Red Cell Distribution Width (RDW) as a Novel prognostic Marker in Diabetic Patients
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ARTICLE INFO

Article history:
Received 25.05.2015
Accepted 28.07.2015

Keywords:
type 2 diabetes, hyperglycemia, cell distribution width (RDW), prognostic marker.

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The red cell distribution width (RDW) is a measure of the variation of red blood cell (RBC) content. The RDW is a measure of variation in size of the circulating erythrocytes which is routinely obtained from a standard Complete Blood Count (CBC). Some disorders including metabolic disease can reason of heterogeneity in the size of circulating erythrocytes. Increased red blood distribution widths are associated with anemia, but it also appears to be associated with other outcomes, like heart attacks, heart failure, death and depression. Researches indicate that evaluated RDW as a marker of macrovascular and microvascular complications in a nationally representative sample of the diabetes patients. Type 2 diabetes has achieved pandemic affects some 300 million people worldwide. This disease is heterogenous and reflects the interaction of several disease processes. The chronic hyperglycemia in diabetes mellitus is associated with long-term damage, also dysfunction and failure of different organs, especially in the eyes, kidneys, nerves, heart. Therefore early detection and timely of diabetes is very important and a lot of research has been done in this field. High RDW is related to disorder of erythropoiesis, reflecting chronic inflammation. RDW may be a significant clinical marker of vascular complications in diabetes and that is independent of traditional risk factors. Studies suggest that changes in RDW is associated with increased incidence of diabetes mellitus (DM) independently of other risk factors and also propose that changes in RDW could be a deputy marker of reduced RBC survival, with lower HbA1c due to shorter period of glucose exposure.

Introduction:
Diabetes mellitus is a metabolic disease in which the body’s inability to produce any or enough insulin therefore elevated levels of glucose in the blood that is increasingly observed as a disease of insulin deficiency due not only to intrinsic pancreatic cell dysfunction but also to the decline of cell mass (1). Untreated diabetes can cause
many acute and chronic complications. Acute complications include lactic acidosis (LA), hypoglycemia, diabetic ketoacidosis and non-ketosis hyperosmolar coma. Serious long-term complications include cardiovascular and cerebrovascular disease also damage to blood vessels within the eye can cause of diabetic retinopathy and ultimately blindness. Increased serum glucose level has multiplex effects on the RBC, including glycation of hemoglobin, reduced deformability and lifespan (2).

Typically, diabetes is classified according to the degree of insulin deficiency and is the most common type 2 diabetes that also called insulin independent diabetes (3).

In patients with type 2 diabetes, studies have shown an association between the degree of hyperglycemia and increased risk of microvascular and macrovascular complications, neuropathy, heart failure, stroke, and is associated with long term damage, dysfunction, and failure of different organs, particularly the eyes, kidneys, nerves, heart and blood vessels therefore timely diagnosis and treatment is very important(4,5).

RDW is calculated as the percentage of the standard deviation of RBC size/mean corpuscular volume. Clinical conditions where RDW is routinely elevated are ineffective red cell production (such as iron deficiency, B12 or folate deficiency and hemoglobinopathies), increased red cell devastation (such as hemolytic), or after blood transfusion (6).

In the CBC routinely 2 types of RDW is being including RDW-SD (RDW standard deviation) and RDW-CV (RDW coefficient of variation).

No statistically remarkable correlation was found between the RDW-SD and diabetics but a statistically significant positive correlation was found between the RDW-CV and diabetics.

Since many tests for the diagnosis and monitoring of type 2 diabetes can be noted that such fasting blood sugar (FBS), random glucose test, HbA1C and glucose tolerance test (GTT).

In this article, we discuss association between RDW and type 2 diabetes in order to evaluate capability of RDW as a novel prognostic marker in diabetic patients.

Incidence:

One of the markers that have recently received considerable attention for its role in diabetes is RDW. RDW is a quantitative measure of the heterogeneity circulating red blood cell size, and is normally assessed in the differential diagnosis of anemia(7,8).

RDW insignificantly a free test which is reported by a complete blood count without extra cost with good prognostic value (5). Increased RDW has been associated with several medical disorders and nutritional deficiencies such as iron deficiency [ID], inflammation, uremia, increased red cell destruction (such as hemolysis), or after blood transfusion and also increased mortality in patients with heart failure, heart attack (7, 9, 10).

It is Interesting that patients with HF are also at higher risk of developing diabetes (11).

Several have guessed that higher levels of RDW may reflect an inflammatory state, which is associated with adverse clinical consequences and leads to impaired erythrocyte maturation (12).

Some studies have shown that RDW has emerged as a potential independent predictor with regard to prognosis in patients with coronary artery disease with or without heart failure (12,13).

Recently many researchers suggest the relationship between RDW and diabetes-associated complications and investigate whether there is any association between RDW, nephropathy, neuropathy and peripheral arterial disease (PAD) in a type 2 diabetic population (14).

Cardiovascular disease (CVD) is the main cause of mortality in patients with diabetes (15).

The recognition of markers of macrovascular and microvascular disease could provide new information about the early diagnosis of diabetes complications and facilitated decision-making in prevention and treatment(16).

New studies indicate that RDW could be a novel prognostic marker that reflects oxidative stress
and chronic inflammation in patients with cardiovascular disease. Since the Diabetes mellitus increases oxidative stress and develops vascular inflammation, looks Increased RDW was considerably related with mortality in patients with stable coronary artery disease (17,18).

**Discussion:**

In line with our recent studies on different markers in diabetes (25-32), this study designed. Management of hyperglycemia and its complications in type 2 diabetes is surely one of the most debated fields in medicine (19). Diabetes mellitus effects a considerable proportion of the population, and has economic subsequences for both the individual and the society. Therefore, the monitoring of diabetes mellitus in order to prevent complications is necessary (20). Red cell distribution width (RDW) is a scalar measure of erythrocyte variability and heterogeneity (18). The normal range for the RDW-CV is 11.5%–14.5%, and upper values display greater variations in cell sizes (20).

Studies conducted in recent years is well illustrated The association between low level RDW with increased incidence of DM in subjects with a low or medium mean corpuscular volume (MCV) and high levels RDW with the development of micro and macro vascular complications, liver disease, alcohol abuse, extension of vascular inflammation and cardiovascular disease (2,21). RDW is effectively a free test that, is reported beside a complete blood count without extra cost by well prognostic value (22).

About RDW levels, studies showed that RDW increased in inflammatory states. also, authors suggested that RDW could be an significant predictor of vascular complications of diabetes mellitus (23). RDW is considered a predictive marker that may reflect an underlying inflammatory process and it is relation to other inflammatory marker like high sensitivity C - reactive protein (hs-CRP). Inflammation may effect on erythropoiesis, circulatory half life and deformability of erythrocytes and thus elevating RDW levels (22).

Inflammation could lead to release of immature red blood cells into the peripheral circulation (24). Increase in RDW indicates the presence of anisocytosis (variation in size of the circulating erythrocytes) which is related to defect of erythropoiesis and decay of erythrocytes and reflecting increased levels of oxidative stress, both of which are signs in type 2 diabetics (22). About RDW levels, studies showed that RDW increased in inflammatory states. also, authors suggested that RDW could be an significant predictor of vascular complications of diabetes mellitus (23). RDW is considered a predictive marker that may reflect an underlying inflammatory process and it is relation to other inflammatory marker like high sensitivity C - reactive protein (hs-CRP). Inflammation may effect on erythropoiesis, circulatory half life and deformability of erythrocytes and thus elevating RDW levels (22).

Inflammation could lead to release of immature red blood cells into the peripheral circulation (24). Increase in RDW indicates the presence of red blood cells with unequal size which is related to defect of erythropoiesis and decay of erythrocytes and reflecting increased levels of oxidative stress, both of which are signs in type 2 diabetics (22). Scholars found that baseline RDW level is significantly higher between individuals with known stroke compared to those without a history of stroke. Many studies confirm among myocardial infarction patients, that elevated RDW is associated with stroke occurrence (12). So this marker can be applied as a prognosticator for macrovascular and microvascular complications of diabetes mellitus (5).

Studies in recent years have demonstrated the relationship between high levels of RDW whit cardiovascular disease and other inflammation complication in type 2 diabetes.
Figure 1. RDW as a laboratory marker for detection of diabetes complications
Table 1. Studies exploring the Correlation between RDW and diabetes mellitus.

<table>
<thead>
<tr>
<th>Research groups</th>
<th>Study subjects</th>
<th>Objectives</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Tsuboi S 2013</td>
<td>560 consecutive diabetic patients (mean age, 66.6 years; male, 80%) with stable CAD.</td>
<td>to assay Impact of red blood cell distribution width on long-term mortality in diabetic patients after percutaneous coronary intervention.</td>
<td>Increased RDW was significantly associated with increased long-term all-cause mortality in diabetic patients after PCI.</td>
</tr>
<tr>
<td>Liu DS et al 2013</td>
<td>48 patients with T1D, 26 patients with DKA, and 30 age- and gender-matched controls.</td>
<td>To investigate the potential role of erythrocyte indices in type 1 diabetes (T1D) patients with DKA.</td>
<td>The RDW/MCV ratio can act as a robust biomarker that is more sensitive than RDW in reflecting the presence of DKA.</td>
</tr>
<tr>
<td>Engström G et al 2014</td>
<td>26 709 non-diabetic participants (aged 45-73 years) from the population-based Malmö Diet and Cancer cohort.</td>
<td>to explore the relationships between RDW and glucose, haemoglobin A1c (HbA1c) and incidence of diabetes mellitus (DM).</td>
<td>RDW is a biomarker that could improve risk assessment for individuals at risk of developing DM.</td>
</tr>
<tr>
<td>Yildiz A et al 2014</td>
<td>131 patients with ISR and 138 patients without ISR who had undergone bare metal stent implantation.</td>
<td>to assess the predictive value of preinterventional RDW on the development of in-stent restenosis (ISR) in patients undergoing stent implantation.</td>
<td>Increased preinterventional RDW significantly predicts bare metal stent restenosis and might represent a useful screening tool to stratify patients according to a higher or a lower risk of ISR after stent implantation in patients with stable and unstable angina pectoris.</td>
</tr>
<tr>
<td>Solak Y et al 2014</td>
<td>367 patients with CKD 1 to 5</td>
<td>to evaluate the association of RDW with endothelial dysfunction in patients with chronic kidney disease (CKD).</td>
<td>RDW as a significant predictor of FMD independent of major confounding factors, such as diabetes, inflammation, anemia and kidney function in CKD.</td>
</tr>
<tr>
<td>Magri CJ, Fava S 2014</td>
<td>196 diabetic patients with proliferative diabetic retinopathy.</td>
<td>to investigate whether there is any association between RDW, nephropathy, neuropathy and peripheral arterial disease (PAD) in a type 2 diabetic population.</td>
<td>RDW was shown to be significantly associated with diabetic nephropathy in a type 2 diabetic population with advanced proliferative retinopathy independent of traditional risk factors, including diabetes duration and glycemic control.</td>
</tr>
<tr>
<td>Uche E 2014</td>
<td>200 participants consisting of 100 diabetics and 100 nondiabetic controls.</td>
<td>to evaluate the relationship between the RDW and fasting blood sugar/blood pressure, and compare the results from diabetics with nondiabetic controls.</td>
<td>A positive correlation between the RDW-CV and blood pressure was established in the diabetics in this study.</td>
</tr>
</tbody>
</table>
Conclusion:
Our searches indicate that Low RDW is associated with increased incidence of DM and high RDW is associated with diabetes complication. Increased RDW is related with all-cause and cardiac mortality rates in diabetic patients. RDW might be beneficial marker that could improve risk assessment for individuals at risk of developing DM and evaluation complication in diabetic patient.

Reference:


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Abyaz et al, 2015
Vol 2. No.3 (September 2015) 66-72


