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Original article

Effect of Iron Deficiency Anemia on HbA1c Levels in Non-Diabetic Females in Brack Alshatti

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ABSTRACT

Background and aims. *Iron deficiency anemia (IDA) is the most common form of anemia in the world. Hemoglobin A1c (HbA1c) is used in diabetic patients as an index of glycaemic control reflecting glucose levels of the previous 3 months. Iron deficiency anemia was reported to affects the levels of HbA1c. This study aims to investigate the effect of iron deficiency anemia on HbA1c levels in non-diabetic Libyan women.* ***Methods***. *The study included 40 cases of non-diabetic women who were diagnosed as having IDA and compared to 46 cases of healthy women group. Hb, RBC, Hct, MCV, MCH, MCHC, FBS, and HbA1c were measured. The statistical analysis was done by using the SPSS version 19 and Excel 2010.* ***Results***. *The results show that the mean HbA1c level was significantly increase among IDA group (4.55±0.91%) compared to control group (4.20±0.6%) (P<0.05). There were no significant differences in the levels of fasting glucose between the IDA and the control group (P> 0.05).* ***Conclusion***. *The HbA1c levels in patients with iron deficiency anemia are considerably elevated compared to the control group. As a result, many studies believe that monitoring these patients using only HbA1c could be misleading. Therefore, physicians should consider this factor before making any treatment decisions.*

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INTRODUCTION

According to the World Health Organization (WHO) iron deficiency is one of the most widespread nutritional complications affecting 4–5 billion people across the world. In developing countries, Anemia is prevalent at epidemic levels among nutritionally compromised individuals and presents a major obstacle to the proper growth increasing the risk for mortality and morbidity [1].

Iron deficiency (ID) and iron deficiency anemia (IDA) are prevalent forms of nutritional deficiency. Globally, 50% of anemia is attributed to iron deficiency. Reduced iron stores have been linked to increased glycation of hemoglobin A1C (HbA1c) [2]. Both anemia and iron deficiency anemia (IDA) are identified by a decrease in Hb concentrations and consequently a reduction in the oxygen-carrying ability of the blood. Iron deficiency (ID) entails as a reduction in total body iron to the extent that iron stores are fully exhausted and some degree of tissue iron deficiency anemia is present. Iron deficiency is generally viewed as a continuum: iron depletion, iron-deficient erythropoiesis (IDE), and iron deficiency anemia (IDA) [1].

The symptoms of IDA are usually non-specific and are typically triggered by blood loss due to hemolysis or increased demand for iron and is characterized by shortness of breath, dizziness, fatigue, frequent infections, loss of appetite etc. Presently about 50% of all cases of anemia are caused by iron deficiency. Globally, iron deficiency accounts for 841,000 deaths. while most of the developed countries regions have less than 2% proportion of disability adjusted life years that are attributable to iron deficiency, countries like Africa, India and Saudi Arabia still are at a high risk of IDA [1].

Protein glycation is a spontaneous reaction that is believed to play a key role in the pathogenesis of many clinical disorders. The glycation of proteins is enhanced by elevated glucose concentrations. The major form of protein glycation with a clinical consideration is glycated hemoglobin (HbA1c)[2].

Glycated hemoglobin is produced by a ketoamine reaction between glucose and the N-terminal valine of both ß-chains of the hemoglobin molecule. The major form of glycated hemoglobin is hemoglobin A1c (HbA1c)[2]. It develops when hemoglobin, a protein within red blood cells that carries oxygen throughout your body, joins with glucose in the blood, becoming 'glycated'. By hemoglobin (HbA1c), clinicians are able to get an overall picture of what our average blood sugar levels have been over a period of weeks/months. For people with diabetes this is important as the higher the HbA1c, the greater the risk of developing diabetes-related complications. The HbA1c fraction is abnormally elevated in patients with chronic hyperglycemic diabetes mellitus and it correlates positively with the metabolic control [3].The HbA1c formation used to assess glycemic status in clinical practice depends on several factors, such as the release of HbA1c in reticulocytes from bone marrow, the synthesis rate of HbA1c (or Hb glycosylation rate), and the mean age of circulating erythrocytes [4].

According to the American Diabetes Association (ADA) guidelines, the value of HbA1c should be kept below 6.5% in all the diabetics. The values which are greater than 6.5% indicate an increased chance of progression to the diabetic complications, especially the microvascular ones [5], When plasma glucose is consistently elevated, the nonenzymatic glycation of hemoglobin increases, this alteration reflects the glycemic history over the previous 2–3 months, since erythrocytes have an average lifespan of 120 days [2].

HbA1c levels are not affected by blood glucose levels alone. They are also altered in hemolytic anemias, hemoglobinopathies, acute and chronic blood loss, pregnancy, and uremia, Vitamin B12, folate, and iron deficiency anemias have also been shown to affect HbA1c levels. The two known factors which can modulate the glycation of proteins are the prevailing concentration of glucose and the half-life of the protein. But evidences in the literature have documented increased glycated protein levels in some nondiabetic pathological states, like iron deficiency anemia. Some authors have also found that on supplementation with iron therapy, there was a significant decrease in the levels of glycated hemoglobin. Evidence has accumulated, which supports the hypothesis that the glycation reaction, apart from the traditional chronic hyperglycemia, can be modulated by the iron status of the patient. If the degree of glycation of other proteins in anemic patients was similar to that of the glycated hemoglobin, it would have important clinical implications [5].

The measurement of HbA1c provides a measure of the mean blood glucose concentration over the preceding 2 to 3 months. However, it has been suggested that the HbA1c level does not only reflect glycaemia, but also that it is sensitive to alterations in Hb concentration. Therefore, when IDA is not diagnosed, the use of HbA1c testing alone may result in a misdiagnosis of DM. Therefore, it is crucial to assess patients for hematological and IDA-associated risk factors that may influence the outcome of this diagnostic investigation [6]. The use of HbA1c for the diagnosis of diabetes is now widely advocated. Anemia is cited as a major confounder to this use; however, the effect of the degree of anemia influences HbA1c levels is not known [7].

Some studies show that HbA1c levels are increased in iron deficiency anemia and attempted to explain on the basis of both modifications to the structure of hemoglobin and level of HbA1c in old and new red blood cells. Some Studies showed that HbA1c levels were higher in patients of iron deficiency anemia and decreased significantly upon treatment with iron. With this background, the objective of the present study was to study the effect of iron deficiency anemia on glycated hemoglobin (HbA1c) in non-diabetic women. If so, the iron deficiency had to be corrected before any diagnostic or therapeutic decision was made based on the HbA1c level [5].

Protein glycation is a spontaneous reaction that is believed to play a key role in the pathogenesis of many clinical disorders. The glycation of proteins is enhanced by elevated glucose concentrations. The major form of protein glycation with a clinical consideration is glycated hemoglobin (HbA1c) Glycated hemoglobin is produced by a ketoamine reaction between glucose and the N-terminal valine of both ß-chains of the hemoglobin molecule. The major form of glycated hemoglobin is hemoglobin A1c (HbA1c) [2].

iron deficiency was associated with higher proportions of HbA1c, which could cause problems in the diagnosis of uncontrolled diabetes mellitus in iron deficient patients. The iron status must be considered during the interpretation of the HbA1c concentrations in Diabetes mellitus. The iron replacement therapy is thus especially important in diabetic pa-patients with iron deficiency, as it would also increase the reliability of the HbA1c determinations [2].

Among non-diabetic and diabetic individuals IDA is associated with higher concentrations of HbA1c. Iron replacement therapy decreases HbA1c in both diabetic and non-diabetic individuals. This implies that the iron states must be considered during the interpretation of HbA1c concentrations in diabetic or non-diabetic patients. Early diagnosis and treatment of ID in diabetic patients can improve their glycemic control and may prevent or delay complications [8]. Iron deficiency was associated with higher proportions of HbA1c, which could cause problems in the diagnosis of uncontrolled diabetes mellitus in iron-deficient patients [9].

MATERIAL AND METHODS

Study design and sampling techniques

A prospective cross-sectional study was conducted to investigate the impact of Iron Deficiency Anemia on Glycated Hemoglobin (HbA1c) in Non-Diabetic Adult Women in Brack. The study included a total of 86 subjects, divided into two groups: 46 healthy females and 40 females with Iron Deficiency Anemia, ranging in age from 20 to 50 years. The study was conducted from June 2019 to September 2019. This study was ethically approved by Libyan Authority for Scientific Research.

Approximately 2 ml each of venous whole blood samples were drawn for complete blood counts analysis (hemoglobin (Hb) and HbA1c analysis, the sample were collected in a tube of ethylene diamine tetra acetic acid (EDTA).

Study experiment

CBC; haemoglobin (Hb), hematocrit (Hct), Red Blood Cell (RBC), mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH) were measured by Automat Analyzer BC-2800 Auto Hematology Analyzer, HbA1c were measured by I-chroma analyzer, and FBS by glucose oxidase/peroxidase method.

Statistical analysis

The statistical analysis of the data was carried out by using the SPSS19 and Excel 2010 under Windows8 computer program packages The data were presented as mean±SD for continuous variables. Group means were compared by student t-test. Pearson's co-efficient of correlation was used to determine the correlation between two variables. P value < 0.05 was considered significant.

RESULTS

The current study included 86 non-diabetic Libyan Females aged (20-50 years) in Brack Alshatti Region. The IDA group were 40(47%) volunteers, while the control group included 46(53%) healthy volunteers (Figure 1). The mean age of IDA group was (33.58±8.75). The mean age of control group was (33.86±7.46) (Table 1).

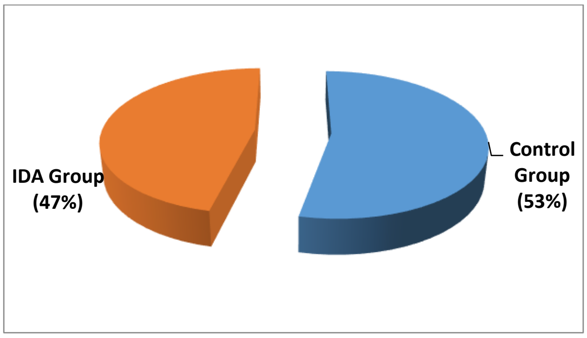

Figure 1. The percentage number of study groups

Table 1. Mean age of control and IDA groups

Group	Number	Age(year) Mean ± SD	T-test	P value
Control group	46	33.86±7.4	0.172	0.15
IDA group	40	33.58±8.7	0.172	

There were significantly decrease ($p<0.05$) in the levels of Hb, Hct, MCV, MCH & MCHC in IDA group when compared to Control group, on the other hand RBC count were not significantly different among the groups of study($p>0.05$) (Table 2).

Table 2. Hematological parameter among control and IDA groups

Parameters	Control	IDA	P.value
Hb (g/L)	12.69±1.01	9.63±1.46	0.001
RBC(10^{12}/l)	4.36±0.32	4.18±0.38	0.06
Hct (%)	4.36±0.32	4.18±0.38	0.001
MCV (fl)	86.23±4.66	71.33±7.98	0.001
MCH (pg/cell)	38.70±8.33	29.80±3.88	0.001
MCHC (%)	29.07±2.06	22.96±3.15	0.001

Table 3 shows there were not significantly different in the level of FBS ($p > 0.05$) in IDA group compared to control group (78.47±12.62, 78.15±14.07) respectively.
The mean of HbA1c in IDA group and control group were (4.55±0.9, 4.20±0.60) respectively. This result showed that there were significantly increased ($p < 0.05$) of HbA1c levels among IDA group compared to control group (Table 3) (Figure 2).

Table 3. Biochemical parameter among control and IDA groups

Parameters	Control	IDA	P-value
FBS	78.47±12.62	78.15±14.07	0.001
HbA1c	4.55±0.91	4.20±0.60	0.03

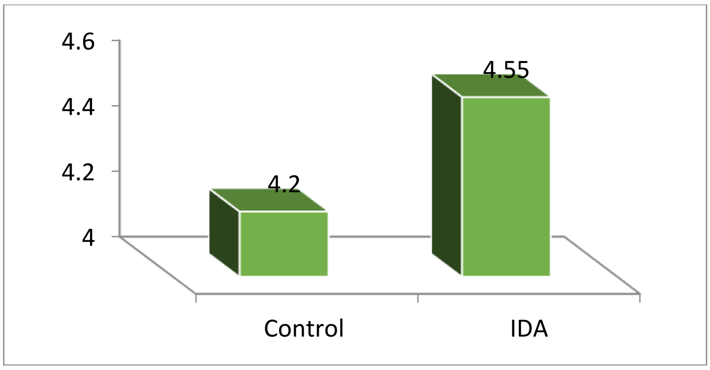

Figure 2. Comparison of HbA1c between IDA and control group

DISCUSSION

HbA1c is the most frequently occurring fraction of haemoglobin A1. It reflects the glycemic status for the previous three months. American Diabetes Association guidelines have not only considered it as the primary target for glycemic control but also included it as a diagnostic criterion [10]. Besides blood glucose, HbA1c levels can be affected by conditions unrelated to diabetes like anemia [11].
The present study showed that there were significantly increased of HbA1c levels among IDA group compared to control group. Similar to our result, Brooks et al. demonstrated the effects of iron deficiency anemia on HbA1c levels. That study was conducted on non-diabetic patients having iron deficiency anemia, before and after treatment with iron. They observed that HbA1 levels were significantly higher in iron deficiency anemia patients and decreased after treatment with iron [12]. Rajagopal et al also indicated that non diabetic with IDA, their HbA1c mean level was significantly higher than non-anemic group. The current study results are also consistent with the study done by El-Agouza et al., who reported that a decline in the Hb level might lead to increase in the glycated fraction at a fixed glucose level, because HbA1C is measured as a percentage of total Hb, Similar results were also reported by [13, 14]. In another study using different method for estimating for HbA1c by cation exchange column chromatography concluded that increased level of HbA1c in IDA group [15]. Mohammed et al. reported that there was a highly significant difference between healthy control, iron deficiency anemia, and non-iron deficiency anemia as regard HbA1c, with the highest level of HbA1c in the iron-deficiency anemia group ([16]. All these results were in agreement with other previous studies conducted by kim et al [17] who reported that HbA1c values were statistically higher among patients with IDA compared to those measured in the individuals without anemia. Brooks et al. also

showed that HbA1c levels were higher in patients of iron deficiency anemia at baseline and decreased on treatment [18]. Vasava et al also showed there was A positive correlation found between iron deficiency anemia and increased HbA1C levels [19].
The mechanisms leading to increased HbA1c levels were not clear , The proposed theories for increased HbA1c levels in IDA were suggested that first: Alteration of quaternary structure of haemoglobin leading to more rapid glycation of globin chain [20 , 21] , second: Increase in the glycated fraction of hemoglobin due to decrease in total hemoglobin at a constant glucose level occurs because HbA1c is measured as a percentage of total Hemoglobin A1c , third: in IDA, reduced red cell production leads to a higher average age of circulating erythrocytes and therefore, increased HbA1c levels [20]. Sluiter et al. gave a different reason to explain the findings of Brooks et al. They were of the view that the formation of glycated hemoglobin is an irreversible process and hence, the concentration of HbA1c in one erythrocyte will increase linearly with the cell's age. In patients with normal blood glucose values but with red cells that are younger than usual, as after treatment of iron deficiency anemia, HbA1 concentration falls. However, if the iron deficiency has been persisting for a long time, the red cell production rate falls, leading not only to anemia but also to a higher than normal average age of circulating erythrocytes and, therefore, of increased HbA1c [20].

CONCLUSION

As a conclusion, HbA1c levels in patients with iron deficiency anemia (IDA) are considerably elevated compared to the control group. Consequently, many studies believe that monitoring Diabetic patients using only HbA1c could be misleading. Therefore, physicians should consider this factor before making any treatment decisions.

Limitation of the Study

A potential limitation of this study is that the budget was limited and not enough to measure important relative parameter for instance oxidative stress biomarker induced by IDA. Also difficulty to find women who have iron deficiency anemia and convince them to participate in this research. And unavailability of the equipment and devices required for research in laboratories of the college, and that forced us to get help from private laboratories.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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تأثير فقر الدم بنقص الحديد على مستويات الهيموجلوبين السكري لدى الإناث غير المصابات بمرض السكر في براك الشطي

أحلام علي بشير

كلية التقنية الطبية - جامعة وادي الشطي ، ليبيا

المستخلص

الخلفية والأهداف. فقر الدم الناجم عن نقص الحديد (IDA) هو أكثر أشكال فقر الدم شيوعًا في العالم. يستخدم الهيموغلوبين (HbA1c) A1c في مرضى السكري كمؤشر للتحكم في نسبة السكر في الدم يعكس مستويات الجلوكوز في الأشهر الثلاثة الماضية. تم الإبلاغ عن أن فقر الدم الناجم عن نقص الحديد يؤثر على مستويات HbA1c. تهدف هذه الدراسة إلى معرفة تأثير فقر الدم الناجم عن نقص الحديد على مستويات HbA1c لدى النساء الليبيات غير المصابات بالسكري. **طُرق الدراسة**. اشتملت الدراسة على 40 حالة لنساء غير مصابات بالسكري تم تشخيصهن على أنهن مصابات بـ IDA ومقارنة بـ 46 حالة من مجموعة النساء الأصحاء. تم قياس Hb و RBC و Hct وMCV و MCH و MCHC و FBS و HbA1c. تم إجراء التحليل الإحصائي باستخدام SPSS الإصدار 19 و Excel 2010. **النتائج**. أظهرت النتائج أن متوسط مستوى HbA1c قد زاد بشكل كبير بين مجموعة IDA (4.55 ± 0.91٪)مقارنة بمجموعة التحكم(4.20 ± 0.6 ٪). (P <0.05) (لا توجد فروق ذات دلالة إحصائية في مستويات الجلوكوز الصائم بين IDA ومجموعة التحكم (P> 0.05). **الخاتمة**. مستويات HbA1c في المرضى الذين يعانون من فقر الدم بسبب نقص الحديد مرتفعة بشكل ملحوظ مقارنة بمجموعة التحكم. نتيجة لذلك ، تعتقد العديد من الدراسات أن مراقبة هؤلاء المرضى باستخدام HbA1c فقط قد يكون مضللاً. لذلك ، يجب على الأطباء مراعاة هذا العامل قبل اتخاذ أي قرارات علاجية.

الكلمات الدالة. فقر الدم الناجم عن نقص الحديد ، IDA، HbA1c ، الهيموغلوبين السكري