VOLUME-6 | ISSUE-3 | MARCH - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

Estimation of anaemic status as the cause behind altered HbA1C level in non diabetic hypothyroid patients

Biochemistry

KEYWORDS: non-diabetic, hypothyroid, HbA1C, anaemia.

PROF. DR. SOMA GUPTA — MBBS, MD (BIOCHEMISTRY) PROF. & HEAD OF THE DEPT.,DEPT OF BIOCHEMISTRY, NRS MEDICAL COLLEGE AND HOSPITAL, KOLKATA, WEST BENGAL, INDIA.

SOUMIKA BISWAS — MBBS , MD (BIOCHEMISTRY) DEMONSTRATOR, DEPT. OF BIOCHEMISTRY , NRS MEDICAL COLLEGE & HOSPITAL ,KOLKATA,WEST BENGAL, INDIA

ABSTRACT

Studies across the world have shown that HbA1C is elevated in non-diabetic patients also suffering from hypothyroidism. The falsely elevated HbA1C level in Hypothyroid patients is often explained by anaemia which is a common associated feature . In this study it was investigated whether elevated A1C in non diabetic hypothyroid patients can be due to anaemia.

Between March 2016 to September 2016, 63 nondiabetic hypothyroid individuals were tested in the Dept. of Biochemistry ,NRSMC & H for TSH ,fT4,fasting blood glucose,HbA1C & complete haemogram. Non-diabetic hypothyroid individuals with anaemia showed elevated HbA1C levels (5.00 +- 0.35 %) than those without anaemia (3.59+- 0.27 %), the rise was approx. 1.39 times. Altered erythrocyte life span is partially responsible for this false elevation in HbA1C levels. Hence this conversion factor might be used to correct the haemoglobin status while using HbA1C as a diagnostic tool for diabetes in such patients.

Introduction:

HbA1C is used for the assessment of glycemic status of the diabetic patients and its use is recommended for diagnosing diabetes by the American Diabetes Association (ADA). But even in the absence of DM ,variation in HbA1C level can be observed in conditions like Haemoglobinopathies, chronic kidney diseases or pregnancy . Conditions that can affect erythrocyte turnover or survival may falsely elevate or lower the A1C levels. Recent studies have shown that false elevation of HbA1C in hypothyroidism even in absence of diabetes . [1]

Decreased production of thyroid hormone is the primary problem of hypothyroidism. It is often complicated by additional conditions like dilutional hyponatremia, anaemia and hyperlipidemia. Anaemia in hypothyroidism can be normochromic normocytic, microcytic hypochromic and macrocytic. The most frequent type of anaemia encountered in hypothyroidism is normochromic normocytic. The etiology of anaemia in hypothyroidism can be explained by nutritional iron deficiency or by the endocrine disorder itself where the lowered thyroid hormone levels repress the bone marrow often resulting in decreased erythrocyte production which may affect the life span of erythrocytes. Altered erythrocyte life span is partially responsible for false elevation in HbA1C levels. This falsely elevated A1C levels in non-diabetic hypothyroid individuals can be explained by anaemia. [2] [3] [4]

Aim & objectives:

The aim of the study was to detect -

1 .) Whether any significant difference exists in HbA1c levels among nondiabetic hypothyroid patients with & without anaemia .

2 .) To find out the conversion factor by which actual value of HbA1C can be obtained.

Review of literature

Hypothyroidism and diabetes are the two of most common endocrine disorders found in Indian subcontinent. The prevalence of thyroid disease in patients with diabetes mellitus is approximately 10-15% . Studies done in hypothyroid patients showed elevated HbA1C not only in the presence of diabetes but also in non-diabetic subjects. Hence the role of HbA1C as a marker of diabetes was questioned in such conditions especially when American Diabetes Association has labeled it as a diagnostic criteria for diabetes mellitus. [5]

Rakesh Dhadhal et al (2015) showed that non-diabetic hypothyroid individuals with anaemia shows elevated A1C levels in prediabetes range. Hence care should be exercised while using HbA1C as a diagnostic tool for diabetes in such patients. [6]

Studies done by Alap L. Christy et al (2013) & Jung Ii Son et al (2013) in hypothyroid patients showed elevated HbA1C not only in the presence of diabetes but also in non-diabetic , anaemic subjects. Hence the role of HbA1C as a marker of diabetes was questioned in such conditions . [1] [7]

P. A. Manjrekar et al (2014) found a positive correlation between iron deficiency anemia and increased A1C levels, especially in the non diabetic & controlled diabetic women and individuals having FPG between 100-126 mg/dl. Hence, before altering the treatment regimen for diabetic patient, presence of iron deficiency anemia should be considered.[8].

Material and Methods:

It was a non interventional, observational, cross sectional study in a tertiary care hospital.. The study took place in Dept of Biochemistry ,NRSMC& H. between March 2016 to September 2016. Adult patients coming to this department were tested for thyroid function ,fasting blood sugar, HbA1c, peripheral smear, Haemoglobin, mean corpuscular Haemoglobin (MCH), mean corpuscular volume (MCV) & mean corpuscular Haemoglobin concentration (MCHC) .

Conditions like confirmed cases of diabetes mellitus (as per criteria of ADA), patients having documented history of gestational diabetes (GDM) or any kind of endocrinopathy which affect for glycemic control, current or prior use of medication with potential to increase or decrease HbA1c (like antidiabetics, corticosteroids, statins, and antipsychotics), pregnant patients or pregnancy-related condition within three months of HbA1c assay, patients having haemoglobin concentration <6 g/dl or >16g/dl., patients having history of blood loss or blood transfusion within two months of HbA1c assay , patients with other life threatening disease, patients with a history of malignancy ,addiction(smoking, alcoholism, drug abuse or any other addiction) ,patients having haemolytic anaemia, other Haemoglobinopathies, anaemia due to other chronic illnesses and abnormal renal function test (Serum Urea, Creatinine) were excluded from our study.

After all the tests a total of 63 non diabetic , hypothyroid ,adult patients were selected randomly from the patients coming to the dept. of Biochemistry & dept. of Endocrinology,NRSMC keeping in mind the inclusion/exclusion criteria. Absence of diabetes was confirmed by proper history taking & fasting blood sugar measurement. Criteria for the absence of diabetes that was used in present study was the criteria submitted by World Health Organiza-

tion (WHO) and American Diabetes Association (ADA) i.e. Fasting blood glucose (FBG) level (≥ 126 mg/dl), plasma blood glucose after two hours from having OGTT is (≥ 199mg/dl) .Presence of hypothyroidism was confirmed by fasting serum TSH & free T4 measurement & history taking.

Presence of anaemia was confirmed by following indices – [Harrison] a) MCV < 90+- 8 fl , b) Hb (adult man) < 16+-2 gm/dl , c) Hb (adult woman , menstruating) < 13+-2 gm/dl , d) Hb (adult woman post menopausal) < 14+-2 gm/dl. TSH & fT4 was done by ELISA method , fasting blood sugar by GOD –POD method , HbA1C – by ion exchange chromatography method & red blood cell indices by automated cell counter.

Statistical analysis :-

After all the clinical tests , 32 non diabetic hypothyroid patients were found to have raised HbA1C level 5.00 +- 0.35 % when compared to other 31 non diabetic hypothyroid patients whose HbA1C level was 3.59+- 0.27 %. After further analysis of other test results like Hb , MCV etc. it was found that the group having raised HbA1C level also had anaemia ,whereas the other group having lower HbA1C level had no anaemic patient in it.

The data was tabulated and presented in table 1 .

Table -1 shows mean value of HbA1C in patients with & without anaemia with standard deviation.

	Red blood indices (Normal)	Red blood indices (anaemic)	total
HbA1C value (%)	3.59+- 0.27 %	5.00 +- 0.35 %	-
No. of patients	31	32	63 patients

After statistical analysis it was found that 32 among 63 nondiabetic hypothyroid patients who had anaemia also had raised HbA1C & the other 31 had normal red blood indices as well as HbA1C.

Independent samples t test

	Levene's test for equality of variances F Sig		95% C.I. of the diff. Lower upper t /sig(2-tailed)/mean diff/ std error diff/				
Equal variances assumed	.771	.386	14.01	0.00	1.403	0.10014	1.20 1.605
Equal variances not assumed			14.01	0.00	1.403	0.10014	1.19 1.606

According to ADA , cut off value of HbA1C for diabetes is 6.5% . Although all the 63 patients had HbA1C value < 6.5 %,but those with anaemia had HbA1C value 5.00 +- 0.35 %. And those who did not have anaemia ,their HbA1C value was 3.59+- 0.27 %.
P value is < 0.0001, so the data were statistically significant.

Discussion & conclusion

After statistical analysis it is evident that non diabetic hypothyroid patients with anaemia had their HbA1C level significantly raised when compared to non diabetic hypothyroid patients without anaemia.

The HbA1C level was found to be 5.0025/3.5995 = 1.39 times higher in anaemic group than the non anaemic group.

This difference is even more marked when the lower limit of the range is compared (3.32 vs. 5.35), the significance of which is not as clinically impacting as the upper limit of the range (diabetes mellitus diagnostic criteria). However, the relatively lower limit of normal for HbA1c in anaemic subgroups may make low values of HbA1c in these patients less indicative of over-enthusiastic glycemic control, as well as less predictive of the increase in mortality associated with such tight control.

According to studies like E English et al(2015) , C Das et al (2012) & E Agouza et al (2002) it was found that iron deficiency anaemia (IDA)(very common finding in hypothyroidism) may result in increased HbA1c values due to an elongation of the erythrocyte lifespan or due to lack of stimulation of erythroid colony development by thyroid hormones or reduction in oxygen distribution to tissues and diminution of erythropoietin level in the absence of thyroid hormones which leads to anemia,. However, it is not known to what degree alterations in erythrocyte indices affect HbA1c values especially around the diagnostic cut point of 6.5% (48 mmol/mol) or the degree of abnormality severity required to result in a significant change.[9] [10]

It was also seen that HbA1C fell significantly after iron treatment in iron deficient anaemic hypothyroid patients, from a mean of 6.15% ± 0.62 to 5.25% ± 0.45 (P < 0.001). In conclusion, iron deficiency must be corrected before making any diagnostic or therapeutic decisions based on HbA1C levels.[11]

The finding of this study is in accordance with some other studies done worldwide like Rakesh Dhadhal (2015) et al [6], Segun Adeoye (2015) et al [12], Erdogan M (2015) et al [13], Alap L. Christy (2013) et al [1], Jung Il Son (2013) et al[7] etc.

This study should have been done on larger sample size, with more parameters like iron & TIBC study, determination of ferritin level of blood to diagnose the amount of iron deficiency in the case and control group.

The use of other surrogates of glycemic control, the measurements of which will not be affected by haemoglobin type and concentration, may circumvent the problem associated with use of HbA1c in this special population. To this end, fructosamine and glycated albumin assays are currently being examined.

References :-

[1] Alap L. Christy, Poornima Manjrekar, Ruby P. Babu, Rukmini M.S., and Anupama Hegde. Elevation of HbA1C in Non-diabetic Hypothyroid Individuals: Is Anaemia the Connecting Link? -A Preliminary Study.J Clin Diagn Res. 2013 Nov; 7(11): 2442–2444.
[2] Horton L, Coburn RJ, England JM, Himsworth RL. The hematology of hypothyroidism 1976. Q J Med. 45(177):101–23.
[3] KC Das, M Mukherjee, TK Sarkar, RJ Dash, GK Rastogi. Erythropoiesis and erythropoietin in hypo and hyperthyroidism. J Clin Endocrinol Metab. 1975;40:211–20.
[4] Fein HG, Rivlin RS. Anaemia in thyroid diseases. Med Clin North Am. 1975;59:1133–45.
[5] Diez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2005;90:4124–27.
[6] Dhadhal R, Chabra RJ, Mangukiya K, Sharma N, Mali KL, Sharma A. A Study of Glycated Hemoglobin (HbA1c) In Non Diabetic Hypothyroid Population.. IJHSR. 2015; 5(3): 127-132.
[7] Jung Il Son, Sang Youl Rhee, Jeong-taek Woo, Jin Kyung Hwang, Sang Ouk Chin, Suk Chon, Seungjoon Oh, Sung Woon Kim, and Young Seol Kim. Hemoglobin A1c May Be an Inadequate Diagnostic Tool for Diabetes Mellitus in Anemic Subjects. Diabetes Metab J. 2013 Oct; 37(5): 343–348.
[8] Alap L. Christy, Poornima A. Manjrekar, Ruby P. Babu, Anupama Hegde,and Rukmini M.S. Influence of Iron Deficiency Anemia on Hemoglobin A1C Levels in Diabetic Individuals with Controlled Plasma Glucose Levels. Iranian Biomedical Journal 18 (2): 88-93 (April 2014)
[9] Emma English & Iskandar Idris & Georgina Smith & Ketan Dhatariya & Eric S. Kilpatrick & W. Garry John.The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review, Diabetologia .
[10] Chanchal Das, Pranab K. Sahana, Nilanjan Sengupta, Debasis Giri, Mukut Roy, and Prasanta Mukhopadhyay. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India.Indian J Endocrinol Metab. 2012 Dec; 16(Suppl 2): S361–S363.
[11] I. El-Agouza, A. Abu Shahla,M. Sirdah.The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis.International journal of laboratory haematology. 2 October 2002.

VOLUME-6 | ISSUE-3 | MARCH - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

[12] Segun Adeoye, Sherly Abraham, Irina Erlikh, Sylvester Sarfraz, Tomas Borda and Lap Yeung. Anemia and Hemoglobin A1c level: Is there a case for redefining reference ranges and therapeutic goals? BJMP 2014;7(1):a706.
[13] Erdogan M, Kösenli A, Ganidagli S, Kulaksizoglu M. Characteristics of anemia in subclinical and overt hypothyroid patients.Endocr J. 2012;59(3):213-20.