Importance of Glycated Hemoglobin in Patients with Altered Thyroid Status

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Abstract: Background: Thyroid hormones have an essential role in metabolism and proliferation of blood cells. Thyroid dysfunction causes anemia by effecting erythropoiesis. In severe cases it can cause leucopenia, thrombocytopenia, and rarely it causes pancytopenia. Glycated hemoglobin (HbA1c) levels differ in disorders of thyroid gland.

Aim: The objective of this study is to measure HbA1c levels and to know its importance in recently diagnosed hyper and hypothyroidism individuals without diabetes.

Methods & Materials: This study was performed in 60 Euglycemic individuals with overt hypo/hyper-thyroidism at OGH in Dec 2018 to Jan 2019 (30 hypothyroid and 30 hyperthyroid) and 30 controls were selected. Baseline HbA1c was estimated by HPLC method and thyroid status was measured by CLIA in all patients and controls and then compared.

Results: HbA1C was found to be significantly higher in hypothyroid group (P <0.05). HbA1c values in hyperthyroid patients were not significantly different from controls.

Conclusion: Baseline HbA1c levels were found to be significantly higher in hypothyroid patients in comparison to hyperthyroid patients and controls despite similar glucose levels. Our study suggests that we should be cautious while interpreting HbA1c data in patients with hypothyroidism.

Key word- HbA1C interpretation, Hypothyroidism, Hyperthyroidism,

I. Introduction

The thyroid gland is located in the neck in front of the larynx, and consists of two lobes connected by narrow. Seen from the front has the shape of a letter H or a butterfly with its wings outstretched. Thyroid gland secretes two important hormones: thyroxine (T4) and triiodothyronine (T3) [1-5]. Thyroid hormones (TH) have crucial role in early brain development, somatic growth, bone maturation, protein synthesis and regulating production of red blood cells. All these functions are regulated by attachment of the active form of thyroid hormone T3 to specific members of the nuclear receptors family (TRα and TRβ). A function of TH in erythropoiesis has been known for more than a century [6,7]. Aberrant production of RBCs and anemia are often observed in patients with thyroid diseases [8]. Thyroid hormone (TH) signals through TH nuclear receptors α (TRα) and β (TRβ), both possessing different splicing isofroms [9]. Although the molecular mechanism(s) underlying TH function on erythropoiesis is unknown, human genome-wide association studies (GWASs) have identified genetic variances in the TRβ locus associated with abnormal hematological traits [10]. Thyroid disorders are frequently accompanied by red blood cell abnormalities. They enhance erythropoiesis via hyper proliferation of immature erythroid progenitors and also by increasing the secretion of erythropoietin (EPO) by inducing erythropoietin gene expression. Thyroid hormones also augment repletion of hypoxia inducible factor 1 (HIF-1) and then motivate growth of erythroid colonies (BFU-E, CFU-E). These hormones also intensify erythrocyte 2, 3 BPG compactness, which enhances the delivery of oxygen to tissues [11,12,13].

Patients with hyperthyroidism observed to have increased erythrocyte mass and patients with hypothyroidism have a decreased erythrocyte mass due to reduction of plasma volume and may undetectable by routine measurement such as hemoglobin concentration [14,15], hence estimation of HbA1C is of helpful.

HbA1C is most commonly used for assessing glycemic status in diabetic patients. In the recent past, the American Diabetes Association has suggested the use of HbA1c as diagnostic tool for prediabetes and
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diabetes. A value between 5.7% and 6.4% represents prediabetes while a value ≥6.5% is considered as diabetes mellitus. Recent studies have shown its counterfeit elevation in hypothyroidism in the absence of diabetes. Glycosylated Hemoglobin A1c (HbA1c) is formed by the glycation of the valine of the β-chain of hemoglobin. Studies have shown variation in HbA1C levels in different conditions like Haemoglobinopathies, chronic kidney diseases, pregnancy even in the absence of diabetes mellitus. Factors effecting HbA1C includes

1. Erythropoiesis
   Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis.
   Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.

2. Altered Hemoglobin
   Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.

3. Glycation
   Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH.
   Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH.
   Variable HbA1c: genetic determinants.

4. Erythrocyte destruction
   Increased HbA1c: increased erythrocyte life span: Splenectomy.
   Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.

II. Aims And Objectives
To evaluate HbA1C levels in euglycemic individuals with altered thyroid status and to know its importance while interpreting data.

III. Methodology
Study was carried in the Department of Biochemistry, Osmania General Hospital, Afzulgunj, Hyderabad, and was approved by the ethical committee. Informed consent was taken from the individuals. This study was performed in 60 Euglycemic individuals with overt hypo/hyper-thyroidism during December 2018 to January 2019 (30 hypothyroid and 30 hyperthyroid) and 30 euthyroid and euglycemic individuals were selected as healthy controls.

Table no.1 - Data of the cases and the control

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO’OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOTHYROID</td>
<td>30</td>
</tr>
<tr>
<td>HYPER THYROID</td>
<td>30</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>30</td>
</tr>
</tbody>
</table>

INCLUSION CRITERIA
1. Hypothyroid patients with TSH >5.5µIU/ml and Hyperthyroids with TSH <0.35µIU/ml
2. Euthyroid and euglycemic individuals as healthy control

EXCLUSION CRITERIA
1. Diabetes Mellitus and Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose
2. Patients with Hemoglobin <10g/dl
3. Renal failure(creatinine clearance <60ml/min)
HbA1c was estimated by using ion exchange HPLC method using BIORAD D 10™ Program , 2ml venous sample was collected in purple vacutainer (k2EDTA). HbA1c reportable range for NGSP -3.8 – 18.5% (IFCC – 18 -179mmol/mol) The HbA1c was compared in hypothyroid and hyperthyroid patients with healthy control population.

Thyroid status was measured by CLIA on ADVIA CENTAUR.
Fasting and oral glucose tolerance test was done on single day by hexokinase method in Beckman coulter AU 5800 Autoanalyzer
Fasting plasma glucose(FBS)- 60-100mg/dl(3.3 to 5.5mmol/L)
1hour glucose levels- <200mg/dl(11.1mmol/L)
2hour glucose levels- <140mg/dl(7.8mmol/L)

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STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for Social Survey (SPSS) for windows version 17.0. The mean and the standard deviation (SD) for all the variables were calculated. Unpaired ‘t’ test was used to study association of HbA1C levels with parameter like FBS, 2h glucose, TSH

IV. Results

The mean serum TSH level in both case groups and that of control group showed statistically significant difference. The levels of serum TSH were significantly higher in the case group which consists of subjects of hypothyroid compared with the control group comprising of normal healthy individuals (p < 0.0001) and levels of serum TSH were significantly lower in another case group which consists of subjects of hyperthyroid compared with the control group comprising of normal healthy individuals.

The mean HbA1c level in the hypothyroid group (mean±SD 5.90± 0.33) and the control group (mean±SD 5.24±0.23) was statistically significant (p < 0.0001) whereas HbA1C levels in hyperthyroid group(mean±SD 5.34± 0.20 ) and the control group(mean±SD 5.24±0.23) was not statistically significant (p=0.0775).

There was no significant difference in fasting and 2h 75 g OGTT plasma glucose values in any of the groups.

Table no:2 Comparison of study parameters in hypothyroid, hyperthyroid patients (cases) and control subjects:

<table>
<thead>
<tr>
<th></th>
<th>HYPOTHYROID</th>
<th>HYPERTHYROID</th>
<th>CONTROL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS mean±SD</td>
<td>83.2±4.2</td>
<td>87.2±3.8</td>
<td>85.4±3.6</td>
<td>0.11</td>
</tr>
<tr>
<td>2h 75g blood sugars mean±SD</td>
<td>108.7±12.8</td>
<td>114.2±12.6</td>
<td>112.4±13.2</td>
<td>0.27</td>
</tr>
<tr>
<td>TSH mean±SD</td>
<td>35.6±14.9</td>
<td>0.12±0.06</td>
<td>3.9±0.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>HBA1C mean±SD</td>
<td>5.90±0.33</td>
<td>5.34±0.20</td>
<td>5.24±0.23</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

P value

Hypo and control | Hyper and control

V. Discussion

In our study, mean baseline HbA1c level was found to be significantly higher in overt hypothyroid patients in comparison to matched control population in spite of having similar glycemic status.

Despite thyroid hormones promoting metabolism of carbohydrates, there is false high or low levels of HbA1C in patients with altered thyroid status.

Several factors other than glycemic status can influence HbA1c levels, including life span of red blood cells (RBC) and conditions affecting RBC turnover. Erythrocytes turnover is increased in thyrotoxic states whereas hypothyroidism has the opposite effect [22].

Our findings were in keeping with the observations by Kim et al [23]. The difference of HbA1c between control and hypothyroid patients at baseline was higher in our study as with the study by Kim et al.
VI. Conclusion

The reasons for elevated HbA1C might be due to the effect of thyroid hormones on altered erythropoiesis. Our study suggests that the effects of the elevated levels of Serum TSH on the HbA1c must be considered and should be interpreted with caution in patients with hypothyroidism. However, to find out the exact mechanism further studies are required on larger cohort.

Conflict of Interest- None

References