A Study to Correlate Anemia with Hba1c Levels in Euglycemic Type 2 Diabetic Patients

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Abstract: _Background_: _Diabetes mellitus (DM) and anemia are both prevalent in India. Glycated hemoglobin (HbA1c) is the gold standard test for the diagnosis of DM and monitoring of glycemic status. Hemoglobin (Hb) being the integral component of HbA1c, there is a possibility that anemia can also affect the level of HbA1c apart from the various other factors._ _Objectives_: _To study the prevalence, type of anemia, and correlation between HbA1c and anemia, including red blood cell (RBC) indices in euglycemic type 2 DM patients. The study was conducted with the objective of studying the correlation between HbA1c and anemia in euglycemic diabetic patients having controlled blood glucose over a period of 3 months._ _Methodology_: _This cross - sectional study was conducted in tertiary care hospital of Uttar Pradesh. All euglycemic diabetic patients with controlled blood glucose over a period of 3 months attending the outpatient department and fulfilling inclusion and exclusion criteria were enrolled in the study._ _Inclusion criteria_: _All euglycemic type 2 DM patients with controlled blood glucose having three consecutive normal blood glucose levels [fasting blood sugar (FBS) —80–130 mg/dL and postprandial blood sugar (PP2BS) test—<180 mg/dL] over a period of 3 months from the outpatient department._ _Exclusion criteria_: _Type 1 DM and latent autoimmune diabetes of adults, patients with hemolytic anemia, pregnancy, chronic alcoholism, chronic kidney disease, chronic liver disease, combined deficiency anemia, patients with increased FBS and PP2BS, acute and chronic inflammatory state, malignancy, anemia of chronic disease, and vitamin B12 deficiency were excluded from our study. Detailed investigations of diabetes and anemia were conducted. The effect of anemia on HbA1c was assessed, and the correlation of anemia with mean HbA1c was analyzed statistically._ _Results_: _The prevalence of anemia in diabetic patients is 56.8%. Normocytic normochromic anemia is the most common, which was observed among 48.86% of diabetic patients. The median HbA1c of anemic patients is higher than nonanemic patients (p < 0.01). There is a negative correlation between Hb and HbA1c (p < 0.01). The correlation of RBC indices, that is, mean corpuscular Hb (MCH), mean corpuscular volume (MCV), and MCH with HbA1c, is also negative (p < 0.01). There is a negative correlation between HbA1c and serum ferritin level, as indicated by the Pearson correlation test (p - value of <0.01)._ _Conclusion_: _Anemia is prevalent in type 2 DM patients without renal involvement, and also normocytic normochromic type is the most common, followed by iron deficiency anemia (IDA). HbA1c levels are significantly affected by the presence of moderate anemia in spite of controlled glycemia._

Keywords: Anemia, Euglycemia, Diabetic

1. Introduction

Diabetes is one of the largest global health emergencies of the 21st century. About 415 million adults are estimated to have diabetes worldwide currently.1 India has an estimated 77 million people with diabetes, which makes it the second most affected in the world, after China. [2]

In addition, approximately 52% of adults with diabetes remain undiagnosed in India. One in six people (17%) in the world with diabetes is from India.3 Glycated Hb (HbA1c) is the most frequently occurring fraction of HbA1. American Diabetes Association guidelines have not only considered it as the primary target for glycemic control but also included it as a diagnostic criterion. Initially, it was believed that HbA1c was only altered by glucose levels; [4, 5] however, certain studies have noted its elevation in conditions other than diabetes, such as hemoglobinopathies, chronic kidney disease, pregnancy, and nutritional anemia. [6, 7]

Diabetes prevalence estimates using HbA1c may be affected by iron deficiency; hence population - based research in areas with a high prevalence of anemia is needed before confirmation of the diagnosis of DM in such population. The mechanism through which iron deficiency and anemia influence HbA1c has yet to be fully elucidated; however, most epidemiologic studies suggest that IDA can result in spuriously high HbA1c values, though some suggest there is lower HbA1c among individuals with IDA or anemia. Mild anemia has little impact on the HbA1c level, whereas moderate to severe anemia can increase the level of HbA1c.

Glycated Hb (HbA1c) levels are expected to be in the control range if the three consecutive blood sugar fasting and postprandial levels measured over a period of 3 months duration are in acceptable control range; any deviation in range would suggest an alteration in the level of HbA1c due to some other factors in which presence of anemia is one such important and common factor. This postulation formed the basis of this study to assess the utility of HbA1c as a marker of glycemic control in anemic diabetics.

Objectives
To study the prevalence and type of anemia in euglycemic type 2 DM patients with normal renal function. Further study the correlation between HbA1c and anemia, including RBC indices and serum ferritin in these euglycemic diabetic patients, having three consecutive controlled blood glucoselevels (FBS 80–130 mg/dL and PP2BS < 180 mg/dL) over a 3 - month duration.

2. Methodology

Study center: Saraswathi Medical College, Hapur

Study design: Cross- sectional study

After the selection of patient with the application of inclusion and exclusion criteria, informed written consent was taken. Detailed medical, past history and general, systemic physical examination and fasting, 2 - hour postprandial blood glucose of last 3 months duration was recorded on a predesigned proforma. All the participants

were further subjected to the following investigations complete blood count, peripheral blood smear, HbA1c, liver and renal function tests, human immunodeficiency virus, and hepatitis B surface antigen.

According to World Health Organization (WHO) cutoff value of Hb for anemia patients was divided into two groups, euglycemic diabetics with anemia and without anemia. The euglycemic diabetic patients with anemia were further investigated with anemia profile to identify the type and cause of anemia. The anemia profile included serum ferritin, vitamin B12, lactate dehydrogenase, and reticulocyte count accordingly. Other investigations like serum iron, total iron - binding capacity, serum folic acid, Hb electrophoresis, and bone marrow were noted if done in any case.

The effect of anemia on HbA1c level and correlation with mean HbA1c was analyzed statistically. Operational definition of anemia as per WHO criteria Hb < 12 g/dL for females and Hb < 13 g/dL for males.

Statistical Analysis
Data were entered in Microsoft Exceland analyzed using excel and IBM Statistical Package for the Social Sciences statistics version 25.

3. Results

The majority of the patients in our study were from the 51–60 years age group. The mean age is 58.43 years, and the standard deviation is 8.79. The gender - wise distribution shows that 55.5% of patients are females and 44.5% are males. Out of 155 cases, a total of 88 patients, 54 females and 34 males, have anemia, so the prevalence of anemia in diabetic patients is 56.8%. Out of the total of 88 anemic patients, 36 had mild anemia, and 52 had moderate anemia. The median HbA1c of moderately anemic patients is statistically significantly higher than mild - grade anemic patients (p < 0.01). Normocytic normochromic anemia is the most common type which was observed among 48.86% of diabetic patients. Microcytic hypochromic anemia was observed among 46.59%, and macrocytic anemia was observed in 4.55% of diabetic patients.

The median Hb, MCV, MCH, and mean corpuscular Hb concentration (MCHC) levels have statistically significant differences between males and females (p < 0.05). Females showed fewer Hb, MCV, MCH, and MCHC values than males. The median HbA1c of anemic patients is higher than nonanemic patients, and this difference is statistically significant (p < 0.01).

There is a negative correlation between Hb and HbA1c as indicated by Pearson correlation test (p - value of <0.01) (Pearson correlation coefficient r = −0.71). It means with the decrease in Hb value; there is an increase in the Hb1Ac level. Correlation of RBC indices, that is, MCH, MCV, and MCHC with HbA1c are also negative as indicated by Pearson correlation test (p - value < 0.01) (r = −0.56, −0.61, and −0.69, respectively). It means there is an increase in Hb1Ac value with a decrease in all RBC indices. There is a negative correlation between HbA1C and serum ferritin

level, as indicated by the Pearson correlation test (p - value of <0.01) (r = −0.48). It means an increase in HbA1c level is seen with a decrease in serum ferritin.

Hemogram	Male		Female		Mann- Whitney *U* test	
	Median	IQR	Median	IQR	Z Value	*p*- value
Hb	10.2	1.9	9.8	0.9	3.8	<0.01
RBC	4.2	1.05	4.1	1.28	1.94	0.051
MCV	71.2	8.4	68.8	10.3	2.37	<0.05
MCH	22.7	5.8	22.05	2.8	2.61	<0.01
MCHC	28.85	2	28.1	2.1	2.33	<0.05

Category of patients	HbA1c		Test statistics
	Median	IQR	Mann- Whitney *U* test
Anemic patients	6.8	0.9	Z Value= -6.559
Nonanemic patients	6.3	0.3	*p*- value < 0.01

HbA1c	MCV		MCH		MCHC	
	Median	IQR	Median	IQR	Median	IQR
≤ 6.5	84.3	7.1	28.5	2.8	34.1	1.5
6.6- 7.5	80.7	15.8	27	6.9	31.3	5.7
7.6- 8.5	67.7	8.4	22.1	4.3	28.2	1.3

4. Discussion

The prevalence of anemia in diabetes is variable in various studies. All studies reveal that anemia is more common in females than males (62.79 vs 49.27% in our study).[8] Similarly, the type of anemia also is variable, and the most common variety is the normocyticnormochromic type.[46.59]% of cases of the microcytic hypochromic type of anemia in our study also revealed low serum ferritin levels suggesting IDA. Macrocytic anemia and low vitamin B12 level were seen only in 4.55% of subjects, like many other studies.[9]

Our study shows that the median Hb1Ac of anemic patients is higher than nonanemic patients. In iron deficiency, red cell production decreases; consequently, an increased average age of circulating red cells ultimately leads to elevated HbA1c levels. As Hb glycation is an irreversible process, Hb subunit α1 (HbA1) levels in erythrocytes will increase with cell age.[10]

Out of the total of 88 anemic patients, 36 had mild anemia and 52 had moderate anemia. The median Hb1Ac of moderately anemic patients is 7.15, which is statistically significantly higher than the median HbA1c of mild anemic patients, which is 6.6.

In our study, there is a negative correlation of RBC indices MCV, MCH, and MCHC with HbA1c, as indicated by the Pearson correlation test (p - value of <0.01).

In our study, there is a negative corelation between HbA1c and serum ferritin level, as indicated by the Pearson corelation test (pvalue of <0.01). Ferritin is a storage form of iron, and it reflects the true iron status. In IDA, ferritin is decreased with an increase in the red cell life span, and an increased red cell life span is associated with increased HbA1c.

Our study shows that the median Hb1Ac of anemic patients is higher than nonanemic patients. In iron deficiency, red cell production decreases; consequently, an increased average age of circulating red cells ultimately leads to elevated HbA1 levels. Different studies have been carried out in both diabetic and nondiabetic groups; however, its distribution in well - controlled diabetics who are on regular therapy is inadequately studied. Although diabetes itself can elevate A1c levels, it has been proven that controlled plasma glucose levels for 3 months correlate very well with controlled HbA1c. Hence, patients with controlled plasma glucose levels are expected to have A1c below 6.5%. Anemic nondiabetic comparison group was not included in our study. Further study needs to be conducted to evaluate the effect of treatment of IDA in euglycemic DM patients on HbA1c values. Berkson's bias as it is a hospital - based study.

5. Conclusion

Anemia is prevalent in type 2 DM patients who are 56.8%. Normocytic normochromic anemia is the most common which was observed among 48.86% of diabetic patients. Median Hb1Ac of moderately anemic patients is statistically significantly higher than mild grade anemic patients. Serum Hb1Ac increases with a decrease in MCV, MCH, MCHC, and serum ferritin.

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