Research Paper Medical Science

Red Blood Cell Distribution Width and Diabetic Vascular Complications

Ilir Alimehmeti Department of International Health, School for Public Health and Primary Care (CAPHRI), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands.

Agron Ylli **Endocrinology Cathedra, Department of Internal Medicine, University of Medicine, Tirana, Albania.**

ABSTRACT

Diabetes has become a major cause of mortality and morbidity, primarily due to various and different diabetic vascular complications (DVC). For predicting and assessing risk of such complications occurrence, research for a common biomarker to all above-mentioned DVC is warranted. Red blood cell distribution width (RDW) has already been associated to cardiovascular morbidity and mortality. Nevertheless, associations with DVC are heterogeneous and controversial, thus requiring a systematic review to be performed. We reviewed systematically four databases: Embase, Pubmed, EBSCO and DOAJ. Seven studies were included in our final review, out of 158 articles identified. RDW was associated with DVC and biomarkers associated with higher DVC incidence. Nonetheless, research was limited and sometimes controversial; therefore a definitive conclusion on the association between RDW and DVC is far from being drawn. However, RDW may be considered a promising biomarker for DVC, but further investigations are needed.

KEYWORDS : RDW, Diabetic Vascular Complications

Introduction:

Diabetes is a major health concern affecting 415 million persons aged 20-79 years old worldwide and having caused around 5 million deaths in 2015, the vast majority of which due to macrovascular and microvascular complications, including myocardial infarction, stroke, peripheral artery disease, diabetic nephropathy and diabetic retinopathy (IDF, 2015). Given the broad specter of such complications, a myriad of biomarkers are already employed for diagnosing and assessing their risk. Thus, in order to evaluate the initiation and the progress of each diabetic vascular complication, the patient is obliged to undergo routinely to different and expensive medical exams and procedures. Therefore research of a common biomarker useful for assessing all diabetic vascular complications is warranted.

Red blood cell distribution width (RDW), an integral part of the complete blood count analysis, is a quantitative measure of the variability in circulating red blood cells size and, its value expressed as a percentage, indicate the heterogeneity in red blood cell dimensions (anisocytosis) (England, 1974). Recent research have reported that elevated RDW levels are associated with acute myocardial infarction (Dabbah, 2010), stroke (Ani, 2009) and peripheral artery disease (Ye, 2011). It follows that the evaluation of RDW as potential candidate for becoming a comprehensive biomarker for vascular diabetic complications is warranted. Nevertheless, yet no systematic review has ever been performed to assess the association of RDW and diabetic complications.

Methods:

PRISMA 2009 methods for conducting and reporting systematic reviews were used (Moher, 2009). A systematic review of all publications published up to January 31st 2016 investigating the association between RDW and one or more diabetic vascular complications was conducted in four databases: Embase, Pubmed, EBSCO and DOAJ. Study design eligibility criteria included cross-sectional, case-control, cohort and trial studies. First, we conducted a sensitive search of all publications using both medical subject headings (MeSH) and free text for erythrocyte indices and diabetes mellitus. Afterwards, titles and abstracts were thoroughly read by two independent investigators for identifying relevant articles fulfilling the above-mentioned eligibility criteria. Full-text publications of all included abstracts were then retrieved. Again, two independent investigators reviewed comprehensively all publications, evaluating the study population, comparison and type of diabetic complication studied. In case of controversy, a third independent and blind reviewer was asked to review the papers subject to controversy and this third decision was key for further including or for discarding the publication, both in the titles and abstracts screening and in the full-text screening. Given the heterogeneity of the single studies, a meta-analysis was regarded unfeasible.

Results:

Figure 1 depicts the flow diagram of the studies included in the final qualitative analysis. A total of 158 articles were identified through database searching, but their number was reduced to 66 after duplication removal. During the phase of titles and abstracts screening, 39 studies were excluded. Of the resulting 27 articles, the full text screening excluded other 20 studies, as the eligibility criteria of study design, study population, comparison and outcome were not met in two, two, eleven and five studies respectively. Finally, seven studies were included for the final qualitative analysis. All studies were published recently, between 2012 and 2014.

Only two studies have investigated the direct relationship between RDW and diabetic vascular complications (Malandrino, 2012; Magri, 2014). In their research, Malandrino and coauthors conducted a cross-sectional study on 2.497 participants with diabetes comparing lowest RDW quartile to highest RDW quartile, identifying higher odds of vascular complication (OR 2.06 [95%CI 1.11, 3.83]), acute myocardial infarction (OR 2.45 [95%CI 1.13, 5.28]), ischemic cerebrovascular disease (OR 4th quartile 2.56 [95%CI 1.21, 5.42]) and diabetic nephropathy (OR 2.33 [95%CI 1.42, 3.82]). Such associations remained significant and mainly unchanged even after adjusting for vascular and RDW covariates. On the other hand, no association between RDW and diabetic retinopathy was found in this study.

Such findings were afterwards supported by a longitudinal prospective study of the association of RDW with coronary heart disease mortality prediction, including 1.439 persons with diabetes from the same study group (Veeranna, 2013). In fact, in their research, Veeranna et al. first found that the proportion of persons with diabetes was higher in the group with RDW >12.6% (14.44% vs. 19.45%, $p<0.001$). Moreover, in their final comparative analysis RDW >12.6% was a predictor of coronary heart disease mortality (HR 1.44 95% CI [1.23–1.68], $p<0.001$), independently of all other know vascular covariates. The association remained significant and unchanged even after additional adjusting for covariates related to RDW, thus warranting the authors to conclude that RDW significantly predicted coronary heart disease mortality in a population cohort free of clinical cardiovascular disease.

The second investigation studying the association between RDW and several diabetes vascular complications was reported by Magri (Magri, 2014). They studied the association between RDW and diabetic nephropathy, diabetic neuropathy and peripheral artery disease, in 196 patients already complicated with diabetic retinopathy. No association

was found between RDW and diabetic neuropathy (p=0.09) or peripheral artery disease (p=0.49), but a strong association was revealed with diabetic nephropathy (OR 1.64 [95%CI 1.15–2.35], p=0.006) even after adjusting for multiple risk factors in multivariate analysis.

Following, Tsuboi et al., studied prospectively the impact of RDW on long-term mortality in patients with diabetes after percutaneous coronary intervention (Tsuboi, 2013). In detail, the authors investigated long-time mortality after a mean follow-up duration of 3.9 years of 560 diabetic patients who were subject to elective percutaneous coronary intervention. After dividing patients in two groups, according to RDW values higher or lower than the median value, they found that the cumulative incidence of all-cause mortality was significantly higher in the high RDW values group (p=0.0015). Likewise, in multivariate Cox-proportional hazards analysis high RDW values were associated with all-cause mortality (HR 2.56, [95%CI 1.12–6.62], p=0.025) after adjusting for all known vascular and RDW covariates. Such results lead the investigators to conclude that RDW might be useful to be used as a biomarker for stratifying risk coronary artery disease patients with diabetes.

Other studies have studied the association of RDW with biomarkers already approved as risk markers for vascular diabetic complication, such as HbA1c and hypertensive response to exercise (Lippi, 2014; Engstrom, 2014; Kucukdurmaz, 2014). In fact, RDW was shown to be positively associated both in elderly people (Lippi, 2014) and non-diabetic individuals (Engstrom, 2014) with HbA1c, which is a well-known predictor of diabetic complications. Given these facts, it may be inferred that RDW is associated with such complications also in these populations. Moreover, another well-known predictor of diabetic vascular complications, hypertensive response to exercise, was shown to be associated to RDW in type 2 diabetes patients (Kucukdurmaz, 2014).

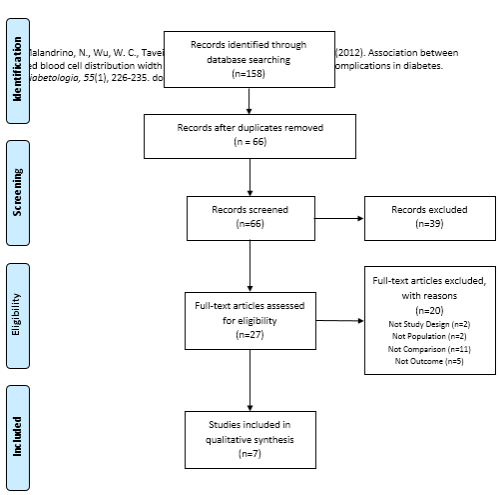
Discussion:

This is the first systematic review investigating the association between red blood cell distribution width and diabetic vascular complications. Such an association may be explained by the fact that, in presence of hyperglycemia, several properties of the red blood cells, including structural and functional properties, present alterations. Glycosylation of cell surface proteins, reduced deformability of the red blood cells and decreased fluidity of the plasma membrane may affect negatively the red blood cells dynamic properties (Keymel, 2011; Lippi 2012). This would impair their flow and lead to the higher vulnerability to vascular injuries. Moreover, diabetic nephropathy itself causes fragmentation of red blood cells, which is well-known cause of red blood cells size heterogeneity (Paueksakon, 2002).

Conclusion:

Given the very small number of research conducted on the topic and the controversial results mentioned above, a final and definitive conclusion is hence quite challenging. Although promising, the association between RDW and diabetic vascular complications should be subject to further study, in order to for such a conclusion to be made.

Figure 1 Flow Diagram



References:

1. International Diabetes Federation. IDF Diabetes, 7 ed. Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org
2. England JM, Down MC. Red-cell-volume distribution curves and the measurement of anisocytosis. Lancet. 1974 Apr 20;1(7860):701-3.
3. Dabbah S, et al. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. American Journal of Cardiology, 105 (2010),312-317.
4. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. Journal of Neurological Sciences, 277 (2009),103-108.
5. Ye Z, et al. Usefulness of red cell distribution width to predict mortality in patients with peripheral artery disease. American Journal of Cardiology, 107 (2011),1241-1245.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
7. Malandrino, N. et al. Association between red blood cell distribution width and macrovascular and microvascular complications in diabetes. Diabetologia 2012;55(1):226-35.
8. Magri CJ, Fava S. Red blood cell distribution width and diabetes associated complications. Diabetes and Metabolic Syndrome 2014;8:13–17.
9. Veeranna, V. et al. Comparative analysis of red cell distribution width and high sensitivity C-reactive protein for coronary heart disease mortality prediction in multi-ethnic population: findings from the 1999-2004 NHANES. International Journal of Cardiology 2013;168(6):5156-61.
10. Tsuboi, S. et al. Impact of red blood cell distribution width on long-term mortality in diabetic patients after percutaneous coronary intervention. Circulation Journal 2013;77(2):456-61.
11. Lippi G. et al. Increased red blood cell distribution width (RDW) is associated with higher glycosylated hemoglobin (HbA1c) in the elderly. Clin Lab 2014;60(12):2095-8.
12. Engstrom, G. et al. Red cell distribution width, haemoglobin A1c and incidence of diabetes mellitus. Journal of Internal Medicine 2014;276(2):174-83.
13. Kucukdurmaz, Z. et al. Red cell distribution width and hypertensive response to exercise in patients with type 2 diabetes mellitus. Clinical and Experimental Hypertension 2014;36(1):32-5.
14. Keymel S, et al. Impaired red blood cell deformability in patients with coronary artery disease and diabetes mellitus. Horm Metab Res 2011;43:760–5.
15. Lippi G, et al. Erythrocyte mechanical fragility is increased in patients with type 2 diabetes. Eur J Intern Med 2012;23:150–3.
16. Paueksakon P, et al. Microangiopathic injury and augmented PAI-1 in human diabetic nephropathy. Kidney Int 2002;61:2142–8.