



ORIGINAL RESEARCH PAPER

Medicine

EVALUATION OF GLYCOSYLATED HEMOGLOBIN (HBA1C) LEVELS IN HYPOTHYROID AND HYPERTHYROID PATENTS

KEY WORDS:

Dr.Pankaj Mohan Shrivastava*

Assistant Professor, Department of Medicine, Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga, Bihar.*Corresponding Author

Dr.(Prof.) K.K. Singh

Professor and Head, Department of Medicine, Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga, Bihar.

ABSTRACT

INTRODUCTION: Almost one-third of the world's population lives in areas of iodine deficiency. Thyroid hormone action has long been recognized as an important determinant of glucose homeostasis. Diabetes and thyroid disorders have a propensity to appear together in patients

OBJECTIVES: To compare and correlate the glycosylated Hb levels and TSH levels in non diabetic patients.

METHODOLOGY: The cross sectional study was conducted among 30 patients of diagnosed thyroid disorders. The biochemical parameters were Hemoglobin, TLC, glycemic control (fasting and post prandial blood glucose levels, glycated haemoglobin A1c), blood urea, serum creatinine and a thyroid profile (TSH, T3, and T4). These parameters were measured and compared with the normal population.

RESULTS: Out of 30 patients 26 were diagnosed as hypothyroid and 4 were diagnosed as hyperthyroid. HbA1c levels were found to be elevated in patients of thyroid disorders (hypothyroidism and hyperthyroidism) as compared to control.

CONCLUSION: Based on this study all the thyroid patients especially hyperthyroid patients should have regular checkup of their glucose levels. Patients should have adequate treatment of the thyroid disorders and thus should prevent themselves from adverse effects of hyperglycemia

INTRODUCTION

Almost one-third of the world's population lives in areas of iodine deficiency. The prevalence of goitre in areas of severe iodine deficiency can be as high as 80%. In iodine-replete areas, most persons with thyroid disorders have autoimmune disease, ranging from primary atrophic hypothyroidism, Hashimoto's thyroiditis to thyrotoxicosis caused by Graves' disease.[1] Thyroid hormone action has long been recognized as an important determinant of glucose homeostasis[2] The role of hyperthyroidism in diabetes was investigated in 1927, by Coller and Huggins proving the association of hyperthyroidism and worsening of diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients suffering from coexisting diabetes[3] 5 adenosine monophosphate-activated protein kinase (AMPK) is a central target for modulation of insulin sensitivity and feedback of thyroid hormones associated with appetite and energy expenditure[4] In hypothyroidism, there is a reduction in glucose-induced insulin secretion by beta cells, and the response of beta cells to glucose or catecholamine is increased in hyperthyroidism due to increased beta cell mass. Moreover, insulin clearance is increased in thyrotoxicosis[5] Possibly, thence, diabetes and thyroid disorders have a propensity to appear together in patients[6]

HbA1C is widely used for the assessment of glycemic status of the diabetic patients and the American Diabetes Association (ADA) recommended its use for diagnosing diabetes[7]. The glycated hemoglobin represents the fraction of hemoglobin that undergoes non-enzymatic glycation over the circulatory life span of the erythrocytes (usually 120 days)[8]

A positive association between thyroid and diabetes mellitus is well recognized but to study the effect of thyroid disorders on glucose metabolism in non diabetic patients (ie patients diagnosed with only thyroid and not diabetes) is an area for extensive research. Our present study was planned to assess correlation between thyroid disorders and non diabetic patients and find out if any association exists between glycosylated haemoglobin levels with those of thyroid hormones in non diabetic patients

Materials and Methods

The cross sectional study was conducted among 30 patients of diagnosed thyroid disorders in the department of medicine at Darbhanga Medical College & Hospital, Laheriasarai, Bihar. The patients who presented with clinical symptoms of thyroid

disorders were followed up and were subsequently diagnosed based on the laboratory findings. The duration of study was 6 months.

30 patients who tested negative for thyroid disorders and who were not using any type of medication, with no mental or physical mutilation and no history of chronic disease were taken as control for the study. Those who agreed to participate were asked to sign a written informed consent form after assurance with regards to confidentiality provided to them. Permission and clearance was taken from the institutional ethics committee.

Inclusion Criteria

1. Patient who presented with symptoms of thyroid disorders and were diagnosed with a specific thyroid disorder.
2. Patient with FBS within the normal range
3. Patients who consent to the participation.

Exclusion Criteria

1. Patient with previously diagnosed thyroid disorder and were on a specific medication
2. Patients with frank diabetes mellitus.
3. Total/subtotal thyroidectomy
4. Patients on I131 treatment, lithium, antithyroid drugs.
5. Radiation exposure
6. Gestational hyperthyroidism
7. Chronic renal failure
8. Abnormal haemoglobinopathy,
9. Hemolytic disorder
10. Recent (< 3 months) blood transfusion

Study Method

All patients were subjected to routine investigations such as:-

1. Hb -- Acid hematin method using sahli's haemoglobinometer
2. TLC -- Thoma zeiss haemocytometer
3. Blood sugar -- Asatoor and king method, 1954
4. Serum Creatinine -- Method of broad and sirota
5. Blood Urea -- Diacetyl monoxime method(DAM)

Special investigations: Glycosylated haemoglobin (Reference range: Non-diabetic—4.5-8.0% , Good control—8.0-9.0%, Fair control—9.0-10.0%, Poor control-- >10.0%) was analysed using commercially available Infinite Glycosylated hemoglobin kits(ACCUREX biomedical private Ltd. Mumbai, India). TSH(reference range 0.44 - 3.45 (microIU/ml)), T3(reference range: 0.49 – 2.02

ng/ml), T4(reference range: 4.7 -12.8(microgram/dl)) estimation was done using ERBA kits (immunoenzymometric assay)

Data analysis

Data was recorded on a pre designed proforma and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond,WA)All data was analyzed using statistical program SPSS package (Chicago, Illinois). t-test, chi square and pearson's correlation were applied with significance levels at 95% CI and p < 0.05 accordingly.

Results

The age in the experimental group varied from 21- 65 with mean age of 42.7 ± 11.05 and that of control varied from 21-64 with a mean of 42.77±10.72 with no significant difference between the two groups(p>0.05). Age and sex distribution of patients are shown in Table 1 and 2.

The various parameters of routine tests were within normal limits and were non significantly different between the study group and control group.

Out of 30 patients 26 were diagnosed as hypothyroid and 4 were diagnosed as hyperthyroid. The comparison of mean levels of serum T3, T4 and TSH between hypothyroid v/s control and hyperthyroid v/s control is given in table 3 and 4 respectively.

TABLE 1: AGE DISTRIBUTION OF STUDY AND CONTROL GROUPS

AGE IN YEARS	STUDY GROUP	CONTROL GROUP
21-30	4	2
31-40	10	11
41-50	10	11
51-60	3	4
61-70	2	3
TOTAL	30	30

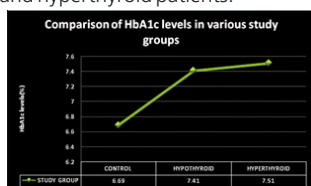
TABLE 2: DISTRIBUTION OF STUDY AND CONTROL

SEX	STUDY GROUP		CONTROL GROUP	
	No. of cases	%age	No. of cases	%age
MALE	4	13.33	4	13.33
FEMALE	26	86.67	26	86.67
TOTAL	30	100	30	100

HbA1c levels in hypothyroid patients were found to be in a range of 7.2-7.79% with a mean of 7.41±0.15% against the range of 5.89-7.2% with the mean of 6.69±0.34% in controls. The difference was found to be highly significant (p<0.001). the HbA1c levels in hyperthyroid patients were found to be in a range of 7.23-7.89% with a mean of 7.51±0.23%, which was significantly(p<0.001) greater than the controls.

Graphical relation between the levels of HbA1c is shown in Graph 1.

Table 5 shows correlation between values of TSH and HbA1c levels in hypothyroid and hyperthyroid patients.



DISCUSSION

As Johnson et al. said, "The thyroid hormones, tri-iodothyronine

and tetra- iodothyronine, are insulin antagonists that also potentiate the action of insulin indirectly." [9]

Thyroid hormones exert both insulin agonistic and antagonistic actions in different organs. However, this occurs in a fine balance necessary for normal glucose metabolism. Deficit or excess of thyroid hormones can break this equilibrium leading to alterations of carbohydrate metabolism[10]

Our study showed significant increase in HbA1c levels in hypothyroid and hyperthyroid patients when compared to controls.

Hypothyroidism

Two theories have been put forward to explain the increased levels of Hba1c levels in hypothyroid patients.

One of those theories blames dysglycemia to be the cause of increased HbA1c levels. Various reasons have been put forward to explain the dysglycemia caused in hypothyroidism.

1. 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[11]
2. Thyroid hormones have been shown to exert some of their actions synergically with insulin. The upregulation of the expression of genes such as GLUT-4 or phosphoglycerate kinase (PGK), involved in glucose transport and glycolysis respectively, is a good proof of concept. Therefore in hypothyroidism insulin resistance in peripheral tissue is present.

Insulin resistance is the cause of increased glucose levels in hypothyroid levels.[12,13]

At the cellular level, thyroid hormones can also increase mitochondrial biogenesis, fatty acid oxidation, and TCA cycle activity . These findings are quite relevant since the role of mitochondrial dysfunction, leading to cellular lipid excess and impaired oxidative metabolism, has been clearly demonstrated in the pathogenesis of type 2 diabetes. Furthermore, it has been described that in skeletal muscle, the lack of thyroid hormones might dysregulate mitochondrial gene expression. PPAR gamma coactivator-1 alpha (PGC-1 alpha), a key transcriptional regulator of mitochondrial content and function, fatty acid oxidation, and gluconeogenesis, has been involved in the process whereby thyroid hormones regulate mitochondrial function . It has been shown that PGC-1 alpha gene expression is increased by T3, as much as 13-fold 6 hours after T3 treatment . The regulation pattern of T3 on PGC-1 alpha is complex and may occur through nongenomic activation of kinases to induce the expression of PGC-1 alpha or through transcriptional upregulation via the presence of a thyroid responsive element (TRE) in the PGC-1 alpha promoter or by genomic upregulation of a transcription factor (via a TRE), which then binds to the PGC-1 alpha promoter and increases PGC-1 alpha transcription. It is hypothesized that PGC-1 alpha can be dysregulated by reduced T3 levels, thus contributing to insulin resistance.[10]

Other theory cites different other causes for increased HbA1c levels in patients of hypothyroidism.

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. The tendency of glycated proteins to accumulate in tissues resisting easy proteolysis and being further source of free radicals.[11]
5. data suggest that thyroid hormone replacement is associated with a decrease in A1C level, which is influenced by increased erythropoiesis rather than by changes in glucose level[8, 14]

Theories almost go against each other in explaining the reason behind increased HbA1c levels in hypothyroid patients. In present study either of the theories can be applicable but anemia was excluded by comparable levels between controls and test patients. Patients with Chronic renal failure were also excluded to remove the effects of Erythropoietin. All patients with any hemoglobin disorders were also excluded to narrow the basis of results. There are a number of factors which play a role in increasing the HbA1c levels and it is difficult to differentiate the causative factors of increase in HbA1c.

This elevation of HbA1c was also demonstrated in a study of 45 hypothyroid patients in which HbA1c was higher than that in control subjects (5.54± 0.43% vs. 5.34±0.31% in hypothyroid patients and controls respectively; p < 0.001)[14]

Another study by Christy et al selected 30 hypothyroid, non diabetic patients with normocytic normochromic anemia and compared these patients with 30 euthyroid non diabetic patients also with normocytic normochromic anemia. HbA1c in the hypothyroid patients was 6.32 ±0.75vs. 5.87±0.46% in the euthyroid group, the difference being statistically significant.[15] The correlation which was seen in this study was also shown by another study which significantly correlated TSH and HbA1c (r =0.46, p<0.05)[16]

Hyperthyroidism

According to Kim H B et al. (1992), The mean values of FBS and HbA1c in hyperthyroid group are higher than those of normal controls. The higher level of FBS and HbA1c in hyperthyroid group compared to normal controls appeared as changes of carbohydrate metabolism.[17]

Permissive influence of T3 is seen in the glycogenolytic and gluconeogenic effects of epinephrine and glucagon. Other hepatic gluconeogenic enzymes that have been found to be positively regulated by thyroid hormones include phosphoenolpyruvate carboxykinase (PEPCK), the enzyme that catalyzes the rate-controlling step of gluconeogenesis [18]

Another mechanism, whereby thyroid hormones are known to increase hepatic glucose output, is through increased hepatic expression of the glucose transporter GLUT2[19]

In another study significant (p = 0.002) increase in the mean value for hemoglobin A1C were found in the hyperthyroid group which is similar to the finding in our study[20]

In another study similar findings were found where HbA1c levels were significantly higher in hyperthyroid group when compared to hypothyroid and euthyroid groups (p<0.001)[21]

Conclusion

From the present study it is concluded that HbA1c levels are increased in both hypothyroid and hyperthyroid patients. Both the disorders have increased levels of HbA1c due to differential actions of thyroid hormones on liver, skeletal muscles and adipose tissue. However many of these actions are complex and based on gene expression changes brought about by thyroid hormones. However an imbalance between the two created by abnormal levels of thyroid lead to a state of hyperglycemia in both conditions.

Based on this study all the thyroid patients especially hyperthyroid patients should have regular checkup of their glucose levels. Patients should have adequate treatment of the thyroid disorders and thus should prevent themselves from adverse effects of hyperglycemia. This study certainly proves the existence of a term called "thyroid diabetes."

TABLE 4: COMPARISON OF MEAN LEVELS OF SERUM T3,T4 AND TSH IN HYPERTHYROID AND CONTROL GROUP

HORMONE	GROUP	NO OF PATIENTS	RANGE	MEAN±SD	t	p	s
T3(ng/ml)	Hyperthyroid	4	2.13-2.67	2.38±0.25	4.32	<0.001	HS
	Control	30	0.54-2.01	1.56±0.38			
T4(microg/dl)	Hyperthyroid	4	15.5-19.97	17.92±1.89	14.78	<0.001	HS
	Control	30	6.2-10.66	8.16±1.14			
TSH(microU/ml)	Hyperthyroid	4	0.03-0.31	0.12±0.13	6.97	<0.001	HS
	Control	30	1.0-3.32	2.21±0.59			

TABLE 5: CORRELATION BETWEEN TSH AND HbA1c IN HYPOTHYROID AND HYPERTHYROID PATIENTS

PARAMETER	r VALUE	p VALUE	SIGNIFICANCE
HbA1c AND TSH (HYPOTHYROID)	0.51	<0.001	HS
HbA1c AND TSH (HYPERTHYROID)	-0.76	<0.001	HS

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TABLE 3: COMPARISON OF MEAN LEVELS OF SERUM T3,T4 AND TSH IN HYPOTHYROID AND CONTROL GROUP

HORMONE	GROUP	NO OF PATIENTS	RANGE	MEAN±S D	T	p	s
T3(ng/ml)	HYPOTHYROID	26	0.12-1.71	1.01±0.34	14.78	<0.001	HS
	CONTROL	30	0.54-2.01	1.56±0.38			
T4(microg/dl)	HYPOTHYROID	26	6.0-8.81	7.05±1.05	3.72	<0.001	HS
	CONTROL	30	6.2-10.66	8.16±1.14			
TSH(microU/ml)	HYPOTHYROID	26	5.0-27.38	7.79±4.42	-6.89	<0.001	HS
	CONTROL	30	1.0-3.32	2.21±0.59			