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LETTER

# Red Blood Cell Distribution Width as a Biomarker in Type 2 Diabetes Mellitus: Technical Notes [Letter]

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## Dear editor

Arkew et al have published an article entitled "Red Blood Cell Parameters and Their Correlation with Glycemic Control Among Type 2 Diabetic Adult Patients in Eastern Ethiopia: A Comparative Cross-Sectional Study" in Diabetes, Metabolic Syndrome and Obesity.[1] I congratulate the authors on their work, which adds to the already extensive literature on the use of the red blood cell distribution width (RDW) as a surrogate biomarker of systemic inflammation in the setting of type 2 diabetes mellitus (T2DM). I would like to add some technical details about the RDW which would be of interest to the readership of the journal who are considering the use of the RDW for this or related purposes.

Commercially available blood analyzers calculate the RDW as the standard deviation (RDW-SD) or the coefficient of variability (RDW-CV) of the red blood cell histogram. Like any other complete blood cell count (CBC) analyte, the RDW may be impacted by preanalytical and analytical phase variables. In the case of the RDW, the most important of these appear to be; 1) time between phlebotomy and analysis, 2) storage temperature, 3) tube type and anticoagulant, and 4) transport conditions, including pneumatic tube transport.[2] Moreover, the determination of the RDW is not standardized among the different instrumentation manufacturers, and in the absence of a recognized RDW standard, there is an additional analytical phase issue.[2] Therefore, when setting up a clinical study that uses CBC data, including the RDW, it is important to consider the potential biases introduced into the data by these preanalytical and analytical phase variables.

To assess the degree to which these issues have been addressed in the study of Arkew et al and the other studies cited in their paper, I extracted the relevant data which are summarized in Table 1.[1,3–8] The preanalytical variables that may impact the RDW were largely unreported, with time between phlebotomy and analysis reported in 1/7 studies and no reporting of storage temperature and transport conditions in any of the studies. It is not surprising that these variables are underreported, since guidelines such as the Standards for Reporting of Diagnostic Accuracy Studies (STARD) do not mandate the reporting of preanalytical and analytical phase variables, despite their obvious importance in the outcomes of many laboratory tests, including the RDW.[9] This is unfortunate, since information about these potential sources of bias are largely unreported outside the laboratory medicine literature and may have important clinical implications. For example, a potential source of error in the RDW is delay between phlebotomy and analysis. Since 6/7 of the studies used outpatient data, a potential time delay may occur if specimens were collected in doctors' offices and/or outpatient clinics and analyzed in a central laboratory. Daves et al have reported that time delays as short as 3 hours have resulted in an erroneous RDW result.[10] A lack of control for these preanalytical phase variables may account in part for the different cutoffs for the RDW and the lack of statistical significance in the study of Adane et al.[3] Due to the lack of standardization of the RDW across different instrumentation platforms, the wide variety of instruments used in these studies, including devices manufactured by Sysmex (Kobe, Japan),[3,6] Abbott (Chicago, IL, USA),[4] Beckman Coulter (Brea, CA, USA),[1,5] and Horiba (Kyoto, Japan),[7] may add additional biases.

**Table 1** Major Clinical and Laboratory Features of the Studies Cited by Arkew et al[1]

| Study [Ref] | Year | Country | Setting | T2DM Sample Size | Control Group(s) Size and Clinical Features | Age (Years, Mean and Range) | RDW, T2DM vs Control | p | Analyzer | Time | Temperature | Preservative | Transport |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adane[3] | 2020 | Ethiopia | OP | 164 | 82, healthy | 50, NR | 44±3.6 vs 44.3±5.0 (SD) | 0.212 | Sysmex KX21N | NR | NR | K2EDTA | NR |
| Alshehri[4] | 2017 | Saudi Arabia | IP | 205 | 200, healthy | 45.5±5.5 | 14.57±3.1 vs 12.63±2.58 (CV) | 0.047 | Cell-Dyn Ruby | NR | NR | EDTA | NR |
| Arkew[1] | 2022 | Ethiopia | OP | 110 | 110, healthy | 43.13±9.43 | 14.20 ±1.03 vs 13.61 ±0.74 (CV) | <0.001 | UniCel DxH 800 | NR | NR | K2EDTA | NR |
| Arkew[5] | 2021 | Ethiopia | OP | 134 | 134, healthy | 43.08±9.30 | 14.00 (13.40–14.70) vs 13.50 (13.10–14.00) (CV) | <0.001 | UniCel DxH 800 | NR | NR | EDTA | NR |
| Biadgo[6] | 2016 | Ethiopia | OP | 148 | 148, healthy | 49.09±8.1 | 47.3±2.6 vs 45.2±3.0 (SD) | <0.001 | Sysmex KX-21N | NR | NR | EDTA | NR |
| Jabeen[7] | 2013 | Pakistan | OP | 170 | 92, healthy | 51.08±0.7 | 14.41±0.14 vs 13.69±0.16 (CV) | 0.001 | Horiba ABX | <2 hrs | NR | EDTA | NR |
| Olana[8] | 2019 | Ethiopia | OP | 70 | 70, healthy | 53.17±11.64 (M); 49.7±9.89 (F) | 14.28±1.862 vs 12.76±0.993 (CV, M); 14.04±1.397 vs 13.08±1.10 (CV, F) | 0.001 (M) 0.012 (F) | NR | NR | NR | EDTA | NR |

**Abbreviations**: ref, reference number; T2DM, type 2 diabetes mellitus; RDW, red blood cell distribution width; OP, outpatient; NR, not reported; SD, standard deviation; K2EDTA, potassium salt of EDTA (ethylene diamine tetra acetic acid); IP, inpatient; CV, coefficient of variation; EDTA, ethylene diamine tetra acetic acid; M, male; F, female.

Another issue with the practical implementation of the RDW as a surrogate biomarker is its limited dynamic range, meaning that the difference between a normal and abnormal result may be quite small. Despite the differences in group means being statistically significant, there may be considerable overlap between individual results in the disease and control groups, impacting the meaningfulness of test results. This is particularly noteworthy for the studies of Arkew et al and Jabeen et al,[1,5,7] where the differences in group means are ~1 fL, despite the statistically significant difference between the two cohorts. Without a rigorous control of the preanalytical and analytical phase variables, individual patient results may be difficult or impossible to interpret.

In summary, I thank Arkew et al for their thought-provoking study, that adds to our understanding of the potential clinical utility of the RDW in T2DM, and more broadly, its use as a surrogate marker of systemic inflammation. I hope that this assessment will add additional context to Arkew et al's work and will be of interest to the readership of Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy who are considering the use of the RDW for this purpose.

## Disclosure

The author reports no conflicts of interest in this communication.

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