NJPPP National Journal of Physiology, Pharmacy & Pharmacology

DOI: 10.5455/njppp.2015.5.290720141
http://www.njppp.com/

RESEARCH ARTICLE

BIOCHEMICAL ROLE OF SERUM FRUCTOSAMINE IN PATIENTS WITH THYROID DISORDERS

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Received
14.07.2014
Accepted
29.07.2014

Key Words
Thyroid; Hypothyroid, Hyperthyroid; Fructosamine

Background: Fructosamine (FA) is the product of a reaction between glucose (sugar) and albumin (protein). It is used to monitor the short-term glycemic changes in patients with diabetes and may have a role in conjugation with glycated hemoglobin.
Aims & Objective: Fructosamine test is used to evaluate the average amount of glucose in blood over a period of 2–3 weeks. FA is a useful indicator to measure the peripheral metabolic function in patients with thyroid disorders. As serum thyroid function tests, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum FA ratios occupied our attention, their inconsistency in the subjects with subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism in relation to the euthyroid healthy control subjects was studied here.
Materials and Methods: This study was conducted on 100 patients with overt hypothyroidism, subclinical hypothyroidism, and hyperthyroidism attending the medical OPD and radioimmunoassay laboratory of the Department of Biochemistry, Jawaharlal Nehru Medical College and Hospital, Ajmer, Rajasthan, India.
Results: The mean glycated hemoglobin level was higher in study group than in controls, and it was not statistically significant. The mean serum FA level was higher in patients with overt hypothyroidism and subclinical hyperthyroidism and lower in those with hyperthyroidism than that in controls. It was found to be highly statistically significant.
Conclusion: The FA values, which are largely higher than FPG and HbA1c values, indicate a higher propensity to glycation and a decrease turnover of the proteins in the patients with overt hypothyroidism and subclinical hypothyroidism; contrary results were observed in individuals with hyperthyroidism.

INTRODUCTION

Glycosylated hemoglobin or hemoglobin A1c (HbA1c) is a widely used glycemic marker and it evaluation is considered as the primary technique to assess glycemic control, along with self-monitoring of blood glucose, by the American Diabetes Association (ADA). Fructosamine (FA) is a generic name given to a compound known as plasma protein ketoamines.[1] It is formed by a spontaneous non-enzymatic reaction between a carbonyl group of a glucose molecule with an amino group of a protein.[2] In blood, FA is primarily glycated albumin, as it is the most abundant protein present. It is also known as glycated serum proteins or glycated albumin, and is used to monitor the plasma glucose concentration over a shorter period (usually 2–3 weeks) to assess diabetes management.[3]

The physiological role of fructosamine 3-kinase has been investigated by incubating human erythrocytes in the presence of the high concentrations of glucose and of a specific inhibitor of this enzyme.[4] It converts glycated hemoglobin to a form of hemoglobin with alkali-labile phosphate, presumably corresponding to fructosamine 3-phosphate residues. This phosphorylation step triggers the spontaneous decomposition of fructosamine 3-phosphate residues to free amine, inorganic phosphate, and 3-deoxyglucosone, which can be oxidized to 2-keto-3-deoxygluconate in the red blood cells. Fructosamine 3-kinase thus initiates a mechanism of protein deglycation in human erythrocytes.[1,5]

Abnormal protein turnover influences FA values, as in thyroid disease (i.e., in patients with thyrotoxicosis and hypothyroidism, in whom protein turnover is increased and decreased, respectively).[6,7] Elevated FA levels could be due to a decreased protein turnover, which thus prolongs the half-life of the proteins. FA is a useful indicator to measure the peripheral metabolic function in patients with thyroid disorders.

The functions of thyroid gland are dependent on the availability of iodine, integrity of the hypothalamus–pituitary axis, and well-developed, functioning thyroid follicular cells.[8] Physiological changes (pregnancy), pathological changes (protein deficiency), and medication (oral contraceptives) alter the levels of thyroid hormones and result in various thyroid disorders.[9]

Diseases of the thyroid gland almost always manifest themselves through symptom resulting due to either excessive or insufficient production of thyroid hormone.[10] The thyroid disease is established on the clinical grounds, and the functional disturbance is assessed by the metabolic state.[11] The functional diagnosis of thyroid disease is based on a carefully taken history, a thorough search for the physical signs of hypothyroidism or hyperthyroidism, and an elegant appraisal of the results of the laboratory tests.[12] The most common cause of hypothyroidism is autoimmune (Hashimoto's) thyroiditis.

Other causes include iodine deficiency and iatrogenic (postsurgical/ radiation/ drug therapies).[13] Autoimmune thyroiditis involves lymphocytic infiltration of the thyroid with production of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies. Autoimmune thyroiditis is associated with other autoimmune conditions including type 1 diabetes mellitus and vitiligo. It is predominant in females.[14] Galactorrhea and amenorrhea occur because of low levels of T_3/T_4 fail to inhibit the hypothalamus, which secretes high levels of thyrotropin-releasing hormone. This stimulates the pituitary to release more prolactin.[15,16] The most common cause of hyperthyroidism is Graves' disease, which is an autoimmune disease in which thyroid-stimulating immunoglobulins bind and activate the thyroid-stimulating hormone (TSH) receptor on thyrocytes. It occurs mostly in 15–35 years old females.[17]

Removing the thyroid gland to correct the hormone imbalance does not correct Graves' ophthalmopathy or myxedema.[13,17] In view of aforementioned controversial findings, we were aimed to evaluate the FA level in patients with hypo- and hyperthyroid disorders.

MATERIALS AND METHODS

This study was conducted on 100 patients with overt hypothyroid, subclinical hypothyroid, and hyperthyroid disorders attending the medical OPD and radioimmunoassay (RIA) laboratory of the Department of Biochemistry, Jawaharlal Nehru Medical College and Hospital, Ajmer, Rajasthan, India. The selected subjects were further grouped as:

- **Group I:** It consisted of healthy control (euthyroid) subjects (n = 50). By routine examinations, we ensured that all the subjects were healthy and there were no signs and symptoms or history of thyroid abnormalities.
- **Group II:** It consisted of patients with overt hypothyroidism (n = 35). It included the patients with the clinically established hypothyroidism.
- **Group III:** It consisted of patients with subclinical hyperthyroidism (n = 30). It included the patients with established subclinical hypothyroidism.
- **Group IV:** It consisted of patients with hyperthyroidism (n = 35). It included the patients with clinically established hyperthyroidism.

Exclusion Criteria: Patients undergoing treatment for any thyroid disorders, patients taking lipid-lowering drugs, patients with diabetes, patients with malignancy, and pregnant women were excluded.

Collection and Analysis of Blood Samples: Informed consent was obtained from all subjects for participating in the study. Blood samples were collected by venipuncture using an aseptic technique. The serum separated from the samples was analyzed for following biochemical parameters.

Blood samples were analyzed for: Blood glucose fasting by using enzymatic glucose oxidase–horseradish peroxidase-based end-point method. HbA1c was determined by ion-exchange resin method.

Serum separated from the samples was analyzed for: Thyroid function tests (T_3, T_4, and TSH) by RIA method. Fructosamine test was conducted using nitroblue tetrazolium method.

RESULTS

In this study thyroid profile (T3, T4, and TSH) and glycemic profile (fasting plasma glucose, HbA1c, serum FA) were analyzed in patients with subclinical hypothyroid, overt hypothyroid and hyperthyroid disorders and compared with normal healthy control (euthyroid) subjects. The mean ages of euthyroid, subjects with overt hypothyroidism, subclinical hypothyroidism, and the hyperthyroidism was 35.0 ± 7.30, 40.51 ± 09.13, 41.48 ±10.11, and 41.16 ± 08.54, respectively.

Table 1: Distribution of the subjects studied in relation to sex

Group Studied	No. of Subjects		Total
	Male	Female	
Euthyroid	20	30	50
Overt hypothyroid	10	25	35
Subclinical hypothyroid	13	17	30
Hyperthyroid	10	25	35
Total	53	97	150

Table 2: Mean age (years) of the subjects studied

Group Studied	Age (Mean ± SD)
Euthyroid	35.00 ± 7.30
Overt hypothyroid	40.51 ± 9.13
Subclinical hypothyroid	41.48 ± 10.11
Hyperthyroid	41.16 ± 8.54

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	>0.05 (NS)
HbA1c (%)	5.03 ± 0.53	6.0 ± 0.58	0.61	>0.05 (NS)
Fructosamine (µmol/l)	260.70 ± 26.06	581.65 ± 51.11	15.81	<0.001 (HS)

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HS, highly significant; S, significant; NS, not significant

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	>0.05 (NS)
HbA1c (%)	5.03 ± 0.53	5.31 ± 0.56	0.52	>0.05 (NS)
Fructosamine (µmol/l)	260.70 ± 26.06	372.93 ± 43.94	10.13	<0.001 (HS)

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HS, highly significant; S, significant; NS, not significant

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	>0.05 (NS)
HbA1c (%)	5.03 ± 0.53	5.15 ± 0.45	0.47	>0.05 (NS)
Fructosamine (µmol/l)	260.70 ± 26.06	162.97 ± 23.46	3.88	<0.001 (HS)

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HS, highly significant; S, significant; NS, not significant

Table 6: Glycemic profile in the subjects studied

Tests	Euthyroid	Overt Hypothyroid	Subclinical Hypothyroid	Hyper-thyroid
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

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c

DISCUSSION

For all subjects, a comparative study of various biochemical parameters was carried out. In keeping with the prevailing hypermetabolic state and increased turnover of the proteins, the FA concentrations were found to be significantly lower in the subjects with hyperthyroidism as against those in the control group. The fasting plasma glucose (FPG) levels were higher. These findings were in agreement with the previously reported data on carbohydrate metabolism and FA levels in hyperthyroidism.[4,6] A significant positive association was found between FPG and FA levels ($r = 0.977$, $p < 0.001$). There exists a state of oxidative stress even in hyperthyroidism, 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 *et al*.,[6] the mean values of fasting blood sugar (FBS) and HbA1c in hyperthyroid group are found to be higher than those in normal controls, but mean values of serum albumin and FA in hyperthyroid group are found to be lower than those in normal controls, with correlation each other. The higher levels of FBS and HbA1c in hyperthyroid group compared to normal controls were due to changes in carbohydrate metabolism. It was revealed that FA was not a reliable indicator of previous serum glucose concentration in hyperthyroidism, which might have originated from the concomitant decreased level of albumin as the greatest fraction of FA.

CONCLUSION

The FA 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 subjects with overt hypothyroidism and the subclinical hypothyroidism; the contrary is true about the subjects with hyperthyroidism.

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Cite this article as: Soni N, Sharma N, Kaushik GG. Biochemical role of serum fructosamine in patients with thyroid disorders. Natl J Physiol Pharm Pharmacol 2015;5:50-53.
Source of Support: Nil
Conflict of interest: None declared