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Integrity loss of glycosylated hemoglobin with deepening anemia

Bünyamin Aydın[1], Aysun Gönderen[2]

[1]Health Sciences University, Kütahya Evliya Celebi Training and Research Hospital, Division of Endocrinology and Metabolism, Kütahya, Turkey
[2]Health Sciences University, Kütahya Evliya Celebi Training and Research Hospital, Division of Hematology, Kütahya, Turkey

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ABSTRACT

Introduction: Iron deficiency anemia (IDA) has been shown to cause a false increase in glycosylated hemoglobin (HBA1c), but how much increase in hemoglobin (Hgb) causes a certain decrease in HBA1c remains unknown. Knowledge of this ratio will enable more accurate clinical diagnosis and follow-up of diabetes. This study aimed to investigate whether IDA causes a decrease in HBA1c and if it does, how much of a decrease it causes.

Material and Method: One hundred and twenty-two patients with IDA made up the study group and sixty-two health volunteers formed the control group. 270 mg ferrous sulphate (=80 mg elemental iron) were administered to the study group each day, orally for 3 months, and a control of age/sex matched healthy participants were monitored. Hgb, serum iron, serum iron binding capacity (SIBC), ferritin and HbA1c levels of all participants were measured and compared at baseline and at the third month of the study.

Results: There was a significant decrease in HbA1c and SIBC levels at baseline and 3 months in the study group ($p<0.001$, $p<0.001$, $p<0.001$ respectively) and a significant increase in serum iron, ferritin and Hgb ($p<0.001$, $p<0.001$, $p<0.001$ respectively). It was found that a 1 mg/dl increase in Hgb level resulted in a 0.113% decrease in HbA1c.

Conclusion: As anemia deepens, HBA1c loses its reliability for diagnosis and follow-up of DM. IDA should be considered before any diagnosis or treatment decisions are made according to HbA1c levels.

Keywords: anemia, diabetes, glycosylated hemoglobin

INTRODUCTION

Anemia is a worldwide public health issue affecting 1.62 billion people or a quarter of the world's population, both in the first world and developing countries. There are a range of anemia types but the most prevalent is IDA, which constitutes one third of all anemia cases in the world (1).

HbA1c is commonly used to diagnose as well as monitor DM (2). The main factor influencing HbA1c is blood glucose, however, circumstances such as IDA, hemolytic anemia, alcohol, pregnancy, blood loss and uremia are believed to alter HbA1c levels independent of glycemic state (3). Relying only on HbA1c measurements for patients with DM is controversial, and studies have shown IDA to cause false high HbA1c values (4-6), though the cause remains elusive (7). Glycosylation of hemoglobin is irreversible, therefore, HbA1c levels in RBC rise with cell age (8). IDA is correlated with longer RBC survival which leads to higher HbA1c levels. In addition, elevated malondialdehyde (MDA) levels in IDA increase Hgb glycosylation. It has been alleged that a combination of these two mechanisms may result in an erroneous increase in HbA1c levels in patients with IDA (9).

Both DM and IDA are very common around the world and as such, the possibility of these two diseases co-existing is also very high (3). Clinical consequences of any correlation between body iron and HBA1c will affect many patients with DM and IDA. Because false raised HBA1c will lead to an incorrect diagnosis of diabetes and inappropriate follow-up and treatment of diabetic patients. If the HBA1c level decreases after iron treatment in a patient with IDA, it is necessary to demonstrate how much increase in Hgb causes a decrease in HBA1c

Corresponding Author: Bünyamin Aydın, aydinbunyamin@yahoo.com
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in order for the decrease in HBA1c to be useful in the diagnosis and follow-up of diabetic patients. There is only one study on this subject in the diabetic patient population without a control group (10), and further studies are needed. Our study was carried out in the non-diabetic patient group in comparison with the control group. Our study was conducted to investigate whether the HBA1c level decreases after iron deficiency anemia treatment and if it does, how much of an increase in Hgb causes a certain decrease in HBA1c.

MATERIAL AND METHOD

The clinical trial protocol was approved by the Ethics Committee of Kütahya Health Sciences University, Kütahya Evliya Çelebi Training and Research Hospital (Date: 08.07.2021 Decision No: 2021/12-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study was carried out between October 2020 and July 2021 in the Department of Endocrinology and Metabolism Diseases of Kütahya Health Sciences University, Kütahya Evliya Çelebi Training and Research Hospital. Patients who met the inclusion criteria were sequentially included in the study after written informed consent was obtained.

Patients with IDA included in the study group did not have any prior diagnosis of DM, were not on any anti-diabetic medication and had fasting plasma glucose (FPG) < 100 mg/dl, HbA1c < 6.5% female hemoglobin (Hgb) < 12 g/dl and male 13 g/dl, mean corpuscular volume (MCV) < 80 (fL), ferritin < 15 ng/ml. Since ferritin, which shows iron stores in the body, is also an acute phase reactant and may be influenced by any infectious circumstance, only patients with normal c-reactive protein (CRP) values were included in the study. Patients on any medication that may influence body weight were excluded from the study as these may alter HbA1c by affecting insulin resistance.

One hundred and thirty four patients of the study group and 66 healthy volunteers in the control group meeting the inclusion and exclusion criteria were included in the study. In the study group, 3 patients who did not comply with treatment and follow up, 6 patients who could not tolerate oral iron treatment and 3 patients whose Hgb failed to increase despite iron treatment were excluded from the study. Also, four patients who failed to comply with follow up were excluded in the control group. The study was completed with 122 patients in total in the study group and 62 healthy volunteers in the control group.

Eligibility

Inclusion criteria: (a) Male and female patients over age 18 (b) No previous diagnosis of DM and not on any anti-diabetic medication (c) For study group, a diagnosis of IDA (male Hgb <13 mg/dl, female Hb <12 mg/dL, MCV <80 (fL), ferritin <15 ng/dl), for control group male Hb >13 mg/dl, female Hb >12 mg/dL, MCV >80 (fL), ferritin >15 ng/dl) (d) CRP within normal range (e) Compliance with treatment and follow up (f) Acceptance of inclusion in the study.

Exclusion criteria: (a) Diagnosed with DM or use of any anti-diabetic medication (b) Diagnosis of anemia other than IDA (c) Patients whose Hgb failed to increase despite oral iron treatment (d) Patients with high CRP values (e) Patients on medications which aid weight loss such as a glucagon like peptid-1 (GLP1) analogue or orlistat (f) Patients on any medication known to affect body weight (g) Patients with abnormal thyroid function tests, on levothyroxine or anti-thyroid medication (h) Patients with a history of surgery for obesity (i) Patients with any endocrinopathy that may result in obesity (Cushing's syndrome, acromegaly, hypothyroidism, etc.) (j) Patients with acute coronary syndrome, heart failure, cerebrovascular disease, pregnancy, chronic liver disease, abnormal renal function tests and malignancy (k) Patients with a history of blood transfusion during the past year (l) Patients who failed to comply with monitoring and treatment (m) Patients who declined to be included in the study.

Treatment and Follow-up

Patients were administered 270 mg/day ferrous sulphate (=80 mg elemental iron) for three months for the treatment of IDA. Age/sex matched healthy participants were followed as the control group. Hb, MCV, hematocrit (Hct), red blood cells (RBC), platelets (PLT), white blood cells (WBC), serum iron, serum iron binding capacity (SIBK), serum ferritin, fasting plasma glucose (FPG), HbA1c, body mass index (BMI), CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine and blood urea nitrogen (BUN) values of patients were measured at the start and following 3 months of treatment with iron and compared.

Biochemical Analysis

Blood samples were obtained in the morning at the start of the study and following 3 months of treatment with iron after at least 10 hours of fasting through the night. Venous fasting blood samples were obtained from one antecubital vein in 8 ml anticoagulant free tubes. Blood in the straight tubes was allowed to coagulate for 30 minutes and centrifuged at 3000 rpm at room temperature. Repeated freezing and defrosting was avoided. HbA1c was measured with high performance liquid chromatography (HPLC) using a TOSOH device, and serum ferritin was measured with electrochemiluminescence immunoassay

(ECLIA) using a Beckman Coulter UniCel Dxl 600 device. Hemogram was evaluated flow cytometrically with a Mindray BC-6800 device. Serum iron, SIBK, CRP, FPG, creatinine, AST, ALT, BUN values were measured with a Beckman Coulter Systems' au5800 series device using spectrophotometry.

Statistical Analysis

The normality of distribution was examined using the Kolmogorov-Smirnov test. Descriptive statistical methods including percentage and mean±standard deviation (SD) or median (min.- max.) were used to provide basic characteristics of the data. A Wilcoxon signed ranks test was used for non-normally distributed continuous variables for the study group (FPG, Hgb, Hct, RBC, MCV, WBC, serum iron, SIBC, ferritin, CRP) and the control group (FPG, Hgb, RBC, MCV, PLT, serum iron, ferritin, CRP). A paired samples t-test was used for normally distributed continuous variables of the study group (HBA1c, BMI, PLT) and control group (HBA1c, Hct, WBC, SIBC, BMI) Statistical analyses were carried out using SPSS23.0 version (IBM Corporation, Armonk, NY, US). When two-tailed p <0.05, differences were considered statistically significant. Regression models were used for increases and decreases in Hgb values. Results were obtained by using Hgb values at baseline and third month. A regression model analysis was carried out using Excel 16.0 (2016).

RESULTS

Baseline Characteristics

The total number of patients included 93 women (76.23%) and 29 men (23.7%) in the study group, and 47 women (75.81%) plus 15 men (24.19%) in the control group. The median age of women was 41.13±8.73 and men 44.21±8.42 in the study group, and 41.04±7.58 for women and men 44.93±4.34 in the control group (**Table 1**). When the baseline and 3 month data were compared, there was no significant difference between the study group and the control group in terms of BMI (p:0.332, p:0.399 respectively) (**Table 2-3**).

Blood Glucose Parameters

While the baseline HbA1c for the study group was 5.90 ±0.37 (%), it was 5.48±0.48 (%) at third month, which was significantly lower (p <0.001). Baseline HbA1c for the control group was 5.52±0.33 (%) and 5.53±0.30 (%) at the third month, showing no statistically significant difference (p:0.578). Baseline and third month FPG (mg/dL) levels for the study group were 94.00 (81-138) and 92.00 (80-142) respectively, and there were no statistically significant difference (p:0.256). Baseline and third month FPG (mg/dL) levels for the control group (mg/dL) were 94.50 (81-128) and 92.00 (80-138) respectively and also showed no statistically significant difference (p:0.071) (**Table 2-3**).

Table. 1 Demographic parameters

Characteristic	Study group (n=122)	Control group (n=62)
Mean age, years	Male : 44.21±8.42	Male: 44.93±4.34
	Female: 41.13±8.73	Female: 41.04±7.58
Sex male/female %	Male: 29 (23.77 %)	Male: 15 (24.19%)
	Female: 93 (76.23 %)	Female: 47 (75.81%)

Table 2. Comparison of baseline and 3rd month values of study group

	Baseline	3rd Month	p
HbA 1c, (%) †	5,90±0,37	5,48±0,48	<0.001
FPG (mg/dL) *	94.00 (81-138)	92.00 (80-142)	0.256
Hgb (g/dL) *	10.25 (5.7-11.8)	12.70 (11.6-15.0)	<0.001
Hct (%) *	32.95 (23.1-38,0)	40.25 (38.1-45.4)	<0.001
RBC (10^6/uL) *	4.40 (2.7-5.6)	4.80 (3.9-6.8)	<0.001
MCV (fL) *	73.00 (62.0-79.0)	82.90 (77.5-92.0)	<0.001
PLT (10^3/uL) †	335.17±77.43	287.52±64.70	<0.001
WBC (10^3/uL)*	7.40 (3.9-7.3)	7.50 (4.2-8.3)	0.190
Serum Iron (ug/dL) *	20.00 (2-57)	58.00 (18-272)	<0.001
SIBC (ug/dL) *	417.50 (273-584)	331.00 (131-481)	<0.001
Ferriti (ug/L) *	3.00 (1-29)	14.00 (3-208)	<0.001
CRP (mg/L) *	1.60 (0.10-4.70)	1.80 (0.20-4.60)	<0.001
BMI (kg/m²) †	26.94±3.32	26.97±3.38	0.332

HBA1c: glycosylated hemoglobin, FPG: fasting plasma glucose, Hgb: hemoglobin, Hct: hematocrit, RBC: red blood cell, MCV: mean corpuscular volume, PLT: thrombocyte, WBC: white blood cells, SIBC: serum iron binding capacity, CRP: c-reactive protein, BMI: body mass index
* Data are presented as median (minimum-maximum and compared by Wilcoxon signed ranks)
† Data are presented as mean±SD and compared by paired samples t test

Table 3. Comparison of baseline and 3rd month values of control group

	Baseline	3rd Month	p
HbA 1c, (%) †	5.52±0.33	5.53±0.30	0.578
FPG (mg/dL)*	94.50 (81-128)	92.00 (80-138)	0.071
Hgb (g/dL)*	13.00 (12.0-14.9)	13.10 (12.0-14.4)	0.441
Hct (%)†	41.37±1.68	40.92±1.32	0.017
RBC (10^6/uL)*	4.80 (4.1-5.8)	4.85 (4.2-6.8)	0.494
MCV (fL) *	84.67±2.81	84.89±2.84	0.558
PLT (10^3/uL)*	281.50 (184-442)	286.00 (175-442)	0.685
WBC (10^3/uL)†	7.10±1.74	7.38±1.75	0.067
Serum Iron (ug/dL)*	61.50 (12-266)	61.50 (20-185)	0.840
SIBC (ug/dL)†	314.08±62,10	308.03±71,05	0.537
Ferritin (ug/L)*	18.00 (6-96)	20.00 (5-113)	0.768
CRP (mg/L)*	1.60 (0.10-4.70)	1.80 (0.20-4.60)	0.592
BMI (kg/m²)†	27.07±3.09	27.11±3.17	0.399

HBA1c: glycosylated hemoglobin, FPG: fasting plasma glucose, Hgb: hemoglobin, Hct: hematocrit, RBC: red blood cell, MCV: mean corpuscular volume, PLT: thrombocyte, WBC: white blood cells, SIBC: serum iron binding capacity, CRP: c-reactive protein, BMI: body mass index
* Data are presented as median (minimum-maximum and compared by Wilcoxon signed ranks)
† Data are presented as mean±SD and compared by paired samples t test

Hematological Parameters

When baseline and third month WBC levels in the study group were compared, no significant differences were observed (p:0.190), however, SIBC and PLT showed significant decreases (p<0.001, p<0.001 respectively), and RBC, MCV, serum iron, ferritin and Hgb showed significant increases (p<0.001, p<0.001, p<0.001,

p<0.001, p<0.001 respectively) (**Table 2**). When baseline and third month serum iron, SIBC, ferritin, Hgb, MCV, RBC, WBC and PLT in control group values were compared, no statistically significant differences were observed (p:0.840, p:0.537, p:0.768, p:0.441, p:0.558, p:0.494, p:0.067, p:0.685 respectively) (**Table 3**).

Regression between Hgb and HbA1c

An increase of 1 mg/dL in Hgb was found to result in a 0.113784 % decrease in HbA1c. The table below shows the progression of the regression method when 1 was added to Hgb values of 3 randomly selected patients.

HbA1c values showed a 0.113784% decrease at the third month of study					
	Baseline HbA1c Study Group	**Baseline Hgb Study Group**	**Hgb at 3rd Month Study Group**	**HbA1C at 3rd Month Study Group**	**Difference**
Patient 1	7.1	11.2	12.9	6.452213505	0
Patient 1	7.1	11.2	13.9	6.338429777	0.113784
Patient 1	7.1	11.2	14.9	6.224646049	0.113784
Patient 2	5.7	10.7	12.1	5.427191807	0
Patient 2	5.7	10.7	13.1	5.313408079	0.113784
Patient 2	5.7	10.7	14.1	5.199624351	0.113784
Patient 3	6	11.1	13.8	5.479490192	0
Patient 3	6	11.1	14.8	5.365706464	0.113784
Patient 3	6	11.1	15.8	5.251922736	0.113784

DISCUSSION

In our study, IDA was found to be correlated with increased HbA1c concentrations with statistically significant decreases observed following iron treatment. The most important finding of our study was that a 1 mg/dL increase in Hgb level causes a 0.113% decrease in HBA1c. We believe this may be due to normalization of RBC survival which was prolonged and decrease in malondialdehyde levels following iron treatment.

The first research to study the influence of IDA on HbA1c levels was by Horton and Huisman (11), who showed HbA1c concentrations to be medium, 5.3%, in 14 healthy individuals and 4.9% in patients with IDA.

Studies were often performed on normoglycemic patient groups and the relationship between IDA and HbA1c evaluated. The baseline HbA1c of 50 patients with IDA without DM and 50 healthy volunteers without IDA or DM were compared and HbA1c was observed to be significantly higher in the group with IDA (12). Similarly, in a study by Son et al. (13), of 112 patients with IDA and 217 healthy individuals without IDA, the baseline HbA1c was proposed to have low specificity in the group with anemia, therefore, HbA1c was a limited parameter for diagnosis of DM. In studies with IDA patients without DM where HbA1c levels were evaluated following iron treatment, HbA1c showed significant decreases with iron and HbA1c was reported to result in the false diagnosis of DM in patients with IDA (4-6, 14-15).

In a review in 2017, it was concluded that IDA is correlated with increased HbA1c concentrations both in diabetic and non-diabetic individuals and iron treatment results in a decrease in HbA1c (7). The findings of our study are consistent with these studies. All data support the idea that iron deficiency should be corrected before making a diagnosis of pre-diabetes or diabetes.

Although the design and results of our study and the studies mentioned above differ, the rationale for research is similar. In short, there is an uncertainty and possibility of error in utilizing HbA1c in the diagnosis and monitoring of diabetes. The International Expert Committee warned clinicians to be wary of any conditions which may affect RBC turnover during the follow-up with diabetes patients (16). IDA is the most prevalent reason affecting RBC turnover. The interpretation of HbA1c based on information from a hematological examination and iron metabolism indices may help to prevent misdiagnosis or under-diagnosis, and HbA1c should be evaluated carefully as a parameter of glycemic control in patients with IDA (17).

The American Diabetes Association (ADA) suggested using only plasma glucose, not HbA1c as a diagnostic criterion for diabetes in patients with IDA (18). In accordance with the ADA, our study also supports not using HbA1c for the diagnosis and monitoring of patients with IDA.

Following the observation that HbA1c decreases with treatment of IDA, the first question is: how much HbA1c decrease is caused by the rise in Hgb. There is only one study on this subject in diabetic patients without a control group, and it was found that 2.2 mg/dL increase in Hgb value caused a 0.4% decrease in HBA1c level (10). In our study, it was determined that 1 mg/dL increase in Hgb value caused a 0.113% decrease in HBA1c value. This means that the deeper the IDA, the more the reliability of HBA1 is lost. This ratio should be supported with multi-centre studies and more patient participation. We believe our study is valuable to future research as it may be the beginning of a new ratio to be included in DM diagnosis and monitoring guidelines.

IDA is more common especially in young women of reproductive age (1). The majority of the patient

population in our study consisted of female patients at this age. The results of our study showed that it is of particular importance whether IDA is coexisting when diagnosing diabetes according to HBA1c in women in this group or when following a diabetic patient. If IDA coexists, it would be more appropriate to diagnose and follow-up diabetes based on the HBA1c level after eliminating the iron deficiency. Gestational diabetes mellitus (GDM), is one of the most widely encountered metabolic disturbances. Macrosomy, neonatal hypoglicemia, neonatal hypocalcemia, neonatal hypomagnesemia and potential respiratory problems of newborn are more prevalent in the newborn of women with GDM (19). For this reason, in a pregnant patient, examining HBA1c level after the iron deficiency is eliminated would enable a more accurate diagnosis of whether it is gestational DM or is it pregestational DM.

The limitations of our study are low patient numbers and study being performed in a single centre. Multi-centre studies with more participants are required.

CONCLUSION

In our study, we found that a 1 mg/dL increase in Hbg causes a 0.113% decrease in HBA1c. This shows that HBA1c loses its reliability in the diagnosis and follow-up of DM as the anemia deepens. Elimination of iron deficiency before any diagnosis or treatment decision is made based on the HbA1c level will prevent patients from being misdiagnosed with diabetes and prevent additional unnecessary intervention in diabetes treatment of diabetic patients. Nevertheless, implementing additional treatment to diabetic patients with IDA based on the high HBA1c will increase the risk of hypoglycemia in patients and will bring additional drug costs to the state economy. Early diagnosis and treatment of IDA in diabetic patients can improve glycemic control and prevent or delay complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Research Ethics Committee of Kütahya Health Sciences University, Kütahya Evliya Çelebi Training and Research Hospital (Date: 08.07.2021 Decision No: 2021/12-04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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