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Change in HbA1c Level with treatment of iron deficiency anaemia in non diabetic patients

N.S Neki[*], Narendra Kumar Meena[**], Kuldip Singh[*], Satpal Aloona[****], Amritpal Singh[*****], Gagandeep Singh[**], Neeraj Joshi[**], Aarti Vaid[**], Deepali Kaushal[**], Amandeep Singh Dhanju[**], Jithesh G[**], Rohit Bhardwaj[**], Bhoj Raj Sharma[**]

Professor[*], Junior Resident[**], Assistant Professor[***],Senior Resident[*****], Department of Medicine, Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, India.

Corresponding Author:
Narendra Kumar Meena, Om Niwas House No-9,Gali No-1
Gopal Nagar, Amritsar, 143001, Punjab, India.
Phone: 9815984812 e-mail: *drnarendra51@gmail.com*

Abstract

Introduction:- Glycatedhaemoglobin(HbA1c) is used as an indicator of a patient's glycemic status over the previous 2-3 months. According to American Diabetes Association (ADA) Guidelines, HbA1c levels should be maintained below 7% in all diabetic patients in order to prevent the development of microvascular complications.

Aims:- To study the effect of iron deficiency anaemia treatment on HbA1c level and to assess whether iron deficiency anaemia affects HbA1c levels.

Material and Methods: 50 non-diabetic with confirmed iron deficiency anaemia (IDA) patients and 50 age-matched healthy subjects were enrolled in this study.

Results: The mean baseline HbA1c level in the patients with IDA (6.12±0.21%) was significantly higher than controls groups(6.12±0.21%). After treatment of iron deficiency anaemia the mean HbA1c levels, significantly decreased from 6.12±0.21% to 5.21±0.16%.

Conclusions: iron deficiency anaemia was associated with higher levels of HbA1c, which could cause problems in the diagnosis of uncontrolled diabetes mellitus in iron deficient patients.

Keywords: Glycatedhaemoglobin,Iron deficiency anaemia, Diabetes Mellitus.

Introduction

Iron deficiency anaemia is the most common form of anaemia in India. Hemoglobin A1c (HbA1c) is a glycated hemoglobin that can be used as an indicator of a patient's glycemic status over the previous 2-3 months. Glycatedhemoglobins including HbA1c and other hemoglobins constitute the HbA1c fraction of adult hemoglobin (HbA).[1] HbA1c is the predominant hemoglobin found in HbA1 fractions. According to the ADA Guidelines 2015, HbA1c levels should be maintained below 7% in all diabetic patients in order to prevent the development of microvascular complications.[2] HbA1c levels are not only affected by blood glucose levels alone but they are also altered in hemolytic anaemias,[3] hemoglobinopathies,[4] acute and chronic blood loss,[5,6] pregnancy,[7,8,9]and uremia,[10,11,12].Vitamin B-12, folate and iron deficiency anaemias have also been shown to affect HbA1c levels. The earliest study to investigate the effect of iron deficiency anaemia on HbA1c levels was conducted by Brooks et al 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.[13]Sluiter et al proposed that the formation of glycatedhaemoglobin is an irreversible process and hence, the concentration of HbA1c in erythrocyte will increase linearly with the cells age. They found that in patients with normal blood glucose levels, but with very young red cells, as would be found after treatment of iron deficiency anaemia, HbA1c concentration was reduced. However, if iron deficiency has persisted for a long time, the red cell production rate would fall, leading not only to anaemia but also to a higher than normal average age of circulating erythrocytes and, therefore, increased HbA1c levels.[14]Later on some another studies showed that HbA1c levels was increased in iron deficiency anaemia patients and decreased significantly after treatment of iron.[15,16]Some studies reported that there were no differences between the HbA1c levels of anemic patients and controls.[17,18] A study conducted by Sinha et al showed that HbA1c levels were lower in patients with iron deficiency anemia and increased significantly upon treatment with iron.[19]We conducted a study to analyze the effect of iron deficiency anaemia on HbA1c level and to assess whether treatment of iron deficiency anaemia affects HbA1c levels.

Materials and Methods

This is a prospective case control observational study in which 50 non diabetic patients with confirmed iron deficiency anaemia presented to outpatient and inpatient department of Guru Nanak Dev Hospital, Amritsar and fulfilling the inclusion and exclusion criteria of the study and matched control group of 50 healthy individuals were evaluated.

Anaemia patients with haemoglobinless than 12 gm% (female, non pregnant),13 gm% (male), Adults >18 years, Serum ferritin value less than 15 microgram/L. Peripheral blood picture showing microcytic hypochromic picture, Iron profile study and serum ferritin suggestive of iron deficiency anaemia were included in this study.

Patients with diabetes, hemolytic anaemia, hemoglobinopathies, chronic kidney disease, pregnancy, chronic alcoholic state, acute blood loss were excluded.

All anaemic patients after fulfilling all inclusion and exclusion criteria were recruited for the study after taking informed consent. Detailed history and clinical examination of the patients was done. The study was conducted after approval from institutional thesis and ethical committee.

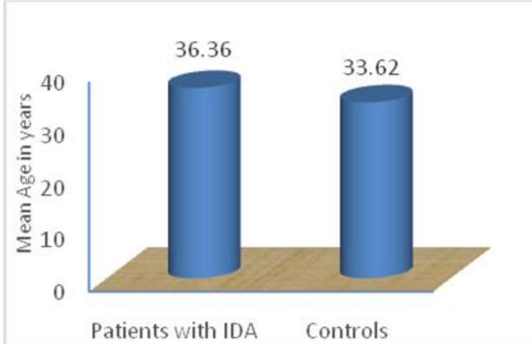
Patients were subjected to Complete Blood Count (CBC), Reticulocytic count, PBF,Iron profile study (serum total iron, TIBC, transferrin saturation),Liver Function Tests, Blood urea, Serum creatinine, Urine pregnancy test (married female with history of amenorrhoea), Blood sugar (fasting and post prandial), Serum Ferritin, USG abdomen and HbA1c. HbA1c was done by glycosylated haemoglobin kit which is based on Ion Exchange Resin Method.

Iron deficiency anaemia patients were re-evaluated 2 months after the completion of treatment. Then change in HbA1c levels with treatment of iron deficiency anaemia in non-diabetic patients was assessed and its statistical significance was evaluated in present study. The data collected was analyzed according to the standard statistical methods to reach a conclusion. Approval from the institutional ethics committee was obtained before starting the study.

Results

Table 1. Age Distribution

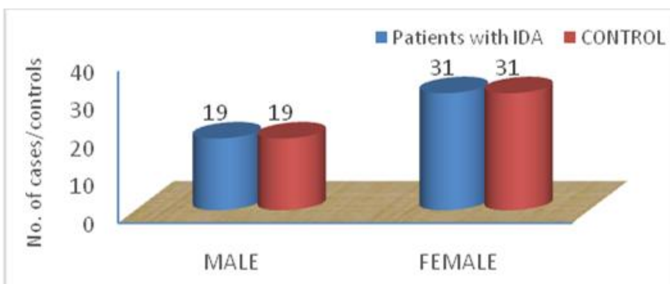
Variable	Type of Patients	N	Mean	SD	P Value
Age	Patients with IDA	50	36.36	8.24	0.079
	Controls	50	33.62	7.13	



The mean age of all the patients with iron deficiency anaemia under study was 36.36±8.24 years whereas the mean age of healthy individuals under study was 33.62±7.13 years. The minimum age in cases was 18 years and maximum age was 50 years. The minimum age in controls was 22 years and maximum age was 48 years.

Table 2. Sex Distribution

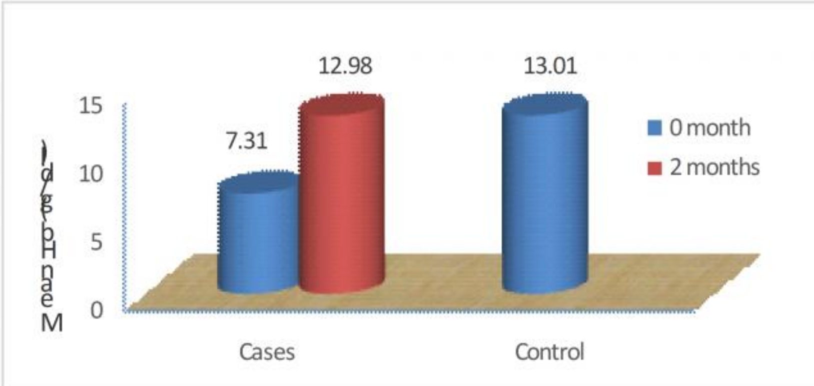
Sex	Statistics	Type of Patients		Total
		Patients with IDA (n=50)	Controls (n=50)	
Male	N	19	19	38
	%	38.0	38.0	38.0
Female	N	31	31	62
	%	62.0	62.0	62.0
Total	N	50	50	50
	%	100.0	100.0	100.0



31 patients (62%) with iron deficiency anaemia were females whereas 19 patients (18%) with iron deficiency anaemia were males. 38(68%) healthy individuals (controls) were females whereas 19(38%) healthy individuals were males.

Table 3. Distribution of Haemoglobin baseline and two months among patients with IDA and controls at 0 month

Type of Patients	N	Lab Parameter	Mean	SD	P Value	
					0m of cases v/s 2m of cases	2m of cases v/s 0m of controls
Cases	50	Hb(0m)	7.31	1.61	0.00	0.11
	50	Hb(2m)	12.85	0.58		
Controls	50	Hb(0m)	13.01	0.69		



The mean haemoglobin value at 0 month of all the patients with iron deficiency anaemia under study was 7.31±1.61 g/dl whereas the mean haemoglobin value at 2 months of all the patients with iron deficiency anaemia under study was 12.85±0.58 g/dl. The mean haemoglobin level of the control group was 13.01± 0.69 g/dl. After 2 months of treatment for iron deficiency anaemia, there was a significant increase in the haemoglobin levels of anemic patients (p<0.01). These data provided evidence that haemoglobin was indeed lower in anemic patients than in healthy controls, and the observed difference was statistically significant (P<0.01).

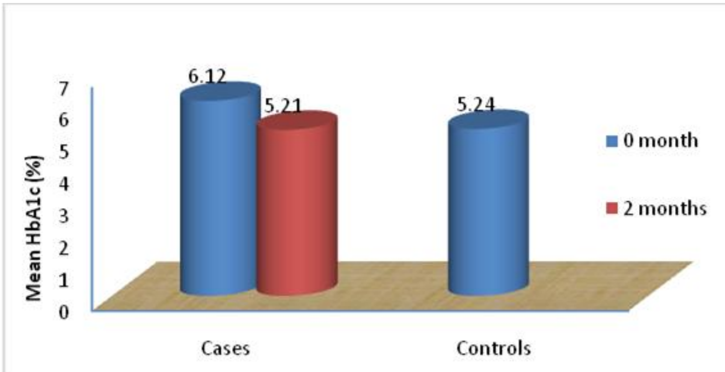
Table 4.Distribution of serum ferritin baseline and two months among patients with IDA and controls at 0 month

Type of Patients	N	Lab Parameter	Mean	SD	P Value	
					0m of cases v/s 2m of cases	2m of cases v/s 0m of controls
Cases	50	S. Ferritin (0m)	7.91	1.24	0.00	0.45
	50	S. Ferritin (2m)	203.74	37.37		
Controls	50	S. Ferritin (0m)	204.90	50.40		

The mean serum ferritin value at 0 month of all the patients with iron deficiency anaemia under study was 7.91±1.24 µg/L whereas the mean serum ferritin value at 2 months of all the patients with iron deficiency anaemia was 203.84±37.37 µg/L. Significance of difference between means of serum ferritin at 0 month and 2 months for patients with iron deficiency anaemia is statistically significant (p<0.05).The mean serum ferritin value at 0 month of healthy individuals under study was 204.90±50.40 µg/L. The significance of difference between means of serum ferritin at 0 month for healthy individuals and 2 months for patient with iron deficiency anaemia is statistically non-significant (p>0.05).

Table 5. Distribution of HbA1c baseline and 2 months among patients with IDA and controls at 0 month

Type of Patients	N	Lab Parameter	Mean	SD	P Value	
					0 m of cases v/s 2 m of cases	2m of cases v/s 0 m of controls
Cases	50	HbA1c (0m)	6.12	0.21	0.00	0.33
	50	HbA1c (2m)	5.21	0.16		
Controls	50	HbA1c (0m)	5.24	0.35		



The mean HbA1c value at 0 month of all the patients with iron deficiency anaemia under study was 6.12±0.21% whereas the mean HbA1c value at 2 months of all the patients with iron deficiency anaemia was 5.21±0.16%.Significance of difference between means of HbA1c at 0 month and 2 months for patients with iron deficiency anaemia is statistically significant ($p<0.05$).The mean HbA1c value at 0 month of healthy individuals under study was 5.24±0.35%. The significance of difference between means of HbA1c at 0 month for healthy individuals and 2 months for patient with iron deficiency anaemia is statistically non- significant ($p>0.05$).

Discussion

In our study, mean HbA1c values at baseline of all the patients with iron deficiency anaemia under study was 6.12±0.21%. The mean HbA1c at baseline of healthy individuals under study was 5.21±0.16%. This is in contrast to the results shown by Brooks et al[14] (9.9% vs 7.9%), Coban et al[15] (7.4% vs 5.9%) and Tarim et al[20] (10.6% vs 7.7%), ($p<0.001$ each), and it was suggested that IDA should be corrected before interpreting HbA1c results.

The HbA1c levels, which were significantly higher in iron deficiency anaemia patients (6.12±0.21%) than in controls (5.21±0.16%),decreased significantly after iron treatment. After treatment of iron deficiency anaemia the mean HbA1c levels, significantly decreased from 6.12±0.21 % to 5.21±0.16%.Our observation of increased HbA1c levels at baseline and the subsequent decrease in HbA1c with iron supplementation was supported by study conducted by Coban et al[15] and El-Agouza et al.[16]

The earliest study to investigate the effect of iron deficiency anaemia on HbA1c levels was conducted by Brooks et al 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. The mechanism leading to increased glycated HbA1c levels were not clear. It was proposed that, in iron deficiency, the quanternary structure of the haemoglobin molecule was altered, and that glycation of the globin chain occurred more readily in the relative absence of iron.[13]Sluiter et al tried to provide an explanation for the above findings. They proposed that the formation of glycatedhaemoglobin is an irreversible process and hence, the concentration of HbA1c in erythrocyte will increase linearly with the cells age. For example, they found that in patients with normal blood glucose levels, but with very young red cells, as would be found after treatment of iron deficiency anaemia, HbA1c concentration was reduced. However, if iron deficiency has persisted for a long time, the red cell production rate would fall, leading not only to anaemia but also to a higher than normal average age of circulating erythrocytes and, therefore, increased HbA1c levels.[14] In 1980, Mitchell et al commented on the study done by Brooks et al. They calculated the absolute amount of HbA1c in each red cell (i.e., the mean corpuscular HbA1c) and found that there were no differences in HbA1c levels before and after iron treatment. They also analyzed the study done by Suilter et al and suggested that red cell age was unlikely to be a significant factor in explaining the change in HbA1c levels during the treatment of iron deficiency anaemia.[17] Later van Heyningen et al reported no differences in HbA1c concentrations when comparing non-diabetic patients with iron deficiency anaemia before and after iron treatment to healthy controls. They believed that the reported differences in HbA1c concentrations before and after iron supplementation were due to difference in the laboratory methods used for measuring HbA1c.[18]Hansen et al also demonstrated that there were no significant difference in HbA1c concentration in iron-deficient patients, vitamin B12 deficiency patients, and healthy controls. They were of the opinion that in iron deficiency anaemia, the erythrocyte survival rate is normal, while in vitamin B12 deficiency anaemia, the erythrocyte survival rate decreases, but the haemolytic component is often minor and affects both mature and immature erythrocyte. Hence they thought that the normal levels of glycatedhaemoglobin are explained. They found that HbA1c levels decreased upon treatment of the anaemia, which was probably due to increased bone marrow erythropoiesis caused by the treatment, leading to production of new immature erythrocytes.[21] In a study by Rai et al, colorimetric assays ion exchange chromatography, and affinity chromatography were compared as method for measuring HbA1c, and no significant differences were found in HbA1c values measured by these methods.[22] Further studies by Coban et al and El-Agouza et al showed that HbA1c levels were higher in patients with iron deficiency anaemia and decreased significantly upon treatment with iron. They argued that 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.[15,16] As evident from the above studies, the exact mechanism through which iron deficiency anaemia affects HbA1c levels remains unclear. The explanations provided in the studies quoted above are merely speculation. Due to variation in results obtained from these multiple studies, we were prompted to conduct our own study to investigate the effects of iron deficiency anaemia on HbA1c levels.

Conclusions

Our study results show that glycatedhaemoglobin(HbA1c) was significantly higher in iron deficiency anaemia patients than in controls groups. It means iron deficiency anaemia leads to rise in HbA1c levels. This may have a practical application in diabetic individuals with iron deficiency anemia where glycosylated hemoglobin alone may give a false picture of poor glycemic control. Therefore, iron status must be considered and iron deficiency must be corrected before making diagnostic or therapeutic decision based on glycosylated hemoglobin values in diabetes mellitus.

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