The relationship between glycated hemoglobin (HbA1c) and normal hemoglobin (HG) level in diabetics and non-diabetic Libyan women

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Abstract

The use of HbA1c for the diagnosis of diabetes is widely advocated despite studies that show there a

re many factors that influence the level of HbA1c, such as RBC parameters hemoglobin concentration and RBCs life span. This study investigates the relationship between HbA1c levels and hemoglobin concentration in diabetic and non-diabetic Libyan females, both pregnant and non-pregnant. Ninety-nine blood samples were collected from Zuwara General Hospital, Al Ain Center for Diabetes and Endocrine Disease, and Al Zawia Diabetes Center. These samples were analyzed using Cobas Integra 400plus for HbA1c and Sysmex XP300 for hemoglobin concentration, with statistical analysis conducted via IBM SPSS Statistics software. The results include: Diabetic non-pregnant women had significantly higher HbA1c levels (8.13±0.44) compared to non-diabetic non-pregnant women (5.18±1.31) ($t = -4.575$, $p < 0.001$). Non-pregnant women had a higher RBC count (5.92±0.33) than pregnant women (4.06±0.50) ($t = -3.001$, $p = 0.012$). A strong positive correlation was found between HbA1c and fasting blood sugar (FBS) in diabetic non-pregnant women ($r = 0.801$, $p < 0.001$). HbA1c and FBS levels did not show significant association with anemia indicators (RBC count and HGB levels) in both diabetic and non-diabetic women, regardless of pregnancy status. Diabetic women, both pregnant and non-pregnant, had higher HbA1c and FBS levels compared to non-diabetic women. Non-pregnant women, irrespective of diabetes status, had higher HbA1c, RBC count, and FBS levels compared to pregnant women. Hemoglobin (HGB) levels did not significantly differ between groups, suggesting pregnancy status and diabetes do not significantly impact HGB levels. The study concludes that further research is needed to identify factors affecting HbA1c levels.

Keywords: Diabetes mellitus, HbA1c, Blood sugar, RBC parameters,

العلاقة بين الهيموجلوبين السكري و مستوى الهيموجلوبين الطبيعي لدى النساء الليبيات المصابات وغير المصابات بالسكري

يوصى على نطاق واسع باستخدام معدل السكر التراكمي (HbA1c) لتشخيص مرض السكري على الرغم من الدراسات التي تظهر أن هناك العديد من العوامل التي تؤثر على مستوى HbA1c، مثل معلمات تركيز الهيموغلوبين في كرات الدم الحمراء وعمر كرات الدم الحمراء. تبحث هذه الدراسة في العلاقة بين مستويات الهيموجلوبين السكري وتركيز الهيموجلوبين العادي في الإناث الليبيات المصابات بداء السكري وغير المصابات به، سواء الحوامل أو غير الحوامل. تم جمع تسعة وتسعين عينة دم من مستشفى زوارة العام ومركز العين للسكري وأمراض الغدد الصماء ومركز الزاوية للسكري. تم تحليل هذه العينات باستخدام Cobas Integra 400plus لـ HbA1c و Sysmex XP300 لتركيز الهيموجلوبين، مع إجراء التحليل الإحصائي عبر برنامج IBM SPSS Statistics. وكانت النتائج كالاتي: كان لدى النساء غير الحوامل المصابات بداء السكري مستويات عالية من HbA1c (8.13±0.44) مقارنة بالنساء غير الحوامل وغير المصابات بداء السكري (5.18±1.31) (t = -4.575، p < 0.001). كان عدد كرات الدم الحمراء لدى النساء غير الحوامل (5.92±0.33) أعلى من النساء الحوامل (4.06±0.50) (t = -3.001، p = 0.012). تم العثور على علاقة إيجابية قوية بين HbA1c وسكر الدم الصائم (FBS) لدى النساء غير الحوامل المصابات بداء السكري (r = 0.801، p < 0.001). لم تظهر مستويات HbA1c و FBS ارتباطًا كبيرًا بمؤشرات فقر الدم (عدد كريات الدم الحمراء ومستويات HGB) في كل من النساء المصابات بداء السكري وغير المصابات بداء السكري، بغض النظر عن حالة الحمل. كان لدى النساء المصابات بالسكري، سواء الحوامل أو غير الحوامل، مستويات أعلى من HbA1c و FBS مقارنة بالنساء غير المصابات بالسكري. كان لدى النساء غير الحوامل، بغض النظر عن حالة مرض السكري، مستويات أعلى من HbA1c وRBC وFBS مقارنة بالنساء الحوامل. لم تختلف مستويات الهيموغلوبين بشكل كبير بين المجموعات، مما يشير إلى أن حالة الحمل والسكري لا تؤثر بشكل كبير على مستويات الهيموغلوبين. وتخلص الدراسة إلى أن هناك حاجة إلى مزيد من البحث لتحديد العوامل التي تؤثر على مستويات HbA1c.

1. Introduction

Diabetes mellitus is a chronic condition marked by high blood glucose levels due to insulin issues. Glycated hemoglobin was initially identified as an unusual Hemoglobin in patients with diabetes over many years ago (Rahbar et al., 1969). It was introduced into clinical use in the 1980s and subsequently has become a cornerstone of clinical practice (Massi-Benedetti, 2006). After that, numerous studies were conducted about correlating it to glucose measurements resulting in the indication that HbA1c could be used as an objective measure of glycemic control. Glycated hemoglobin, especially HbA1c, reflects average blood glucose over 2-3 months (Livshits et al., 2012). Glycated hemoglobin is the product of the irreversible reaction between glucose and hemoglobin by non-enzymatic glycation, which depends on the blood glucose level, the glycation time and the red blood cell lifespan (Koenig RJ, eta al.,1976) It's vital for diabetes screening and monitoring. Compared to the Oral Glucose Tolerance Test (OGTT), HbA1c testing is quicker, more convenient, and less affected by various factors (Saudek C D,2006). It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycemic control in people with diabetes. Additionally, HbA1c levels correlate with the progression of diabetic complications, making it an essential tool in diabetes management and research. HbA1c is endorsed by international committees and the American Diabetes Association for diagnosing diabetes, with strict quality assurance and standardized assays essential. Aligning criteria with international reference values ensures reliability as shown in **Table 1** (English and Lenters-Westra, 2018).

However, HbA1c values can be affected by various factors such as the method of detection, presence of other health conditions (comorbidities), the mean age of erythrocytes in the circulation and medications taken by the patient. These factors can influence the accuracy of HbA1c measurements and their correlation with plasma glucose levels, sometimes not reflecting plasma glucose accurately (Diabetes Control, 1993; Bloomgarden, 2009;). To ensure the reliability of HbA1c results, it's essential to follow standardized testing protocols and use validated laboratory methods. Additionally, clinicians should consider the patient's medical history, including comorbidities and medications, which can influence HbA1c levels (Colagiuri et al., 2011). Regular calibration and quality control measures in laboratories help maintain accuracy. Clinicians may also compare HbA1c results with other measures of glycemic control, such as fasting plasma glucose and continuous glucose monitoring, to confirm consistency and accuracy.

Table 1: The international reference values of HbA1c

Blood glucose mg/dl	status	HbA1c %
97 - 110	Normal	4.4 - 5.5
110 - 130	Pre-Diabetes	5.5 - 6.0
130 - 155	Diabetes Good control	6.0 - 6.8
155 - 184	Diabetes	6.8 - 8
184 up to	Diabetes Poor control	8 up to

There are several conditions can affect the accuracy of HbA1c measurement. These include hemoglobinopathies (abnormalities in hemoglobin), such as sickle cell disease or thalassemia, which can alter the structure of hemoglobin and interfere with HbA1c testing (Weykamp, C., 2013). Additionally, conditions that affect red blood cell turnover, such as anemia or recent blood loss or transfusion, can also impact HbA1c results. Furthermore, certain medical treatments or conditions that affect erythropoiesis (red blood cell production), such as chronic kidney disease or erythropoietin therapy, may affect HbA1c levels (Ng,J M et al., 2010; Rasche, F M et al., 2017). It's important for healthcare providers to consider these factors when interpreting HbA1c results in patients with these conditions.

It's possible for someone to be identified as having diabetes based on HbA1c levels but not meet the criteria for diabetes based on direct glucose measurements. This can occur due to various factors such as differences in the time frames being assessed by each test (Ahmad J and Rafar D., 2013). Moreover, anemia occurs when there are no enough red blood cells or the red blood cells do not function properly. It is diagnosed when a blood test shows a hemoglobin value of less than 12.0 gm/dl in a woman (McLean et al.,2009). Therefore, anemia often involves a decrease in the number of red blood cells or a reduction in hemoglobin levels. When the blood volume is diluted due to decreased red blood cell concentration, it can falsely lower HbA1c levels, (Jandric et al., 2012; Elsheikh E et al., 2023). This is because HbA1c is measured as a percentage of total hemoglobin, and if the overall hemoglobin level is reduced, the HbA1c percentage may appear lower than it

actually is. While anemia can also affect men, the prevalence is generally lower compared to women, particularly outside of specific life stages like pregnancy and menstruation.

HbA1c measurements during pregnancy in diabetic patients help assess minimal perinatal risk for the mother and maximize fetal health (Rafat D and Ahamd J., 2012). Stringent glycemic control before and during pregnancy reduces risks like congenital malformations, overweight infants, and complications during pregnancy and delivery associated with poor glycemic management. Pregnant women are particularly susceptible to anemia due to the increased demands on their bodies during pregnancy. Anemia occurs when there's a deficiency in red blood cells or hemoglobin, which are responsible for carrying oxygen to tissues throughout the body. During pregnancy, a woman's blood volume expands to accommodate the needs of the growing fetus, which can dilute the concentration of red blood cells and hemoglobin in the bloodstream, leading to anemia (Lemaitre M et al., 2022). This retrospective study examines the relationship between HbA1c levels, blood sugar, hemoglobin concentration, and red blood cells in diabetic and non-diabetic Libyan females during clinic visits. It also explores the impact of Iron Deficiency Anemia on HbA1c levels in diabetic and non-diabetic pregnant and non-pregnant Libyan women. And enhance understanding in the field, leading to better patient care and guiding future research endeavors. The study investigated the relationship between cumulative blood sugar measured by HbA1c and fasting blood sugar (FBS) and anemia indicators measured by red blood cell (RBC) count and hemoglobin (HGB) levels in diabetic and non-diabetic, pregnant and non-pregnant women.

2. Material and Methods

2.1 Samples Collection

A total of 99 venous blood samples were collected from diabetics and nondiabetics pregnant and non-pregnant Libyan female into tubes containing K_2EDTA as an anticoagulant from Zuwara General Hospital, Al Ain Center for diabetes and endocrine disease-Surman, and Al Zawia Diabetes Center in Libya. The samples were collected during the period from October to December 2022. The participants mean age were ranged from 24 to 80 years. The baseline demographics of the study subjects are shown in **Table 2**.

Table 1 Participants information

Pregnant		Non-pregnant	
Diabetic	Non-diabetic	Diabetic	Non-diabetic
42	31	12	12

2.2 Samples analysis

The samples were analyzed in the Surman Central Laboratory and the Alweqaia Laboratory-Sabratha. Analysis of HbA1c sample was performed using Cobas Integra 400 plus, and Complete Blood Count (CBC) was measured by Sysmex XP300. The statistical analyses were performed with IBM SPSS Statistics software version 29.0. The correlation between different variables was calculated using the Spearman correlation equation for ranked non-linear variables. A p-value of less than or equal to 0.001 was considered statistically significant.

The samples were analyzed in hematology unit for CBC to determine Red Blood Cell (RBCs) count. RBCs are counted accurately using automatic discriminators to separate the cell population based on complex algorithms. The hemoglobin concentration counted using Sysmex XP300 Automated Hematology Analyz using a non-cyanide method. For Glycated Hemoglobin (HbA1c) the samples were analyzed in biochemistry unit by Cobas Integra 400plus, using absorbance photometry Technique.

3. Results and discussion

A total of 99 Libyan females were take part in this study, with mean age of 24-80 years. Among these, 42 were pregnant with diabetes and 31 pregnant non-patients. The non-pregnant women had 12 diabetes and 12 non-diabetes. The study investigated the relationship between cumulative blood sugar measured by HbA1c and fasting blood sugar (FBS) and anemia indicators measured by red blood cell (RBC) count and hemoglobin (HGB) levels in diabetic and non-diabetic, pregnant and non-pregnant women. **Table 3** shows the mean values and the standard deviation for the measured parameters in diabetic and non-diabetic participant.

Table 3 The mean values and the standard deviation for the measured parameters

The parameter	Non-diabetic		Diabetic	
	Pregnant	Not-pregnant	pregnant	Not-pregnant
HbA1c	4.72±0.38	5.18± 1.31	6.19±1.31	8.13± 0.44
HGB	11.93±1.69	12.51±1.59	11.48±1.59	12.12±1.71
FBS	79.86± 13.13	92±12.77	126.94±43.55	182.23±12.49
RBC	4.06±0.50	5.92± 0.33	4.27±0.33	7.312±2.08

The results in **Table 3** shown that diabetic pregnant women having a higher mean HbA1c level (6.19±1.31) compared to non-diabetic pregnant women (4.72±0.38). Additionally, a significant difference was found in RBC count ($t = -2.021$, $p = 0.049$), with diabetic pregnant women having a higher mean RBC count (4.27±0.33) compared to non-diabetic pregnant women (M = 4.06±0.50). Regarding FBS, a significant difference was found ($t = -4.738$, $p < 0.001$), with diabetic pregnant women having a higher mean FBS (126.94± 43.55) compared to non-diabetic pregnant women (79.86±13.17).

The results of the studied population of non-diabetic pregnant women shown that there was no significant correlation between HbA1c and RBC count ($r = 0.094$, $p = 0.614$) or between FBS and RBC count ($r = 0.121$, $p = 0.591$). Similarly, no significant correlation was found between HbA1c and HGB levels ($r = -0.179$, $p = 0.336$). However, there was a non-significant correlation between FBS and HGB levels ($r = 0.003$, $p = 0.991$). Additionally, a non-significant correlation was observed between HbA1c and FBS ($r = 0.206$, $p = 0.357$). Overall, the findings suggest that cumulative blood sugar levels, as measured by HbA1c and FBS, are not significantly associated with anemia indicators (RBC count and HGB levels).

The comparison results between non-diabetes and diabetes of not pregnant women shown that there was a significant difference in HbA1c levels between the two groups ($t = -4.575$, $p < 0.001$), with diabetic non-pregnant women having a higher mean HbA1c level (8.13±0.44) compared to non-diabetic non-pregnant women (5.18±1.31). However, no

significant difference was found in RBC count (t = -1.436, p = 0.165) or HGB levels (t = 0.562, p = 0.580) between the two groups. Regarding FBS, a significant difference was observed (t = -4.572, p < 0.001), with diabetic non-pregnant women having a higher mean FBS (182.23±12.49) compared to non-diabetic non-pregnant women (79.86± 13.17).

Results of comparison between not pregnant and pregnant women for non-diabetes shown that there was a significant difference in HbA1c levels between the two groups (t = -3.339, p = 0.002), with non-pregnant women having a higher mean HbA1c level (5.18±0.454) compared to pregnant women (M = 4.72±0.388). The results are consistent with previous studies (Chowdhury et al., 2020; Abdulkafi et al., 2019) that shown that in pregnant women without diabetes, HbA1c levels may decrease slightly during the first trimester and then gradually increase as pregnancy progresses, returning to pre-pregnancy levels postpartum. These changes are generally considered normal and not indicative of any underlying health issues. Additionally, a significant difference was found in RBC count (t = -3.001, p = 0.012), with non-pregnant women having a higher mean RBC count (5.92±0.33) compared to pregnant women (4.06±0.50). However, no significant difference was observed in HGB levels between the two groups (t = -0.997, p = 0.325). Regarding FBS, a significant difference was found (t = -2.574, p = 0.015), with non-pregnant women having a higher mean FBS (92.0±12.77) compared to pregnant women (79.86±13.13). During pregnancy, pregnant women typically experience lower fasting blood sugar (FBS) levels compared to non-pregnant women. This phenomenon occurs due to several physiological changes that take place in the body during pregnancy. These include increased insulin sensitivity, higher insulin production, glucose utilization by the fetus, and glycogen storage results in lower fasting blood sugar levels in pregnant women compared to non-pregnant women (Osman et al., 2022).

Comparison between not pregnant and pregnant women for diabetes results in show that there was a significant difference in HbA1c levels between the two groups (t = -2.937, p = 0.010), with non-pregnant women having a higher mean HbA1c level (8.13±0.44) compared to pregnant women (M = 6.19±1.31). Additionally, a significant difference was found in RBC count (t = -4.133, p = 0.001), with non-pregnant women having a higher mean RBC count (7.312±2.08) compared to pregnant women (M = 4.27±0.33). However, no significant difference was observed in HGB levels between the two groups (t = -1.216, p = 0.230). Regarding FBS, a significant difference was found (t = -2.648, p = 0.022), with non-pregnant women having a higher mean FBS (182.23±12.49) compared to pregnant women (126.94±43.55). In diabetic patients, where blood glucose levels are often elevated due to insulin resistance or insufficient insulin production, there is an increased formation of HbA1c. Since RBCs have a relatively long lifespan, HbA1c provides a valuable measure of average blood glucose levels over several months, offering insight into long-term glycemic control.

The relationship between HbA1c and RBCs in diabetic patients is primarily related to the lifespan of RBCs and the mechanism by which HbA1c is formed and certain medical conditions. It's important to note that HbA1c levels can be influenced by these factors other than blood glucose levels. However, in diabetic patients, monitoring HbA1c levels remains a key method for assessing overall glycemic control and the effectiveness of diabetes management strategies (Valadan et al., 2022).

In the studied population of diabetic pregnant women, the results indicate that there was no significant correlation between HbA1c and RBC count (r = -0.130, p = 0.418) or between FBS and RBC count (r = -0.131, p = 0.641). Similarly, no significant correlation was found between HbA1c and HGB levels (r = -0.166, p = 0.300) or between FBS and HGB levels (r = -0.051, p = 0.857). However, a significant positive correlation was observed between HbA1c and FBS (r = 0.666, p = 0.004). This finding suggests that higher levels of HbA1c are associated with higher FBS levels in diabetic pregnant women. Overall, the results did not reveal any significant associations between cumulative blood sugar levels and anemia indicators in the studied population of diabetic pregnant women, except for the positive correlation between HbA1c and FBS.

The results from the studied population of non-diabetic, non-pregnant women show that, there was no significant correlation between HbA1c and RBC count (r = 0.469, p = 0.124) or between FBS and RBC count (r = -0.246, p = 0.440). Similarly, no significant correlation was found between HbA1c and HGB levels (r = 0.429, p = 0.164) or between FBS and HGB levels (r = 0.356, p = 0.256). Additionally, there was no significant correlation between HbA1c and FBS (r = -0.124, p = 0.700). Overall, the findings suggest that cumulative blood sugar levels, as measured by Hba1c and FBS, are not significantly associated with anemia indicators (RBC count and HGB levels) in the studied population of health, non-pregnant women.

The results in the studied population of diabetic, non-pregnant women, indicate that there was no significant correlation between HbA1c and RBC count (r = -0.132, p = 0.668) or between FBS and RBC count (r = -0.131, p = 0.669). Similarly, no significant correlation was found between HbA1c and HGB levels (r = -0.140, p = 0.649) or between FBS and HGB levels (r = -0.095, p = 0.758). However, a significant strong positive correlation was observed between HbA1c and FBS (r = 0.801, p < 0.001). This finding suggests that higher levels of HbA1c are associated with higher FBS levels in diabetic, non-pregnant women. Overall, the results did not reveal any significant associations between cumulative blood sugar levels and anemia indicators in the studied population of diabetic, non-pregnant women, except for the strong positive correlation between HbA1c and FBS.

4 Conclusion

cumulative glucose analysis has been recommended only for the determination of glucose control among persons who have already received the diagnosis of diabetes. Glycated hemoglobin has several advantages as a diagnostic test: it has higher repeatability and can be assessed in the non-fasting state, and is the preferred test for monitoring glucose control (Virtue et al., 2004). However glycated hemoglobin should be used to assess blood sugar in the absence of anemia because the conflicting inverse association between anemia and cumulative glucose which led to under-diagnosis, and contributed to misdiagnosis or under-diagnosis resulting in adverse consequences (English et al., 2015). The aim of this study was to determine the potential extent to which cumulative glucose is affected by anemia in diabetic and non-diabetic women. The study results indicated that cumulative blood sugar levels, as measured by HbA1c and FBS, do not appear to be significantly associated with anemia indicators (RBC count and HGB levels) in non-diabetic or diabetic women, regardless of pregnancy status.

Diabetic women, both pregnant and non-pregnant, tend to have higher levels of HbA1c and FBS compared to their non-diabetic counterparts. Non-pregnant women, both diabetic and non-diabetic, tend to have higher levels of HbA1c, RBC count, and FBS compared to their pregnant counterparts. HGB levels did not show significant differences between the groups, suggesting that pregnancy status and diabetes may not significantly impact HGB levels in the studied populations. This can be due random sample collection and to the supplements that women take during pregnancy based on the advice of the supervising doctors (Xiang et al., 2022).

It's important to note that HbA1c levels can be influenced by factors other than blood glucose levels, such as variations in RBC lifespan, hemoglobin variants, and certain medical conditions. However, in diabetic patients, monitoring HbA1c levels remains a key method for assessing overall glycemic control and the effectiveness of diabetes management strategies (Soumya et al., 2015). Further studies are needed to identify the key factors that affect HbA1c levels and complete what our study lacks such as identification of the relationship between HbA1C and hematological indices such as the average red blood cell size (MCV) Hemoglobin amount per red blood cell (MCH) which, help diagnose the cause of anemia.

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