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Research Article

THE EFFECT OF IRON REPLACEMENT ON HBA1C IN IRON DEFICIENCY ANEMIA: A BEFORE & AFTER STUDY

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ABSTRACT

Glycated haemoglobin (HbA1c) is used in diagnosis & monitoring of diabetes mellitus & was found to be affected by many factors other than blood glucose; iron deficiency anemia is one of them. In our study 50 patients of iron deficiency anemia were included. All were non-diabetic based on fasting blood sugar (FBS), post prandial blood sugar (PPBS) level & history. HbA1c level, serum ferritin & iron level were calculated before & after 6 months of iron replacement. It was found that after iron therapy HbA1c level was significantly decreased & serum ferritin & serum iron level were significantly increased. Serum ferritin & iron level were negatively correlated to HbA1c before therapy & after that serum iron was positively correlated but serum ferritin remained negatively correlated to HbA1c level. Importantly FBS before & after treatment remained significantly positively correlated as was PPBS. HbA1c level was reduced with iron replacement in iron deficiency anemia independent of blood sugar.

INTRODUCTION

Glycated haemoglobin (HbA1c) is a marker of long term (previous 2-3 months) average plasma glucose concentration. It is formed by irreversible glycation of valine amino acid at N-terminal of beta chain of haemoglobin (Telen MJ *et al*, 1998). Diabetes mellitus is defined by HbA1c $\geq$ 6.5 & HbA1c $\leq$ 5.6 is considered normal. HbA1c can be expressed as a percentage (DCCT unit) or as a value in mmol/mol (IFCC unit). HbA1c level is measured by three methods: -(1) chromatography (2) boronate affinity assay (3) immunoassay. HbA1c level is also affected by many factors independent of hyperglycemia like hemolysis, chronic renal failure, hemoglobinopathies, drugs like antiretrovirals, ribavarin, alcohol intake, vit. C & E, intra - erythrocyte pH, vitamin B_{12} deficiency, iron deficiency, administration of erythropoietin & chronic liver disease (Rohlfing CL *et al*, 2008; Bry L *et al*, 2001; Gallegher EJ *et al*, 2009). These factors affect HbA1c level by many mechanism like alteration in glycation, change in lifespan of RBC, change in rate of erythropoisis, combination of these mechanism & measuring technique. Since iron deficiency anemia is very commonly encountered clinical problem so it is necessary to explore relationship between iron deficiency anemia (IDA) & HbA1c level to rectify its interpretation more correctly. There are many studies showing reduced level of HbA1c after iron replacement which was previously elevated due to iron deficiency anemia, in both diabetic as well as non diabetic population (Coban E *et al*, 2004; Lippi G *et al* 2011; EL-Agouza I *et al* 2002; Tarim O *et al*, 1999; Rafat D *et al*, 2012; Sundaram RC *et al* 2007; Gram-Hansen P *et al*, 1990). Many studies show correlation between iron, red blood cell indices & HbA1c (Koga M *et al*, 2007; Hardikar PS *et al*, 2012; Koga M *et al*,2010). Reduction in HbA1c after iron replacement is postulated due to the formation of new red cells & alteration in glycation rate of haemoglobin (Brooks AP *et al*, 1980; Kim C *et al*, 2010).

Indian studies are lacking to show effect of iron replacement on HbA1c & explore relationship of HbA1c with s.iron, s.ferritin & haemoglobin level .Objective of this study was to explore effect of iron replacement on HbA1c & relationship between iron indices & HbA1c.

MATERIALS AND METHODS

Location of study, its design & duration

This study was prospective study with before & after iron replacement design. It was conducted in SMS hospital, Jaipur after approval of institutional ethical committee. Study population included 50 IDA patients attending OPD or

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admitted in wards of Deptt. of Internal Medicine . Study was conducted between February 2015 to January 2016. Non-diabetic patients defined on basis of their FBS & PPBS & history were included in study.

Data Collection & Relevant Investigations

The detailed history was taken & complete physical examination was done. Blood samples were sent in hospital laboratory for complete blood count, PBF(peripheral blood film), MCV, reticulocyte count, serum iron, serum TIBC (total iron binding capacity), serum ferritin, transferrin saturation, FBS (after 8 hour overnight fast), PPBS (after 2 hour of 75 gram oral glucose), RBS, serum creatinine, serum urea. Plasma sugar was measured by glucose oxidase method & HbA1c was measured by turbimetric immunoassay (Standardised according to IFCC reference method).

Non diabetic subjects with iron deficiency anemia were included in study with following criteria

Criteria for Iron Deficiency Anaemia (IDA)

1) Haemoglobin < 13 gm% in male & < 12 gm% in female
2) PBF showing microcytic hypochromic anaemia
3) MCV < 74 fl
4) S. Iron < 55 µg /dl
5) Serum Ferritin level < 16 µg/l
6) Serum transferrin saturation<18%

Criteria For Non Diabetic Status

1. Fasting blood sugar < 110 mg/ dl
2. Post prandial blood sugar < 140 mg/dl
3. Random blood sugar < 200 mg/dl
4. No history of insulin treatment &/or oral hypoglycemic drugs, Diabetes mellitus

Exclusion Criteria

1) Patient of chronic kidney disease (GFR < 60 ml/min/1.73 m^2), calculated by Cockcroft-Gault equation.
2) Known case of diabetes mellitus or newly diagnosed diabetes mellitus
3) Hemolytic anemia
4) Chronic alcoholic
5) Those unable to give informed consent.
6) Patients taking drugs known to affect HbA1c level

Statistical data were analysed with SPSS version 16 using Paired T test for comparison of means before & after treatment & confidence interval of difference with T-value & P- value were calculated. Carl-Pearson correlation coefficient was used for relationship between HbA1c & various variable like s.iron, s.ferritin & hemoglobin.

RESULTS

The values of outcome variables are summarised in table no.1. There are 50 subjects in study population out of which 28 are females & 22 are male. Before iron treatment the mean haemoglobin of group was 8.43± 0.73, mean serum iron level was 24.61±12.96, mean serum ferritin level was 10.48±2.78 & mean serum transferrin saturation was 7.76±4.51. All these values are showing features of iron deficiency anemia. All the patients were non diabetic & mean fasting plasma sugar was 82.42±9.70 while the mean post prandial blood sugar was 126.86±9.12. The mean HbA1c was 4.71 ± 0.64. Patients were treated with oral iron therapy for 6 months. The patients having haemoglobin less than 8 gm /dl were also given IV infusion of iron. After 6 months of iron therapy the mean Hb increased to 13.12 ± 0.83 (gm/dl), mean serum iron level increased to 70.84 ± 7.28 (µg/dl), mean serum ferritin level increased to 62.11 ± 6.86 (µg/l) & mean transferrin saturation increased to 26.73 ± 2.43. These all values were significantly increased (p <0.05) in after group. The mean HbA1c was decreased to mean value of 3.85 ± 0.79 & the difference between before & after therapy was statistically significant (P <0.05) as shown in table no. 1. Importantly the subjects are still non diabetic based upon plasma sugar measurement & the mean value of FBS & PPBS were 82.10 ± 9.86 (gm/dl) & 126.58 ± 9.36 (gm/dl) & difference was not statistically significant (p value >0.05).

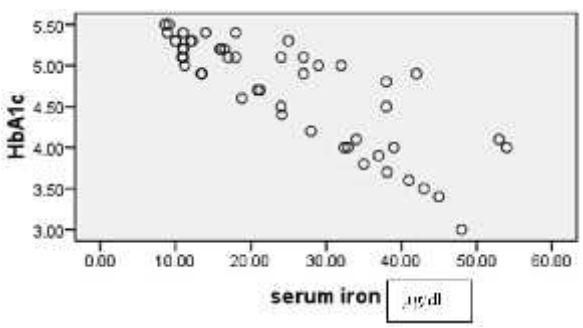
Table 1 Outcome variable of patients in the study

S. No.	Measured variable	Study population		P value
		Before iron replacement	After iron replacement	
1	Total no. of patients	50	50	
2	Total no. of female patients	28	28	
3	Total no. of male patients	22	22	
4	Mean Hb (gm/dl)	8.47± 0.73	13.12± 0.83	<0.05
5	Mean serum iron (µg/dl)	24.61±12.96	70.84±7.28	<0.05
6	Mean % transferrin saturation	7.76±4.51	26.73±2.43	<0.05
7	Mean serum Ferritin (µg/l)	10.48±2.78	62.11±6.86	<0.05
8	Mean HbA1c level %	4.71 ± 0.64	3.85 ± 0.79	<0.05
9	Mean FBS (mg/dl)	82.42±9.70	82.10±9.86	>0.05
10	Mean PPBS(mg/dl)	126.86±9.12	126.58±9.36	>0.05

Table no. 2 explains relationship between HbA1c & serum iron, serum ferritin as well as with mean haemoglobin before & after iron therapy. Correlation between outcome variable & HbA1c was calculated as Carl Pearson coefficient (r) & level of significant was p value < 0.05. The serum iron, serum ferritin & hemoghlobin were negatively correlated to HbA1c in before group with p value <0.05 (as shown in Graph 1a,1b,1c respectively).

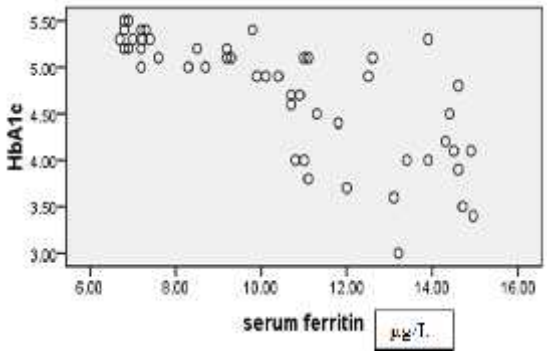
Table 2 Correlation between iron indices & HbA1c level

	Before iron therapy correlation with HbA1c level		After iron therapy correlation with HbA1c level	
	r value	p value	r value	p value
Hb	-0.327	<0.05	-0.081	>0.05
Serum iron	-0.826	<0.05	0.765	<0.05
S. ferritin	-0.748	<0.05	-0.907	<0.05

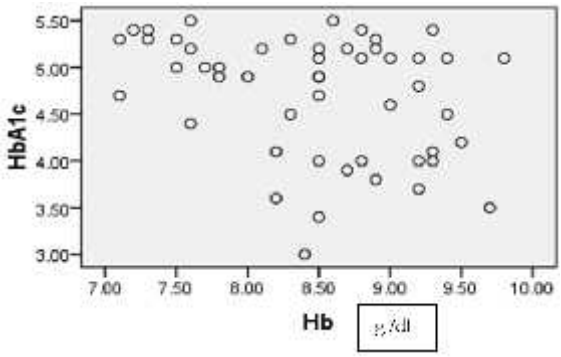


Graph 1a Scatter plot showing relationship between HbA1c & serum iron (before Iron therapy)

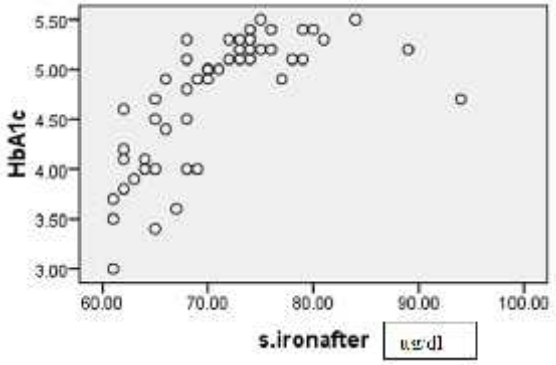
The r value for haemoglobin was-0.327, for serum iron it was -0.826 & for ferritin it was-0.748. After iron therapy in same individuals, the haemoglobin & ferritin were negatively correlated to HbA1c (graph 2b, 2c respectively) but serum iron was positively correlated to HbA1c (figure 2a).



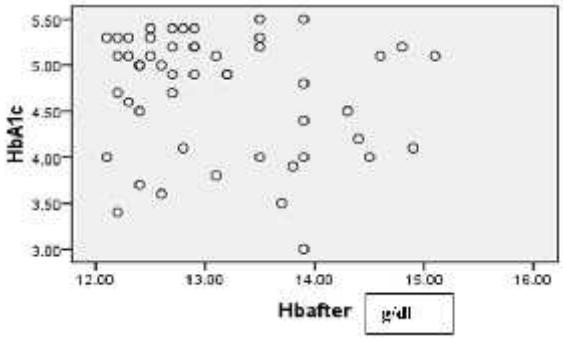
Graph 1b Scatter plot showing relationship between HbA1c & s. ferritin (before Iron therapy)



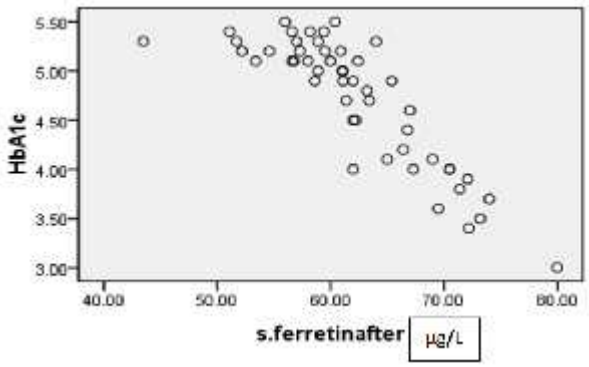
Graph 1c Scatter plot showing relationship between HbA1c & Hb (before Iron therapy)



Graph 2a Scatter plot showing relationship between HbA1c & s.iron (After Iron therapy)



Graph 2b Scatter plot showing relationship between HbA1c & Hb (After Iron therapy)



Graph 2c Scatter plot showing relationship between HbA1c & S.Ferritin (After Iron therapy)

The r value for haemoglobin was -0.081 but it was statistically non significant (p was 0.57) & it was -0.907 for ferritin & it was highly significant. (p was <0.001). The r value for serum iron & HbA1c after iron therapy was 0.765. (p was <0.05)

DISCUSSION

In our study as the before & after groups were having same subjects**,** individual factors which may create bias are reduced to minimum as the age & sex ratio was same. Other factors which may affect HbA1c level were carefully excluded from the subjects eg. CRF, alcoholism hemoglobinopathies, particular drug exposure. The measurement of HbA1c was done with same method & in same laboratory.

Iron therapy & mean HbA1c

In our study mean HbA1c level of subjects having iron deficiency anemia (IDA) decreased significantly (p value >0.05) after iron therapy. Mean FBS & mean PPBS showed minute difference which was not significant (p value >0.05). Although multiple daily glucose readings should to be taken to compare average plasma sugar level over 3 months before & after therapy. But it was not possible in our study. Catherine *et al* (2010) found that iron deficiency anemia was associated with higher HbA1c distribution in comparison to normal subjects. It was 5.32 in iron deficiency in comparison to 5.27 in normal healthy women. Coban *et al* (2004) in their study found that mean HbA1c decreased significantly after iron treatment from a mean of 7.4% ± 0.8 to 6.2% ± 0.6 ($p < 0.001$). Tarim *et al* (1999) found that HbA1c in IDA patients decreased from 7.6 ± 2.6 to 6.2 ± 1.4% after iron therapy ($P > 0.05$), despite similar glucose levels.

Correlation of anemic outcome variables & HbA1c level

In our study we found out the relationship between HbA1c & iron indices (s.iron, s.ferritin) & also hemoglobin. The most consistent & robust correlation was between serum ferritin & HbA1c. Before iron therapy & after iron therapy it was negatively correlated with s.ferritin & Carl Pearson coefficient r was -0.74 & - 0.90 respectively (p value <0.001) which means iron store was deciding factor in therapy for HbA1c difference. But serum iron was not having conclusive relationship, as it was negatively correlated before therapy & positively correlated after therapy. So iron store marker i.e. serum ferritin rather than simple s. iron level was better explanatory for effect. Koga *et al* (2007) in their study found negative correlation between HbA1c & haemoglobin & also

with MCH & MCV that was significant. They concluded that erythrocyte indices were associated with HbA1c independent of plasma sugar. Hardikar PS *et al* (2012) found that lower Hb, lower MCH, lower MCV & higher red cell distribution width were associated with higher HbA1c. Further they found that lower s. ferritin concentration predicts higher HbA1c supporting an association with iron deficiency despite normal glucose tolerance. They concluded that use of HbA1c to diagnose prediabetes & diabetes in nutritionally compromised population might produce misleading estimates of prevalence. Reduction in HbA1c after iron replacement is postulated due to the formation of new red cells & alteration in glycation rate of haemoglobin (Brooks AP *et al*, 1980; Kim C *et al*, 2010). The proposed mechanism for increased glycation of haemoglobin moiety in iron deficiency anemia is lipid peroxidation & increased malondialdehyde in iron deficiency anemia (Sundaram RC *et al*, 2007).

The limitation of study

The limitation of this study is that , although in our study there was no significant difference in FBS & PPBS in before & after group; multiple daily glucose readings should be obtain to measure the glycemia level over 3 months which is determinant of HbA1c, instead of comparing mean FBS & mean PPBS.

CONCLUSION

Iron deficiency anemia is associated with increased HbA1c. Iron therapy reduced the increased HbA1c in IDA patients. Iron deficiency anemia is independent factor affecting HbA1c. So interpretation of HbA1c should be done carefully keeping the fact in mind that it is accurately valid after correction of anemia.

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