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ORIGINAL RESEARCH

Red Blood Cell Parameters and Their Correlation with Glycemic Control Among Type 2 Diabetic Adult Patients in Eastern Ethiopia: A Comparative Cross-Sectional Study

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Background: Diabetes has been proposed to inflict an insult on the hematopoietic milieu marked by changes in hematological indices including red blood cell parameters. Thus, this study aimed to assess the red blood cell parameters and their correlation with glycemic control in type 2 diabetic adult patients in comparison with apparently healthy individuals.

Methods: A comparative cross-sectional study was conducted at the chronic illness clinic of Hiwot Fana Comprehensive Specialized University Hospital from May 20 to July 10, 2022. A total of 220 (110 type 2 diabetic patients and 110 controls) study participants were selected by a simple random sampling technique. Five milliliters of venous blood were collected by the vacutainer blood collection technique. Red blood cell parameters and blood glucose levels were determined using UniCel DxH 800 and Biosystems A25 analyzers, respectively. Independent sample *t*-test and Pearson correlation test were used for the data analysis. P-value <0.05 was considered statistically significant.

Results: Statistically significant difference was observed in RBC parameters of T2DM patients and the control group. The mean RBC count, Hgb, Hct ($P < 0.001$), and MCHC ($P = 0.002$) in patients with type 2 diabetes was significantly lower than in the control group. However, the mean of RDW was significantly increased in type 2 diabetic patient groups than in the control group ($P < 0.001$). The mean RBC count, Hct, and Hgb in patients with good glycemic control were significantly higher than the patients with poor glycemic control. Besides, a statistically significant negative correlation was observed between glycemic control and RBC count, Hgb, and Hct level in diabetic patients.

Conclusion: In this study, a statistically significant difference was observed in red blood cell parameters of type 2 diabetic patients compared to the control group. A significant negative correlation was noted between glycemic control and RBC parameters in type 2 diabetic patients. Therefore, evaluation of RBC parameters should be considered for better management of patients with type 2 diabetes mellitus.

Keywords: Eastern Ethiopia, glycemic control, red blood cell parameters, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a rapidly growing global health emergency and one of the four (cardiovascular disease, cancer, and respiratory disease) priority non-communicable diseases targeted for action by world leaders.[1] Diabetes is classified into two major types, type 1 and type 2 diabetes. Type 2 diabetes (T2DM) is the majority of the DM burden, comprising 90–95% of cases and characterized by peripheral insulin resistance or reduced production of insulin.[2] The burden of DM among adults has rapidly increased from 108 million in 1980 to 537 million cases and 6.7 million deaths in 2021.[3] More

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than 75% of the global diabetes burden is shouldered by low- and middle-income countries and the number of diabetes cases is estimated to increase to 783 million globally by 2045.[3] The prevalence of diabetes in sub-Saharan Africa is markedly increased. Recent international data showed that 24 million (4.5%) adults in the Africa Region and 1.9 million (3.3%) adults in Ethiopia had diabetes.[3]

Diabetes mellitus is associated with various pathological changes including metabolic, cellular, and blood disturbances resulting in vascular complications.[4] It has been documented that several blood components including red blood cells (RBCs), white blood cells (WBCs), platelets, and the hemostasis systems are affected by diabetes.[5] Light of evidence showed that qualitative and quantitative change of RBCs are common in diabetic patients.[6] It has been documented that, hyperglycemia is responsible for the complications and adverse outcomes of diabetes.[7] The persistent hyperglycemia in diabetes is associated with metabolic, structural, and functional changes in RBCs due to the glycation of hemoglobin (Hgb) and membrane proteins.[8,9] In addition, chronic inflammation and raised production of oxygen-free radicals are also associated with endothelial tissue damage and RBC dysfunction.[10,11] Besides, glycation of RBCs leads to increased aggregation and reduced deformability due to reduced membrane fluidity. These changes have been shown to unfavorably increase blood viscosity that affects microcirculation and leads to microangiopathy.[12] Indeed, these changes could have an adverse effect on RBC parameters such as RBC count, Hgb, hematocrit (Hct), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), and red cell distribution width (RDW).[9,13]

Anemia is the most common hematological abnormality in T2DM patients and is often unrecognized, and its prevalence varies in different populations worldwide.[14–16] The cause of anemia in T2DM is multifaceted that includes declining kidney function, functional erythropoietin deficiency, oral antidiabetic drugs, oxidative stress, advanced glycation end products (AGEs), chronic hyperglycemia, and inflammation.[17] As a result, anemia could occur early in patients with diabetes, even without overt nephropathy. Also, anemia is a significant adverse prognostic factor to increase the risk of diabetic complications including nephropathy, retinopathy, and cardiovascular disease due to hypoxia-induced organ damage.[18] Indeed, an array of these modifiable risk factors is neglected, and if untreated, it is associated with poor quality of life, increased length of hospital stay, and all-cause mortality in diabetes populations.[17]

Generally, maintaining good glycemic control is mainly recommended to minimize the progression of diabetic complications. Early normalization of blood glucose may block the pathological processes that are closely related to and initiated by hyperglycemia like oxidative stress and glycation of membrane proteins and lipids. Laboratory investigations for the management of diabetic patients are fasting blood glucose, glucose in the urine, glycated hemoglobin (HbA1c), and parameters of lipid status.[4] Analysis and interpretation of hematological parameters such as WBC, RBC, Hgb, Hct, RDW, and other platelet parameters could contribute to the following-up of the progression of degenerative complications in diabetes.[19] Although the prevalence of anemia and hematological parameters in T2DM has been assessed somewhere in Ethiopia,[20,21] the relationship between RBC parameters and glycemic control was not well characterized. Therefore, this study aimed to assess the red blood cell parameters and their correlation with glycemic control in type 2 diabetic adult patients in comparison with healthy controls at Hiwot Fana Comprehensive Specialized University Hospital.

Materials and Methods

Study Design, Period, and Setting

A comparative cross-sectional study was conducted from May 20 to July 10, 2022, at the Chronic Care Clinic of Hiwot Fana Comprehensive Specialized University Hospital (HFCSUH), Eastern Ethiopia. The hospital is found in Harar town, at a distance of 526 km from Addis Ababa, the capital city of Ethiopia, at an elevation of 1885 meters. There are four hospitals, eight health centers, and two private clinics that provide healthcare services in Harar town. Hiwot Fana Comprehensive Specialized University Hospital gives comprehensive healthcare services to the entire population of Eastern Ethiopia. Also, the hospital plays a pivotal role in providing teaching, research, and other community services. During the study period, the chronic follow-up clinic at HFCSUH provides regular follow-up service for more than 410 (110 type I and 300 type II) DM patients.

Study Participants

All adult patients with T2DM attending a chronic care clinic of HFCSH during the study period and volunteered to give informed written consent were enrolled in the study. In addition, age- and sex-matched healthy individuals were involved as a control group. The control groups were volunteer non-remunerated blood donors, HFCSH staff, and patient attendants. On the other hand, patients with cardiac, renal, and liver disease, patients with HIV/AIDS, bronchial asthma, patients who were taking erythropoietin, insulin, hematin factors, blood transfusion in the past three months, hypertensive patients, smokers, alcoholics, pregnant women, patients below the age of 18 and above 65 years were excluded from this study. Healthy individuals who had a history of chronic diseases and those who did not volunteer to participate were excluded from the study. The health condition of the control groups was evaluated according to the national blood bank service blood donor questionnaire, and screening was done for transfusion-transmitted infectious diseases (HIV, Hepatitis, Syphilis, and malaria).

Sample Size Determination and Sampling Technique

As recommended by Van Voorhis and Morgan in the rules of thumb, 30 participants are required per group to detect real differences, which gives 80% power.[22] Thus, a total of 220 (110 T2DM and 110 controls) study participants were engaged in this study. A simple random sampling technique was used to select the study participants. A random number generator was used to reduce the effect of selection bias in the study, and every subject in the target population had an even chance to be selected.

Operational Definitions

RBC Parameters

These are hematological tests that include RBC, Hgb, HCT, MCV, MCH, MCHC, and RDW.[23]

Glycemic Control

American Diabetes Association recommends measuring hemoglobin A1c to determine glycemic control. If HgbA1c is unavailable and unaffordable, average fasting blood sugar (FBS) can be considered. Accordingly, the previous 2 months' fasting blood sugar (FBS) level and the current result were used to determine the average FBS level. Based on this, study participants were categorized as having poor glycemic control (FBS $\geq$ 152 mg/dl) and good glycemic control (FBS $<$ 152 mg/dl), which is equivalent to 7% HgbA1C.[24]

Data Collection and Laboratory Methods

Socio-demographic data like age, sex, residence, occupation, and educational status were collected by a pretested structured questionnaire. Duration of diabetes and fasting blood sugar levels of the previous two months were tracked review of the patient's medical records. The anthropometric data such as height, weight, and waist circumference (WC) were collected by following the anthropometric measurement protocol. Body mass index (BMI) was determined as weight in kilograms divided by height in meter squared.

Five milliliters of venous blood sample (2mL in a serum separator tube and 3mL in a K2EDTA tube) were collected using a vacutainer blood collection system from each diabetic patient. Again, three milliliters of venous blood were collected into a K2EDTA test tube from each control group. Fasting blood glucose was estimated from a serum separator tube by glucose oxidase method,[25] using Biosystems A25 (Costa Brava, Spain) clinical chemistry analyzer. Red blood cell parameters were determined by UniCel DxH 800 (Beckman Coulter, USA) hematology analyzer by following the electrical impedance and spectrophotometry principle.[26]

Data Quality Assurance and Management

The questionnaire prepared in the English language was translated into Amharic & Afan Oromo and translated back to the original version. A pre-test was done on 5% of the sample size, and training was given to the data collectors. Manufacturer's instructions and standard operating procedures were strictly followed in all processes of laboratory analysis. Low, normal, and high control materials were used for the hematological analyzer, and normal and pathological

controls were applied for glucose measurement. All laboratory investigations were analyzed within two hours of specimen collection. Generally, all phases of quality assurance protocols were maintained.

Statistical Analysis and Interpretation

The completeness and consistency of data were checked and entered into Epidata version 3.1. A statistical Package for Social Sciences version 25 software was used for data analysis. Data normality was checked by Shapiro–Wilk and Kolmogorov–Smirnov test. Categorical variables were reported as frequency and percentages, and continuous variables were reported as mean with standard deviation. Chi-square tests were used to determine statistical differences between the study group for categorical variables. Comparison of RBC parameters between diabetic and control participants as well as between diabetic patients with good glycemic control and poor glycemic control was done by independent sample *t*-test. The correlation of RBC parameters with glycemic control was examined by Pearson's correlation (r). In any condition, P-value <0.05 was considered statistically significant.

Ethical Considerations

Ethical clearance was obtained from the Institutional Health Research Ethics Review Committee of the College of Health and Medical Sciences of Haramaya University with letter reference number IHRERC/092/2022. A letter of cooperation was written to HFCSUH, and permission was obtained from the hospital administration. Written informed consent was obtained from each study participant after explaining the objective and procedures of the study. The data were kept confidential, and participation was voluntary. Laboratory results with abnormal findings were sent to clinicians for proper treatment and management of patients. The study was carried out according to the Declaration of Helsinki.

Results

Socio-Demographic, Anthropometric, and Clinical Characteristics of Study Participants

In the current study, 220 (110 type 2 diabetic patients and 110 controls) study subjects participated. The mean age (mean ±SD) was 43.13 ± 9.43 for type 2 diabetic patients and 43.00 ± 8.82 years for controls. Around 73 (67.40%) study participants were males for both T2DM patients and controls. Of the total study participants, around 20 (18.20%) and 36 (32.70%) were government employees for type 2 diabetic patients and controls, respectively. The majority of study participants, 113 (84.3%) and 107 (79.9%) were urban dwellers of type 2 diabetic patients and controls, respectively. Statistically, a significant increment was found in WHR ($p < 0.001$), and BMI ($p < 0.001$) in T2DM controls. The mean value of FBG was 159.93 ± 27.40 and the mean duration of DM since diagnosis was 7.65 ± 3.40 years in type 2 diabetic patients. The majority of T2DM patients 99 (90.00%) were taking metformin (Table 1).

Comparison of RBC Parameters of the Study Participants

A statistically significant difference was observed in the RBC parameters of type 2 diabetic patients and the control group. The mean RBC count, Hgb, Hct ($P < 0.001$) and MCHC ($P = 0.002$) in patients with T2DM patients was significantly lower than in the control group. However, a significantly higher value of RDW was found in type 2 diabetic patients than in the control group ($P < 0.001$) (Table 2).

Comparison of RBC Parameters of T2DM Patients Based on Glycemic Control

A statistically significant difference was observed in RBC parameters of T2DM patients with good glycemic control and poor glycemic control. The mean RBC count, Hct ($P = 0.002$), and Hgb ($P = 0.028$) in patients with good glycemic control were significantly higher than the patients with poor glycemic control. However, a statistically significant change was not found in other RBC parameters in the patients with good glycemic control and patients with poor glycemic control ($P > 0.05$) (Table 3).

Table 1 Socio-Demographic, Anthropometric, and Clinical Characteristics of Study Participants, at Hiwot Fana Comprehensive Specialized University Hospital, Eastern Ethiopia, 2022 (n = 220)

Variables		T2DM (n = 110)	Control (n = 110)	P-value
Age (years), mean ± SD		43.13±9.43	43.00±8.82	0.920
Sex, n (%)	Male Female	73 (67.40) 37 (33.60)	73 (67.40) 37 (33.60)	0.184
Occupation, n (%)	Government employee Private employee Private worker Others	20 (18.20) 9 (8.20) 29 (26.40) 52 (47.30)	36 (32.70) 18 (16.40) 35 (31.80) 21 (19.10)	<0.001*
Educational status, n (%)	Unable to read and write Able to read and write Primary school High school and above	11 (10.00) 18 (16.40) 34 (30.90) 47 (42.70)	4 (3.60) 8 (7.30) 32 (29.10) 66 (60.00)	0.100
Residence, n (%)	Urban Rural	94 (85.50) 16 (15.70)	87 (14.50) 23 (20.90)	0.170
BMI (kg/m2)		24.98±3.80	22.40±1.95	<0.001*
WHR		0.90±0.02	0.85±0.02	<0.001*
Glycemic level (mg/dl), mean ± SD		159.93±27.40	_	_
Duration of DM (year), mean ± SD		7.65±3.4	_	_
Anti-DM drug, n (%)	Metformin Sulfonylureas	99 (90.00) 11 (10.00)	_ _	_ _

Note: *p-value <0.05 is considered as statistically significant.

Table 2 Comparison of Red Blood Cell Parameters of Study Participants at Hiwot Fana Comprehensive Specialized University Hospital, Eastern Ethiopia, 2022 (n = 220)

Parameters	T2DM (n = 110) Mean ± SD	Control (n = 110) Mean ± SD	p-value
RBC ($10^6/\mu L$)	5.00±0.42	5.30±.0.43	<0.001*
Hgb (g/dl)	15.36±1.2	16.50±1.10	<0.001*
Hct (%)	45.24±3.14	47.70±3.23	<0.001*
MCV (fl)	91.14±4.35	90.34±4.26	0.171
MCH (Pg)	30.94±1.85	31.20±1.60	0.260
MCHC (%)	34.20±0.94	34.5±0.89	0.002*
RDW (%)	14.20 ±1.03	13.61 ±0.74	<0.001*

Note: *p-value <0.05 is considered as statistically significant.

Correlations of RBC Parameters with Glycemic Control Among T2DM Patients

In the correlation analysis, RBC count (r = −0.239, p = 0.012), Hgb (r = −0.193, p = 0.044) and Hct (r = −0.265, p = 0.005), showed a statistically significant negative correlation with glycemic control. However, significant correlation was not found between other RBC parameters and glycemic controls and other clinical variables.

Table 3 Comparison of Red Blood Cell Parameters of Type 2 Diabetic Adult Patients Based on Glycemic Control Status, at Hiwot Fana Comprehensive Specialized University Hospital, Eastern Ethiopia, 2022 (n = 110)

Parameters	Good Glycemic Control (n = 53) Mean ± SD	Poor Glycemic Control (n = 57) Mean ± SD	p-value
RBC (10^6/μL)	5.12±0.40	4.87±0.45	0.002*
Hgb (g/dl)	15.60±0.92	15.16±1.11	0.028*
Hct (%)	46.20±2.94	44.34±3.06	0.002*
MCV (fl)	90.40±3.94	91.84±4.64	0.081
MCH (Pg)	30.54±1.51	31.31±2.06	0.280
MCHC (%)	33.98±1.00	34.23±0.91	0.098
RDW (%)	14.17 ±1.00	14.23 ±1.10	0.764

Note: *p-value <0.05 is considered as statistically significant.

Discussion

It has been documented that qualitative and quantitative changes in red blood cells of diabetic patients are common and a significant cause of premature death in these patients.[6,27] In the present study, a statistically significant difference was observed in the RBC parameters of T2DM patients and the non-diabetic group. The mean RBC count, Hct, and Hgb values were significantly lower in T2DM patients than in the control group. This finding is in harmony with reports from India,[28] Libya,[29] Sudan,[30] and Ethiopia.[20,21] The relative decrease in RBCs count, Hct, and Hgb level might be that long-term hyperglycemia causes the generation of free oxygen radicals and irreversible glycation of hemoglobin and RBC membrane proteins. All these acts in concert lead to decreased deformability, increased aggregation, aging of RBCs, and decreased survival of RBCs.[10,12,31] The reduced deformability and increased aggregation in RBCs unfavorably increase blood viscosity that affects the microcirculation, leading to microangiopathy, again results increased RBC destruction.[12] However, contrary to our report, pieces of literature from Pakistan[32] and Ethiopia[33] reported increased RBC count and Hgb level in type 2 diabetic patients than in the non-diabetic group. This might be due to the effect of hyperinsulinemia, in which insulin has a synergetic effect with erythropoietin and stimulates erythroid progenitors resulting in increased erythropoiesis.[34]

In addition, MCHC values were found significantly lower in the diabetic patients as compared to the non-diabetic group. Similarly, studies conducted in Saudi Arabia[35] and Sudan[30] reported that the MCHC value was decreased in T2DM patients than in the controls. Erythrocytes stayed in hyperglycemic conditions throughout their life span and are subjected to several structural and functional changes including hypochromia, anisocytosis, and poikilocytosis.[36] Hypochromia is indicated by decreased MCHC and is a common finding in iron deficiency anemia, thalassemia, and anemia of inflammation.[37] It has been accepted that DM is associated with long-term inflammation and increased inflammatory cytokines like interleukin 6 and interleukin-1.[17,38] Thus, inflammation inducible cytokines and hepcidin plays a significant role in the development of microcytic hypochromic red blood cells by retention of iron in reticuloendothelial cells.[39] However, contrary to the current findings, pieces of literature from India,[28] Libya,[29] and Gondar, Ethiopia,[21] reported a higher value of MCHC in T2DM patients. The increased MCHC value in diabetic patients may be associated with morphological and functional modifications of RBCs due to chronic hyperglycemia. Hyperglycemia increases the attachment of hemoglobin to the inside of the RBC membrane network including band 3 and spectrin proteins.[40] This may result in the formation of spherocytic cell and alter the mechanical properties of RBCs. The Hgb attachment to the spectrin network also increases the intracellular or cytosolic viscosity of the RBCs that are associated with MCHC.[41]

Regarding RDW, the current data showed that RDW values were significantly increased in type 2 diabetic patients as compared to the non-diabetic groups. This report is in agreement with several studies conducted in Pakistan,[32] Saudi Arabia,[35] and Ethiopia.[20,21,33,42] An increased RDW shows the presence of anisocytosis among the circulating RBCs, which is associated with a defect in red blood cell production and rapid destruction of RBCs.[43] Long-lasting

inflammation and a higher level of oxidative stress are common in the diabetic environment, and they are known to reduce RBCs' survival resulting in variation in erythrocyte size and lower red blood cell count.[44]

In the present study, the mean RBC count, Hct, and Hgb were significantly decreased in patients with poor glycemic control as compared to patients with good glycemic control. The finding is supported by some work of literature from India,[45] and Ethiopia.[46] The possible mechanism could be due to many biochemical changes in the RBC membrane including impaired ATPase (Na^+/K^+ ATPase and Mg^{2+} ATPase) activities. Chronic hyperglycemia increases sorbitol accumulation in erythrocyte and this affects Na+/K+-ATPase activity leading to osmotic imbalance, reduced deformability, and cellular death.[47,48] It has been reported that the activity of RBCs ATPase was significantly decreased in T2DM patients with higher glucose. In addition, a significant negative correlation was reported between ATPase and hyperglycemia.[47] Hyperglycemia also increases the rate of membrane lipid peroxidation and enhanced Ca^{2+} intracellular levels, ultimately triggering the process of eryptosis.[40,48] Therefore, the interplay between inflammation, oxidative stress, and the undesirable effects of hyperglycemia on the mechanical and hemodynamic features of the RBCs can be inferred to the lower values of red blood cells and their parameters in patients with uncontrolled glycemic levels.

This study also included the correlation of RBC parameters and glycemic controls in diabetic patients. In the correlation analysis, a statistically significant negative correlation was determined between glycemic control and RBC count, Hgb, and Hct. The negative correlation between RBC, Hct, and Hgb with glycemic control in diabetes might be due to oxidative stress resulting from the imbalance between free radicals and the body's antioxidant defense systems. Evidence showed that diabetic patients were susceptible to oxidative stress and higher blood glucose level had an association with free radical-mediated lipid peroxidation, leading to reduced RBC survival. The persistent hyperglycemia is the primary cause of glucose autoxidation, glycation of hemoglobin, membrane protein, and activation of polyol pathway with increased oxidative stress.[49] The red blood cell is a central focus of oxidative stress because it is thought to undergo a high rate of endogenous and exogenous H_2O_2 production from hemoglobin autoxidation, glycoxidation, and lipoxidation.[10,50] In addition, diabetic nephropathy is one of the complications of diabetes due to changes in metabolic and hemodynamic pathways such as hyperglycemia, oxidative stress, glomerular hyperfiltration, and glomerular and tubular epithelial hypertrophy.[51] When there are structural and functional changes in the kidney like damage to the peritubular fibroblasts, there is erythropoietin deficiency and low Hgb that leads to anemia.[17,51]

The present study has to be interpreted in the light of limitations. One limitation of this study is that we cannot determine a cause–effect relationship due to the cross-sectional nature of our study design. In addition, morphological evaluation and other contributing factors closely linked with RBC parameters like micronutrient levels in the study participants were not determined.

Conclusion and Recommendation

The current study showed that there was a statistically significant difference in RBC parameters (RBC count, Hct, Hgb, and MCHC) of type 2 diabetic patients compared to the control group. This study also highlights that there was a statistically significant decrement in the mean RBC count, Hct, and Hgb in patients with poor glycemic control as compared to patients with good glycemic control. Besides, red blood cell count, hematocrit, and hemoglobin were inversely correlated with glycemic control. Therefore, in addition to an assessment of glycemic control, regular evaluation of RBC parameters should be considered for better management of type 2 diabetic patients and to prevent the occurrence of major complications.

Abbreviations

AGE, Advanced Glycation End Products; BMI, Body Mass Index; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; K2EDTA, Dipotassium Ethylene Diamine Tetra Acetic acid; FBS, Fasting Blood Sugar; HbA1c, Glycated hemoglobin; Hct, Hematocrit; Hgb, Hemoglobin; HFCSUH, Hiwot Fana Comprehensive Specialized University Hospital; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Cell Hemoglobin Concentration; MCV, Mean Corpuscular Volume; RBC, Red Blood Cell; RDW, Red blood cell Distribution Width; T2DM, Type 2 Diabetes Mellitus; WHR, Waist-to-Hip Ratio.

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Author Contributions

All authors made a significant contribution to the work reported in the conception, study design, execution, acquisition, analysis and interpretation of data; took part in drafting, revising and critically reviewing the manuscript. All authors have agreed on approval of the final manuscript to be published in the current journal and to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest related to this work.

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