Association of the Elevated Red Blood Cell Distribution Width with the Risk of Developing Diabetes Mellitus

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Abstract

Objective The aim of this study was to determine whether elevated levels of RDW-coefficient of variation (CV) are associated with the development of diabetes mellitus (DM) in a population of healthy middle- and old-aged individuals.

Method We conducted a retrospective cohort study. A total of 2,688 individuals (aged 49-66 years) without a DM diagnosis, impaired fasting glucose, or anemia at baseline were grouped according to the RDW-CV quartile, and the onset of DM during a 4-year period was recorded for each group.

Results The correlation coefficients for the RDW-CV and waist circumference and for the RDW-CV and HbA1c were 0.114 and 0.133, respectively. The relative risks of future DM in RDW-CV quartiles II, III, and IV (high) compared with RDW-CV quartile I (low) were 1.9 [95% confidence interval (CI) 1.0-3.6, \( p=0.057 \)], 1.6 (95% CI 0.8-3.0, \( p=0.157 \)), and 2.2 (95% CI 1.2-4.0, \( p=0.015 \)), respectively. After adjusting for sex, age, waist circumference, hemoglobin A1c, triglycerides, high density lipoprotein-cholesterol (HDL-C), and high-sensitivity C-reactive protein, the multivariate relative risk for the highest vs. the lowest RDW-CV quartile was 1.8 (95% CI, 1.1-3.4, \( p=0.046 \)).

Conclusion These data indicate that an elevated RDW-CV is associated with an increased incidence of DM.

Key words: diabetes mellitus, red blood cell distribution width, incidence

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Introduction

Diabetes mellitus (DM) is estimated to affect over one hundred million Chinese persons, and its incidence has dramatically increased in recent years, especially in the middle-elderly population (1). Notably, as many as two-thirds of individuals with DM remain undiagnosed or untreated. These individuals have a higher risk of cardiovascular disease, renal dysfunction, diabetic foot, retinopathy and other complications, and they require long-term medication and regular monitoring of the blood glucose or hemoglobin A1c (HbA1c) concentration. The HbA1c concentration represents the average blood glucose level over the previous three months, is free of short-term fluctuations, and can be monitored long term and controlled according to individual circumstances to an appropriate level to reduce the risk of serious complications (2). Very recently, a relationship between the elevated red blood cell (RBC) distribution width (RDW) and higher HbA1c concentrations was found in a large cross-sectional study (3).

The RDW, an index of the heterogeneity of RBCs determined using an automated hematology analyzer that has been used in the past to assist in the identification of the type of anemia, is commonly elevated in patients with iron deficiency anemia and megaloblastic anemia. Moreover, in acute blood loss or hemolysis, the RBCs released into the bloodstream are more immature than normal, which can result in an increased RDW, whereas a normal RDW is typically present in cases of aplastic anemia, which is anemia caused by leukemia or myelodysplastic syndrome (4). Although the RDW is mainly used to identify the different types of anemia, cumulative evidence from recent studies suggests that it can also be used to predict cardiovascular events and heart failure (5, 6).

The RDW is known to be associated with HbA1c; how-
ever, to the best of our knowledge, the relationship between
the RDW and the development of DM remains controversial. Therefore, we evaluated whether an elevated RDW-
coefficient of variation (CV) can independently predict a fu-
ture risk for DM in healthy middle- and old-aged individu-
als.

Materials and Methods

Study participants

We used a retrospective cohort design. Participants were
enrolled at our screening center, where the employees of a
large company annually undergo routine medical examina-
tions. The participants ranged from 49 to 66 years of age in
2011 and were consecutively referred to our screening cen-
ter for annual routine medical checkups from January 2011
to December 2014. Candidate participants (n=3,452) self-
reported their medical history and prescription drug use,
family history, and smoking at baseline. A family history of
DM was defined as a father, mother, brother or sister with
DM. Candidate participants were excluded if one or more of
the following conditions were met: (1) self-reported DM at
baseline; (2) hemoglobin concentration <130 g/L in men or
<115 g/L in women; (3) HbA1c >6.0% (42 mmol/mol); (4)
fasting plasma glucose >6.1 mmol/L; and (5) missing values
for any covariates of interest. After exclusion, 2,688 indi-
viduals, including 1,747 men and 941 women, were enrolled
into the study cohort.

Within the next four years, new cases were confirmed if
one or more of the following conditions were met: (1) self-
reported DM or hypoglycemic agent use and (2) DM diag-
nosed by a routine medical checkup. The DM diagnosis was
made by the attending physician according to the criteria
used in the report “Definition and diagnosis of diabetes mel-
litus and intermediate hyperglycemia: report of a WHO/In-
ternational Diabetes Federations IDF consultation (7).” The
hospital record room was contacted for available supporting
documentation. Candidate participants who were found to
have prevalent DM or were confirmed to be using a hypo-
glycemic agent before enrollment, but had not been identi-
fied as having prevalent DM at baseline were excluded. DM
was confirmed if participants were found to have prevalent
DM or were confirmed to be using a hypoglycemic agent
during the observation period. A total of 98 participants,
including 67 men and 31 women, developed confirmed DM
during the 4-year observation period. The distribution of
cases according to the year of confirmed diagnosis was as
follows: 41 cases in year 2, 28 cases in year 3, and 29 cases
in year 4.

Laboratory procedures

Fasting blood specimens were collected in the morning
from 7:30-9:00. Fasting was defined as not having con-
sumed a meal for more than eight hours. Whole blood sam-
ple were collected in EDTA-K2 and were used for hemato-
logical and HbA1c level determination; hematological test-
ing was performed using the Sysmex XE-2100 (Sysmex Corporation, Kakogawa, Japan) automated hematolo-
gy analyzer. Hemoglobin was measured by spectrophotometry, and
RBC counts were detected by laser diffraction and flow cy-
tometry. The mean corpuscular volume (MCV) and RDW-
CV were also measured by the XE-2100 analyzer. The
RDW-CV was calculated using the following formula: RDW-CV = [Standard deviation of MCV/mean MCV] ×
100%. HbA1c was measured by a high-pressure liquid ion
exchange chromatography assay (HLC-723G7, TOSHO Cor-
poration, Tokyo, Japan). Serum samples were assayed for
fasting plasma glucose, triglycerides, creatinine, high density
lipoprotein-cholesterol (HDLC) and high-sensitivity C-
reactive protein (hs-CRP) levels. Fasting plasma glucose
was measured by a hexokinase assay, triglycerides were mea-
ured by a glycerol phosphate oxidase assay, creatinine was
measured by an enzymatic assay, HDLC was measured by a
surfactant clearance assay, and hs-CRP was measured by a
high-sensitivity latex enhanced immunoturbidimetric assay.
For all assays, the samples were centrifuged within an hour
of collection, and testing was completed within four hours
by AU2700 (Olympus Corporation, Tokyo, Japan) analysis.
Throughout the study, routine internal quality control proce-
dures and an external quality assessment scheme were used
to validate the reliability of the results. In addition, as severe
lipemia and hemolysis could interfere with the assessments,
samples with a concentration of triglycerides greater than 5
mmol/L or a free hemoglobin value higher than 5 g/L were
scheduled for re-acquisition. Height, weight and waist cir-
cumference were measured at the screening center by two
trained nurses, and the body mass index (BMI) was calcu-
lated as weight divided by height squared (kg/m²).

Statistical analysis

Statistical analyses were performed using the statistical
package SPSS version 19.0 (SPSS Inc., Chicago, USA). For
normality tests, normally distributed continuous variables
were expressed as $\bar{x} \pm sd$ and were compared by a one-
way analysis of variance (ANOVA) [followed by the least
significant difference (LSD) test for multiple comparisons
between groups]. Because the distributions of CRP, triglyc-
erides (TG) and HDLC were skewed, those variables were
expressed as the median (5th-95th), and differences in the
distributions of these variables between groups were deter-
mined using the non-parametric Kruskal-Wallis test. For
categorical variables, differences between groups were ex-
amined using the $\chi^2$ test. Spearman’s partial correlation coef-
ficients were calculated for the correlations between the
RDW-CV and waist circumference and between the RDW-
CV and HbA1c. Single- and multiple-factor unconditional
logistic regression analyses were used to determine the rela-
tive risks (RRs) after adjusting for potential confounding
factors. The level of statistical significance was always set at
p<0.05.
Table 1. Baseline Characteristics (n=2,688).

|                | I 11.0-12.2% (n=667) | II 12.3-12.5% (n=576) | p       | III 12.6-12.9% (n=747) | p       | IV 13.0-17.3% (n=698) | p       |
|----------------|----------------------|-----------------------|---------|------------------------|---------|-----------------------|---------|
| Male/Female, % | 57/43                | 65/35                 | 0.002   | 67/33                  | < 0.001 | 70/30                 | < 0.001 |
| Age, y         | 56.9±5.1             | 57.3±5.1              | 0.312   | 57.5±5.0               | 0.365   | 57.3±5.2              | 0.196   |
| BMI, Kg/m²     | 23.5±2.8             | 23.5±2.7              | 0.871   | 23.8±3.0               | 0.048   | 23.4±2.8              | 0.647   |
| WC, cm         | 81.0±9.5             | 82.5±9.0              | 0.007   | 82.9±9.8               | < 0.001 | 83.1±9.7              | < 0.001 |
| HbA1c, %       | 5.24±0.35            | 5.29±0.33             | 0.009   | 5.32±0.34              | < 0.001 | 5.33±0.31             | < 0.001 |
| Hemoglobin, g/L| 137.8±11.6           | 138.1±11.8            | 0.620   | 138.2±11.3             | 0.515   | 138.0±12.0            | 0.753   |
| MCV, fL        | 91(86-97)            | 91(85-97)             | 0.161   | 90(86-97)              | 0.108   | 91(84-98)             | 0.005   |
| TG, mmol/L     | 1.21(0.53-3.06)      | 1.21(0.53-3.56)       | 0.560   | 1.17(0.59-3.09)        | 0.942   | 1.12(0.52-2.80)       | 0.188   |
| HDL-C, mmol/L  | 1.51±0.36            | 1.52±0.34             | 0.671   | 1.54±0.37              | 0.109   | 1.56±0.36             | 0.005   |
| hs-CRP, mg/L   | 0.60(0.20-3.10)      | 0.60(0.20-3.30)       | 0.736   | 0.70(0.20-3.40)        | 0.582   | 0.70(0.20-3.60)       | 0.357   |
| Creatinine, μmol/L | 66.8±14.6        | 67.3±13.1             | 0.591   | 68.7±14.1             | 0.010   | 68.0±14.9            | 0.104   |
| Smoking, yes/no| 164/503              | 151/425               | 0.514   | 219/528                | 0.096   | 259/439               | < 0.001 |
| Hypertension, yes/no | 85/582          | 61/515                | 0.896   | 89/658                 | 0.916   | 91/607                | 0.779   |
| Cardiomyopathy, yes/no | 0/667       | 2/574                | 1.746   | 0/698                  | 0.734   |
| Nephropathy, yes/no | 0/667        | 0/576                | 1.746   | 0/698                  | 0.692   |
| Dyslipidemia, yes/no | 217/450    | 208/368              | 268/479 | 231/467               | 0.839   |
| DM family history, yes/no | 36/631   | 44/532               | 57/690  | 35/663                | 0.809   |

Differences in the study variables across RDW-CV quartiles were tested by the Kruskal-Wallis test (for skewed variables), one-way ANOVA (for continuous variables), and the χ² test (for categorical variables). Differences relative to the lowest RDW-CV quartile were evaluated by the LSD test or the Kruskal-Wallis test. Continuous variables are expressed as mean±sd, and skewed variables are expressed as the median (5th-95th).

WC: waist circumference, HbA1c: hemoglobin A1c, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, hs-CRP: high-sensitivity C-reactive protein.

Results

The RDW-CV was used to categorize the participants into quartiles. The baseline characteristics of the entire population are shown in Table 1. As predicted, the highest RDW-CV group had a higher mean waist circumference (p<0.001 for trend) and higher HbA1c (p<0.001 for trend), and the RDW-CV was significantly positively associated with the waist circumference (r=0.11, p<0.001) and HbA1c (r=0.13, p<0.001). Hemoglobin and age were not significantly different among the RDW-CV quartiles (p=0.73 for trend and p=0.073 for trend, respectively). The influence of anemia on the RDW-CV was ruled out.

Therefore, we evaluated whether the relationship between the RDW-CV and the risk of future DM was independent of the waist circumference and HbA1c. As shown in Table 2, the correlation between the RDW-CV level and future DM had a reduced strength after adjusting for HbA1c and the waist circumference.

Then, to assess potential combinatory effects, we computed the relative risk of DM after dividing the population into 8 groups according to a waist circumference cut-off value of 85 cm for men and 80 cm for women and a 75th percentile RDW-CV cut-off value (Fig. 1, 2). Within each of those 8 groups, the relative risk of future DM was higher in the higher RDW-CV subgroup than in the lower RDW-CV subgroup, however, these differences were not significant, and the RR of DM was highest for individuals with both a high waist circumference and high RDW-CV levels.

Next, we determined the RRs of incident DM with an RDW-CV value of 85 cm for men and 80 cm for women and a 75th percentile RDW-CV cut-off value (Fig. 1, 2). Within each of those 8 groups, the relative risk of future DM was higher in the higher RDW-CV subgroup than in the lower RDW-CV subgroup, however, these differences were not significant, and the RR of DM was highest for individuals with both a high waist circumference and high RDW-CV levels.

In the subgroups of participants who were smokers or non-smokers, the relative risk of DM was highest for individuals with both high RDW-CV levels and smoking status, however, this difference was not significant (Fig. 4).

Finally, we calculated the crude and adjusted RRs of DM.
The RRs of DM in the II, III, and IV groups relative to the RR of the I group were 1.9 [95% confidence interval (CI), 1.0-3.6, p=0.057], 1.6 (95% CI, 0.8-3.0, p=0.157), and 2.2 (95% CI, 1.2-4.0, p=0.015), respectively. After adjusting for sex, age, waist circumference and HbA1c, TG, HDL-C, and hs-CRP levels, the multivariate RR for the highest vs. the lowest quartile of the RDW-CV was 1.8 (95% CI, 1.1-3.4, p =0.046) (Table 3).

Discussion

In the present study, elevated RDW-CV values were associated with the development of DM during the 4-year follow-up period, although this difference had borderline significance after adjusting for multivariate confounding factors. In addition, our study expands on previous works that studied other known risk factors for DM by revealing positive correlations between the RDW-CV and the waist circumference and between the RDW-CV and HbA1c. In other words, the RDW was associated not only with HbA1c, but also with the waist circumference.

Over the past few years, the association between an elevated RDW and cardiovascular disease has become increasingly clear. According to epidemiologic studies, an elevated RDW is a prognostic marker of heart failure and is strongly related to the risk of a cardiovascular event (5, 6). Moreover, an accumulating body of evidence suggests that the RDW is a useful parameter for predicting mortality in pa-
tients with stroke (8) and heart failure (5). Similar results have also been observed in acute kidney injury (9), peripheral artery disease (10), and pulmonary embolism (11). Although the definitive mechanism of the relationships between the RDW and these diseases remains unclear, Lippi et al. hypothesized that the relationships between an elevated RDW and hs-CRP and between an elevated RDW and the erythrocyte sedimentation rate could be due to chronic low-grade systemic inflammation (12). However, Förhész et al. hypothesized that suppressed erythrocyte maturation, oxidative damage, impaired kidney function and consequent decreased erythropoietin secretion, and iron, vitamin B12, and folate deficiencies may be involved in the relationships between an elevated RDW and various diseases (13).

There are several alternative explanations for our results: first, the ability of the RDW-CV to predict a future risk of DM may be an epiphenomenon of underlying DM risk factors. For instance, an increased waist circumference due to subcutaneous and visceral fat deposition can exacerbate insulin resistance and also induce the secretion or expression of some proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α (14). Tumor necrosis factor-α has been found to promote the development of insulin resistance (15) and inhibit the growth of burst-forming unit erythroid cells and colony-forming unit erythroid cells to reduce the production of RBCs (16, 17). In addition, interleukin-6-nearly 30% of in vivo systemic IL-6 stems from subcutaneous adipose tissue (18)-can induce the hepcidin expression (19). This mechanism, inflammation-mediated iron abnormal metabolism, is also potentially important in the relationship between the RDW-CV and the DM risk.

Chronic inflammation plays a crucial mediating role in the pathogenesis of type 2 DM (20, 21), and the RDW has been found to be related to the expression of inflammatory biomarkers (12); thus, inflammation-mediated abnormal iron metabolism is another important and perhaps central mechanism of RDW elevation. Inflammation induces the hepcidin expression (19), and hepcidin then inhibits intestinal iron absorption and macrophage iron release. Indeed, a strong independent relationship between elevated ferritin levels and an increased incidence of DM events has been found in previous studies (22). Moreover, earlier studies showed that proinflammatory cytokines inhibit erythropoietin-induced erythrocyte maturation (23), which may cause RDW elevation. However, to weaken the effect of this factor, we excluded individuals with anemia and also adjusted for the hemoglobin level; therefore, it is unlikely that these results are entirely due to abnormal iron metabolism. Future studies with a more complete evaluation of bone marrow hematopoiesis in individuals with DM may provide further insight into the mechanisms of the interaction between hematologic factors and DM.

Another underlying mechanism that may (at least partially) explain our finding is the correlation between the RDW-CV and HbA1c. Because an increased blood glucose level would impair erythrocyte deformability and exacerbate aggregation (24), it would thus make RBCs more prone to lysis when passing through capillary vessels and splenic cords, which would be reflected in part by an increase in the RDW-CV.

In the present analysis, the smoking rates steadily increased across the RDW-CV quartiles. Similar results were also observed in the study by Engström et al. (25). This finding suggests that smoking increases the level of RDW-CV. Cigarette smoking is known to be linked to insulin resistance in peripheral tissues (26) and impaired glucose tolerance (27). Moreover, cigarette smoking has also been found to temporarily increase the serum glucose concentration (28). Furthermore, there is prospective evidence of a strong relationship between smoking and the incident occurrence of DM (29). Therefore, the link between the RDW-CV
Additional, Engström et al. did not exclude participants with anemia, which may have affected their results. Finally, although the RDW-SD and RDW-CV are indicators of RBC heterogeneity, they may not be identical.

There are several limitations associated with this study. First, we did not exclude a minority of subjects, such as those who had undergone blood transfusions, had experienced heart failure (5), and had coronary heart disease (6). Because those factors may be responsible for the higher RDW-SD and RDW-CV values in those individuals, the inclusion of those individuals at study enrollment may have affected our results. Second, undiagnosed DM, impaired fasting glucose or impaired glucose tolerance at study entry may have biased our results. Nevertheless, to reduce the impact of those factors, we excluded individuals with a baseline fasting plasma glucose of more than 6.1 mmol/L or an HbA1c value of more than 6.0% from our initial sample. Finally, although we excluded participants with anemia, we did not correct for the folic acid or vitamin B12 levels.

Despite these limitations, our findings support the conclusion that an elevated RDW-CV predicts the development of DM over 3-4 years in middle-aged and older Chinese adults. Additionally, as the RDW-CV can be easily and inexpensively measured clinically, the combination of the waist circumference and HbA1c are anticipated to provide a better indication of future DM risk.

The authors state that they have no Conflict of Interest (COI).

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Table 3. Crude and Adjusted Relative Risks of Type 2 Diabetes Mellitus.

|    | I     | II    | p     | III   | p     | IV    | p for trend |
|----|-------|-------|-------|-------|-------|-------|------------|
|    | 11.0-12.2% | 12.3-12.5% | p     | 12.6-12.9% | p     | 13.0-17.3% | p     |
| Diabetes/no | 15/652 | 24/552 | 0.072 | 26/721 | 0.168 | 33/665 | 0.013 | 0.088 |
| Crude analysis relative risk (95% CI) | 1.0 | 1.9(1.0-3.6) | 0.057 | 1.6(0.8-3.0) | 0.157 | 2.2(1.2-4.0) | 0.015 | 0.088 |
| Adjusting for all risk factors relative risk (95% CI) | 1.0 | 1.8(0.9-3.4) | 0.097 | 1.3(0.8-3.0) | 0.425 | 1.8(1.1-3.4) | 0.046 | 0.201 |

All risk factors: gender, age, waist circumference, hemoglobin A1c, triglyceride, high density lipoprotein-cholesterol, and high-sensitivity C-reactive protein.

and DM may be partially due to the impact of smoking.

Very recently, independent relationships between a decreased RDW-standard deviation (SD) and an increased risk of developing DM, increased waist circumference and lower HbA1c were found in Sweden (25). To the best of our knowledge, no published reports with similar results in other populations exist. Our findings expand on those of previous analyses to include a large cohort of healthy middle- and old-aged Chinese individuals and show an association between the RDW and the incidence of DM that does not appear to be generalizable to other ethnic groups. Moreover, the different follow-up durations (over 14 years vs. 4 years) may have resulted in differences in the baseline conditions.

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