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Original Article

Effect of Iron Deficiency Anaemia on HbA1c Levels among Non-Diabetic Females

Heba Ben Halem[1]*, Abdullah Almaedani[2]

[1]*Department of Life Sciences, School of Basic Sciences, Libyan Academy, Al Jabal Al Akhdar, Libya*
[2]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Omar Al Mukhtar, Al Bayda, Libya*
Email. *Heba.ben90@gmail.com*

Abstract
Iron deficiency anaemia (IDA) and Diabetes Mellitus both represent significant global public health concerns. HbA1c is one of the most used methods for diagnosis and monitoring of Diabetes. While several studies have explored the relationship between IDA and HbA1c, the findings are still inconsistent. Therefore, identifying the factors contributing to these inconsistencies is crucial for improving clinical interpretation and diagnostic accuracy of HbA1c, particularly in patients with IDA. This study aimed to investigate the impact of IDA on HbA1c levels, assessing the role of its severity on HbA1c levels and contributing to a better understanding of the reasons behind the conflicting findings. A cross-sectional case-control study was carried out at AL Wahda Hospital in Darna city, Libya, spanning from January 2025 to June 2025 and included 212 non-diabetic females aged 15-49, divided into 106 diagnosed with IDA (study group) and 106 age- and sex matched non-anemic (Control group). Medical history was obtained from each participant, and the following laboratory tests were performed: HbA1c, CBC, and Serum ferritin. Statistical analysis was performed using SPSS software version 26, applying the Kolmogorov–Smirnov test, Sign test, General linear model test and Kruskal Wallis test. Serum ferritin and haemoglobin had a statistically significant impact on HbA1c levels (P = 0.03) and (P=0.05), respectively. However, no statistically significant difference was found in the mean HbA1c between females with IDA and those without IDA (5.52 ± 0.40 vs 5.48 ± 0.52, P= 0.54), although a mild decrease was observed in the mean HbA1c of females with IDA compared to those without IDA. In addition, the study revealed no statistically significant differences in HbA1c levels across anaemia severity groups (P = 0.42). These findings suggest that HbA1c is significantly associated with serum ferritin and haemoglobin in non-diabetic females. However, this study may provide additional insights regarding the relationship between IDA and HbA1c within the context of previously inconsistent studies. Therefore, in IDA patients, reliance solely on HbA1c results may potentially lead to overestimation or underestimation of glycemic control, and HbA1c need to be interpreted cautiously in anaemic patients.
Keywords. Iron Deficiency Anaemia, Glycated Haemoglobin (HbA1c), Non-Diabetics, Serum Ferritin.

Introduction

Iron deficiency anaemia (IDA) is a major public health problem affecting about 30-50% of the world's population. IDA affects individuals of all ages, but young children, women of reproductive age, pregnant women and menstruating adolescent girls are the most commonly affected [1]. Iron deficiency (ID) is defined as a pathophysiological condition characterised by inadequate iron storage due to the progressive depletion of iron stores that develops as a result of decreased iron intake caused by impaired nutrition, decreased intestinal absorption secondary to gastrointestinal conditions, or the use of proton pump inhibitors; increased iron demands as observed in pregnancy; or increased iron loss usually due to bleeding. Heavy menstrual bleeding in reproductive-age women (HMB) is considered the most common cause of ID [2]. ID is viewed as a spectrum, ranging from iron depletion and iron-deficient erythropoiesis to iron deficiency anaemia. IDA is the most severe stage of iron deficiency, in which both iron stores and circulating iron levels are significantly reduced, leading to decreased Hb levels and the appearance of IDA symptoms [3].

Glycated Haemoglobin (HbA1c) is a glucose-modified haemoglobin formed by binding of glucose to the beta chain of haemoglobin [4]. HbA1c is considered a crucial, reliable biomarker of long-term glycemic control [5]. According to the American Diabetes Association (2011), HbA1c levels between 5.7% and 6.4% are a diagnostic marker of prediabetes, and HbA1c ≥ 6.5% is a diagnostic marker for DM [6]. However, studies indicate that HbA1c levels can be significantly affected by several non-glycemic factors; these factors include conditions that change red blood cell lifespan and Haemoglobin structure, such as IDA [5]. In addition, several studies suggest that IDA might influence HbA1c, potentially leading to a false increase or decrease in HbA1c levels and consequently misinterpretation of glycemic control, which may contribute to inaccurate clinical decisions regarding the management of diabetes or prediabetes [7]. Although inconsistent results have been reported in several previous studies regarding the relationship between IDA and HbA1c, the underlying mechanisms contributing to these inconsistencies remain unexplored. In addition, the prevalence of IDA among Libyan women of reproductive age is notably high, and limited data are available about the Libyan population. Accordingly, this study is designed to investigate the impact of IDA on HbA1c levels and to assess the role of its severity on HbA1c levels in non-diabetic Libyan females in order to enhance the understanding of the conflicting findings found in previous studies.

Methods

Study Design and Sample Population

A cross-sectional case-control study was carried out at AL Wahda Hospital in Darna city, Libya, spanning from January 2025 to June 2025. A total of 212 non-diabetic females aged 15-49 years were selected, divided into two groups: females diagnosed with IDA (study group) and females having no evidence of IDA (Control group). Females with IDA were diagnosed

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based on serum ferritin level (< 15 ng/ml) and haemoglobin level (<12 g/dl). Medical history was obtained from each participant, and blood samples were collected for the following laboratory measurements: HbA1c, CBC, and serum ferritin.

Exclusion Criteria

Participants with a confirmed diagnosis of diabetes mellitus, anaemia caused by factors other than iron deficiency, or a history of renal or liver diseases were excluded; also, pregnant and lactating women were excluded.

Laboratory Procedure

HbA1c was measured by using Ion-Exchange High-Performance Liquid Chromatography (IE-HPLC). The results were expressed as a percentage (%) according to the National Glycohemoglobin Standardisation Program (NGSP). Serum ferritin was measured using an electrochemiluminescence immunoassay (ECLIA). The results were expressed in ng/ml, with a reference range of 15–150 ng/ml for females. CBC was measured using an automated haematology analyser (Dymind, China).

Statistical Analysis

The data were analysed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were represented by percentage and frequency, while continuous variables were represented as mean ± SD. The sample size was determined by using the statistical program Epi Info (version 7.2.6.0), with a two-sided confidence level of 95% and a power of 80%, considering a control-to-case ratio of 1:1. The Kolmogorov–Smirnov test determined data normality and nonparametric tests were used. Statistical significance was set at $p < 0.05$. The sign test was used to compare mean HbA1c levels between study and control groups; the General Linear Model test (GLM) was used to clarify the impact of iron status markers (Haemoglobin and Ferritin) on HbA1c levels, and the Kruskal Wallis test was used to compare HbA1c levels across different levels of anaemia.

Ethical Approval

This study was reviewed and approved by the Al-Jabal Al Akhdar Committee for Bioethics (JCB), reference number: NBC: 004. H. 25. 29, under the Libyan Authority for Scientific Research and Libyan National Committee for Biosafety and Bioethics. Permission from Al Wahda Hospital, Darna was also obtained.

Results

The study sample included 212 female participants, with 106 in each of the control and study groups. An analysis of the age distribution between the two groups was conducted. *No statistically significant difference in either the mean age (P=0.97) or age distribution (P=0.19) was found between the control and study groups. The two groups were approximately matched in age. Furthermore, the (37-49 year) age group represented (50%) of the total sample. This distribution shows that the majority of the participants fall within middle adulthood, which could support the validity of group comparisons, as a result of the relatively balanced age distribution* (Table 1).

Table 1. Demographic and age distribution of the participants between the control and study group.

Age distribution	Control group	Study group	Total	P value
N	106	106	212	_
Mean ± SD (years)	35.76 ± 10.55	35.71 ± 8.70	_	0.97
Age distribution (years)				
15_25	21	14	16.5%	
26_36	30	41	33.5%	0.19
37_49	55	51	50%	
Total	106	106	100%	

Note: Data are presented as mean ± SD.

Laboratory Parameters of the Participants in The Control and Study Groups

The study group showed significantly lower haemoglobin and serum ferritin levels, indicating impaired iron status. In contrast, the control group maintained normal haematological parameters (Table 2).

Table 2. Laboratory parameters of the participants in the control and study groups

Variable	Control group	Study group
Hb (g/dl)	12.22 ± 0.45	9.91 ± 1.18
Ferritin (ng/ml)	45.65 ± 30.37	9.72 ± 3.72

Comparison of HbA1c Levels Between the Control Group and The Study Group

The study demonstrated that the Mean HbA1c of the control group was 5.52 ± 0.40, while the Mean HbA1c of the study group was 5.48 ± 0.52, and P= 0.54, indicating that there was no statistically significant difference between the two groups. However, a mild decrease was observed in the mean HbA1c of the study group compared to the control group (Table 3).

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Table 3. Comparison of HbA1c levels between the control group and the study group.

HbA1c	N	Mean	SD	Minimum	Maximum	P-value
Control group	106	5.52	0.40	4.66	6.30	0.54
Study group	106	5.48	0.52	3.88	6.30	

Data are represented as mean ± standard deviation (SD), N= 106 per group, P= 0.54, indicating no statistically significant differences.

Impact of (Serum Ferritin and Haemoglobin) on HbA1c Levels

Serum ferritin had a statistically significant impact on HbA1c levels (P = 0.03). Moreover, Hemoglobin also demonstrated a borderline significant effect on HbA1c levels (P= 0.05) (Table 4).

Table 4. Impact of serum ferritin and haemoglobin on HbA1c levels.

Source	Type III sum of squares	df	Mean square	F	P value
Ferritin	29.282	160	0.183	25.330	0.03
Hemoglobin	0.784	6	0.131	18.076	0.05

F-values and corresponding P-values are demonstrated above each column, indicating a statistically significant effect (P < 0.05).

Comparisons of HbA1c Levels Across Different Levels of Anaemia

No statistically significant differences in HbA1c levels across anaemia severity groups (P = 0.42) (Table 5).

Table 5. Comparisons of HbA1c levels across different levels of anaemia

	Severity of anaemia	N	Mean Rank	P value
HbA1c	**Mild 11_11.9**	20	46.75	0.42
	Moderate 8_10.9	81	56.15	
	Severe ≤ 8	5	47.70	
	Total	106		

Discussion

This study demonstrated that both iron status markers, serum ferritin and haemoglobin, have a statistically significant association with HbA1c levels in non-diabetic females. This finding indicates that IDA could influence HbA1c measurements. Nevertheless, the comparative analysis showed no statistically significant difference in the mean HbA1c between females with IDA and females without IDA; the HbA1c levels were numerically lower in females with IDA, suggesting that IDA may decrease HbA1c levels. Previous studies that investigated the influence of IDA on HbA1c levels had conflicting findings. Some studies reported lower HbA1c levels in individuals with IDA [8–10]. In contrast, other studies reported higher HbA1c levels in individuals with IDA [3,11,12]. Whereas Bindayel found no correlation between them [13]. These inconsistencies across the scientific literature may be attributed to several interrelated factors that require a detailed exploration. Possible biological mechanisms and methodological reasons contribute to inconsistent findings in the existing literature.

RBC Lifespan and Age Distribution

In chronic IDA without coexisting hematologic or systemic conditions, the decrease in RBC production increases the average age of circulating RBCs, resulting in a prolonged RBC lifespan (older RBCs), thereby providing more time for glycation, which may lead to false elevation in HbA1c levels at the same glucose exposure [14,15]. However, in case of acute IDA, such as severe bleeding, the bone marrow increases erythropoiesis to compensate for blood loss [16]. This generation of new (young RBCs) decreases the average age of circulating erythrocytes, resulting in shortened RBC lifespan and providing less time for glycation, which may lead to a false reduction in HbA1c levels independent of glucose exposure [17]. Also, in the regenerative phase following iron therapy, the bone marrow becomes highly active, resulting in increased young RBCs and decreased average age of circulating erythrocytes [17]. This shortened RBC lifespan provides less time for glycation, which may lead to a false reduction in HbA1c levels independent of glucose exposure [18]. Importantly, cross-sectional studies rarely measure how long IDA has been present; instead, they evaluate only different stages of anaemia, which may lead to conflicting findings.

Haemoglobin Structural Changes and Oxidative Stress

IDA alters the quaternary structure of haemoglobin, which may disturb haemoglobin interaction and create conditions that enhance the glycation process, which occurs on the N-terminal valine of the β-globin chain [19,20]. Simultaneously, IDA increases oxidative stress, which in turn promotes haemoglobin glycation through elevated malondialdehyde levels [19]. This oxidative stress may also facilitate glucose auto-oxidation to dicarbonyl intermediates, representing a crucial step in the Maillard reaction leading to enhanced haemoglobin glycation [21]. The alteration of haemoglobin structure, along with increased oxidative stress, may explain the variability observed in HbA1c levels in the case of IDA [19].

HbA1c as A Percentage

Recent research defines HbA1c as the ratio of glycated haemoglobin (HbA1c) to total haemoglobin (tHb), which consists of

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both glycated and non-glycated haemoglobin.

Formula conceptually $\%\ HbA1c = \left(Glycated\ Haemoglobin - Total\ Haemoglobin \right) x\ 100$

Generally, the conventional laboratory assessments of HbA1c require separate determination of HbA1c and tHb; the process of separation increases the loss or degradation of HbA1c, resulting in decreased accuracy of the assay [22]. More specifically, in individuals with IDA, the total amount of haemoglobin decreased, resulting in an increase in the glycated haemoglobin fraction even at the same glucose exposure [23]. Consequently, the percentage can be elevated, leading to false elevation in HbA1c readings [23,24]. Furthermore, multiple studies have reported that IDA can lead to false elevation in HbA1c readings without a corresponding increase in blood glucose [11,25]. HbA1c is a reliable indicator for diagnosing and controlling diabetes, but conditions such as IDA and other hemoglobinopathies can lead to conflicting results [26].

Assay Techniques

Differences in the laboratory techniques used for HbA1c assays such as (ion-exchange HPLC, affinity chromatography and immunoassay) may shift the results up or down in IDA [19]. Multiple studies indicated that methodological variations in assay techniques are the primary cause of opposite directions across studies [19,27]. Additionally, differences in population characteristics and the severity of anaemia may further modulate these mechanisms, contributing to the inconsistency in the literature. In addition, no statistically significant differences were found in HbA1c levels across anaemia severity groups. The lack of a statistically significant effect in this study may be attributed to most cases occurring within the range of mild to moderate anaemia. This unequal distribution of the participants may not be sufficient to detect the real effect of anaemia severity on HbA1c levels. On the other hand, many studies have shown that HbA1c levels are negatively correlated with the severity of anaemia; HbA1c levels decreased as the severity of anaemia increased [8,9]. In contrast, other studies have shown that HbA1c levels are positively correlated with the severity of anaemia; HbA1c increased as the severity of anaemia increased [11]. However, several limitations should be considered in this study, including that underrepresentation of participants with severe anemia may limit the ability to detect statistical differences between anaemia severity groups. In addition, the lack of intervention and follow-up limits the ability to evaluate HbA1c response to iron therapy and long-term outcomes. Furthermore, the duration of iron deficiency anaemia was not documented, which may give an indication of RBC turnover and its influence on HbA1c levels. Future studies with larger and more balanced sample sizes are required, in addition to considering alternative glycemic biomarkers, such as fructoseamine and glycated albumin, as they reflect glycemic control over a shorter duration (2-3 weeks) and are less affected by RBC turnover, providing further insights for developing alternative blood sugar measurements in cases of IDA.

Conclusion

This study demonstrates that HbA1c levels are significantly associated with serum ferritin and haemoglobin in non-diabetic females, although the mean HbA1c didn't differ significantly between females with and without IDA, indicating that IDA could influence HbA1c measurements. In IDA patients, relying solely on HbA1c results may potentially lead to overestimation or underestimation of glycemic control. The conflicting reports in previous studies highlight the need for further research and suggest that IDA should be considered an important modifier when interpreting HbA1c measurements.

Conflict of interest. Nil

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