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**INTERNATIONAL JOURNAL OF  
 ADVANCED RESEARCH (IJAR)**

Article DOI:10.21474/IJAR01/5320  
 DOI URL: <http://dx.doi.org/10.21474/IJAR01/5320>



### RESEARCH ARTICLE

#### ESTIMATION OF GLYCATED ALBUMIN, SERUM FRUCTOSAMINE AND LIPID FRACTION IN THE PATIENTS WITH THYROID DISORDER.

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#### Manuscript Info

##### Manuscript History

Received: 03 July 2017  
 Final Accepted: 05 August 2017  
 Published: September 2017

##### Key words:-

glycated albumin, serum fructosamine, lipid profile, thyroid disorders.

#### Abstract

**Background:** Thyroid disorders are the commonest disorders worldwide. Thyroid disorders leads to change in lipoprotein, carbohydrate and protein metabolism. Glycation is the process of non-enzymatic addition of sugar to protein, DNA, and lipids.

**Aim:** To study the lipid and glycemic abnormalities in the patients of overt hypothyroidism, subclinical hypothyroidism and hyperthyroid patients, and compare the same with euthyroid subjects,

**Methodology:** The present was conducted on 300 subjects, of either sex of various age groups. Study included diagnosed thyroid disorder patients (200) attending Medical OPD, patients admitted in medical and surgical wards and patients coming in Radioimmunoassay (RIA) laboratory, Biochemistry Department J.L.N. Medical College & Hospital, Ajmer. The results of patients were compared with the hundred healthy subjects of either sex of similar age group.

The indices included:- Serum Fructosamine assayed by Nitro-Blue Tetrazolium Kinetic Method, Serum Glycated Albumin by Enzyme Linked Immunosorbent Assay, Fasting blood glucose by GOD-POD Method, serum lipid profile was estimated by enzymatic CHOD-POD for total cholesterol. Total Triglyceride by-GPO-PAP method, HDL by CHOD-POD Phosphotungstate Method, LDL cholesterol and VLDL cholesterol were calculated by Freidwald's formula.

**Results:** The mean serum fructosamine and glycated albumin levels were high in hypothyroid patients in comparison to healthy control, vice a versa was found in hyperthyroid patients which was statistically significant. Significant increased in level of total cholesterol, triglycerides, LDL-cholesterol VLDL cholesterol and decreased level of HDL was found in hypothyroid patients. The fasting blood glucose level were high in all the thyroid disorder patients but the results were within the reference range.

**Conclusion:** Present study indicates that monitoring of lipid profile in patients of thyroid dysfunction would be helpful in preventing cardiovascular disease, also serum fructosamine and glycated albumin are better short term markers of glycemic index in the patients of thyroid disorder.

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**Introduction:-**

Thyroid hormones play a key role in the regulation of synthesis, metabolism and mobilization of lipid, carbohydrates and protein. Thyroid diseases are medical conditions impairing the functions of the thyroid gland. Imbalance in production of thyroid hormone arises from dysfunction of the thyroid gland itself or pituitary gland, which produces the thyroid stimulating hormone (TSH), which is regulated by thyrotropin-releasing hormone produced by the hypothalamus. The concentration of TSH increases with age, requiring age related correction. (M.I. Surk's et al; 2007).

Hypothyroidism and hyperthyroidism are the two principal pathological conditions that involve the thyroid gland. Other thyroid disorders include Subclinical hypothyroidism and Overt hypothyroidism, etc (Komorica E et al.; 2012). Hypothyroidism is defined as deficiency of thyroid hormone secretion and action. Common causes are autoimmune disorders like Hashimoto thyroiditis, iodine deficiency, removal thyroid gland etc. Subclinical hypothyroidism is defined as asymptomatic state, characterized by normal concentration of T<sub>4</sub> and T<sub>3</sub> and elevated level of thyroid stimulating hormone.

Overt hypothyroidism is defined as clinical syndrome of hypothyroidism associated with elevated TSH level (thyroid stimulating hormone) and decreased serum levels of T<sub>3</sub> and T<sub>4</sub>. Hyperthyroidism is defined as a hypermetabolic state caused by excessive production of thyroid hormones. Some clinicians prefer the term "thyrotoxicosis". Common causes are Grave's disease, Hashimotothyroiditis toxic nodule etc. Hyperthyroidism exhibits an enhanced excretion of cholesterol and an increased turnover of low density lipoprotein-cholesterol (LDL-C), resulting in a decrease in the total cholesterol and LDL-C levels and in raised high density lipoprotein-cholesterol (HDL-C) levels.

Fructosamine (FA) is glycated protein, the generic name for plasma proteins ketoamines. It is formed by a spontaneous on-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 (Johnson et al :1999). Serum Fructosamine, glycated albumin is generally used for assessing the glycemic changes in diabetics over a 2-3 week period. When the fructosamine and glycated albumin values were compared between the hypothyroid and the hyperthyroid patients, it was found that the fructosamine and glycated albumin levels 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 (Hara et al:1990). Studies correlating various glycemic parameters in thyroid disorders were not diagnostically significant. So the present study was conducted to monitor the serum fructosamine level, glycated albumin level in thyroid disorder patients as diagnostic marker to measure the short term glycemic index, also to measure the level of lipid profile in the thyroid disorder patients.

**Material & Method:-**

The present study was conducted on 200 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 100 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=100). 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=70). It included the clinically established patients of hypothyroidism. GROUP III: Subclinical Hyperthyroid patients (n=60). It included the clinically established patients of sub clinical hypothyroidism. GROUP-IV: Hyperthyroid patients (n=70). It included the clinically established patients of hyperthyroidism. The fasting lipid profile [ Total cholesterol (TC), Triglycerides (TG), HDL-C, LDL-C, very low density lipoprotein-cholesterol (VLDL-C), the thyroid profile ( Total T<sub>3</sub>, T<sub>4</sub> and TSH) and the glycemic profile which consisted of FPG, serum fructosamine and Glycated albumin were calculated in all the groups. Clinically diagnosed cases of hypo and hyperthyroid disorder were taken. 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 serum lipid profile was estimated by the enzymatic CHOD-POD method for TC {3}, GPO-POD method for TG {9} and by the CHOD-POD/ Phosphotungstate method for

HDL-cholesterol [8]. These estimations were carried out by using semi automated analyzer. LDL-Cholesterol and VLDL-Cholesterol were calculated by Friedwald's formula. FPG was estimated by the GOD-POD method, HbA1c was estimated by the ion-exchange resin method and Serum Fructosamine was estimated by the NBT reduction method [5], Glycated albumin by enzyme linked immunosorbent assay. The results were expressed as mean  $\pm$  standard deviation (SD). P-value <0.05 was considered statistically significant.

**Study design:** Perspective, case control study.

#### Observation:-

**Table 1:-** Glycemic Profile in Subject Studied

Test	Euthyroid Subjects	Overt hypothyroid	Sub-clinical hypothyroid	Hyperthyroid
FBG (mg/dl)	84.24 $\pm$ 11.23	90.65 $\pm$ 13.51	87.80 $\pm$ 13.14	92.36 $\pm$ 12.2
HbA1C%	5.03 $\pm$ 0.53	6.0 $\pm$ 0.58	5.3 $\pm$ 0.56	5.12 $\pm$ 0.43
Fructosamine ( $\mu$ mol/l)	260.70 $\pm$ 76.06	581 $\pm$ 51.11	372 $\pm$ 43.94	162 $\pm$ 23.46
Glycated albumin (%)	14.1 $\pm$ 1.4	20 $\pm$ 2.5	18 $\pm$ 2.0	11 $\pm$ 2.0

Serum fructosamine levels were low in the hyperthyroid patients against the control group (162 $\pm$ 23.46 V/s 260.70  $\pm$  26.06) (p< 0.001 (H.S.)). Whereas the fasting plasma glucose levels were higher 92.31 $\pm$ 12.2 in comparison to euthyroid subjects. Significant positive correlation was found between the FPG and fructosamine level (r = 0.977, p < 0.001). Glycated albumin levels were significantly high in the overt hypothyroid patients (20 $\pm$ 2.5) and subclinical hypothyroid patients in comparison to euthyroid subjects (14 $\pm$ 1.4) (p value was < 0.001).

**Table 2:-** Lipid profile in subjects studied

Test	Euthyroid	Overt hypothyroid	Subclinical hypothyroid	Hyperthyroid
TC (mg/dl)	184.7 $\pm$ 14.70	254.74 $\pm$ 13.04	249.46 $\pm$ 11.71	193.72 $\pm$ 13.11
TG(mg/dl)	117.12 $\pm$ 21.55	162 $\pm$ 11.33	155.93 $\pm$ 15.15	129.02 $\pm$ 15.18
HDL(mg/dl)	45.98 $\pm$ 11.33	42.54 $\pm$ 8.10	43 $\pm$ 7.89	46.65 $\pm$ 11.61
VLDL(mg/dl)	23.42 $\pm$ 4.31	32.55 $\pm$ 3.39	31.18 $\pm$ 3.02	174.58 $\pm$ 14.05
LDL(mg/dl)	115 $\pm$ 6.50	179.65 $\pm$ 21.55	174.58 $\pm$ 14.05	121.27 $\pm$ 17.53

TC- total cholesterol: TG –triglyceride: VLDL- very low density protein.

#### Results:-

The present study was conducted on 300 patients of various age group. These were further divided into four groups. Group I-comprised 100 euthyroid subjects. Group II-70 overt hypothyroid subjects, Group III-60 subclinical hypothyroid patients, Group IV -70 hyperthyroid subjects.

The mean serum fructosamine levels were higher in overt hypothyroid (581.65 $\pm$ 51.11) and subclinical hypothyroid (372.93 $\pm$ 43.94) patients in comparison to euthyroid subjects (260.70 $\pm$ 20.06), vice a versa was found in the hyperthyroid patients which was highly significant(table1). Serum fructosamine levels were highly significant (P<0.001) and correlated among the different groups of thyroid disorders.

Mean glycated albumin levels were higher in overt hypothyroid patients and subclinical hypothyroid patients 18.0 $\pm$ 2.0, in comparison to euthyroid subjects and vice a versa was found in hyperthyroid patients where it was significantly low 11 $\pm$ 2.0 in comparison to euthyroid patients 14 $\pm$ 1.4 as shown in Table 1.

The postulation put forward for the abnormally high fructosamine and glycated albumin levels in absence of clinical hypoglycemia in hypothyroid patients are:

Deterioration of protein metabolism which further decreases turnover of proteins and increase of half life of protein, Increase in glycation of protein via auto oxidative glycation in case of oxidative stress Increase in protein carbonylation, serum malondialdehyde and decreased glutathione level in hypothyroid cases explains increased peroxidation of lipids this might be a contributing factor for increased radical mediated protein glycation, Low grade inflammation and free radical formation causes manifold increase in immunoglobulin, production this explains glycation of these immunoglobulin. Disturbance in glucose homeostasis with decreased glucose absorption and

utilization leads to insulin resistance, this further causes glycation of protein. The tendency of glycated proteins to accumulate in tissues, resisting easy proteolysis are further source of free radicals.

Above findings were similar to the data reported by Kondaveti. S. et al. (2014). Thyroid hormone promotes albumin metabolism. Hyperthyroidism is a hypermetabolic state and there is increased turnover of proteins but, in hypothyroidism albumin metabolism is prolonged. Glycated albumin levels decrease in the patients with nephrotic syndrome, which shortens the half life of serum albumin and increases in the patients with liver cirrhosis, which prolongs the half life of serum albumin. In present study it was found that mean HbA<sub>1c</sub> level was slightly raised in overt hypothyroid and subclinical hypothyroid patients in comparison to euthyroid subject and vice versa was found in hyperthyroid patients but the levels were within the normal range as diabetic patients were excluded. Mean fasting glucose levels were found to be slightly higher in thyroid disorder compared to euthyroid subjects (70-110mg/dl) but difference was not found to be statistically significant (Table 1).

Table 2 shows a significant increase in the level of total cholesterol (254.74±13.04), triglyceride (162.75±19.67), and decreased level of HDL (42.54±8.10) VLDL (32.55±3.39) LDL (179.65±21.55) was observed in overt hypothyroid patients in comparison to the euthyroid subjects. Similar results were found in subclinical hypothyroid patients and vice versa was found in the hyperthyroid patients.

### Discussion:-

A comparative study of various biochemical parameter like serum fructosamine, glycated albumin, glycated haemoglobin, lipid fraction was carried out. Keeping in mind that thyroid hormone affects protein and carbohydrate metabolism so, in hyperthyroidism there was increase in protein turnover as Hyperthyroidism is a hypermetabolic state but, in hypothyroidism albumin metabolism is prolonged. Serum fructosamine, glycated albumin, levels were increased in hypothyroidism and decreased in hyperthyroidism. FBG were high in hyperthyroidism and low in hypothyroidism. These findings were in agreement with the previously reported data on carbohydrate metabolism. A significant positive association was found between FBG level FA level ( $p < 0.001$ ) which is highly significant.

R. Rangaswamy et al. (2013) concluded that, serum fructosamine values were found to be significantly correlated among the different group of thyroid disorders ( $P = 0.001$ ). In thyroid disorder, the sensitivity, specificity, PPV, NPV in hypothyroidism is 100%, 96.4%, 100%, 100% and hyperthyroidism is 75%, 92.9%, 42.6% and 100% respectively. Albumin values negatively correlated with hypothyroidism which was statistically significant. Significant correlation was found between T<sub>3</sub>, T<sub>4</sub>, TSH and fructosamine levels. It was concluded that it is useful to consider serum fructosamine as diagnostic indicator in patients with thyroid disease.

All the hypothyroid cases had normal FPG values (90.65 ± 13.51 mg/dl) 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 normoglycaemia of the hypothyroid patients, fructosamine was greatly increased in them, which could be due to the decreased turnover of the plasma proteins in hypothyroidism.

According to Kim H B et al. (1992), The mean values of FBS and HbA<sub>1c</sub> 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 HbA<sub>1c</sub> in hyperthyroid group compared to normal controls appeared as changes of carbohydrate metabolism. And it was revealed that fructosamine was not reliable 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.

In overt hypothyroid subjects:- 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, Agedepa D et al 1979.; Staub J J et al.; 1992, Abrams J J et al.; 1981, In hypothyroid patients, despite the reduced activity of  $\beta$ -hydroxy  $\beta$  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. {Deschamphelire 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, thereby increasing the risk of atherosclerosis.

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  $\mu$ U/ml for TSH for the SCH patients. Also, the mean age of the patients was much lower ( $41.48 \pm 10.11$ ) 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.

### Conclusion:-

The Serum fructosamine and glycated albumin levels values were 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. So it is better short term glycemic marker in the patients of thyroids disorder.

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 fraction in patients with thyroid dysfunction would be helpful in preventing cardiovascular diseases.

### Acknowledgement:-

I am highly indebted to the staff & my colleagues who helped me to accomplish my project.

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