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Biochemistry

INFLUENCE OF IRON DEFICIENCY ANAEMIA ON HBA1C IN TYPE 2 DIABETIC AND NON-DIABETIC

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ABSTRACT **Introduction:** Haemoglobin A1c [HbA1c] has been adopted by physicians as a surrogate for monitoring glycemic control. There exists concern that other factors beyond serum glucose concentration may affect glycation rates. **Aim:** This study aimed to analyse the effect of Iron deficiency anaemia on HbA1c levels in type 2 diabetic patients having both controlled and uncontrolled fasting blood sugar levels compared with non-diabetic. **Methods:** The study group comprised 600 patients with type 2 diabetes. Out of this, 360 uncontrolled diabetic with IDA patients (FBS > 125 mg %) and 240 controlled diabetic without IDA patients (FBS < 115 mg %) compared with 460 non-diabetics, out of this 200 with IDA and 260 without IDA. **Results:** In controlled diabetes without IDA, the HbA1c was 6.9 ± 0.8%, while uncontrolled diabetes with IDA, subjects who had FBS > 125 mg % had significantly higher HbA1c of 8.1 ± 0.5% value. Odds ratio for HbA1c for non- diabetic patients with IDA and without IDA was non-significant. **Conclusion:** The study emphasizes the need to exercise caution when applying HbA1c reference ranges to anaemic populations.

KEYWORDS : Iron deficiency Anaemia [IDA], Type 2 Diabetes Mellitus, HbA1c

Introduction

The American Diabetic Association (ADA) recommends HbA1c levels as diagnostic criteria for diabetes mellitus. Physicians have adopted HbA1c levels as a convenient way to screen for diabetes, as well as to monitor therapy. There exists concern that because HbA1c is formed from the glycation of the terminal Valine unit of the β-chain of haemoglobin, it may not be an accurate surrogate to ascertain glycaemic control in certain conditions that affect the concentration, structure and function of haemoglobin.

Kim et al (2010) stated that iron deficiency is associated with shifts in HbA1c distribution from < 5.0 to ≥ 5.5 % and significant increases was observed in the patients absolute HbA1c levels 2 months after treatment of anaemia [1]. HbA1c is also affected by pregnancy [2, 3], uraemia [4], haemolytic anaemia [5], haemoglobinopathies [6], acute and chronic blood loss, Vitamin B12 and folate deficiencies [7]. There is a dearth of literature onHbA1c levels in the anaemia population and a reference range for this unique population does not currently exist.

Iron deficiency anaemia is one of the most prevalent types of malnutrition and common in India. Ferritin is the form in which iron is stored, and testing amount of ferritin reflects the iron status. Globally, 50% of anaemia is attributed to iron deficiency [8]. Studies have shown that reduced iron levels are correlated with increased levels of HbA1c leading to false high levels of HbA1c in non-diabetic individuals [9, 10]. The earliest study to investigate the effects of iron deficiency anaemia on HbA1c levels was conducted by Brooks et al. [9] who assessed HbA1c levels in 35 non-diabetic patients having iron deficiency anaemia both before and after treatment with iron. They observed that HbA1c levels were significantly higher in iron deficiency anaemia patients and decreased after treatment with iron.

Anaemia with type 2 diabetes remains unidentified because both of them share similar symptoms such as lethargy, pale skin, chest pain, irritability, numbness/coldness in the hands and feet, tachycardia, shortness of breath and headache [11]. A high incidence of anaemia was observed in diabetics without renal insufficiency, and also suggested that poor glycemic control and old age are associated with the incidence of anaemia in diabetic patients with normal renal function [12].

In the light of the uncertainty in the influence of anaemia on HbA1c, it is imperative that clinicians are aware of the caveats with HbA1c values when they make management decisions in the anaemic populations. The study attempts to discern clinical differences in HbA1c levels in patients with anaemia compared to non-anaemic population of both type 2 diabetes and non-diabetics, and also to quantify and show the direction of such difference if they indeed exist.

Materials and Methods

Subjects:

The study is a retrospective chart review of patients with and without anaemia of both type 2 diabetes and non-diabetics. 1060 patients of Chennai medical college hospital and research centre, Irungalur, Trichy, TN., who consulted during April 2016 to December 2016 were selected. The study participants were residents of in and around Tirchy, Tamil Nadu, South India.

The study reviewed electronic medical records of selected patients, extracting data on fasting blood glucose, HbA1c, serum ferritin, peripheral smear and haemoglobin and red cell indices. Other information obtained electronically were socio demographic factors (Gender, age, ethnicity, smoking status and duration of T2DM) and clinical findings on first visit [blood pressure (BP), medications, eGFR and diabetic complications]. To be included in the study, all patients were 30 – 70 years of age.

Exclusion criteria included those who had history of unstable cardiovascular and peripheral diseases; those with chronic illnesses; those with recent blood loss or donated blood recently; those who have haemolytic anaemia or genetic differences in the haemoglobin molecule (haemoglobinopathy) such as sickle-cell disease and other systemic disorders that could result in anaemia and pregnancy, overt thyroid dysfunction, chronic kidney disease, chronic liver disease, on corticosteroid therapy.

The presence of anaemia was defined by a haemoglobin level < 13.0 g/dL in men and < 12.0 g/dL in women, Hct < 40% in males and < 36% in females, mean corpuscular volume (MCV) < 80 fl, MCH < 26 pg/cell, MCHC < 32 g/dl and peripheral smear showing microcytic hypochromic picture were considered to have IDA and confirmed by their serum ferritin levels (<15μg/L) [13]. Fasting blood glucose and HbA1C were estimated using Mindray BS-420 chemistry analyser. Hb, Hct, MCV, MCH, MCHC were measured by using Mindray BC-5300 Auto Haematology analyser. Serum ferritin by Biorad lab.

Absolute HbA1c levels were calculated from the measured HbA1c levels by using the formula [13], Absolute HbA1c (g/dl) = (HbA1c * Hb) ÷ 100

Statistical Analysis

Descriptive data are presented as means and standard deviations (SD). Data analysis between two groups was compared using two-tailed independent sample t-test. Two-tailed Pearson's partial correlation coefficient was used to determine age-adjusted correlations between variables. Logistic regression analysis was used for the analysis of associations between anaemia and independent variables. Data were analysed using IBM SPSS statistics 20. P value < 0.05 was considered as significant.

RESULTS

Demographic and clinical characteristics of patients are as shown in **Table 1**. For this current study, out of total 1060 subjects of both gender (Male = 560, Female = 500) were selected (Table-1). As our aim was to examine prevalence of iron deficiency anaemia in diabetic patient, 600 diabetic patients were divided into two groups according to their FBS levels. 360 were uncontrolled diabetics (FBS > 125 mg %) with IDA (A) and 240 were controlled diabetics (FBS < 115 mg %) without IDA (B). Table 1 revealed that the incidence of anaemia was higher in patients with poorly controlled diabetes than controlled diabetes (P < 0.05) and the odds of anaemia were higher in diabetic females than diabetic males (P < 0.05).

FBS and HbA1c levels: (Fig: 1, Table 3): The well-controlled diabetes with normal FBS < 115 mg % had HbA1c of 6.9 ± 0.8%, while subjects who had FBS > 125 mg % had significantly higher HbA1c of 8.1 ± 0.5% value. Odds ratio for HbA1c > 5.0 % for non-diabetic patients with IDA and without IDA were 5.5 ± 0.8 and 5.1 ± 0.01 and it was non-significant.

Haemoglobin, ferritin and HbA1c: The data in Table 3 provided evidence that haemoglobin was indeed lower in anaemic patients than in healthy control and the observed difference was statically significant (< 0.05).

The Serum ferritin level of IDA with uncontrolled diabetes was significantly lower compared to controlled diabetes without IDA and non-diabetes (with and without IDA). Additionally the Absolute HbA1c levels were low in anaemia compared to controlled diabetic and control group.

Table 1: Prevalence of Anaemia Vs. Gender with FBS in Diabetic and NonDiabetic

N = 1060					
Diabetic (n = 600)***			Non-Diabetic (n = 460)		
	Female (n = 300)	Male (n = 300)		Female (n = 200)	Male (n = 260)
IDA (A) (n = 360) FBS > 125 mg %	200*** (55.6%)	160 (44.4%)	IDA (C) (n = 200)	60 (30 %)	140 (70 %)
No IDA (B) (n = 240) FBS < 115 mg %	100 (41.7%)	140 (58.3%)	No IDA (D) (n = 260)	140 (53.9%)	120 (46.1 %)

A: Diabetic (FBS > 125 mg %) with Iron deficiency anaemia
B: Diabetic (FBS < 115 mg %) without Iron deficiency anaemia
C: Non-Diabetic with Iron deficiency anaemia
D: Non-Diabetic without Iron deficiency anaemia

Table 2: Comparison of red cell indices

	Diabetic with IDA	Diabetic without IDA	Non Diabetic with IDA	Non Diabetic without IDA
Hb (g/dL)	10.4 ± 0.08	14.3 ± ***0.16	11.46 ± 0.08	14.4 ± ***0.2
Haematocrit (%)	32.1 ± 0.3	39.6 ± *** 0.4	37.07 ± 0.3	42.2 ± ***0.8
MCV (fl)	75.4 ± 0.2	85.1 ±*** 0.4	78.56 ± 0.22	86.2 ± **0.2
MCH (pg/cell)	26.3 ± 0.3	29.7 ± ** 0.15	25.9 ± 0.2	29.9 ± **0.3
MCH-Conc (%)	30.6 ± 0.2	33.51 ± ** 0.15	31.1 ± 0.24	34.1 ± **0.2

Fig 1: Comparison of haemoglobin and HbA1c in type 2 diabetic and non-diabetic (with and without IDA):

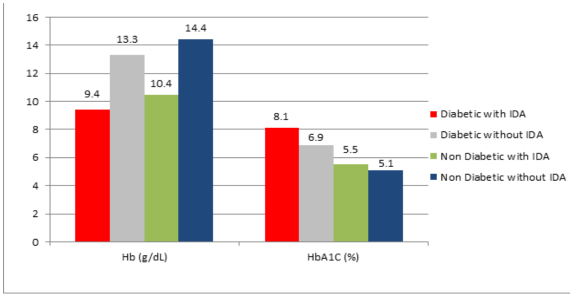

Table 3: Comparison of haemoglobin and HbA1c, Absolute HbA1c and Serum ferritin levels in diabetics and non-diabetics (with and without IDA)

	A	B	C	D
Hb (g/dl)	9.4 ± 0.08***	13.3 ± 0.16	10.46 ± 0.08	14.4 ± 0.2
HbA1C (%)	8.1 ± 0.5***	6.9 ± 0.8	5.5 ± 0.8	5.1 ± 0.04
Absolute HbA1C (g/dl)	0.762	0.98	0.58	0.74
Sr. Ferritin (ng/ml)	16.9 ± 6.1***	196.9 ± 65.0	140.6 ± 59.4	210.0 ± 40.6

Discussion

In the present cross-sectional study, diabetic patients with IDA had high incidence of anaemia (60%). Anaemia along with diabetes is an alarming condition because of increased risk of developing eye disease, heart disease or a stroke therefore the life span of patients who have anaemia along with diabetes is less as compare to people who have diabetes without anaemia [15].

Our study shows that Diabetic with Iron deficiency anaemia is more common among women than men. This was observed in a similar study by Nitin Sinha et al [8], who reported females to be more affected with IDA than males. HbA1c levels in IDA with FBS >125mg% compared to diabetes with controlled FBS < 115mg% without IDA. Our results show that there is a positive correlation between haemoglobin and HbA1c concentrations. HbA1c levels tend to be higher in cases of iron deficiency. On treatment with iron supplements, the HbA1c levels decrease [8, 9, 14]. On improvement of Hb, a significant decrease HbA1c was observed in type 2 diabetes, however no such significant difference caused in non-diabetic cases. Corroborating our study, studies by Cogan et al, and el Agouza et al showed that the HbA1c levels were higher in patients with IDA and decreased significantly on treatment with iron supplements. According to them, elevated HbA1c levels in iron deficiency anaemia could be explained by the assumption that if serum glucose remains constant, a decrease in the haemoglobin concentration might lead to an increase in the glycated fraction [10].

Thus our findings suggest that a reduction of blood glucose levels and the targeting of acceptable glycated haemoglobin levels would help reduce the risk of anaemia in the diabetic population. There is an urgent need for proper diabetic care and management for diabetic senior citizens, who have limited food choices and are more vulnerable to iron deficiency anaemia. Therefore, physicians should recommend them to take iron and vitamin supplement and take nutritious iron-rich diet.

As high incidence of anaemia was observed in diabetes mellitus we recommend that routine haematological tests along with blood glucose level should be mandatory in diabetic outpatient clinics in order to make optimal therapeutic decisions for treatment of anaemia in type 2 diabetes mellitus.

Conclusion

The study emphasizes the need to exercise caution when applying HbA1C reference ranges to anaemic populations. It makes the case for defining HbA1c reference ranges and thus therapeutic goals for IDA. Redefining such reference ranges may increase the sensitivity of HbA1c in diagnosing type 2 diabetes in anaemic population. We recommended that absent of risk factors and symptoms reliable to type 2 diabetes, marginal elevation in HbA1c levels in anaemic patients should warrant confirmation of diagnosis using FBS and PPBS.

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