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ORIGINAL ARTICLE

ERYTHROCYTOSIS AS A RISK FACTOR FOR TYPE II DIABETES MELLITUS: A SINGLE CENTRE EXPERIENCE IN IRAQ

Dleir Yasin Taha[1], Najmaddin Salih Hussein Khoshnaw[2], Hisham Alrawi Getta[3]
Aveen Mohammad Abdulqadir[4], Rafl M. Kamil[5]

[1]Department Biology, Shar Hospital, Ministry of Health, KRG, Iraq, [2]Department of Clinical Science, College of Medicine, University of Sulaimani, KRG, Iraq, [3]Department of Pathology, University of Sulaimani, College of Medicine, Sulaymaniyah, Iraq, [4]Department of Medical Laboratory Science, American University of Iraq-Sulaymaniyah, Iraq, [5]Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Background: Type 2 diabetes (T2DM) is a serious and common chronic disorder. Appreciating risk factors for developing T2DM will improve screening, early detection, and treatment in high-risk individuals. Insulin-like growth factor-1, associated with insulin resistance, has been observed to stimulate erythropoiesis, increasing hematocrit levels. In this study, we aimed to determine whether disorders in glucose metabolism could be related to high RBC count levels and, hence, may be an independent risk factor for T2DM.

Materials & Methods: In this cross-sectional study, two hundred healthy male blood donors aged 17-65 with no history of T2DM were recruited. The hematological parameters such as RBC, Hb, Hct, and other RBC parameters were measured. HbA_{1c} and fasting blood sugar were also measured.

Results: The HbA_{1c} was normal in most cases (84.5%). In comparison, 31 donors (15.5%) had high HbA_{1c}. RBC count was also normal in 121 (60.5%) of the donors, while 79 donors (39.5%) had a high RBC count. We noticed that 25 (31.6%) of the 79 donors with high RBC counts also reported having a high HbA1c level, with a ($p < 0.002$).

Conclusion: There was a statistically significant correlation between the HbA_{1c} level and the RBC count. Therefore, a high RBC count may be a risk factor for T2DM on its own.

KEY WORDS: Hematocrit; Insulin Resistance; Polycythaemia; Type 2 Diabetes Mellitus.

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INTRODUCTION

Numerous complex genetic, environmental, and metabolic variables combine to cause type 2 diabetes (T2DM), a common and serious chronic illness. T2DM and its aftereffects are a major global public health issue that impact almost every population in both developed and developing countries, resulting in high rates of diabetes-related morbidity and mortality.[1] According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes worldwide in 2021, and this number is projected to increase to 643 million by 2030.[2] More than 90% of these cases are classified as T2DM, making it one of the most common chronic diseases globally.[3] In the Middle East and North Africa region, the prevalence of diabetes is among the highest worldwide, and in Iraq, recent reports estimate that about 14% of adults are affected by diabetes, reflecting a steady rise in its incidence, hence, the incidence of T2DM has been increasing, particularly in emerging nations.[4] Individuals with a significant familial predisposition to T2DM, advanced age, obesity, and a sedentary lifestyle are the ones most likely to be at the greatest risk.[5,6] Insulin resistance increases the likelihood of an individual having

Corresponding Author:

Dr. Najmaddin Salih Hussein Khoshnaw
Clinical Hematologist
Department of Clinical Science, College of Medicine
University of Sulaimani, Sulaimaniyh, Iraq.
E-mail: najmaddin.salih@gmail.com

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impaired glucose tolerance and T2DM. Individuals with insulin resistance exhibit several risk factors that are similar to those observed in individuals with T2DM, including: hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, hypertension, hyperuricemia, and prothrombic state.[7-9] Present initiatives to prevent T2DM involve targeting environmental risk factors by reducing obesity rates and encouraging regular physical activity.[10] Understanding the risk factors associated with the development of T2DM will enhance the process of identifying, detecting, and treating the condition in persons who are at a higher risk.[11]

Another risk factor is blood viscosity, a fundamental biological factor, is influenced by hematocrit, serum proteins, and the red blood cell (RBC) aggregation level. Polycythemia, also known as erythrocytosis, are classified into two forms: Primary polycythemia, and polycythemia vera, the former is caused by a clonal aberration in the bone marrow, and the later develops due to increased erythropoietin.[12,13] Additionally, Insulin-like growth factor-1 (IGF-1), which is linked to insulin resistance, has been found to promote the production of red blood cells, increasing hematocrit levels. In addition, elevated hematocrit levels can raise the thickness of the blood, which is negatively correlated with the extent of glucose elimination. If this situation continues, it can result in insulin resistance.[14,15]

Prior research has identified a correlation between red blood cell count and problems related to glucose metabolism. It has also shown a correlation between elevated red blood cell count, hematocrit level, and serum iron content in patients and increased insulin resistance.[16,17] As far as we know, the relationship between a high red blood cell count and insulin resistance has yet to be investigated in our area. Therefore, the objective of the present study was to determine whether erythrocytosis may represent an independent risk factor for the development of T2DM. By focusing on healthy male donors, this study aimed to clarify the association between elevated red blood cell count and impaired glucose metabolism, thereby contributing to early identification of individuals at increased risk for T2DM.

MATERIALS AND METHODS

Between November 2021 and April 2022, the central blood bank in Sulaimani City, located in the Kurdistan Region of Iraq (KRI), served as the location for the present cross-sectional study. The research was carried out accordingly after obtaining permission from Sulaimani Directorate of Health (approved number 20/1). All of the participants gave their consent after being given the information that was pertinent to the study. The total number of the study participants was 200 male blood donors who were in a good health condition, their ages ranged between 17-65 and had no history of T2DM. This sample size was determined by power analysis with 80% statistical power, a 95% confidence level, and an expected effect size of 0.25.

We were able to gather data on the respondents' ages, genders, smoking habits, experiences as donors, and any personal or family medical histories thanks to the questionnaire that was created for this study. Each participant provided five millilitres of venous blood for the collection of blood samples. Red blood cell count (RBC), haemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red blood cell distribution width (RDW) were among the haematological parameters that were measured after the blood samples had been thoroughly mixed. We used an electronic particle counter built by Swelab in Sweden called Alfa Plus for these observations. In addition, the levels of HbA_{1c} were computed with the use of an automated biochemical analyzer (Cobas c311, Roche Diagnostics, Germany). Next, the serum was collected using vacuum tubes that included a clot activator. The serum was then analyzed with the same automated biochemical analyzer to calculate the levels of fasting blood sugar (FBS).

Regarding the participants' inclusion criteria, apparently healthy male blood donors aged 17-65 years, with no known history of diabetes mellitus, hematological disorders, or chronic systemic diseases, and who consented to participate voluntarily were included. And individuals with a previous diagnosis of diabetes or prediabetes, anemia or polycythemia vera, chronic renal or hepatic disorders, recent blood transfusions (within the past three months), or those taking medications known to affect glucose or hematological parameters (e.g., corticosteroids, erythropoietin) were excluded.

A statistical package for the social sciences (SPSS version 25.0) was utilized to represent the obtained data as the mean plus or minus the standard deviation for all continuous variables that were normally distributed. The threshold for statistical significance was established at a level of $p < 0.05$. Concerning the comparison of categorical data, the Chi-square test was utilized within the framework of normalcy.

RESULTS

A total of 200 healthy male blood donors aged 18-64 years participated in the study (mean 36.7 $\pm$ 9.2 years). Most participants (93%) were adults aged 25-64 years. HbA_{1c} levels were within the normal range for the majority, while a smaller proportion showed elevated values indicative of prediabetes or diabetes as shown in Table 1. Only a few donors were smokers, and none reported a family history of diabetes.

Table 1: The age groups, HbA_{1c}, and smoking status of the studied healthy subjects

Parameters	N (%)
Age	
Youth (15-24 years)	14 (7.0)
Adults (25-64 years)	186 (93.0)
Total	200 (100)
HbA_{1c} Levels	
Normal ≤ 5.6 %	169 (84.5)
Prediabetes 5.7 - 6.4 %	16 (8.0)
Diabetes ≥6.5 %	15 (7.5)
Total	200 (100)
Smoking Status:	
Smoker	10 (5)
Non-smoker	190 (95)
Total	200 (100)

The mean donation period among participants was 4.6 ± 3.7 years, with nearly half having donated for 1-3 years as shown in Table 2.

Table 2: The duration of donation in the studied healthy patients

Donation (years)	N (%)
1 - 3	97 (48.5)
4 - 6	65 (32.5)
7 - 9	10 (5.0)
≥10	28 (14)
Total	**200 (100)**

Also, most donors showed normal hematological profiles for hemoglobin, hematocrit, and RBC count, as summarized in Table 3.

Table 3: The hematological parameters in subjects with erythrocytosis and high HbA_{1c} levels

Hematological parameters	N (%)
Hemoglobin Levels (Hb):	
Normal	163 (81.5)
High	37 (18.5)
Total	200 (100)
Hematocrit Levels (Hct):	
Low	1 (0.5)
Normal	145 (72.5)
High	54 (27.0)
Total	200 (100)
RBC Counts:	
Normal	121 (60.5)
High	79 (39.5)
Total	200 (100)

*According to WHO classification, the normal Hb for males is 14.0-16.5 g/dL; the normal Hct for males is 40-49%; the normal RBC count for males is 4.5-5.5× 10^{12}/L.

Moreover, a significant association was observed between elevated RBC count and high HbA_{1c} levels ($p < 0.002$), as presented in Table 4.

DISCUSSION

Our study showed an independent relationship between RBC count and increased HbA_{1c} levels among healthy male blood donors, suggesting that erythrocytosis may represent a novel hematologic marker for early metabolic dysfunction and predisposition to T2DM. Most participants in this study were adults aged 25-64 years as shown in Table 1, suggesting that this age range can be associated with the onset of insulin resistance

Table 4. Illustrates the number of enrolled subjects with erythrocytosis and high HbA_{1c} levels

Hematological parameters	N (%)	Normal HbA_{1c}	High HbA_{1c}	*p* value
RBCs normal	121 (100)	115 (95)	6 (5)	0.002*
RBCs high	79 (100)	54 (68.4)	25 (31.6)	
Total	200 (100)	169 (84.5)	31 (15.5)	

**Indicates significancy.*

and metabolic disorders. Comparable subclinical changes have been documented in prediabetic individuals across several recent cohorts. For instance, Arkew *et al.* reported that even modest elevations in HbA_{1c} correlated with altered red cell parameters and deteriorating glycemic control in Ethiopian adults.[16] The minimal smoking prevalence in the present cohort (5%) eliminates a key confounder, as smoking is known to elevate hematocrit via chronic hypoxia and oxidative stress.

Approximately half of the donors (48.5%) had a blood donation history of 1-3 years, while smaller proportions had longer histories, as regular blood donation can lead to mild iron depletion and improved insulin sensitivity, still our results revealed that 39.5% of donors exhibited elevated RBC counts. Therefore, we can suggest that intrinsic stimulation of erythropoiesis is independent of iron stores and possibly mediated by endocrine or metabolic factors. Additionally, increased insulin or IGF-1 activity could account for this persistent erythrocytosis. In one study, they observed a similar pattern in the city of Rio de Janeiro of T2DM patients, where higher hematologic indices predicted vascular complications, implying that hematologic alterations might precede or parallel metabolic deterioration rather than follow it.[18]

Our hematological analysis showed that 18.5% of participants had elevated hemoglobin and 27% had increased hematocrit, while 39.5% showed high RBC counts. Using these findings we can state that the concept of elevated erythrocyte mass may pre-exist before overt metabolic abnormalities appear, as increased RBC concentration elevates blood viscosity, reducing capillary perfusion and tissue oxygenation according to literature.[19] On the other hand, impaired oxygen delivery can limit oxidative glucose utilization in skeletal muscle and hepatocytes, promoting insulin resistance as confirmed by Sun *et al.*[20] by showing that increased blood viscosity in T2DM correlates directly with hyperglycemia and fibrinogen elevation, implying a feed-forward loop between viscosity and glycemic control. Our results extend this knowledge by identifying a similar pattern in healthy, normoglycemic individuals, which may represent the earliest detectable stage of this pathophysiological process.

Moreover, the most critical finding in this study is the statistically significant relationship between high RBC counts and elevated HbA_{1c} levels ($p < 0.002$). Among participants with normal RBC counts, only 5% demonstrated elevated HbA_{1c}, compared with 31.6% among those with high RBC counts. This threefold increase underlines the potential role of erythrocytosis as an independent predictor of early dysglycemia. Similar to one study conducted by Nah *et al*., who reported that hematological parameters, including RBC and hematocrit, were strongly correlated with pancreatic β-cell dysfunction and insulin resistance in prediabetes.[21] Additionally, Abbas *et al*., also reported in a Yemeni cohort that elevated RBC indices in non-diabetic individuals were associated with higher FBS and homeostatic model assessment for insulin resistance (HOMA-IR) scores.[22]

Our findings also suggest that the concept that erythrocytosis is an active participant in metabolic dysregulation. As elevated RBC counts may induce microvascular stress and oxidative injury, creating a pro-inflammatory milieu that impairs insulin sensitivity. Conversely, hyperinsulinemia and elevated IGF-1, a characteristics of early insulin resistance, may further stimulate erythropoietin-driven erythropoiesis. This mechanism was also proposed by Cho *et al.*, which integrates vascular flow properties into the pathogenesis of diabetes.[14,23] Moreover, our data suggest that such processes may initiate well before clinical hyperglycemia, providing an opportunity for early detection and intervention. According to these findings and analysis, we can state that the significant relationship between RBC count and HbA_{1c} could be leveraged as early screening indicators for metabolic risk. Routine inclusion of RBC indices in metabolic screening panels could help identify individuals at risk for prediabetes or insulin resistance long before biochemical markers or symptoms emerge. Furthermore, interpreting HbA_{1c} in the context of RBC count is essential, as elevated erythrocyte mass or altered lifespan can influence HbA_{1c} independently of plasma glucose, potentially leading to diagnostic misclassification if not accounted for.

The major strength of this research is the examination of a healthy, well-characterized population, eliminating many confounding influences common in diabetic cohorts. In addition to the utilization of standardized biochemical and hematological assessments. Moreover, the significant correlation between erythrocytosis and HbA_{1c} in a non-diabetic sample provides a novel contribution to diabetes risk stratification literature, especially in the context of Middle Eastern populations.

Certain limitations of the study include: the cross-sectional design, which precludes inference of causality, whether erythrocytosis predisposes to or results from impaired glucose metabolism cannot be definitively established. Also, the exclusive inclusion of male participants restricts generalizability, as gender differences in erythropoiesis and insulin sensitivity. Subsequently, factors such as iron status, erythropoietin levels, and serum IGF-1 were not measured, limiting mechanistic interpretation. Therefore, future studies are recommended to include both sexes and assessing hormonal and oxidative markers, which are essential to clarify the temporal and biological dynamics underlying this association.

CONCLUSION

This study demonstrated a significant association between RBC count and high HbA_{1c} levels among healthy male blood donors, indicating that erythrocytosis may serve as an independent risk factor for T2DM. Therefore, incorporating hematological parameters such as RBC count and hematocrit into routine assessments may enhance early identification of individuals at risk for T2DM.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	DYT, NSHK
Acquisition, Analysis or Interpretation of Data:	DYT, NSHK, HAG, AMA, RMK
Manuscript Writing & Approval:	DYT, NSHK, HAG, AMA, RMK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.