Research Article

Assessment of Red Blood Cell Parameters as a Biomarker for Glycaemic Control in Patients of Type 2 Diabetic Mellitus: A Cross-Sectional Study

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ABSTRACT

Introduction: Continuous exposure to hyperglycaemia in red blood cells leads to continuous glycation of the haemoglobin protein, which causes changes in the structure and function of the haemoglobin molecule. Besides the glycation of proteins, hyperglycaemia has various other effects on red blood cells (RBCs) like change in the mechanical properties and internal viscosity of RBCs, increased aggregation, and osmotic fragility, thus leading to changes in erythrocyte structure and hemodynamic properties. These changes may be reflected by one or all the erythrocyte parameters such as red blood cell count, haemoglobin, HCT, MCV, MCH, MCHC, and RDW.

Aims/ objective: To assess red blood cell parameters as a biomarker for long-term glycaemic control among patients of type 2 diabetes mellitus in tertiary care centre of eastern India.

Materials and Method: Approximately 2.5 ml of blood was dispensed into test tubes labelled with ethylene-diamine-tetra-acetic acid (EDTA) anticoagulant to check erythrocyte parameters. The remaining 2.5 mL of blood was collected in a separate EDTA test tube for HbA1c analysis. Red blood cell parameters were analysed using a fully automated haematology analyser. Patients with HbA1c <7% were defined as having good glycaemic control and patients with HbA1c ≥7% were defined as having poor glycaemic control.

Results: RBC count was significantly (p<0.05) reduced in patients with HbA1c ≥7% compared to patients with HbA1c <7%. Haemoglobin was also lower in patients with HbA1c ≥7% but this difference was not quite statistically significant. Meanwhile, MCV, MCH, and RDW were significantly (p<0.05) elevated in T2 DM patients with HbA1c ≥7%. A statistically significant correlation was detected between RBC count, MCV, MCH, and RDW parameters with HbA1c level in patients of type 2 diabetes mellitus.

Conclusion: Type 2 diabetes mellitus was found to be associated with lower red blood cell count and haemoglobin level. Endocrinologist should assess these parameters routinely in patients of type 2 diabetes mellitus.

Keywords: Type 2 Diabetes Mellitus, Red Blood Cells, Haemoglobin, HbA1c.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2023.v79i02.030

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v79i02.030

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease associated with high blood sugar levels caused by the body's inability to produce an adequate amount of the hormone insulin or to effectively use the insulin produced by the body.[1] It is a heterogeneous group of metabolic disorders characterized by various defects in the regulation of metabolism of carbohydrate, fat, or protein. [2] Diabetes mellitus is characterized by hyperglycaemia, glycosuria, hyperlipidaemia, and negative nitrogen balance in the body. Uncontrolled level of blood glucose level could be related with multiple organ damage causing disability and life-threatening health disorders like cardiovascular diseases (CVD), nerve damage leading to various neuropathy, kidney damage characterized by diabetic nephropathy, diabetic foot leading to lower-limb amputation, and ocular disease (mainly affecting the retina) leading to vision loss and blindness. [1, 2]

The most common laboratory tests used to screen and monitor blood glucose status in the clinical management of diabetes include fasting blood glucose (FBS), random blood glucose (RBS), oral glucose tolerance test (OGTT) and glycated haemoglobin test (HbA1c). [3] HbA1c is a variant of haemoglobin, formed by the condensation of a glucose molecule with amino acid at the N-terminus in the β chain of haemoglobin. The HbA1c blood test provides the average blood glucose level of a diabetic patient over the past 2-3 months, which is the expected lifespan of red blood cells (RBCs).[4] HbA1c is an effective biomarker and it is most effective for long-term blood glucose monitoring. compared with other glucose-based tests because it is less affected by factors such as food intake, stress, exercise, and immediate treatment responses.[5]

RBC parameters are components of complete blood count (CBC), which include a panel of analytical tests usually utilized to distinguish between different types of anaemia.

[6] RBC parameters comprises of red blood cell (RBC) count, haematocrit (HCT), haemoglobin, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red cell distribution width (RDW). [7]

Continuous exposure to hyperglycaemia in red blood cells leads to continuous glycation of the haemoglobin protein, which causes changes in the structure and function of the haemoglobin molecule.[8] Besides the glycation of proteins, hyperglycaemia has various other effects on red blood cells (RBCs) like change in the mechanical properties and internal viscosity of RBCs, increased aggregation, and osmotic fragility, thus leading to changes in erythrocyte structure and hemodynamic properties. These changes may be reflected by one or all of the erythrocyte parameters such as red blood cell count, haemoglobin, HCT, MCV, MCH, MCHC, and RDW. [9, 10]

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.14 Lack of HbA1c tests in health care facilities is one of the hindrances for clinicians to make long-term management decisions about patients of type 2 diabetes mellitus.15 16,17

Some recent evidence also indicates that red blood cell parameters can be used to monitor diabetes control and progression of complications.[11,12] A retrospective study conducted in a developing country in diabetics and non-diabetics also concluded that values of RBC parameters are proportional to HbA1c and blood glucose, so they are important tools for the evaluation of patients with type 2 diabetes mellitus.[13]

Although HbA1c testing continues to be the gold standard for assessing long-term glycaemic control, its accessibility and affordability in routine diagnostic services remains limited in developing countries. [14] Lack of HbA1c testing in healthcare facilities is one of the barriers preventing clinicians from making long-term management decisions for the patinets of type 2 diabetes mellitus. [15] Reports also indicated that the absence of HbA1c assessment was an important predictor of frequent hospital readmission in patients of type 2 diabetes mellitus. [16, 17]

Furthermore, it has been reported that limited access to HbA1c testing appears to be an important indicator of poor glycaemic control in patients with type 2 diabetes and a significant barrier to improved glycaemic control. [18] In developing countries such as India, HbA1c testing is not readily available in public health facilities in rural areas and is a relatively costly test in some private sectors. Therefore, there is a need to find readily available tools for monitoring glycaemic status in resource-constrained countries. Hence, this study was aimed to assess red blood cell parameters as a biomarker for long-term glycaemic control among patients of type 2 diabetes mellitus in tertiary care centre of eastern India.

MATERIALS AND METHODS

This was a cross-sectional study done in tertiary care centre of eastern India after approval of Institutional Ethics Committee. The study was done in department of pathology in collaboration with department of general medicine from August 2020 to July 2021.

Inclusion Criteria

Patients with diagnosis of type 2 diabetes mellitus of either sex of age greater than or equal to 18 years.

Exclusion Criteria

Patients with known anaemia or any other haematological disorders, Patients with chronic kidney or liver disease, patients who have received blood transfusion during 3 months before data collection, patients with history of recurrent malaria, pregnancy, and lactation.

After interview and review of detailed medical records, a 5 mL venous blood sample was collected from each eligible subject by aseptic technique using a sterile 5 mL syringe. Approximately 2.5 ml of blood was placed in labelled test tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant for testing RBC parameters. The remaining 2.5 mL of blood was drawn into another of her EDTA tubes for analysis of HbA1c. Samples were then transported to the laboratory unit for analysis on the same day of sample collection to prevent haemolysis of whole blood. RBC parameters were analysed with a fully automated haematology analyser.

Based on the ADA medical criteria in Diabetes Mellitus 2020 Recommendation, we divided glycaemic control in T2-DM patients into two groups.[19] Patients with HbA1c <7% were defined as good glycaemic control and those with HbA1c ≥7% were defined as poor glycaemic control.

Statistical analysis

Data were checked for completeness and entered into Microsoft Excel 365 and exported to Statistical Package for Social Science (SPSS) software version 25 for statistical analysis. To determine glycaemic status, study participants were divided into two groups (poor and good glycaemic control) based on HbA1c levels. An independent t-test analysis was then utilized to compare the means of her RBC parameters between the two groups. Pearson's bivariate correlation coefficient (r) was utilized to evaluate the strength of association between each RBC parameter and HbA1c level. In all cases, P-values less than 0.05 were considered statistically significant.

OBSERVATIONS AND RESULTS

Table 1: Comparison of baseline demographic and clinical characteristics

Variables	Good Glycaemic Control (n=44)	Poor Glycaemic Control (n=68)	P-value
Age in years (mean ± SD)	53.38 ± 13.37	52.20 ± 11.71	0.62*
Sex			
Male (%)	27 (61.36)	45 (66.18)	0.60
Female (%)	17 (38.64)	23 (33.82)	0.60
Residence			
Urban	26 (59.09)	42 (61.76)	0.67
Rural	19 (40.91)	26 (38.24)	0.67
Duration of Diabetes	5.84 ± 1.98	6.57 ± 2.16	0.0687*
*Unpaired t test **Chi-square Test			

Most of the patients were males and of age group 40-60 years. Duration of diabetes was slightly higher in patients with poor glycaemic control but this difference was not quite statistically significant.
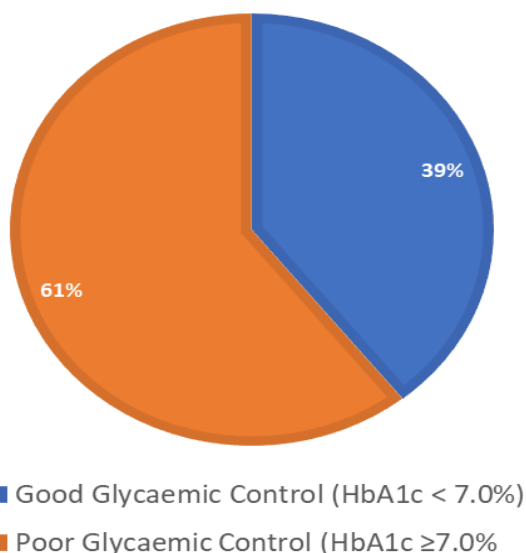

Figure 1: Proportion of patients with Good and Poor Glycaemic Control

RBC count was significantly (p<0.05) reduced in patients with HbA1c ≥7% compared to patients with HbA1c <7%. Haemoglobin was also lower in patients with HbA1c ≥7% but this difference was not quite statistically significant. Meanwhile, MCV, MCH, and RDW were significantly (p<0.05) elevated in T2 DM patients with HbA1c ≥7%.

Table 2: Comparison of RBC parameters between two groups

Variables in Mean ± SD	Good Glycaemic Control (n=44)	Poor Glycaemic Control (n=68)	P-value (Unpaired t test)
RBC in 10^6/mm³	4.68 ± 0.49	4.27 ± 0.68	0.0008 S
Haemoglobin in g/dl	13.92 ± 1.34	13.41 ± 1.54	0.074 NS
PCV in %	42.62 ± 3.98	41.18 ± 5.26	0.124 NS
MCV in fl	89.48 ± 6.66	92.53 ± 7.46	0.030 S
MCH in pg	29.23 ± 2.54	30.68 ± 2.82	0.006 S
MCHC in g/dl	33.11 ± 0.82	33.07 ± 0.81	0.799 NS
RDW in %	13.59 ± 1.16	14.42 ± 1.15	<0.0001 ES

S: Significant   NS: Not Significant   ES: Extremely Significant

Table 3: Pearson's Correlation Analysis Between RBC Parameters and HbA1c in Patients of Type 2 Diabetes Mellitus

Variables in Mean ± SD	Pearson's Correlation (r) with HbA1c (%)	P-Value
RBC in 10^6/mm³	-0.31	0.001
Haemoglobin in g/dl	-0.16	0.15
PCV in %	-0.11	0.25
MCV in fl	0.29	0.002
MCH in pg	0.26	0.003
MCHC in g/dl	-0.03	0.75
RDW in %	0.52	<0.0001

A statistically significant correlation was detected between RBC count, MCV, MCH, and RDW parameters with HbA1c level in patients of type 2 diabetes mellitus.

DISCUSSION

In the current study, patients with HbA1c ≥7% had lower RBC counts than the HbA1c <7% group, and the difference was statistically significant. It is possible that chronic exposure to high glucose results in nonenzymatic glycation of haemoglobin and membrane proteins, accelerating red blood cell senescence and ultimately reducing red blood cell counts in patients with persistent hyperglycaemia. [25] This might also be due to changes in fluid and electrolyte balance. Erythrocyte cation pump protein (Na+/K+-ATPase and Ca2+-ATPase) activity was significantly decreased in patients of type 2 diabetes mellitus with increased blood glucose levels and was significantly negatively correlated with FBS levels. [26, 27]

A significant negative correlation was also observed between red blood cell counts and HbA1c values. This finding is consistent with a previous study reporting a decrease in RBC count in patients of type 2 diabetes mellitus with poor glycaemic control. [28,29] However, in contrast to our results, studies conducted in Bangladesh found no significant difference in RBC count between patients of type 2 diabetes mellitus with poor glycaemic control and patients of type 2 diabetes mellitus with good glycaemic control. No mean difference and no correlation with HbA1c levels were reported.[30] A possible hypothesis for this difference is that this is due to the relatively small sample sizes used in previous studies. In the present study, haemoglobin levels were significantly decreased in type 2 diabetic patients with HbA1c ≥7%. This result is consistent with the finding of a previous study (r=0.148, p=0.56) conducted in India.[31] However, in contrast to our findings, there was a statistically significant inverse association between haemoglobin and HbA1c in patients with type 2 diabetes from a study by Rashid et al. (r=−0.979, p<0.05).[32] This discrepancy may be due to differences in study populations, with previous studies including type 2 diabetes mellitus patients with known diabetic nephropathy.

For RDW, data showed a significant increase in patients with HbA1c ≥7%. Chronic inflammation and oxidative stress due to hyperglycaemia may be a possible mechanism for increasing RDW levels in patients of type 2 diabetes mellitus. [33] This result is consistent with a study conducted in Egypt that reported higher level of RDW in patients of type 2 diabetes mellitus with uncontrolled glycaemia.[34] However, in contrast to the current results, a study conducted in Bangladesh did not observe a significant mean difference in RDW between type 2 diabetic patients with good glycaemic control and those with poor glycaemic control of type 2 diabetic patients however a positive correlation was found between RDW and HbA1c levels.[30] This discrepancy may be due to differences in the glycaemic status of the study population, and previous studies have shown that study participants were patients having well controlled glycaemic control.

Our study also found a significant positive correlation between RDW and HbA1c levels. This is consistent with previous studies conducted in Pakistan and India.[35,36] However, our findings contrast with another study conducted in India, showing that RDW was not significantly correlated with HbA1c levels in diabetic patients.[37] This reason for these findings may be the small number of patients enrolled in previous studies.

The study also found that in type 2 diabetic patients with HbA1c ≥7%, MCV and MCH values was significantly increased, whereas there was no significant difference in MCHC between the two groups. Besides, both MCV and MCH had significant correlation with the level of HbA1c. The reason behind increased MCV in patients with poor glycaemic control could be influx of glucose to erythrocytes through insulin-independent glucose transporter (GLUT-1) leading to high intracellular glucose concentration resulting in the rapid diffusion of water into the cell then flattens the biconcave disk and bloats the cell.[38] The possible mechanism for the increase in MCH levels in type 2 diabetes mellitus patients with poor glycaemic control may be due to elevated cytoplasmic viscosity. A recent research reported that the secondary structure of haemoglobin was affected (increase in proportion of β-pleated sheet and decrease in proportion of α-helix content) in patients of type 2 diabetes mellitus with higher level of HbA1c.[39] However, our finding is in contrast to an earlier study done in Pakistan, which reported that there was no significant correlation 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) in patients of type 2 diabetes mellitus.[35] The possible reason for the difference might be due to variation in the glycaemic status of the study population.

However, the result of this study should be interpreted in the light of some limitations. First, the study design was cross-sectional and therefore causal-effect relationship between studied variables could not be analysed. Second, the sample size of this study was not large enough and our study was also single-cantered, so it could be difficult to generalize the findings to the whole population of type 2 diabetes mellitus patients. Finally, some potential confounding factors that are closely related with RBC parameters such as the nutritional status of iron, folic acid, and vitamin B12 in the patients were not determined and subsequent subgroup analysis was not done.

CONCLUSION

Type 2 diabetes has been found to be associated with low red blood cell counts and haemoglobin levels. Endocrinologists should regularly assess these parameters in patients with type 2 diabetes. Patients with type 2 diabetes and poor glycaemic control had decreased RBC counts and haemoglobin and increased MCV, MCH and RDW. Red blood cell count was inversely correlated, whereas MCV, MCH, and RDW were directly correlated with HbA1c level. A multi-center prospective study with a large sample size is needed to definitively examine the relationship between RBC parameters and HbA1c and validate their role in blood glucose monitoring in patients of type 2 diabetes mellitus.

Ethical clearance: Institutional Ethics Committee of Medinirai Medical College & Hospital, Palamu

International Journal of Pharmaceutical Sciences Review and Research
Available online at www.globalresearchonline.net
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