination of water molecule. It is a useful indicator to measure the peripheral metabolic function in patients with thyroid disorders (16), FA (glycated albumin) is generally used for assessing the glycemic changes in diabetics over a 2-3 week period. When the fructosamine values were compared between the hypothyroid and the hyperthyroid patients, it was found that the fructosamine levels and the fructosamine per albumin ratio were

significantly lower in the patients with Grave's disease than in the normal subjects, while they were significantly higher in the patients with primary hypothyroidism (14,31). Studies correlating various glycemic parameters in thyroid disorders are not well documented. Therefore in the present study an attempt will be made to compare the FA, HbA1c and the lipid fractions in subclinical hypothyroid as well as in the overt hypothyroid and hyperthyroid subjects.

MATERIALS AND METHODS

The present study was conducted on 100 overt hypothyroid, subclinical hypothyroid and hyperthyroid patients attending the Medical OPD and Radio Immuno Assay (RIA) Laboratory of the Biochemistry Department of JawaharLal Nehru Medical College & Hospital, Ajmer. The results of patients were compared with 50 healthy control subjects of either sex of similar age group (25-55 years). The selected subjects were further grouped as: **GROUP- I:** Healthy Control (Euthyroid) subjects (n=50). It was ensured by routine examinations that all the subjects were healthy and there were no signs and symptoms or positive history of thyroid abnormalities. **GROUP-II:** Overt Hypothyroid patients (n=35). It included the clinically established patients of hypothyroidism. **GROUP-III:** Subclinical Hyperthyroid patients (n=30). It included the clinically established patients of sub clinical hypothyroidism. **GROUP-IV:** Hyperthyroid patients (n=35). It included the clinically established patients of hyperthyroidism. The fasting lipid profile [Total cholesterol (TC), Triglycerides (TG), HDL-C, LDL-C, very low density of lipoprotein-cholesterol (VLDL-C), TC/HDL and LDL/HDL ratios], the thyroid profile (Total T3,T4 and TSH) and the glycemic profile which consisted of FPG, HbA1c and serum fructosamine were estimated / calculated in all the groups. The diagnoses of hypo and hyperthyroidism were established, based on the clinical signs and symptoms and the T3, T4 and TSH estimations. Patients on treatment for any thyroid disorder, lipid lowering drugs, diabetes, malignancy and pregnant women were excluded. The study was approved by the Ethics committee of our college.

Blood samples were collected by venipuncture by aseptic technique. The serum separated from the samples were analyzed for following biochemical parameters. The estimation of thyroid profile was done by using a Radio Immuno Assay (RIA) method. The serum lipid profile was estimated by the enzymatic CHOD-POD method for TC (4), by the GPO-POD method for TG (12) and by the CHOD-POD/ Phosphotungstate method for HDL-cholesterol (10). These estimations were carried out by using semi automated analyzer. LDL-Cholesterol and VLDL-Cho lesterol were calculated by Friedwald's formula (13) and the TC/HDL and the LDL/HDL ratios were noted. FPG was estimated by the GOD-POD method (29), HbA1c was estimated by the ion-exchange resin method (30) and serum fructosamine was estimated by the NBT reduction method (6). The results were expressed as mean ± standard deviation (SD). P-value < 0.05 was considered statistically significant.

RESULTS

The present study had been concluded on 150 subjects with age group (25-55 years). These were further divided into 4 groups. Group I comprised of 50 subjects who were euthyroid (control), Group II comprised of 35 subjects who were overt hypothyroid patients, Group III comprised of 30 subjects who were subclinical hypothyroid patients and Group IV comprised of 35 subjects who were hyperthyroid patients**.** Among the 50 euthyroid subjects, 20 subjects were males while 30 subjects were females, overt hypothyroid subjects include 10 males and 25 females, subclinical hypothyroid subjects include 13 males and 17 females while 10 males and 25 females were present in hyperthyroid subject group. The mean ages of euthyroid, overt hypothyroid, subclinical hypothyroid and the hyperthyroid subjects were 35.0 ± 7.30; 40.51± 09.13; 41.48±10.11 and 41.16± 08.54 respectively**.**

Table:1 shows the serum TSH and the total thyroid hormone levels of the 4 groups. As compared to the euthyroid subjects, the mean TSH level was higher with lower T_3 and T_4 values in the Group II subjects and vice versa in the Group IV subjects. Normal T_3 and T_4 values and raised TSH levels (upto 20 µIU/ml) were considered in Group III subjects. **Table:2** shows a significant increased in the levels of TC, TG, LDL-cholesterol, VLDL-cholesterol, TC/HDL and LDL/HDL ratios and decreased levels of HDL-cholesterol were observed in overt hypothyroid & subclinical hypothyroid subjects and elevated HDL-cholesterol observed in hyperthyroid subjects as compared to the healthy control subjects. The Mean ± SD value of FPG, HbA1c and serum fructosamine levels in euthyroid healthy control subjects was 84.24±11.23, 5.03±0.53 and 260.70±26.06, and in overt hypothyroid subjects it was 90.65±13.51, 6.0±0.58 and 581.65±55.11. The FPG and HbA1c levels were increased and the increase in fructosamine level was observed statistically highly significant ($p<0.001$) in overt hypothyroid subjects as compared with euthyroid subjects **(Table:3). Table:4** shows Mean ± SD values of FPG (87.80±13.14), HbA1c (05.31±0.56) and serum fructosamine (372.93±43.94) were elevated in subclinical hypothyroid subjects as compared to euthyroid subjects having values: FPG (84.24±11.23), HbA1c (05.03±0.53) and serum fructosamine (260.70±26.06) respectively. Serum fructosamine level was observed statistically highly significant ($p<0.001$) in SCH subjects when compared with euthyroid subjects.

Table 1 : Mean T3, T4, TSH among the different groups.

Tests	Euthyroid	Overt hypothyroid	Subclinical hypothyroid	Hyperthyroid
Serum T3(ng/ml)	1.34±0.20	0.52±0.14	0.76±0.34	2.94±0.14
Serum T4 (µg/dl)	9.2±1.41	3.91±1.31	6.0±1.23	17.81±2.39
Serum TSH(µIU/ml)	2.13±0.53	26.15±15.13	11.60±5.81	0.09±0.03

Table 2 : Lipid parameters in the subjects studied.

Tests	Euthyroid	Overt hypothyroid	Subclinical hypothyroid	Hyperthyroid
TC (mg/dl)	184.7±14.70	254.74±13.04	249.46±11.71	193.72±13.11
TG (mg/dl)	117.12±21.55	162.75±19.67	155.93±15.13	129.02±15.18
HDL(mg/dl)	45.98±11.33	42.54±8.10	43.70±7.89	46.65±11.61
VLDL (mg/dl)	23.42±04.31	32.55±3.39	31.18±3.02	25.80±3.03
LDL (mg/dl)	115.3±6.50	179.65±21.55	174.58±14.05	121.27±17.53
TC/HDL ratio	4.01±0.81	5.98±1.29	5.70±1.0	4.15±0.95
LDL/HDL ratio	2.50±0.21	4.22±1.09	4.06±0.32	2.59±0.13

Table 3: Comparison of glycemic profile in Euthyroid and Overt hypothyroid group.

Tests	Euthyroid	Overt hypothyroid	t-value	P- Value
FPG(mg/dl)	84.24±11.23	90.65±13.51	1.03	p>0.05 (NS)
HbA1c (%)	5.03±0.53	6.0±0.58	0.61	p>0.05 (NS)
Fructosamine (µmol/L)	260.70±26.06	581.65±51.11	15.81	P<0.001 (HS)

**p-value < 0.001 Highly Significant (HS), *p-value<0.05 Significant (S), p-value>0.05 Non Significant (NS)

Table 4: Comparison of glycemic profile in Euthyroid and Subclinical hypothyroid group.

Tests	Euthyroid	Subclinical hypothyroid	t-value	P- Value
FPG(mg/dl)	84.24±11.23	87.80±13.14	0.98	p>0.05 (NS)
HbA1c (%)	5.03±0.53	5.31±0.56	0.52	p>0.05 (NS)
Fructosamine (µmol/L)	260.70±26.06	372.93±43.94	10.13	P<0.001 (HS)

**p-value < 0.001 Highly Significant (HS), *p-value<0.05 Significant (S) p-value>0.05 Non Significant (NS)

Table 5 : Comparison of glycemic profile in Euthyroid and Hyperthyroid group.

Tests	Euthyroid	Hyperthyroid	t-value	P- Value
FPG(mg/dl)	84.24±11.23	92.31±12.24	1.36	p>0.05 (NS)
HbA1c (%)	5.03±0.53	5.15±0.45	0.47	p>0.05 (NS)
Fructosamine (µmol/L)	260.70±26.06	162.97±23.46	3.88	P<0.001 (HS)

**p-value < 0.001 Highly Significant (HS), *p-value<0.05 Significant (S), p-value>0.05 Non Significant (NS)

Table 6: Glycemic profile in the subjects studied.

Tests	Euthyroid	Overt hypothyroid	Subclinical hypothyroid	Hyperthyroid
FPG(mg/dl)	84.24±11.23	90.65±13.51	87.80±13.14	92.31±12.24
HbA1c (%)	5.03±0.53	6.0±0.58	5.31±0.56	5.15±0.45
Fructosamine (µmol/L)	260.70±26.06	581.65±51.11	372.93±43.94	162.97±23.46

Table:5 illustrates the mean value of FPG and HbA1c levels were elevated in the hyperthyroid subjects, even with lower serum fructosamine levels. Seumfructosamine was observed statistically significant ($p<0.001$) in hyperthyroid subjects when compared with euthyroid subjects. **Table:6** has compared the FPG, HbA1c and the serum fructosamine concentrations of the study groups. FPG and HbA1c were elevated in the Group II, Group III and Group IV subjects. The increase in serum fructosamine level was observed statistically highly significant ($p<0.001$) in Group II and Group III and vice versa in the Group IV subjects.

DISCUSSION

In overt hypothyroid subjects:-

A lack of thyroid hormones in hypothyroidism causes an elevation of the LDL-cholesterol synthesis due to an increase in the cholesterol synthesis and absorption, a decrease in the hepatic lipase and the lipoprotein lipase activities, defects in the receptor- mediated catabolism of LDL-cholesterol (Liberopoulos EN et al 2002), an increase in the oxidation of plasma cholesterol, mainly TC and LDL-cholesterol and a decrease in the HDL receptors on the hepatocytes.

The mean levels of serum cholesterol were significantly higher in hypothyroid patients than that of healthy controls in our study. This finding is consistent with other studies. Liberopoulos E N et al.; 2002, Agedeppa D et al 1979.;, Staub J J et al.;1992, Abrams J J et al.;1981, In hypothyroid patients, despite the reduced activity of β-hydroxy β methyl glutaryl Co A (HMG-CoA) reductase, there is often an increase in the serum total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol and intermediate density lipoprotein (IDL) cholesterol. In addition incompletely degraded VLDL particles enriched in cholesterol and apo- E accumulate in thyroid subjects. A defective receptor mediated LDL catabolism and changes in intravascular metabolism as defined by decreased activities of lipoprotein lipase & hepatic lipase, seem to contribute to these alterations. Muls E et al.;1985, In a study in support of this hypothesis, Kutty M K et al.;1978, it was observed that serum cholesterol levels were significantly elevated only in severely hypothyroid patients when compared with controls.

Regmi A et al. (2010) said, overt hypothyroidism has always been associated with hypercholesterolemia, there is much controversy in association of subclinical hypothyroidism and hypercholesterolemia. Deschampheleire M et al.; 1999, In this study, all the parameters of lipid profile i.e., TC, HDL, LDL and TG were found to be increased in subclinical hypothyroidism and the difference was statistically significant. Increase of total cholesterol and LDL can be attributed to the effect of thyroid hormone on expression of LDL receptors and cholesterol 7-alpha

hydroxylase (CYP7A), a rate limiting enzyme in bile acid synthesis. Decreased thyroid function not only increases the number of LDL particles but also promote LDL oxidation, there by increasing the risk of atherosclerosis.

All the hypothyroid cases had normal FPG values (90.65 ± 13.51 mg/dl) [Table 3,6] as per the reference range (70-110 mg/dl), but the mean value was higher as compared to that in the normal euthyroid controls. Despite the normoglycaemiaof the hypothyroid patients, fructosamine was greatly increased in them, which could be due to the decreased turnover of the plasma proteins in hypothyroidism.

The postulations for the abnormally high fructosamine levels in the absence of clinical hyperglycemia in the hypothyroid patients are:-

1. Decreased metabolism leading to decreased turnover of proteins and thus prolonging their half - life.
2. Increased oxidative stress causing increased glycation of proteins.
3. Low grade inflammation adding to the free radical formation and its effects. Raised immunoglobulins in response to inflammation and preferential glycation rates of immunoglobulins.
4. Altered glucose homeostasis with decreased absorption and conversely decreased utilization also associated with hyper insulinemia and insulin resistance probably causing transient elevations in the glucose concentrations thus contributing to glycation of serum proteins.
5. The tendency of glycated proteins to accumulate in tissues resisting easy proteolysis and being further source of free radicals.

In subclinical hypothyroid subjects:-

The lipid derangements which were observed in the overt hypothyroid subjects were replicated in the SCH subjects also, to a similar extent [Table 2]. The fructosamine levels were not as high as those in the hypothyroid group. The above findings were recorded inspite of choosing a low cut off value of 5.6-20 μIU/ml for TSH for the SCH patients. Also, the mean age of the patients was much lower (41.48±10.11) than the older age (> 60) which was reported in other studies (Arrigo T et al.; 2008, Papi G et al.; 2007). In view of the cardiovascular risk which was involved, the SCH patients thus need to be cautiously monitored and if the clinical features suggest, they should be treated as overt hypothyroid cases.

In hyperthyroid subjects:-

There exists a state of hypermetabolism in hyperthyroidism, resulting in increased muscle protein breakdown and enhanced metabolic activities (Brennan M D et al.; 2006, Riis A L et al.; 2005). A reversal of the findings in hypothyroidism can be expected in the hyperthyroid subjects. Surprisingly, the LDL-cholesterol concentration and the LDL/HDL ratio remained elevated as compared to those in the euthyroid controls. The TC and the TG values were also slightly higher, but they were not statistically significant. The HDL-cholesterol levels did not differ in the hyperthyroid and the euthyroid pools. Most of the studies that have compared the cholesterol levels in hypo and hyperthyroidism (Sundaram V et al.; 1997, Diekman M J M et al.; 2000), have reported significantly lower LDL-cholesterol levels in hyperthyroidism as compared to those in the hypothyroid subjects (raised HDL-cholesterol). The thyroid hormone (T_3) is known to affect the LDL-cholesterol levels. The promoter of the LDL receptor gene contains a thyroid hormone responsive element (TRE) and T_3 modulates the gene expression of the LDL-receptor (Shin DJ et al 2003). Accordingly, lower levels of LDL-cholesterol can be expected with raised T_3 levels.

Sundaram V et al. (1997), and Oge A et al. (2004), studied the LDL-cholesterol oxidation in hypo and hyperthyroidism and found that in both the cases, the LDL-cholesterol oxidation was increased as compared to that in the euthyroid cases. They attributed this to the increased generation of free radicals that accompanied the lipid peroxides in hyperthyroidism. Hyperthyroidism is not usually associated with atherosclerosis. The cardiac com-plications are usually arrhythmia or congestive heart failure, which are secondary to the hypermetabolic state (Jayaprasad N et al.; 2005). The aspect of the LDL-cholesterol oxidation in hyperthyroidism and the role of the enhanced LDL-cholesterol oxidation in the cardiac disease process in these patients requires further debate.

In keeping with the prevailing hypermetabolic state and the increased turnover of the proteins, the fructosamine concentrations were found to be significantly lower in the hyperthyroid subjects as against those in the reference control. The FPG levels were higher. These findings were in agreement with the previously reported data on carbohydrate metabolism and the fructosamine levels in hyperthyroidism (Weijers R N et al.; 1990, Ford H C et al.; 1987, Kim H B et al.; 1992). A significant positive association was found between fasting plasma glucose (FPG) and fructosamine ($r = 0.977$, $p < 0.001$). There exists a state of oxidative stress even in hyperthyroidism (Mohan Kumar K M et al.; 2004), which should have raised the possibility of the proteins getting glycated, but the protein turnover must be largely in excess of the probabilities of their glycation.

According to Kim H B et al. (1992), The mean values of FBS and HbAlc in hyperthyroid group are higher than those of normal controls but those of serum albumin and fructosamine in hyperthyroid group are lower than those of normal control with correlation each other. The higher level of FBS and HbAlc in hyperthyroid group compared to normal controls appeared as changes of carbohydrate metabolism. And it was revealed that fructosamine was not

relable indicator of previous serum glucose concentration in hyperthyroidism. That may be originated from the concomitant decreased level of albumin as the greatest fraction of fructosamine.

CONCLUSION

The lipid profile is unfavorably altered in thyroid dysfunction. Dyslipidemia is one of the established risk factor in cardiovascular disease. Therefore, this study indicates that monitoring of lipid in patients with thyroid dysfunction would be helpful in preventing cardiovascular diseases. The fructosamine values which are largely in excess of the FPG and HbA1c values, indicate a higher propensity to glycation and a decrease turnover of the proteins in the overt hypothyroid and the subclinical hypothyroid subjects,vice versa is true of the hyperthyroid subjects.

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