Effect of Iron Deficiency Anemia on Glycated Hemoglobin and Glycated Albumin Levels in Non-Diabetic Patients: Role of Malondialdehyde

Medhat A Ghazy[1], Tamer A Elbedewy[1], Nivin Baiomy[2], Hossam Hodeib[2]

[1] Internal Medicine Department, Faculty of Medicine, Tanta University, Egypt
[2] Clinical Pathology Department, Faculty of Medicine, Tanta University, Egypt
E-mail: tamerelbedewy2006@ yahoo.com, tamer.elbedawi@med.tanta.edu.eg

Abstract: Background/aim: HemoglobinA1c (HbA1c) is used to assess the long-term glycemic control. Glycated albumin (GA) is a short-term glycemic marker, not influenced by hemoglobin disorders. The studies about the effect and mechanism of iron deficiency anemia (IDA) on HbA1c are conflicting and not yet known. IDA promotes oxidative stress. Malondialdehyde (MDA) found to be elevated in oxidative stress. The aim of our work to investigate the effect of IDA before and after treatment on HbA1c and GA levels in non-diabetic patients and the role of MDA in this effect. **Subjects and methods:** Prospective study was conducted with 105 participants divided into two groups. Group I comprised 85 IDA patients treated with intravenous iron, 60 patients respond to treatment which complete the study. Group II included 20 apparently healthy participants as control group. Complete blood count, iron profile, HbA1c, GA and MDA were measured before treatment and after 12 weeks from the beginning of intravenous iron infusion. **Results:** HbA1c and MDA are significantly higher in IDA before treatment than the controls. HbA1c and MDA decreased significantly by iron therapy. Insignificant difference between the controls, IDA patients as regard GA. Significant negative correlations between HbA1c and hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), serum ferritin, serum iron and transferrin saturation**.** Significant positive correlations between HbA1c and total iron binding capacity (TIBC) and serum MDA**. Conclusions**: GA rather HbA1c is better glycemic marker in IDA. Caution should be used when diagnosing diabetes among IDA patients using HbA1c. MDA may play a role in HbA1c elevation in IDA.
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1. Introduction

Glycemic markers are indispensable in routine practice to guide diabetes therapy as well as in clinical trials to investigate the efficacy of medications on patients' glycemic control. Glycemic markers cover different periods of glycemic control, they also provide different information on glucose metabolism and may reflect different pathways [1].

Hemoglobin A1c (HbA1c) has been widely used to assess the long-term glycemic control and the risk for the development of complications in diabetes. More recently, there has been a move towards the use of HbA1c for the diagnosis of type 2 diabetes at a value of 6.5% [2]. It appears that glycation of hemoglobin is not simply a concentration dependent process, and factors other than glucose are likely to be involved [3]. HbA1c is affected by a variety of conditions, such as hemolytic anemia, chronic renal failure, and the presence of hemoglobin variants. Under these circumstances, HbA1c cannot be used as a glucose control measure; and alternative markers should be considered [4, 5].

Glycated albumin (GA), fructosamine, and 1, 5-anhydroglucitol (1, 5-AG) are non-traditional markers of hyperglycemia that are not routinely used in clinical practice. There is ongoing debate about whether these markers may have utility as measures of glycemic control in the management of diabetes [6–7].

Glycated albumin is an alternative marker reflecting short-term glycemic control, which is influenced less by disorders of hemoglobin metabolism. Since albumin is glycosylated at approximately 10 times the rate of hemoglobin, GA is more sensitive to the change of blood glucose levels [8]. However, GA is influenced by the pathologic conditions affecting albumin metabolism, such as nephrotic syndrome, liver cirrhosis and thyroid dysfunction [9].

Some studies showed that HbA1c levels were higher in patients with iron deficiency anemia. The results of these studies are conflicting, and the exact mechanism underlying the effects of iron deficiency anemia on HbA1c levels is not yet known [10, 11]. Iron deficiency anemia is known to promote oxidative stress and lipid peroxidation due to inadequate tissue oxygen and free radical production [12]. Malondialdehyde (MDA) is a product of lipid peroxidation and has been found to be elevated in

conditions of oxidative stress [13-15]. Recently, lipid peroxides *per se* can enhance the process of protein glycation [16].

So the aim of our work to investigate the effect of iron deficiency anemia before and after treatment on glycated hemoglobin and glycated albumin levels in non-diabetic patients and the role of malondialdehyde in this effect.

2. Subjects and Methods

Study Population

This prospective study was conducted on 105 participants divided into two groups. The first group (Group I) comprised 85 iron deficiency anemia (IDA) patients treated with intravenous iron, 60 patients respond to treatment and complete the study and 25 patients were non-responders and excluded from the study. The second group (Group II) included 20 (sex and age) matched apparently healthy participants (non-IDA) as control group. This study was conducted at Tanta University Hospitals, Internal Medicine Department, between January 2014 and June 2015. This study was carried out in accordance with the guidelines of the declaration of Helsinki and its subsequent amendments. Written consent was obtained from all participants prior to enrollment in the study.

Patients with a history of acute blood loss, hemolytic anemia, hemoglobinopathies, kidney disease, hemodialysis, liver cirrhosis, pregnancy, diabetes mellitus, impaired fasting glucose, or im-paired glucose tolerance were excluded.

Patients were diagnosed to be anemic according to The World Health Organization definition of anemia as a hemoglobin level <13 g/dL in men and <12 g/dL in non-pregnant women [17]. IDA was diagnosed when serum ferritin values <12 µg/L [18].

All patients were asked to provide a detailed history and were subjected to complete physical examination before treatment administrated.

IV Iron Administration:

The total iron dose required for iron repletion was calculated according to Ganzoni formula [19].

Cumulative iron deficit = [body weight (kg) × (target hemoglobin – actual hemoglobin) (g/dL) × 2.4] + iron depot (mg), where target hemoglobin in this formula for body weight ≥35 kg is 15 g/dL and iron depot is 500 mg.

Treatment was administered 3 times / week (every other day) until iron repletion was achieved. At each visit, the patient was placed in the supine position and underwent a vein cannulation of the forearm. This was connected through IV tubing to a 200 mL bag of 0.9% isotonic saline solution, to which 200 mg of iron sucrose were added. Each infusion was administered over 2 hours. Patients were observed carefully during the infusion and for at least 2 hours after completion of infusion [20].

Therapy was considered effective when serum ferritin level reached between 200 and 300 ug/L or transferrin saturation reached between 30% and 40% with normal hemoglobin level after 12 weeks from the beginning of intravenous iron infusion [21,22].

Laboratory Testing:

All laboratory investigations were done at Clinical Chemistry and Hematology Units, Clinical Pathology Department at the start of the study (before IDA treatment), and after 12 weeks from the beginning of intravenous iron infusion (after IDA treatment). Morning 12-hours overnight fasting venous blood sample (5 ml) was collected by trained laboratory technicians. The levels of hemoglobin, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) were measured by an automated counter (PCE-210N-ERMA INC). Serum ferritin was estimated by ferritin ELISA coated microtiterstrips (CalbiotechInc, Spring Valley, CA, USA). Serum iron and total iron binding capacity (TIBC) were estimated by colorimetric method. Transferrin saturation was calculated by dividing serum iron/TIBC [23,24].

Principle of (HbA1c) measurement:

Serum HbA1c was measured via high-performance liquid chromatography using a (Hemoglobin A1C Chromatographic – spectrophotometric ion exchange cod - 11045) (BIOSYSTEMS, reagents and instruments). HbA1c measurements were standardized to the reference method according to the Diabetes Control and Complications Trial (DCCT) assay and the National Glycohemoglobin Standardization Program (NGSP) standards using the following formulas: %HbA1c-NGSP = 0.86 x %HbA1c-BioSystems + 0.24. The reference interval was (4.0% and 6.0%) for HbA1c [25].

After preparing the hemolysate, where the labile fraction is eliminated, hemoglobins are retained by a cationic exchange resin. Hemoglobin A1c (HbA1c) is specifically eluted after washing away the hemoglobin A1a+b fraction (HbA1a+b), and is quantified by direct photometric reading at 415 nm [26].

Principle of (GA) measurement:

Serum GA was determined by an enzymatic method utilizing an albumin-specific proteinase, ketamine oxidase, albumin assay reagents (LUCICA GA-L; Asahi Kasei Pharma Co., Tokyo, Japan). Glycated albumin was expressed as a percentage of total serum albumin according to the manufacturer's instructions, that is, [(glycated albumin)/ (serum albumin)×100/1.14+2.9]%. The reference interval for GA was 11.0% to 16.0%.

In the enzymatic assay, endogenous glycated amino acids and peroxide are first eliminated by ketoamine oxidase and peroxidase reaction. Second, GA is hydrolyzed to amino acid or peptide by an albumin-specific proteinase, and then the glycated amino acid or peptide is oxidized by ketoamine oxidase producing hydrogen peroxide, which is measured quantitatively. Third, the albumin concentration is measured by the bromocresol purple (BCP) method.

Principle of (MDA) measurement:

The level of malondialdehyde (MDA) in serum was determined according to **Ohkawa *et al.*** [27] using MAK085 SIGMA Lipid Peroxidation (MDA) Assay Kit. In this kit, MDA content of samples was determined by the thiobarbituric acid (TBA) activity. MDA of the serum sample reacts with TBA to form a coloured pigment, the absorption of which is measured by spectrophotometer at 535nm. The results are presented in (nmol/ml).

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 17 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. Comparison of continuous data between (IDA patients and controls) was made by using unpaired t- test for parametric data and Mann-Whitney test for nonparametric data. Comparison of continuous data between (IDA patients before and after treatment) was made by using paired t- test. Fisher's exact was used for comparison between Categorical data. Spearman & Pearson tests for correlations between different parameter (nonparametric & parametric respectively) were used. *P*-value ≤ 0.05 was considered statistically significant.

3. Results

Our study included 60 adult patients with iron deficiency anemia (group I) (21 men (35%) and 39 women (65%)); their ages ranged between 22 and 62 years (mean age 41.57±10.214 years). The control group (group II) included 20 healthy participants (8 men (40%) and 12 women (60%)); their ages ranged between 24 and 55 years (mean age 42.25±8.967 years). There were insignificant differences between group I and group II as regard age and sex. Comparison between the laboratory characteristics are shown in **(Table 1)**.

Table (1): Laboratory characteristics of the studied groups.

Variables	Group Ia (IDA before treatment) (No=60) Mean ± SD (Range)	Group Ib (IDA after treatment) (No=60) Mean ± SD (Range)	Group II (control) (No=20) Mean ± SD (Range)	*P1*	*P2*	*P3*
Hemoglobin (g/dl)	8.75±1.128(6.5-10.7)	12.56±0.601 (12-13.7)	13.41±1.035(12-15.2)	**<0.0001***	**<0.0001***	**<0.0001***
Mean corpuscular volume (MCV) (fl)	69.17±3.823(60-75)	88.47±4.969 (81-98)	89.75±4.844(81-97)	**<0.0001***	0.2885	**<0.0001***
Mean corpuscular hemoglobin (MCH) (pg)	22.78±1.757(20-26)	29.03±1.594 (27-32)	29.1±1.447(27-31)	**<0.0001***	0.802	**<0.0001***
Serum ferritin (ug/L)	7.42±2.29(3-11)	236.15±24.576 (202-286)	114.6±36.107(70-180)	**<0.0001***	**<0.0001***	**<0.0001***
Serum iron (ug/dL)	30.67±9.257(15-49)	102.45±22.621(72-164)	107.85±27.396(72-162)	**<0.0001***	0.4329	**<0.0001***
Total iron binding capacity (TIBC) (ug/dL)	389.12±56.342 (260-487)	293.7±49.821(233-444)	306.1±56.252(240-450)	**<0.0001***	0.3711	**<0.0001***
Transferrin saturation (%)	8.30±3.394(3.1-15)	33.91±2.747 (30-39.9)	34.995±4.431(25.9-42.2)	**<0.0001**	0.7667	**<0.0001***
Hemoglobin A1c (HbA1c) (%)	6.53±0.661 (5-7.8)	4.81±0.458 (4-5.5)	4.96±0.437 (4.2-5.7)	**<0.0001***	0.0800	**<0.0001***
Glycated albumin (GA) (%)	13.32±1.139 (11.4-15.2)	13.43±1.161 (11.1-15.4)	13.72±1.428 (11.2-15.9)	0.2692	0.2353	0.8585
Serum malondialdehyde (MDA) (nmol/ml)	2.57±0.5014 (1.77-3.5)	1.15±0.2476 (0.76-1.6)	1.04±0.2107(0.7-1.45)	**<0.0001***	0.0645	**<0.0001***

P1: Group I before treatment vs. control; P2: Group I after treatment vs. control; P3: Group I before treatment vs. after treatment
*: Significant, IDA; Iron deficiency anemia

As regard glycemic markers, our results showed significantly higher levels of hemoglobin A1c (HbA1c) in iron deficiency anemia patients before treatment (group Ia) when compared with both the controls and iron deficiency anemia patients after treatment (group Ib), and also showed an insignificant difference between the controls and iron deficiency anemia patients after treatment as regards HbA1c. Our results revealed insignificant difference between the controls, iron deficiency anemia patients before treatment and iron deficiency anemia patients after treatment as regard glycated albumin (GA) **(Table 1).**

Our results showed significantly higher levels of serum malondialdehyde (MDA) in iron deficiency anemia patients before treatment when compared with both the controls and iron deficiency anemia patients after treatment, and also showed an insignificant difference between the controls and iron deficiency anemia patients after treatment as regard MDA **(Table 1).**

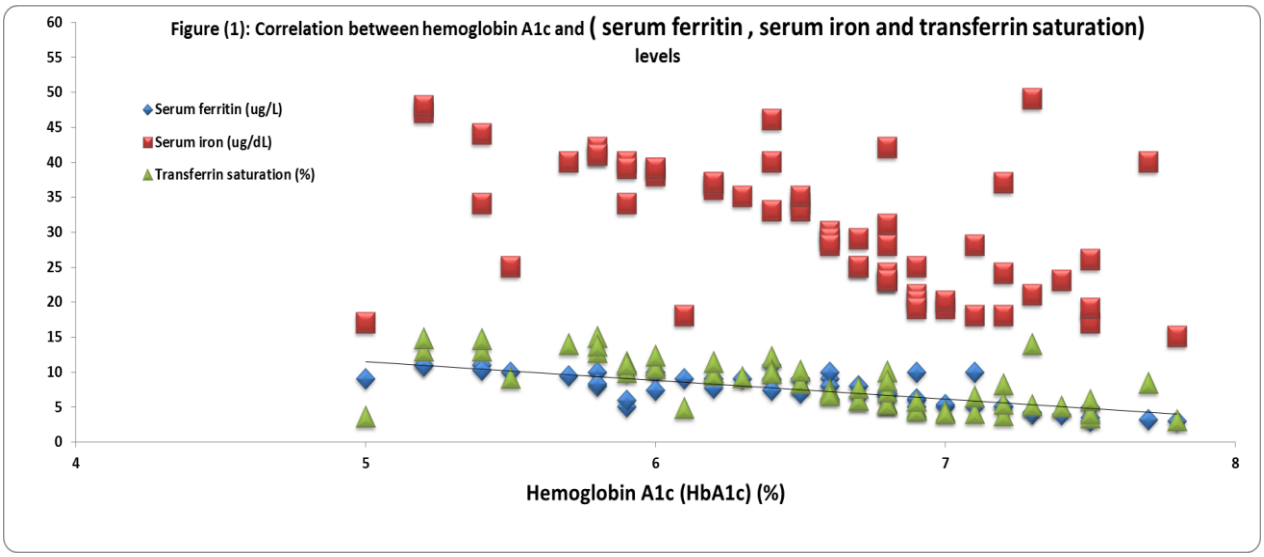
The results of our study (before treatment) (group Ia) showed significant negative correlations between hemoglobin A1c (HbA1c) on one hand and hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), serum ferritin, serum iron and transferrin saturation on the other hand **(Figure 1).** Significant positive correlations were observed between hemoglobin A1c (HbA1c) on one

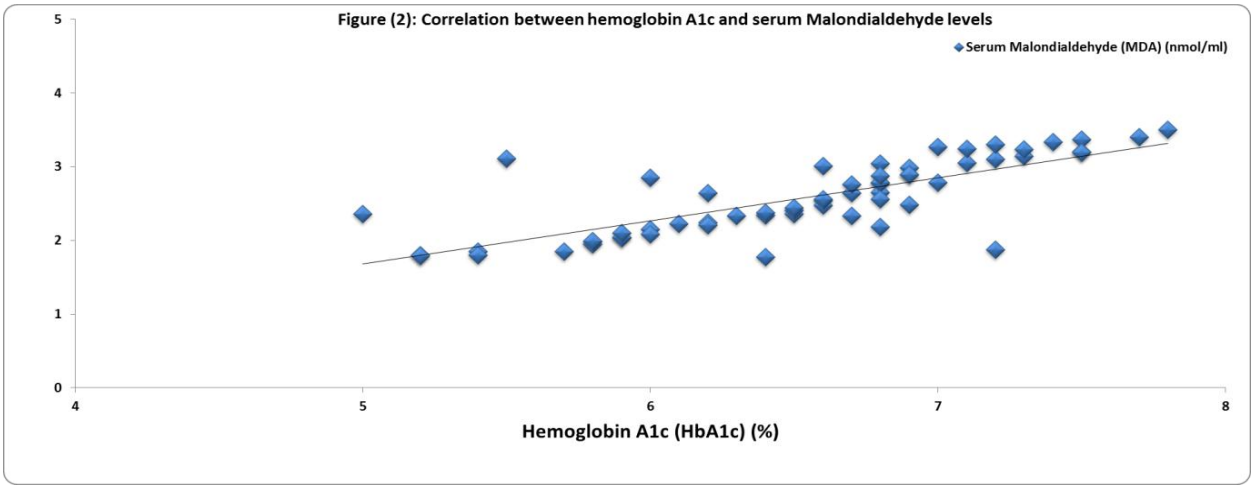
hand and total iron binding capacity (TIBC) and serum malondialdehyde (MDA) on the other hand **(Figure 2).** Other correlations between hemoglobin A1c (HbA1c) and glycated albumin (GA) and other variables are shown in **(Table 2).**

Table (2): Correlations between glycemic markers (hemoglobin A1c and glycated albumin) and different variables among iron deficiency anemia patients before treatment (group Ia).

Variables	Hemoglobin A1c (HbA1c) (%)		Glycated albumin (GA) (%)	
	r	*P*- value	r	*P*- value
Age (years)	- 0.05263	0.6896	- 0.01279	0.9227
Hemoglobin (g/dl)	- 0.3354	**0.0053***	- 0.05216	0.6923
Mean corpuscular volume (MCV) (fl)	- 0.3176	**0.0134***	0.1189	0.3654
Mean corpuscular hemoglobin (MCH) (pg)	-0.2890	**0.0251***	0.01475	0.9110
Serum ferritin (ug/L)	-0.7770	**<0.0001***	-0.07930	0.5470
Serum iron (ug/dL)	- 0.5192	**<0.0001***	- 0.1371	0.2963
Total iron binding capacity (TIBC) (ug/dL)	0.7537	**<0.0001***	0.08982	0.4949
Transferrin saturation (%)	- 0.7013	**<0.0001***	- 0.1255	0.3392
Hemoglobin A1c (HbA1c) (%)	--------	--------	0.08262	0.5303
Glycated albumin (GA) (%)	0.08262	0.5303	--------	--------
Serum malondialdehyde (MDA) (nmol/ml)	0.7733	**<0.0001***	0.05782	0.6608

***:** Significant**.**





4. Discussion:

Iron deficiency is the most prevalent forms of anemia, globally, 50% of anemia is attributed to iron deficiency with absence iron stores [28]. An earlier study showed that reduced iron stores have a link with increased glycation of hemoglobin A1c (HbA1c), leading to false-high values of HbA1c in non-diabetic individuals but the exact mechanism are unknown [29].

Glycation and lipid peroxidation are spontaneous reactions that are believed to play a key role in the pathogenesis of many clinical disorders. Glycation of proteins is enhanced by elevated glucose concentrations [14]. Since cellular energy metabolism is dependent on oxygen, anemia has a wide range of clinical consequences. Iron is required by the enzymes involved is oxidative metabolism. IDA leads to increased oxidative stress and increased lipid peroxidation, however the mechanism is not completely clarified [30]. Malondialdehyde (MDA), the end product of lipid peroxidation, is a good marker of free radical–mediated damage and oxidative stress [31].

Our study showed significantly higher levels of hemoglobin A1c (HbA1c) in iron deficiency anemia patients (IDA) before treatment when compared with the controls. HbA1c decreased significantly by iron therapy in patients with IDA with insignificant difference between the controls and IDA patients after treatment.

This results were conceded with **Kim *et al.* 2010 [32];** who investigated the influence of iron deficiency on HbA1c among non-diabetic adults in huge multicenter study and found after adjusting for age and ethnicity that HbA1c was higher in iron-deficient subjects.

Koga *et al.* 2010[33]; also searched for the effect of iron deficiency state compared with the controls on HbA1c in non-diabetic premenopausal women and found that iron deficiency and IDA had significant higher HbA1c levels when compared with normal controls.

Also, **Shanthi *et al.*2013 [34]** and **Shekhar *et al.* 2014 [35];** demonstrated that HbA1c level in the non-diabetic patients with IDA was higher than that in the control group. **Shanthi *et al.* 2013 [34];** suggested that IDA changes the quaternary structure of hemoglobin leading to increased glycation.

According to the explanation provided by **Sluiter *et al.* 1980;** hemoglobin glycation is an irreversible process. Hence, HbA1 levels in erythrocyte will be increased with cell age. In iron deficiency, red cell production decreases, consequently an increased average age of circulating red cells ultimately leads to elevated HbA1 levels [36].

On the other hand, **Sinha *et al.* 2012 [37]** and **Kalasker *et al.* 2014 [38];** found that the mean HbA1c level in anemic non diabetic patients were significantly lower than that in the control group that increased with iron replacement therapy. The authors did not discuss why their data conflicts with other studies but it may be due to the severity of anemia as the participants in this study had low mean hemoglobin levels (6.2 gm%); the duration of anemia was not given.

Four studies evaluated HbA1c levels in non-diabetic patients, before and after iron therapy of IDA. Three studies reported a significant decrease in HbA1c after iron therapy.

Gram-Hansen *et al.* 1990 [39]; in small study found significant decrease in HbA1c after 3 weeks of iron therapy. **El-Agouza *et al.* 2002 [10];** showed that HbA1c decrease after 20 weeks of follow up but this study did not include control subjects for comparison. Also, **Coban *et al.* 2004 [11];** found significant decrease in HbA1c which not reach to the control levels after 3 months of iron therapy; however, the iron indices had not fully normalized at that time.

In contrast, **Sinha *et al.* 2012 [37]** found that mean HbA1c at baseline in anemic patients was significantly lower than that in the control group, after 2 months of iron therapy for IDA, the HbA1c was significantly higher than the controls. No explanation of the results was presented.

The present study showed significant negative correlations between HbA1c on one hand and hemoglobin, MCV, MCH, serum ferritin, serum iron and transferrin saturation on the other hand**.** Also, significant positive correlations were observed between HbA1c on one hand and TIBC and serum MDA on the other hand**.**

Koga *et al.* 2007 [40], Hardikar *et al.* 2012 [41] and **Shanthi *et al.* 2013 [34];** demonstrated negative correlations between HbA1c and Hemoglobin, MCV and MCH levels. **Kalasker *et al.* 2014 [38];** observed a significant negative correlation between hemoglobin and HbA1c in patients and controls. **Koga *et al.* 2010 [33];** found that serum iron, transferring saturation and log ferritin inversely associated with HbA1c.

In the opposite side of our results, **Sinha *et al.* 2012 [37];** found significant positive correlation between hemoglobin and HbA1c levels in patients at baseline and after 1 month of treatment. However, there was no correlation at the end of the 2-month treatment period. **Hardikar *et al.* 2012 [41];** showed positive correlation between HbA1c and serum ferritin. **Ford *et al.* 2011 [42];** stated that increase HbA1c is associated with increased ferritin.

As regards glycated albumin (GA), our results revealed insignificant difference between the controls,

iron deficiency anemia patients before and after treatment.

In the same direction of our results, the only study **Koga *et al.* 2010 [33];** found that no effect of iron deficiency and IDA on glycated albumin in non-diabetic premenopausal women when compared with normal controls.

One study evaluated serum GA levels, before and after iron therapy of IDA. **Koga *et al.* 2009 [43];** who observed that mean serum GA did not change significantly before and after iron therapy but this study done in 4 diabetic patients with IDA—2 men and 2 women.

As regard malondialdehyde (MDA), our results showed significantly higher levels of serum MDA in IDA patients before treatment when compared with the controls. MDA decreased significantly by iron therapy in patients with IDA with insignificant difference between the controls and IDA patients after treatment.

Sundaram *et al.* 2007 [14]; stated that non-diabetic IDA is associated with higher MDA, iron replacement therapy lowers MDA. MDA is also evaluated in IDA Helicobacter pylori (H pylori) infected patients and evaluated the effect of therapy by **Vijayan *et al.* 2007 [44];** who found MDA was significantly higher in IDA H pylori infected patients compared with the controls. In IDA H pylori infected patients, MDA level decreased significantly after one month of treatment in patients received both iron therapy and anti-H pylori therapy but insignificant changes were found in the levels of MDA in IDA H pylori infected patients after one month of treatment in patients received only iron therapy.

Conclusions:

In IDA patients, HbA1c is not an accurate glycemic marker, and it does not accurately reflect the glycemic control. GA rather than HbA1c better reflects glycemic control status in IDA. Caution should be used when diagnosing diabetes among IDA patients using HbA1c. MDA may play a role in HbA1c elevation in IDA.

Conflicts of interest:

There is no conflict s of interest.

Authors' Contribution:

All the authors read and approved the final paper. All the authors contributed equally.

Corresponding Author:
Tamer A Elbedewy
Department of Internal Medicine, Tanta University, Egypt
E-mail: tamerelbedewy2006@ yahoo.com
tamer.elbedawi@med.tanta.edu.eg

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