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The Association between Red Blood Cell Distribution Width and Metabolic Syndrome in Adolescent Girls

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Abstract

Background: Metabolic syndrome (MetS) is characterized by metabolic and anthropometric abnormalities which are associated with an increased risk of cardiovascular disease (CVD). Red blood cell distribution width is a candidate biomarker for CVD.

Method: Nine hundred and eighty-eight girls who were between 12 to 18 years old were enrolled. Anthropometric parameters and blood pressure were measured, together with biochemical and hematological variables, using routine measures. International diabetes federation (IDF) criteria were used for the diagnosis of MetS.

Result: Some of the demographic parameters such as weight, neck circumference (NC), waist circumference (WC) and hip circumference (HP) were significantly different between the groups with and without MetS, as may be expected. Significantly higher values for red blood cell distribution width (RDW) were observed only in subjects with waist circumference (P= 0.017) and fasting blood glucose levels (P= 0.038). RDW measures were directly associated with MetS status (r=0.076 (P =0.043)), WC (r=0.097 (P =0.016)), and fasting blood glucose (FBG) (r= -0.085 (P =0.037)). It was found that the RDW had specificity and sensitivity for MetS-based IDF criteria 48.01 and 77.78, respectively. RDW related cure area (95% CI) for MetS was reported to be 0.588 (0.380- 0.796).

Conclusion: We found that an elevated RDW was associated with the presence of MetS and with some its components; but ROC analysis revealed that a weak specificity in spite of good sensitivity of RDW for MetS, along with a low AUC may make it unusable for the diagnostic prediction of MetS in this population.

Key Words: *********Achievement goals, cheating behavior.

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1- INTRODUCTION

Metabolic syndrome (MetS) is defined by a cluster of several metabolic abnormalities and is associated with insulin resistance and adipose tissue dysfunction and distribution (1, 2). The definition of MetS is complicated especially in children and adolescents; often adult MetS definitions are adopted for children and adolescents and applied for these age groups. Redefining the adults' criteria and the finding of new more specific markers for children are dynamic areas in MetS research (3). Some of the adopted MetS definitions for children are listed in **Table 1**. MetS is associated with several cardiovascular risk factors including insulin resistance, glucose intolerance, atherogenic lipid profile, hypertension, obesity, coagulation disorder, and elevated levels of inflammatory markers (4). These risk factors play a role in the progression of cardiovascular diseases (CVD). One candidate biomarker for CVD risk is the red blood cell distribution width (RDW). The RDW is a ratio of heterogeneity in red blood cell size, which is measured by dividing the standard deviation (SD) of erythrocyte volumes to the mean corpuscular volume (MCV) (i.e., RDW=SD/MCV). RDW is measured routinely as part of the complete blood count (CBC). Several studies have suggested that RDW may be a useful marker for the CVD diagnosis and prognosis. These results indicate that an increased RDW is associated with arterial hypertension and it may be a novel predictor for CVD mortality (5, 6). In addition to hypoxia, the erythropoiesis process is influenced by chronic inflammation which can affect RDW (7). Chronic inflammation and oxidative stress may be involved in elevated RDW in the MetS (8). Pro-inflammatory cytokines play a major role in inhibition of EPO-induced RBC maturation, which results in RDW elevation (9). Furthermore, insulin resistance and high insulin level are involved in initiation of inflammation; this condition may be related to high RDW through affecting oxidative stress on RBCs for shortening the life span (8). However, the relationship between RDW and MetS remains unclear.

RDW is a novel marker that may reflect the presence of an inflammatory state (10). The association between RDW and MetS may be due to the elevated levels of inflammatory markers (11-13). In the present study, we have investigated the association between RDW and MetS in adolescent girls and aim to determine its utility in the diagnosis of MetS in adolescent girls.

2- MATERIALS AND METHODS

2-1. Participants

As part of an ongoing sub-national study, nine hundred eighty eight girls between 12 and 18 (14.56 ± 1.53) years old were recruited using random cluster sampling. Demographic data were collected by a researcher-made questionnaire. All the cases and their parents filled the written informed consent forms which were approved by the Ethic Committee of Mashhad University of Medical Sciences.

2-2. Anthropometric measurements and definitions

Anthropometric values such as height, weight, neck circumference (NC), waist circumference (WC) and hip circumference (HP) and blood pressure were measured by a trained research staff. Right arm blood pressure was measured following a few minutes of rest in the sitting position. For the weight measurement, a 0.01 Kg digital scale was used in thin clothing. Waist circumference was also measured at the midway between the lower rib margin and iliac crest (subjects should be in standing state and

wearing only underwear at the end of normal expiration) (14). Finally, the neck circumference was also measured midway of the neck (15). IDF criteria were used for the diagnosis of MetS (16). Age-adjusted IDF criteria for the adolescents and adults were applied for >16 and 10 to <16 years old, respectively. MetS is diagnosed due to the observation of obesity plus two or more risk factors such as hyperglycemia, hypertriglyceridemia, etc.

Table-1: some metabolic syndrome definitions adopted to pediatrics (3)

Criterion	IDF (43)	NCEP-ATP III (44)	Cook et al., 2003 (45)	De Ferranti et al., 2004 (46)	Goodman et al., 2004 (47)	Papadopoulou-Alataki et al., 2004 (48)
Approach	-	-	Modified- NCEP		Modified- WHO	Modified- EGIR
Obesity; WC (P or cm)	≥ 95th P	≥ 95th P	≥ 90th P	> 75th P		≥ 94 cm for male; ≥ 80 cm for female
Obesity; BMI (P)	-				≥ 95th P	-
FBG (mg/dL)	≥ 100	≥ 110	≥ 110	≥ 110	≥ 110	≥ 110 - > 126
BP (mmHg)	SBP/ DBP ≥ 130/ ≥ 85	-			SBP/ DBP ≥ 130/ ≥ 85	SBP/ DBP ≥ 140/ ≥ 90
BP (P)	-	SBP /DBP ≥90th P	SBP≥ 90th P	SBP> 90th P	-	
TG (mg/dL)	≥ 150	≥ 136	≥ 110	≥ 100	≥ 130	≥ 177
HDL (mg/dL)	< 40	< 35	≥ 40	< 50	≥ 39	< 38.67
Insulin (P)	-				Insulin top quartile in nondiabetics	≥ 75th P
Definition	obesity plus 2 or more	3 or more	3 or more	3 or more	IR, Hyperglycemia, or known DM plus 2	IR or hyperinsulinemia plus 2 or more

NCEP-ATP III: National Cholesterol Education Program's Adult Treatment Panel III; IDF: International Diabetes Federation; WC: Waist circumference; FBG: fasting blood glucose; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MetS: metabolic syndrome; DBP: diastolic blood pressure; SBP: systolic blood pressure. P: percentile; IR: insulin resistance; DM: diabetes melitus.

2-3. Hematological and biochemical measurements

All participants underwent routine blood tests including fasting blood glucose, serum lipid profile, and serum hs-CRP. Blood samples were taken after 12 hours of overnight fasting. Biochemical tests were performed with enzymatic methods using the commercial kits (Pars Azmoon Teb, Tehran, Iran) and high sensitivity C-reactive protein levels were measured by

commercial kits (Bioscience, Germany). The high sensitivity C-reactive protein was measured quantitatively using particle enhanced turbidimetric assay. Blood parameters were measured using the Sysmax device (Sysmax LLC, Arizona, USA) (17).

2-4. Data analysis

Statistical analyses were performed using the SPSS (SPSS, Chicago, IL). Medians ($Quartile_3$-$Quartile_1$) and means ± standard deviation (SD) were considered for non-normal and normal data, respectively. Kolmogorov-Smirnov test was applied for the normality test. Mann-Whitney U test was used to compare the non-normal data. Kolmogorov-Smirnov test and Analysis of variance (ANOVA) were also used for the comparison of data with normal distribution. Estimation of correlation between quantitative and qualitative variables was done via Pearson and Spearman rho tests, respectively. Point bi-serial correlation test was performed for correlation estimation between quantitative and qualitative variables.

3- RESULTS

MetS was determined using the IDF criteria in 988 schoolgirls. Mean age of the participants was 14.56±1.53 years (range 12 to 18). The prevalence of MetS among this population was estimated as 1.2% using the adopted IDF criteria for pediatrics.

Anthropometric data are shown in **Table 2**.

Table-2: Anthropometric measures in participants with or without metabolic syndrome

Parameters	MetS*	Non-MetS*	p-value**
Age (years)	13.75 ± 0.58	14.57 ± 0.49	0.042
Height (cm)	161.75 ± 1.64	157.59 ± 0.198	0.019
Weight (cm)	78.25 ± 4.33	52.58 ± 0.374	0.001
Neck circumference (cm)	34.42 ± 0.557	31.07 ± 0.075	0.001
Hip circumference (cm)	108.83 ± 2.87	91.57 ± 0.291	0.001

* means ± standard deviation.

**Comparison of two groups was done by Kolmogorov-Smirnov test.

All parameters were significantly different between the groups. As expected, weight in the MetS group was higher than in the non-MetS group with statistically significant differences. Neck circumference (NC) in subjects with MetS was significantly higher than that in healthy subjects (P=0.001). Moreover, hip circumference (HP) in subjects with and without MetS was 108.83±2.87 and 91.57±0.291, respectively.

The RDW values were compared for all parameters of IDF definition in MetS and non-MetS cases. RDW values ranged from 7.9% to 22.8% with a mean of 12.94±1.26 for all participants, while this measure in individuals with MetS was 14.45±0.75 which was significantly greater than that for the non-MetS participants with 12.91±0.05 (P=0.019). We categorized our participants into two groups by the use of RDW 14%, which was found to predict MetS in Caucasian adults (18); in subjects with RDW values <14%, MetS prevalence was estimated to be 0.9% in comparison to 7.5% in subjects with RDW≥14%. Among all components of MetS-based IDF definition, RDW values were statistically significant for the waist circumference and FBG (**Table 3**).

Table-3: RDW values in components of IDF criteria in two groups.

Variables	Metabolic syndrome status	RDW means ± SD	p-value
High WC (cm)	Non-MetS	12.9 ± 1.26	0.017
	MetS	13.17 ± 1.23	
High FBG (mg/dL)	Non-MetS	12.94 ± 1.26	0.038
	MetS	12.76 ± 1.21	
High SBP (mmHg)	Non-MetS	12.93 ± 1.24	0.444
	MetS	13.55 ± 2.29	
High DBP (mmHg)	Non-MetS	12.94 ± 1.26	0.659
	MetS	12.62 ± .74	
High TG (mg/dL)	Non-MetS	12.92 ± 1.24	0.287
	MetS	13.01 ± 1.57	
HDL (mg/dL)	Non-MetS	12.96 ± 1.34	0.926
	MetS	12.91 ± 1.07	
MetS based IDF	Non-MetS	12.91 ± 0.05	0.019
	MetS	14.45 ± 0.75	

Means ± standard deviation. Comparison of two groups was done by Kolmogorov-Smirnov test. WC: Waist circumference, FBG: fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglyceride, HDL: high density lipoprotein.

In subjects with WC that met the criteria, the mean RDW (13.17±1.23) was significantly higher than that in non-MetS individuals (12.9±1.26). However, RDW in FBG criterion, showed lower levels in subjects with MetS compared to that in Non-MetS participants (P=0.038). Using the hypertension criteria, only for systolic blood pressure did we observe that the RDW mean was higher in MetS cases, but this difference was not significant (P=0.444). Also in diastolic blood pressure (DBP) no significant differences were found between RDW means, while DBP means showed the lower values in MetS cases. Triglyceride values and HDL, however, showed higher (13.01±1.57 vs. 12.92±1.24 (P=0.287)) and lower (12.91±1.07 vs. 12.96±1.34 (P=0.926)) values of RDW means in subjects with MetS, respectively; but these differences were not significant.

The associations between RDW and anthropometrics such as weight (r=0.033 (P=0.414)), NC (r=0.058 (P=0.141)) and HP (r=0.016 (P=0.692)) were not statistically significant even for waist circumference (WC). The associations between RDW and each one of IDF criteria were also assessed to determine the correlation between MetS and RDW. Only obesity was shown to be significantly related to RDW (r=0.097 (P=0.016)), and FBG was also inversely correlated with RDW (r=-0.085 (P=0.037)). The results regarding the association between IDF metabolic syndrome definition and RDW are shown in **Table 4**.

ROC analysis showed that the RDW specificity and sensitivity for MetS based IDF criteria were 48.01% and 77.78%, respectively. Area under curve (95% CI) of RDW for MetS was 0.588 (0.380-0.796). In spite of acceptable sensitivity, low specificity of RDW for MetS made it not to be a good marker for diagnosis of MetS in this population or age group. The receiver operating curve (ROC) is illustrated in **Fig. 1**.

Table-4: Correlation between RDW and MetS components

Components of MetS						MetS based IDF criteria
WC	FBG	TG	SBP	DBP	HDL	
0.097 (.016)	-0.085 (.037)	-0.043 (.287)	0.031 (.445)	-0.018 (.659)	0.004 (.928)	0.076 (.043)

Association was estimated by point- biserial correlation test and it was reported by r (p-value). WC: Waist circumference, FBG: fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglyceride, HDL: high density lipoprotein.

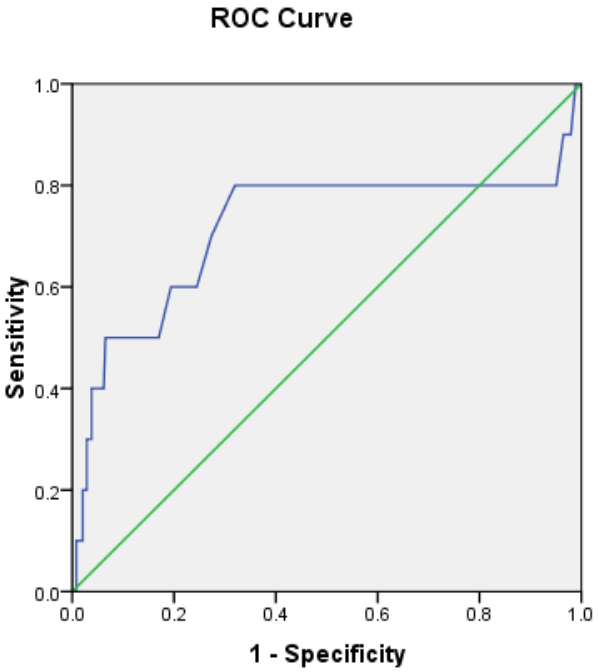

Fig. 1: ROC of RDW on MetS (IDF criteria)

4- DISCUSSION

In the present study, we aimed to investigate the association between RDW and metabolic syndrome (MetS), in order to determine the susceptibility of RDW for MetS diagnosis in children and adolescents. RDW is introduced as a new potential marker related to chronic inflammation in cardiac events (7, 12, 19-23). It's being inexpensive and easy to access by cell blood count (CBC), have made it an interesting marker for detection of chronic inflammatory processes; but its sensitivity and specificity for these processes has not been clearly proved, yet. Such processes play an important role in the development and progression of MetS (24); therefore, RDW can be a potential marker for MetS, as well. However, its relation with MetS is unclear. Our findings show a positive association between MetS and RDW. Among MetS components, only WC and FBG significantly associated with RDW; and FBG and RDW had an inverse correlation. In this study, no significant association was found between RDW and some anthropometric indices including weight, WC, NC, and HP. In addition, the association between hypertension parameters (i. e. SBP and DBP) and RDW were not statistically significant.

MetS is a complicated condition that involves a variety of risk factors such as genetic and environmental factors. This pathophysiological status can increase the susceptibility to cardiovascular diseases (CVDs) and type 2 diabetes (25, 26). Insulin resistance and adiposity are the main reasons to increase the prevalence of MetS. Therefore, elevated fasting blood glucose and hyperglycemia may play an important role in changing the mechanical properties of the erythrocytes, reduction of survival rate, and production of non-homogenous RBCs (27, 28). Abnormalities in metabolic and inflammatory markers have been observed in MetS patients. Altered hemorheological properties have been associated with obesity and can be involved in RDW increasing mechanisms (29). Increases in the value of RDW has been reported in some clinical states including arterial hypertension (30), diabetes mellitus (31), overweight (22), and MetS (8, 11, 32-34). In line with the present study, Vaya et al., demonstrated an independent association between RDW and MetS, while central obesity showed the strongest association (35); and inverse associations between FBG and RDW were observed in both studies. The negative correlation between RDW and FBG has been also reported by Yan et al (33). These observations may be attributed to different mechanisms from hyperinsulinemia which affect red blood cell membrane in metabolic diseases (35, 36).

According to the findings of the present study, in subjects with RDW ≥ 14%, the prevalence of MetS was almost seven times more than that in subjects with RDW < 14%. This finding is confirmed by a cross-sectional study in the Ibermutuamur Cardiovascular Risk Assessment (ICARIA) plan and prospective research in Tel Aviv Prospective Angiographic Survey (TAPAS) (18, 37); but more research is needed to confirm the applicability of this cutoff in children and adolescents.

In this study, the RDW levels in MetS were significantly higher in comparison to the healthy cases. It seems that the increased inflammation can be a cause of the association between RDW and MetS in which the pro-inflammatory cytokines inhibit maturation of EPO-induced erythrocyte maturation and affect the RDW levels (9, 20).

In contrast to Laufer Perl et al.'s research, the present study has observed no significant association between RDW and hypertension in spite of the increasing RDW in cases with high SBP; this difference in findings may be attributed to different populations or prevalence of MetS, and/or to the number of participants (18).

Oxidative stress and elevated inflammation in obese individuals with MetS have been suggested as possible mechanisms of susceptibility to cardiovascular events (38-40). Our findings showed no association between higher anthropometrics such as weight, WC, NC, and HP; but point-biserial correlation test showed that there is a significant association between RDW and ordinal WC in MetS; this may reveal that not only obesity, but perhaps obesity related inflammation, atherosclerosis, and systemic inflammation can be the key factors in the association between MetS and adverse cardiac manifestations (41). Therefore, RBC maturation defect results in the inflammatory state, and may lead to anisocytosis which reflects in higher RDW in MetS (10, 21). Inflammation is associated with impaired erythropoiesis and it has been observed that some inflammatory cytokines such as TNF-α, IL-1β, and IL-6 affect the erythropoiesis process through the signal desensitization of bone marrow erythroid progenitors. Therefore, RBC maturation is impaired, and anisocytosis occurs.

There is an important correlation between elevated RDW and subclinical atherosclerosis signs such as increased intimal-medial thickness and carotid plaques (42). In this study also, some anthropometric indexes that represent central obesity measure were found to have no significant correlation with RDW; but in MetS condition, central obesity index (WC) showed a positive association with the increased RDW. These findings may tell us that mere consideration of obesity is not enough, and perhaps the subclinical inflammation associated with obesity must receive even more attention.

4-1. Limitations of the study

It should be noted that the study population is only composed of schoolgirls who cannot be representative of the general population. Another limitation of the present study is that serum levels of inflammatory and biochemical markers which can affect RDW, were not measured.

5- CONCLUSION

In general, we found that an elevated RDW was associated with MetS in adolescent schoolgirls; however, our findings cannot confirm the susceptibility of predicting MetS through RDW, in spite of its being cost effective and easily accessible. The low specificity of it for MetS made it unusable in this studied population. Nevertheless, mechanisms that are involved in increasing the RDW values in MetS condition are unclear and further studies are required for determining them.

6- COMPETING INTERESTS

None.

7- FUNDING

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8- ABBREVIATION

Analysis of variance: ANOVA

Area under curve: AUC

Body mass index: BMI

Cardiovascular disease: CVD

Cell blood count: CBC

Coronary artery disease: CAD

Erythropoietin: EPO

Fasting blood glucose: FBG

High density lipoprotein cholesterol: HDL-C

High-sensitivity C-reactive-protein: hsCRP

Hip circumference: HP

Interleukin: IL

International diabetes federation: IDF

Mean corpuscular volume: MCV

Metabolic syndrome: MetS

Neck circumference: NC

Receiver operating characteristic: ROC

Red blood cell distribution width: RDW

Standard deviation: SD

Systolic and diastolic blood pressures: SBP or DBP

Total cholesterol: TC

Triglyceride: TG

Tumor necrosis factor- α: TNF-α

Waist Circumference: WC

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17425

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