Original Article

Evaluating the Association of Red Blood Cell Parameters and Glycemic Control in Type 2 Diabetic Patients at Tien Giang General Hospital

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Abstract

Background: Red blood cell distribution width (RDW), a hematologic index, is a quantitative measure of the range in volume and size of red blood cells. Hyperglycemia in patients with type 2 diabetes is considered to promote the formation of glycosylated hemoglobin (HbA1C) and to shorten the lifespan of red blood cells by reducing their deformability and increasing their osmotic fragility and adhesiveness. **Objectives:** To evaluate the association between red cell distribution width (RDW), mean corpuscular volume (MCV), and mean corpuscular hemoglobin content (MCHC) of red blood cells and glycemic control in patients with type 2 diabetes. **Methods:** This retrospective study included 107 patients with type 2 diabetes who were undergoing treatment at Tien Giang General Hospital from April to August 2019. Gender, age, complete blood count, plasma glucose, HbA1C, cholesterol, and triglyceride data were collected. The patients were divided into two groups: group I (HbA1C≤6.5–6.9%; n=51) and group II (HbA1C≥7.0%; n=56). **Results:** RWD was 13.32 for the group I and 13.95 for group II. MCHC was 32.21 for the group I and 32.84 for group II. RDW and MCHC were significantly higher in patients without good glycemic control (HbA1C≥7.0%) than with good HbA1C control (6.5–6.9%). RDW showed a significant correlation between glucose concentration and MCHC. HbA1C and MCHC were also significantly correlated. **Conclusion:** Good glycemic control is associated with lower RDW and MHC values in patients with type 2 diabetes. Therefore, RDW and MCHC can be used as prognostic markers to assist in blood glucose control in these patients.

Keywords: Type 2 Diabetes, HbA1C, Red Blood Cell Distribution Width, Tien Giang

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia [43,45] resulting from defects in insulin secretion, insulin action, or both. [1] It is a noteworthy worldwide issue. [44] In Vietnam, the current estimates for the future prevalence of type 2 diabetes (T2DM) indicate a significant impact on the country's economy. Suburban areas, in particular, are facing considerable increases in economic burden in terms of expenditures on hospitalizations, which will place health budgets under pressure in the foreseeable future. [2]

In 2015, 3.5 million Vietnamese people were reported as diabetic by the World Diabetes Association IDF Diabetes Atlas, and this number is forecasted to rise to 6.1 million by 2040. [3] According to a 2015 Ministry of Health survey, 68.9% of people with hyperglycemia have not had their condition detected, and only 28.9% of people with diabetes are managed at health facilities. The annual cost per patient is presently estimated at the US $246.10 (95% CI 228.3–267.2), which accounts for about 12% (95% CI 11–13) of Vietnam's gross domestic product (GDP) per capita in 2017. Of this per-patient cost, US $127.30, US $34.40, and US $84.40 were spent on direct medical costs, direct nonmedical costs, and indirect costs, respectively. [4] One study reported the increases from 2013 to 2017 in the total and per-patient costs in a Vietnamese private hospital as US $3,527,530.50 and US

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How to cite this article: Van Ta, T., Bich Thi Nguyen, H., Thanh Tran, H., The Pham, H. Evaluating the Association of Red Blood Cell Parameters and Glycemic Control in Type 2 Diabetic Patients at Tien Giang General Hospital. Arch Pharma Pract 2019;10(4):153-9.

$733,245.30, respectively. [5] Another study found statistically significant differences between the quality of life in patients with T2DM in terms of age, residence, marital status, education level, alcohol drinking, exercise, body mass index (BMI), DM treatment, family history, and presence of complications. [6] These economic and quality of life issues point to a need for comprehensive testing for determining patients at risk of developing T2DM.

One widely accepted method for diabetes diagnosis in the general population is the measurement of glycated hemoglobin (HbA1c). [7] This measure has several important advantages over fasting plasma glucose because it is less vulnerable to pre-analytical factors, it exhibits a much lower biological variability, it is less influenced by acute stress and conventional drugs that may impair glucose metabolism, and it provides dichotomized information with just one measurement. [8] Another potentially useful screening measure is the red cell distribution width (RDW), which is an index that reflects the heterogeneity of the volume of red blood cells (RBCs). [9] Traditionally, RDW has been widely used for differential diagnosis of anemia, and it can be measured by most hematologic analyzers. [10] Currently, several lines of evidence now show that increased RDW values are convincingly associated with a number of human disorders, including cardiovascular disease, cancer, infections, and diabetes. [11-15]

Some recent studies have shown that the RDW may improve the risk assessment for individuals at risk of developing type 2 diabetes. More specifically, Veeranna et al., using the Third National Health and Nutrition Examination Survey (NHANES) database, reported that RDW increased progressively across categories of HbA1c ($p < 0.001$ for the trend) among 15,343 US non-diabetic adults who were free from cardiovascular disease. [16] Similarly, in a large population-based cohort study of 26,709 non-diabetic Swedish individuals, Engström et al. found that the RDW was positively associated with HbA1c levels, with a relationship showing an increase in HbA1c of 0.10% per each standard deviation increase in RDW. [17]

Diabetes mellitus is well established to have microvascular complications, and these are linked to increases in HbA1c. [18] This suggests that alterations in RDW might be useful in the diagnosis and monitoring of glycemic status, as well as for assessing complications in patients with diabetes. Therefore, the aim of the current study was to evaluate RDW in patients with T2DM and to assess the relationship between RDW and HbA1c.

Materials and Methods

This study was performed as a retrospective search of the database of the laboratory information system of the clinical chemistry laboratory of Tien Giang General Hospital (Vietnam). We retrieved the combined results of CBC and HbA1c tests performed in outpatients from April to August 2019. Tien Giang General Hospital is located in My Tho City, Tien Giang Province, Vietnam. It is a 1000-bed general hospital with full departments/divisions and qualifies as a class-1 hospital. This hospital is an established, fully equipped hospital with modern medical equipment. It is capable of performing diagnoses and treatment of high technology to meet the healthcare needs of the people in the province and the region, thereby enabling people to access high-tech medical services.

Study sample identification

The hospital electronic database contains information on primary diagnosis, age, gender, and biochemical values such as glycemic index, HbA1C, cholesterol, triglycerides, complete blood count (CBC), and RDW. Diabetes was diagnosed when one of the following criteria was met: 1) the diagnosis of diabetes was previously established and documented in the patient's medical records; 2) the patient had a current prescription for oral hypoglycemic medication or insulin. Diabetes mellitus was diagnosed according to the American Diabetic Association (ADA) guidelines: HbA1c $\geq$ 6.5% or fasting blood glucose (FBG) $\geq$ 126 mg/dl or two-hour plasma glucose $\geq$ 200 mg/dl during an oral glucose tolerance test (OGTT).

Patients with acute or chronic inflammatory disease, severe liver or renal insufficiency, morbid obesity, malignancy, valvular heart disease, heart failure, or prior coronary intervention, or who had experienced acute coronary syndrome within 30 days prior to coronary angiography, were excluded from the study. Subjects were also excluded if they had a history of anemia and blood transfusion. Anemia was defined as hemoglobin concentration < 13 mg/dl in men and < 12 mg/dl in women. Patients were also deemed ineligible for this study if they had been discharged from or transferred to the hospital, lacked the medical record information needed for the research, or did not agree to disclose personal information.

Laboratory measurements

Blood samples were drawn during admission from each patient, after overnight fasting, for routine chemistry. Mean corpuscular volume (MCV), mean corpuscular hemoglobin content (MCHC), and RDW values were measured with an ADVIA 2010i instrument (Siemens Healthineers). HbA1c, cholesterol, and triglyceride index were determined by a high-performance liquid chromatography method using an AU680 system (Beckman Coulter). All tests were performed in the clinical chemistry laboratory of Tien Giang General Hospital.

Statistical analysis

Data were analyzed using Excel 2010. Descriptive statistics were employed for qualitative variables, which were expressed as frequencies and percentages, while continuous variables were presented as means ± standard deviations (SD). For further analysis, HbA1c values were used to divide

the patients into two groups—a well-controlled group that had HbA1c <7.0% and a poorly controlled group that had HbA1c ≥7.0%. The Pearson correlation coefficient was applied to assess correlations between RDW and clinical/laboratory parameters. Statistical analysis was considered significant at $p < 0.05$.

Ethical approval

The study protocols were approved by the Hospital' Committee. Ethical issues are globally recognized as important in research, so these matters were thoroughly taken into account in the present study. A solid understanding and agreement among the participants were maintained during the data collection process. We ensured that no harm was inflicted upon the respondents by guaranteeing the privacy of their sociodemographic information. All the data collected in this work were used only for research purposes. During the data collection, each participant was guaranteed anonymity through the assignment of an alphanumeric identity code.

Results

Characteristics of the study participants

A total of 107 patients, including 47 females (42.52%) and 60 males (57.47%), met the selection criteria. The patients' age ranged from 25 to 80 years. The patients were divided into two groups according to their disease status: 56 patients (52.87%) were assigned to the poorly controlled group I and 51 patients (41.13%) with HbA1C in the range of 6.5–6.9% were placed in the well-controlled group II. A statistically significant difference was noted between the two groups. The values of age, HbA1C, cholesterol, MCHC, and RDW were higher in group II than in group I. By contrast, triglycerides and MCVs were higher in group I than in group II (Table 1 and Table 2).

Relationship between RDW and the level of glycemic control among T2DM subjects

Analysis of the blood glucose level and MCHC and RDW showed a significant correlation between these parameters (Figure 1 and Figure 2). Similarly, HbA1C and MCHC also showed a significant correlation (Figure 3). These results demonstrate that glycemic control of patients with type 2 diabetes is strongly correlated with increased RDW and MCHC values.

Discussion

Diabetes mellitus is a metabolic disease that is secondary to either insulin deficiency or a decreased responsiveness of tissues to insulin and is associated with derangements in the metabolism of carbohydrates, lipids, and proteins. Hence, insulin is a very important hormone for maintaining metabolic homeostasis. Persistent hyperglycemia resulting from insulin deficiency leads to the devastating and life-threatening complications of diabetes. For this reason, frequent monitoring of blood sugar is a key step in the management of diabetes. Traditionally, fasting and random or postprandial blood sugar levels have been used in glycemic monitoring. However, in recent years, HbA1c has been added as a tool for diagnosis or monitoring diabetes, as well as for predicting the complications, mortality, and morbidity of diabetes mellitus.

Persistently elevated plasma glucose is non-enzymatically glycated to hemoglobin A to form HbA1c. Consequently, the concentration of HbA1c depends on the level and duration of glucose in the plasma, which is measured clinically as an index of diabetic control over a period of eight to 12 weeks. Like HbA1c, RDW is another RBC parameter, but it is routinely reported in most simple laboratory investigations of the CBC, at no additional cost. It is essentially a marker of the variation in cell volume within the red cell population, which is reported as an index of heterogeneity in the size of circulating erythrocytes. [19] The RDW has been extensively investigated in various studies on the etiology and diagnosis of anemia. [20] More recently, however, its diagnostic and prognostic role has been identified in various diseases, many of which have shown an association between RDW and adverse outcomes, such as increased mortality, poor prognostic marker recognition in patients with heart failure or ischemic heart disease, and a higher incidence of atrial fibrillation and heart failure. [21-25]

In our study, we found a statistically significant correlation between the CBC index and HbA1c, in agreement with the findings of Suryavanshi et al. ($r = -0.235$, $p = 0.001$) [25] while Salimon et al. found in their study that a significant correlation occurs more frequently in males than in females ($r = 0.400$ vs. $r = 0.04$). [26, 27] Another study by Sherif et al. has also shown a positive correlation between RDW and HbA1c but the correlation did not reach statistical significance ($p = 092$). [28] Similarly, Lippi et al. also demonstrated a significant correlation between HbA1c and RDW even after adjustment for age and gender. [29] Our findings corroborate the findings of a significant and positive association of RDW with HbA1c, such that an increase in HbA1c of 0.10% accounted for a 1 SD increase in RDW. [17]

A relationship between RDW and the complications of diabetes (microvascular and macrovascular) has also been reported. [29] Higher values of RDW were associated with an increased probability of developing vascular complications, heart failure, myocardial infarction, stroke, and nephropathy. [30] The RDW values are known to become elevated under conditions of increased red cell destruction or when red cell production is ineffective. [20] A number of possible mechanisms have been proposed to explain RDW increases, including nutritional deficiency (e.g., vitamin B12, iron, or folic acid) and bone marrow depression or inflammation that extends the red blood cell lifespan as a homeostatic adaptation. [20, 31, 32] Importantly, inflammation is a common finding in patients with DM and probably explains why DM is called a "pro-inflammatory state." [33-35]

The pro-inflammatory state associated with T2DM has suggested that RDW can be used as a marker of inflammation in this disease. [28, 33] The RBCs are affected by hyperglycemia in ways other than the formation of HbA1che, as hyperglycemia also leads to reduced cellular deformability of the RBCs, altered mechanical properties, and increases in adhesion and osmotic fragility. High glucose levels cause the rearrangement of erythrocyte membranes, defects in oxygen binding activity of Hb, and alterations in the mechanical features of the cell membrane and general aspects of the cell wall. [36, 37] These changes lead to an altered erythrocyte structure and changes in the hemodynamic characteristics of RBCs. [38, 39] However, the effect of hyperglycemia goes beyond structural changes, as marked effects are observed on the RBC lifespan, which leads to high variability in erythrocyte volumes. [40]

Tight glycemic control was found to result in a modest, but consistent, increase in RBC half-life when compared to poor control. [41] In addition, impairment of Na^+/K^+-ATPase activity leads to electrolyte disturbances, resulting in an increase in the cell size and increased osmotic fragility that in turn, contributes to the development of microvascular complications. Furthermore, microscopy examination and state-of-the-art technological measurements of the RBCs in DM patients reveal augmentation of aggregate shapes and sizes, as well as reduced deformability, when compared to healthy controls. The changes in deformability result in increased blood viscosity and a probable increase in shear stress on the endothelial wall. [36, 42] The interplay between inflammation and the undesirable effects of hyperglycemia on the mechanical features of the erythrocytes can, therefore, be inferred to impact RDW values.

Limitations

Our study has several limitations. One was that the study was a single-center analysis, and the results should thus be interpreted with caution. In order for our results to be generalized, a multi-center replication should be performed to diversify the patient groups. A second limitation is that the sample size of patients enrolled in the study was not large (107 patients). This means that the results should again be interpreted with caution and used as a basis for larger studies. Another limitation is the absence of some information closely associated with RDW, such as genetic polymorphism, menstruation, or nutritional deficiencies of iron, folate, and vitamin B12. Further studies should be conducted to investigate how these factors affect RDW and how they affect the relationship between RDW and glycemic measurements

Recommendation

RDW is a routinely performed, low-cost, and widely available marker that correlates well with glycemic control. Moreover, it was significantly and positively associated with HbA1c. The findings of this study suggest that RBC survival rates, on average, are higher in subjects with high RDW, leading to higher HbA1c due to the increased duration of glucose exposure. RDW is an easily measurable biomarker that could improve the assessment of individuals at risk of developing DM. Therefore, RDW may be a significant and accessible biomarker in T2DM patients that would be useful in clinical detection and evaluation. Further studies should be conducted to investigate how various factors affect RDW and how they affect the relationship between RDW and glycemic measurements. Studies on a larger scale are also required to verify this relationship and role in glycemic monitoring in patients with diabetes.

Conclusion

Overall, diabetic patients with good glycemic control show no adverse alterations in RDW and MCHC. The RDW and MCHC values were lower in patients with well-controlled glycemia than in patients with poor control. The positive correlation between MCHC and RDW with blood glucose concentration and HbA1C was statistically significant. These results suggest that RDW, as a routinely tested laboratory parameter in our clinical practice, may be a valuable addition to the risk assessment arsenal for glycemic control in T2DM.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Acknowledgments

The authors express their gratitude to the Director Board and healthcare staffs of all hospitals for their supporting and offering a great opportunity for our research to be conducted at their sites.

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Table 1. Baseline characteristics and laboratory findings of the study groups

Variables	Well-controlled group (n=51)	Poorly controlled group (n=56)	Total patients (n=106)
Age (years old)	49 (25–75)	56 (35–80)	51 ± 12.60
Gender (Male/Female)	21/30	26/30	51/56
Blood glucose level (mmol/L)	7.17 (5.5–14.18)	17.52 (6.7–29.1)	17.32 (6.7–29.1)
HbA1C (%)	6.62 (6.5–6.9)	9.02 (7–14.9)	7.10 (6.8–14.9)
Cholesterol (mmol/L)	4.78 (3.62–6.46)	5.32 (3.69–8.01)	5.04 (3.62–8.01)
Triglyceride (mmol/L)	2.25 (1.01–13.32)	2.23 (0.13–20.83)	2.25 (0.13–20.83)

Table 2. Distribution of complete blood count results in relation to glycemic control status

Variables	Well-controlled group (n=51)	Poorly controlled group (n=56)	Total patients (n=106)
RDW (%)	13.32 (11.50–20.80)	13.95 (11.50–19.60)	13.52 (11.50–20.80)
MCV (fL)	84.31 (60.70–92.50)	82.07 (61.10–100.90)	83.10 (60.70–103.90)
MCHC (g/dL)	32.21 (29.62–34.43)	32.84 (29.62–35.17)	32.38 (29.62–35.17)

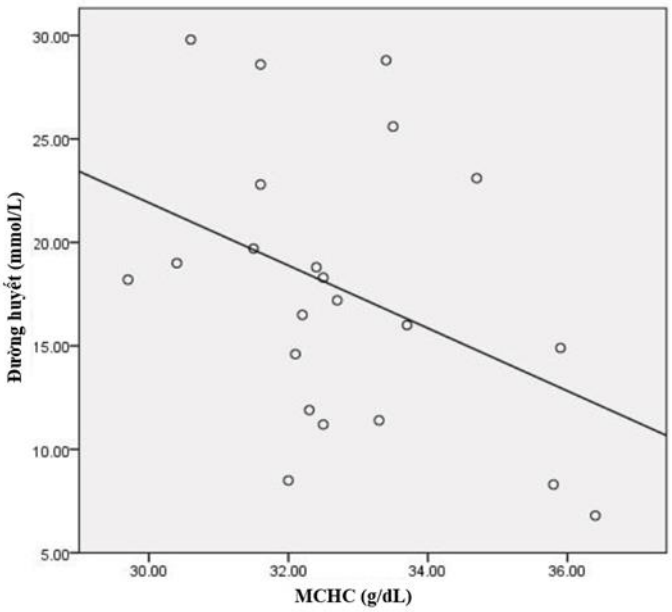

Figure 1. Correlation between MCHC and blood glucose level values

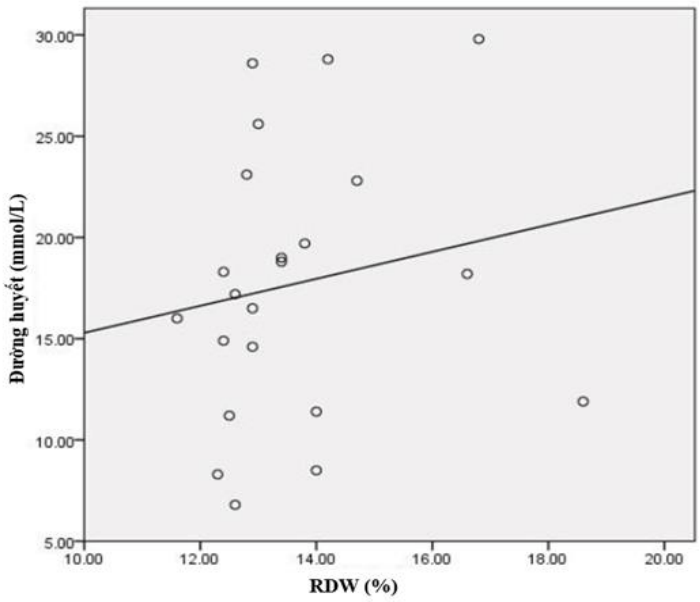

Figure 2. Correlation between RDW and blood glucose level values

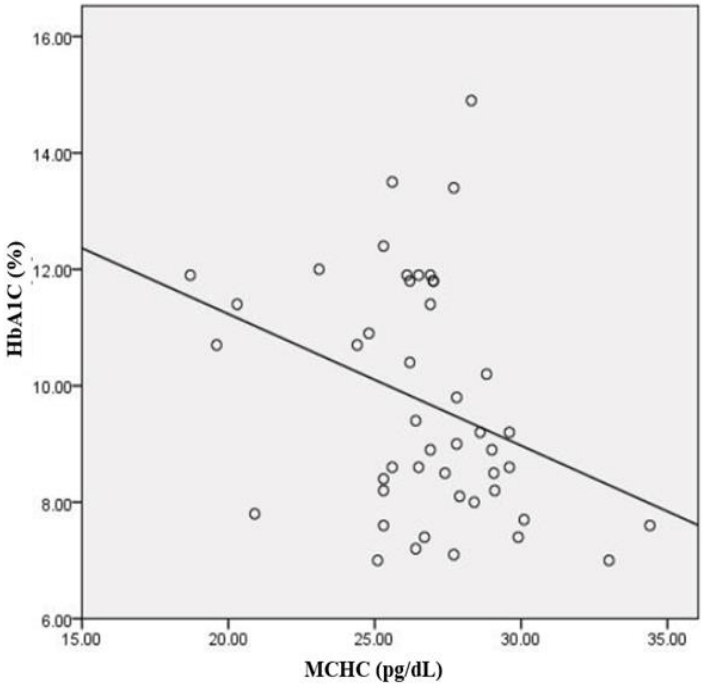

Figure 3. Correlation between MCHC and HbA1c values