Evaluation of Red Blood Cell Parameters as a Biomarker for Long-Term Glycemic Control Monitoring Among Type 2 Diabetic Patients in Southwest Ethiopia: A Cross-Sectional Study

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Evaluation of Red Blood Cell Parameters as a Biomarker for Long-Term Glycemic Control monitoring among Type 2 Diabetic Patients in Southwest Ethiopia: a cross-sectional study

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2 DM) is a common type of DM characterized by hyperglycemia. Glycation of hemoglobin and related proteins in DM can affect the physiological and structural properties of red blood cells. Although glycated hemoglobin (HbA1c) test continues to be the gold standard for the assessment of long-term glycemic control accessibility and affordability of the test in routine diagnosing service are still limited in developing countries. Hence, this study was aimed to assess red blood cell parameters as a biomarker for long-term glycemic monitoring among T2 DM patients.

Methods: Facility-based cross-sectional study through a consecutive sampling technique was conducted among 124 T2 DM patients at the chronic illness follow-up clinic of Jimma Medical Center (JMC) from July 27 to August 31, 2020. A structured questionnaire was used to collect socio-demographic and clinical-related data. Five milliliters of the blood specimen was collected from each eligible T2 DM patient. HbA1c and red blood cell parameters were determined by Cobas 6000 and DxH 800 fully automated analyzers respectively. Data were entered into Epi-data software version 3.1 and exported to SPSS 25 version for analysis. Independent t-test and Pearson's correlation coefficient were used to address the research questions. A P-value < 0.05 was considered statistically significant.

Results: The mean age of study participants was 51.84± 11.6 years. 60.5% of T2 DM patients were in poor glycemic control. There was a significant mean difference between good and poor glycemic controlled T2 DM patients in red blood cell count (4.79±0.5 vs 4.38±0.8), hemoglobin (14.13±1.4 vs 13.60±1.6), mean corpuscular volume (89.52±4.7 vs 92.62±7.5), mean corpuscular hemoglobin (29.63±1.6 vs 30.77±2.9), and red cell distribution width (13.68±1.1 vs 14.63±1.2) respectively. Red blood cell count was inversely correlated (r=-0.280, p=0.002) with HbA1c while mean corpuscular volume (r=0.267, p=0.003), mean corpuscular hemoglobin (r=0.231, p=0.010), and red cell distribution width (r= 0.496, p=0.000) were positively correlated with level of HbA1c.

Conclusion: Red cell count, mean corpuscular volume, mean corpuscular hemoglobin, and red cell distribution width could be useful indicators to monitor the glycemic status of T2 DM patients instead of HbA1c, though large prospective studies should be considered.

Keywords: T2 DM, Hyperglycemia, HbA1c, Red blood cell parameters.

Background

Type 2 Diabetes mellitus (T2 DM) is a common type of DM characterized by hyperglycemia, due to insulin resistance and relative impairment in insulin secretion [1]. Although the pathogenesis of T2 DM is multifactorial, chronic hyperglycemia is the major factor for the development of both micro and macro-vascular complications [2,3]. Thus the strict control of hyperglycemia is the main therapeutic objective to prevent or delay complications associated with DM [4].

The most common laboratory tests used for screening and monitoring of glycemic status in the clinical management of DM comprises, Fasting Blood Sugar (FBS), Random Blood Sugar (RBS), Oral Glucose Tolerance Test (OGTT), and glycated hemoglobin (HbA1c) test [5]. The HbA1c is a hemoglobin variant, formed by condensation of a glucose molecule with N-terminal residue in the β-chain of hemoglobin. Analysis of HbA1c in the blood provides the average blood glucose levels of diabetic patients during the past 2-3 months, which is the expected life span of Red Blood Cells (RBCs) [6]. HbA1c is the most effective biomarker of long-term glycemic monitoring than other glucose-based tests because it is less influenced by factors like food ingestion, stress, exercise, and immediate therapeutic responses [7].

RBC parameters are components of Complete Blood cell Count (CBC) which comprises a panel of analytic tests usually used to differentiate different types of anemia [8]. RBC parameters include Red Blood Cell count (RBC), hematocrit (HCT), hemoglobin (HGB), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red cell Distribution Width (RDW) [9].

Continual exposure of hyperglycemia in RBCs results persistent glycation of hemoglobin protein which causes the structural and functional change of hemoglobin molecule [10]. Besides the glycation of proteins, hyperglycemia has several other effects on RBCs like change in the mechanical properties and internal viscosity of RBCs, increased aggregation, and osmotic fragility, consequently leading to changes in erythrocyte structure and hemodynamic characteristics [11,12]. These changes may be reflected by any one or all of red blood cell analytical parameters such as RBC count, HGB, HCT, MCV, MCH, MCHC, and RDW.

Although the HbA1c test continues to be the gold standard for the assessment of long-term glycemic control, accessibility and affordability of the test in routine diagnosing service are still limited in developing countries especially in rural Africa [13]. Lack of HbA1c tests in health care facilities is one of the hindrances for clinicians to make long-term management decisions about DM patients [14]. Reports also showed that the absence of HbA1c measurement was an important indicator of frequent hospital re-admission in T2 DM patients [15,16]. Moreover, it has been reported that limited access to the HbA1c test appeared to be a key predictor of poor glycemic control and is a significant obstacle to improving glycemic control in T2 DM patients [17]. In Ethiopia, HbA1c assay is not readily available in public health facilities even at referral hospitals, and is a relatively expensive test in some private sectors [18]. Therefore, there is a need to find easily available means of monitoring glycemic status for resource-restricted countries. Hence this study was aimed to evaluate red blood cell parameters as a biomarker for long-term glycemic monitoring among T2 DM patients in southwest Ethiopia.

Methods

Study setting, design and period

A facility-based cross-sectional study design was carried out on type 2 DM patients at the chronic illness follow-up clinic of Jimma Medical Center (JMC). JMC is located in Jimma town at 353 km to the Southwestern of Addis Ababa, the capital of Ethiopia. It has different units and clinics that provide specialized services for clients. Among these, there is a separate chronic illness follow-up clinic in which diabetes mellitus patients are regularly monitored every Monday and Tuesday of the week. The study was conducted from July 27 to August 31, 2020.

Exclusion criteria

T2 DM patients with the following criteria were excluded from the study after verified by checking their medical records.

- Critically ill T2 DM patients to the extent unable to communicate
- T2 DM patients with known anemia and /any hematologic disorder
- T2 DM Patients with confirmed chronic liver and kidney disease
- Patients with known human immune HIV, tuberculosis, and/ any type of malignancy
- Patients who transfused blood in the last 3 month prior to data collection
- T2 DM patients with a history of recurrent malaria and

- T2 DM patients who are pregnant.

Sample size determination and sampling technique

The minimum sample size required for the study was estimated using a single population proportion formula as follows: $n = \frac{N(\mathrm{Z}\alpha/2)^2 P(1-P)}{d^2 (N-1)+(\mathrm{Z}\alpha/2)^2 P(1-P)}$ Where

n = Minimum sample size required for the study

N = Number of T2 DM patients on follow-up care in JMC, which is 2700

$Z_{\alpha/2}$ = Confidence Interval (CI) at 95% which is 1.96 (where $\alpha = 0.05$)

d =Margin of error tolerated which is 4%

P = Assumed the highest proportion of DM in the Ethiopian adult population 5.2 % [19].

By substituting to the above formula, $n = \frac{2700\ (1.96)^2 \text{ x } (0.052)(0.948)}{(0.04)^2(2700-1)+(1.96)^2 \text{ x } (0.052)(0.948)}$,

The minimum sample size n becomes **~ 113,** adding 10 % of non -response rate, a total of **124** study participants were enrolled in the study using a consecutive sampling technique.

Data collection and blood sample analysis

An interviewer-administered structured questionnaire adapted from the WHO STEPS instrument [20], was used to collect socio-demographic profile, behavioral related factors, and clinical data of eligible participants.

After the interview and detailed review of the medical record, five milliliters (5ml) of the venous blood sample was collected from each eligible study participant using 5 cc sterile syringes, through the aseptic technique. About 2.5 ml of blood was dispensed into a labeled test tube containing Ethylene-Diamine-Tetra Acetic acid (EDTA) anticoagulant for testing of RBC parameters. The remaining 2.5 ml of blood was collected in a separate EDTA test tube for the analysis of HbA1c. The specimen then was transported to JMC laboratory unit for analysis on the same date of specimen collection to prevent whole blood hemolysis. RBC parameters were analyzed by a fully automated hematology analyzer, UniCel DxH 800 (Beckman coulter, USA). Whereas, HbA1c was determined by a fully automated Cobas® 6000 chemistry analyzer (Roche diagnostic, Germany).

Operational definitions

Red blood cell parameters are defined by a panel of tests which comprises (RBC count, HCT, HGB, MCV, MCH, MCHC, and RDW) [8].

Glycemic control: were categorized into two groups in T2 DM patients based on the ADA Standards of Medical Care in Diabetes 2020 recommendation [21].

Good glycemic control: HbA1c < 7%; Poor glycemic control: HbA1c ≥ 7 %

Statistical analysis

Data were checked for completeness and entered into Epi-data software version 3.1 and exported to Statistical Package for Social Science (SPSS) software version 25 for statistical analysis. All variables were cleaned through running frequencies to avoid missing values and checked for fulfillment of assumptions using histograms, boxplots and, scatter plots before analysis. To determine the level of glycemic status, study participants were grouped into two (poor and good glycemic control) according to their HbA1c value. Then, an independent t-test analysis was used to compare the mean of RBC parameters between the two groups. Pearson's bivariate correlation coefficient (r) was used to determine the strength of association between each RBC parameter and HbA1c level. In all cases, P values less than 0.05 were considered to be statistically significant.

Data quality management

To ensure data quality, training, and adequate orientation were given for all data collectors. Accuracy, clarity, and completeness of data were reviewed and checked daily by the principal investigator. Sample collection, handling, processing, and analysis were performed by strictly following Standard Operational Procedures (SOPs) to address the quality issues in each analytical phases to guarantee accurate test results. Moreover, all reagents used were checked for their expiry date and both instruments were calibrated every day before the actual sample test according to the manufacture's recommendation.

Results

Socio-demographic characteristics of study participants

A total of 124 eligible T2 DM patients had participated in this study. Out of which 63.7 % and 36.3 % were males and females respectively. The overall average age of the study participants was 51.84 ± 11.6 years ranging between 30-83 years old. The majority of the study participants (85.5%) were married, 58.1% were residing in urban areas (Table 1).

Table 1: Socio-demographic characteristics of T2 DM patients on follow up care in JMC, Southwest Ethiopia, 2020 (N=124)

Variables		Sex		
		Male N=79 (63.7%)	Female N=45 (36.3%)	Total N=124 (100%)
Age in a year [a]	Mean (± SD)	52.27 (±12.2)	51.09 (±10.6)	51.84 (± 11.6)
Marital status	Single	5 (4.0%)	0 (0.0%)	5 (4.0%)
	Married	71 (57.3)	35 (28.2%)	106 (85.5%)
	Divorced	2 (1.6%)	4 (3.2%)	6 (4.8%)
	Widowed	1 (0.8%)	6 (4.8%)	7 (5.6%)
Educational status	No formal education	12 (9.7%)	17 (13.7%)	29 (23.4%)
	Primary	31 (25.0%)	14 (11.3%)	45 (36.3%)
	Secondary	18 (14.5%)	6 (4.8%)	24 (19.4%)
	Above secondary	18 (14.5%)	8 (6.5%)	26 (21.0%)
Residence	Urban	47 (37.9%)	25 (20.2%)	72 (58.1%)
	Rural	32 (25.8%)	20 (16.1%)	52 (41.9%)
Family history DM	Yes	17 (13.7%)	12 (9.7%)	29 (23.4%)
	No	62 (50.0%)	33 (26.6%)	95 (76.6%)

Note**:** [a]Age, a continuous variable presented as mean ± standard deviation.

RBC parameters in T2 DM patients

The total number of T2 DM patients was categorized into Good Glycemic Control (GGC) and Poor Glycemic Control (PGC). 60.5% of T2 DM patients were in PGC. An independent t-test analysis was used to compare mean values of RBC parameters between the two groups. RBC count and HGB were significantly ($p<0.05$) reduced in patients with HbA1c ≥7% compared to patients with HbA1c < 7%. While, MCV, MCH, and RDW were significantly ($p<0.05$) elevated in T2 DM patients with HbA1c ≥7% (Table 2).

Table 2: Mean of RBC parameters among T2 DM patients on follow-up care in JMC, Southwest Ethiopia, 2020 (N=124)

Parameters	Total T2 DM N= 124 Mean ±SD	GGC (HbA1c<7%) N=49 Mean ±SD	PGC (HbA1c≥7%) N=75 Mean ±SD	P-value
RBC (10^6/μL)	4.59 ±0.7	4.79 ±0.5	4.38 ±0.8	0.001*
HGB (g/dl)	13.82 ±1.5	14.13 ±1.4	13.60 ±1.6	0.05*
HCT (%)	41.85 ±4.9	42.71 ±4.1	41.29 ±5.3	0.099
MCV (fl)	91.39 ±6.7	89.52 ±4.7	92.62 ±7.5	0.005*
MCH (pg)	30.32 ±2.6	29.63 ±1.6	30.77 ±2.9	0.007*
MCHC (g/dl)	33.09 ±0.8	33.11 ±0.8	33.07 ±0.8	0.799
RDW (%)	14.10 ±1.2	13.68 ±1.1	14.63 ±1.2	0.000*

Note:* statistically significant at p<0.05; GGC = Good Glycemic Control; PGC = Poor Glycemic Control.

Correlation of RBC parameters and HbA1c in T2 DM patients

Bivariate Pearson's product-moment correlation analysis was used to examine the relationship between red blood cell parameters and the HbA1c level in T2 DM patients. A statistically significant correlation was detected between RBC count, MCV, MCH, and RDW parameters with HbA1c level in T2 DM patients (Table 3).

Table 3: Pearson correlation analysis between RBC parameters and HbA1c in T2 DM patients on follow-up care in JMC, Southwest Ethiopia, 2020 (N=124)

Parameters	HbA1c (%) Pearson correlation (r)	P-value
RBC (10^6/μL)	-0.280	0.002**
HGB (g/dl)	-0.102	0.258
HCT (%)	-0.076	0.402
MCV (fl)	0.267	0.003**
MCH (pg)	0.231	0.010*
MCHC (g/dl)	-0.029	0.749
RDW (%)	0.496	0.000**

Note:* Correlation is significant at 0.05 (two-tailed);** Correlation is significant at 0.01 (two-tailed); P-value <0.05 is considered statistically significant.

Discussion

In the current study, RBC count was lowered in patients with HbA1c ≥7% than HbA1c<7%, groups, and the difference were statistically significant (Table 2). This is because chronic exposure to high glucose results in non-enzymatic glycation of hemoglobin and membrane proteins, leading to accelerated aging of RBCs ultimately might decrease RBC count in patients with persistent hyperglycemia [22]. The other possible mechanism could be due to altered fluid-electrolyte balance. It has been reported that the activity of erythrocytes membrane cat-ion pump proteins (Na^+/K^+-ATPase and Ca^{2+}-ATPase) was significantly reduced in T2 DM patients with elevated blood glucose levels and a significant negative correlation with the level of FBS was observed [23,24]. A significant negative correlation was also observed between RBC count and HbA1c level (Table 3). The finding is consistent with the previous studies conducted in Saudi [25] and Serbia [26], which reported decreased RBC count in poor glycemic controlled T2 DM patients. However, in contrast to our finding, a study conducted in Bangladesh reported no significant mean difference of RBC count between poor and good glycemic controlled T2 DM patients (p=0.608), and no correlation to HbA1c level [27]. The possible hypothesis for this difference might be due to the relatively small sample size used in the previous study. In the present study, the HGB level was significantly reduced in T2 DM patients with PGC (Table 2). This finding is in accordance with the previous study (r= 0.148, p= 0.56) conducted in India [28]. But in contrary to our finding, there was a statistically significant inverse correlation between HGB and HbA1c in T2 DM patients from the study of Rashid et al (r= -0.979, p< 0.05) [29]. The discrepancy might be due to differences in the study population, T2 DM patients with known diabetic nephropathy were included in the previous study.

Regarding RDW, our data revealed that it was significantly elevated in patients with PGC (Table 2). Chronic inflammation and oxidative stress due to hyperglycemia could be the possible mechanism to elevate the value of RDW in PGC T2 DM patients [30]. The result is in harmony with the study conducted in Egypt that reported a significantly (p=0.035) elevated level of RDW in T2 DM patients with uncontrolled glycemia [31]. But in contrast to the current finding a study conducted in Bangladesh reported no significant (p=0.2) mean difference of RDW was observed between poor and good glycemic control T2 DM patients, although a positive correlation was detected between RDW and HbA1c

level [27]. The discrepancy might be due to differences in the glycemic status of the study population, relatively well-controlled T2 DM patients were enrolled in the previous study.

A significant positive correlation was also found between RDW and HbA1c levels in our study (Table 3). This is consistent with the previous studies conducted in Pakistan [32] and India [33]. However, our finding is contrary to another study conducted in India reported that no significant correlation ($r= 0.04$, $p> 0.05$) between RDW and HbA1c levels in T2 DM patients [34]. The difference might be due to the small number (only 50 T2 DM) of patients involved in the previous study.

This study also found that MCV and MCH were significantly increased in T2 DM patients of HbA1c ≥7%, but no significant difference of MCHC among the two groups (Table 2). Besides, both MCV and MCH were significantly correlated with the level of HbA1c (Table 3). Increased MCV in patients with poor glycemic control could be due to an influx of glucose to erythrocytes via insulin-independent glucose transporter (GLUT-1) causing high intracellular glucose concentration which results in the rapid diffusion of water into the cell then flattens the biconcave disk and bloats the cell [35]. The possible hypothesis for the elevation of MCH in hyperglycemic T2 DM patients might be due to increased cytoplasmic viscosity. A recent study reported that the secondary structure of hemoglobin was altered (increased β-pleated sheet and decreased α-helix content) in T2 DM patients at an elevated level of HbA1c [36]. But our finding is in contrast to an earlier report in Pakistan stated that no significant correlation was found between the level of HbA1c with MCV ($r=-0.127$, $p=0.167$), MCH ($r=-0.109$, $p=0.238$), and MCHC ($r=0.051$, $p=0.583$) of T2 DM patients [32]. The possible reason for the difference might be due to variation in the glycemic status of the study population.

However, the findings of this study have to be interpreted in light of some limitations. First, this was a cross-sectional study design and therefore can't infer a causal-effect relationship between studied variables. Second, the sample size enrolled in the study was not large enough and it was a single-centered study, so maybe difficult to generalize the result to the whole T2 DM patients in the population. Finally, some potential confounding factors closely associated with RBC parameters like the nutritional status of iron, folate, and vitamin B12 in the study participants were not determined/ absent.

Conclusions

RBC count and HGB were decreased, while MCV, MCH, and RDW were increased in PGC than GGC T2 DM patients. Besides RBC count was inversely correlated, whereas MCV, MCH, and RDW were directly correlated with the level of HbA1c. Red blood cell parameters such as RBC count, MCV, MCH, and RDW could be useful indicators to monitor the glycemic status of patients with T2 DM instead of the HbA1c test. But more multi-centered, prospective studies with a large sample size are required to clearly examine the relationship between RBC parameters with HbA1c then to verify their role in glycemic monitoring in patients with T2 DM.

Abbreviations

CBC: Complete Blood Count; FBS: Fasting Blood Sugar; HbA1c: Glycated Hemoglobin; JMC: Jimma Medical Center; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; RBCs: Red Blood Cells; RDW: Red cell Distribution Width; T2 DM: Type 2 Diabetes Mellitus.

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Authors' contributions

MA conceive and design the study. BZ actively involved in the guidance of conception of research and critical review of the manuscript. TS, KK, MF, and MT were involved in the proposal development and data collection. MA and BZ were actively working on data analysis, writing the research report, and were major contributors in drafting the manuscript. All authors have read, provide critical feedback, and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical clearance & approval was obtained from the Institutional Review Board (IRB) of Jimma University, Institute of Health Sciences (approval number: IHRPG1/716/20). Written informed consent was also obtained from each study participant after a clear orientation of the study objective, benefit, and procedures. Confidentiality of participant's information was kept using unique codes rather than personal identification. The specimen collected from each study participant was used solely for the intended purpose. The study was conducted in accordance with the declaration of Helsinki. Furthermore, prevention approaches to COVID-19 transmission were strictly followed in every procedure of data collection according to the recommendations set by WHO.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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