Elevated red blood cell distribution width in healthy smokers

Sigara içen sağlıklı bireylerde artmış kırmızı kan hücre dağılım aralığı

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ABSTRACT

Objectives: Red blood cell distribution width (RDW) has been reported to be a marker of morbidity and mortality for some cardiovascular and pulmonary diseases. We aimed to evaluate RDW values in otherwise healthy smokers.

Study design: Two hundred and twenty consecutive subjects with current smoking and 230 age- and gender-matched healthy subjects without smoking history were enrolled. Number of cigarettes smoked per day and duration of smoking, evaluated as pack years, were recorded. Complete blood count, high-sensitivity C-reactive protein (hs-CRP) levels and lipid profile were analyzed in all study participants.

Results: The mean RDW values were higher in smokers than in nonsmokers (13.9±1.2 *vs.* 13.1±0.8, p<0.0001). The mean leukocyte count, mean platelet volume and hs-CRP levels were also significantly greater in smokers when compared to nonsmokers (8440±1.750 *vs.* 7090±1550, p<0.0001; 8.7±0.8 fL *vs.* 8.3±0.6 fL, p<0.0001; 2.42±0.53 mg/L *vs.* 1.46±0.52 mg/L, p<0.0001, respectively). Significant positive correlations between RDW and number of cigarettes smoked per day and between RDW and duration of smoking were identified (r=0.565 and r=0.305, respectively).

Conclusion: Elevated RDW is associated with cigarette smoking and may be a useful indicator of inflammatory activity in smokers.

ÖZET

Amaç: Kırmızı kan hücreleri dağılım genişliğinin (KHDG) bazı kardiyovasküler ve pulmoner hastalıklarda morbidite ve mortalite için önemli bir risk faktörü olduğu bildirilmiştir. Biz bu çalışmada sigara içen sağlıklı bireylerde KHDG değerlerini araştırmayı hedefledik.

Çalışma planı: Sigara kullanmakta olan 220 sağlıklı birey ile yaş ve cinsiyet uyumlu daha önce sigara kullanım öyküsü olmayan 230 sağlıklı birey çalışmaya alındı. Günlük içilen sigara sayısı, paket-yıl olarak hesaplanan sigara kullanım süresi kaydedildi. Tüm hastalarda tam kan sayımı, yüksek duyarlıklı C-reaktif protein (hs-CRP) ve lipit profilleri ölçümleri yapıldı.

Bulgular: Ortalama KHDG değerleri sigara içenlerde içmeyenlere göre daha yüksekti (13.9±1.2 ve 13.1±0.8, p<0.0001). Ortalama beyaz küre sayısı, ortalama trombosit hacmi ve hs-CRP seviyeleri de sigara kullananlarda kullanmayanlara göre daha yüksekti (sırasıyla, 8440±1.750 ve 7090±1550, p<0.0001; 8.7±0.8 fL ve 8.3±0.6 fL, p<0.0001; 2.42±0.53 mg/L ve 1.46±0.52 mg/L, p<0.0001). Günlük tüketilen sigara sayısı ve sigara kullanım süresi ile KHDG arasında anlamlı pozitif bir ilişki saptandı (sırasıyla, r=0.565 ve r=0.305).

Sonuç: Artmış KHDG sigara kullanımı ile ilişkilidir ve sigara içenlerde enflamatuvar aktivitenin bir belirteci olabilir.

Cigarette smoking is an important public health problem and a major cause of morbidity and mortality.[1] Numerous epidemiologic studies strongly support the assertion that cigarette smoking in both men and women increases the incidence of chronic obstructive pulmonary disease, cardiovascular disease and cancer.[2] The World Health Organization has proposed that smoking is the single most important preventable health risk in the world.[3] Despite the warnings of health hazards of cigarette smoking, the prevalence of smoking continues to be remain high in most countries,[4] thereby remaining a major public health concern.

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Red blood cell distribution width (RDW) is a measurement of the variability in size of circulating erythrocytes. It is an objective measure of the heterogeneity in red blood cell size (coefficient of variability of red blood cell volume) obtained from the red blood cell size distribution curves and is routinely reported as part of a standard complete blood count.[5] In clinical practice, RDW is generally used for the differential diagnosis of anemia.[6] Recently, however, higher RDW was found to be a strong and independent predictor of increased risk of mortality and adverse cardiovascular outcomes in patients with obstructive sleep apnea, pulmonary hypertension, acute pulmonary embolism, community-acquired pneumonia, stable angina, acute myocardial infarction, heart failure, peripheral arterial disease, stroke and older age.[7-16] The association between adverse events and RDW in the various reported clinical settings generally appears to be independent of any association between RDW and anemia. In addition, clinical and experimental studies have noted that systemic markers of inflammation are elevated in smokers.[17]

In the present study, we aimed to assess RDW levels in otherwise healthy smokers and healthy volunteers. Smoking characteristics such as quantity consumed and duration of smoking were included in investigating the relationship between smoking and RDW.

PATIENTS AND METHODS

Two hundred and twenty consecutive subjects with current smoking and 230 age- and gender-matched healthy subjects with no history of smoking were included in this cross-sectional study. The study population was composed of individuals admitted to our clinic for general health screening tests. The study was approved by the local ethics committee and all voluntary participants gave written informed consent before participating in the study.

Smoking status information was obtained by a general questionnaire. Current smokers were defined as individuals who smoked ≥1 cigarette per day regularly for at least one year. Non-smokers were defined as those who had never smoked. Smoking characteristics such as the number of cigarettes smoked daily and the number of pack years of smoking, which represents a combined measure of dose and duration of smoking, were also elicited. The number of pack years of smoking was calculated by multiplying the number of packs smoked per day (1 pack contains 20 cigarettes) by the number of years over which time that amount was smoked.

Abbreviations:

BMI	*Body mass index*
CBC	*Complete blood cell count*
FEV1	*Forced expiratory volume in 1 second*
FVC	*Forced vital capacity*
hs-CRP	*High-sensitive C-reactive protein*
LV	*Left ventricular*
MPV	*Mean platelet volume*
RBC	*Red blood cell*
RDW	*Red blood cell distribution width*
sPAP	*Systolic pulmonary artery pressures*
WBC	*White blood cell*

Baseline clinical characteristics including age, gender, body mass index (BMI) and habitual exercise were recorded and a complete physical examination was performed. BMI was calculated as weight in kilograms divided by the square of height in meters. Habitual exercise was defined as (1) mild to moderate aerobic exercise, (2) with a frequency of at least once a week and (3) for 30 min or more per session.

A spirometry test was performed using a handheld spirometer (ZAN 100, ZAN, Messgeraete Gmbh, Germany) in efforts to exclude individuals with confounding conditions, such as chronic lung diseases from the study. After subjects were trained in the forced vital capacity (FVC) maneuver, their FVC, forced expiratory volume in 1 second (FEV1), and ratio of FEV1 to FVC (FEV1/FVC) were measured at least 3 times with the subject in seated position wearing nose clips. The largest FVC and FEV1 from among all acceptable spirograms were selected and expressed as percent predicted of normal.

All subjects underwent two-dimensional and pulsed- and tissue-Doppler echocardiographic evaluation to exclude additional confounding factors, such as heart failure, pulmonary hypertension and valvular diseases. Measurements of left ventricular (LV) internal dimensions, wall thicknesses and of left atrium dimension, peak systolic pulmonary artery pressures (sPAP) pulsed- and tissue-Doppler parameters were made according to the recommendations of the American Society of Echocardiography.[18] The Pulsed Doppler mitral inflow velocities were obtained from the apical four-chamber view with the sample volume placed just below the mitral leaflet tips and peak transmitral flow velocity in early diastole (E), late diastole (A) and E/A ratio were measured. Tissue Doppler imaging of the mitral annulus was obtained

by placing sample volume at the lateral corner of the mitral annulus and peak early diastolic (Em), peak late diastolic (Am) myocardial velocities, E/Em and Em/Am ratios were measured. Peak sPAP was calculated by using the maximal velocity of tricuspid regurgitation on echocardiography. The LV mass index was calculated by the method described by Devereux and Reichek.[19]

Venous blood samples were collected from an antecubital vein in the morning between 08.00 and 10.00 AM, after an overnight fast, into vacuum tubes containing EDTA. Subjects were required to stop smoking for at least 45 minutes to 1 hour before blood collection. Samples were immediately processed for the determination of RDW, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean platelet volume (MPV), white blood cell (WBC), red blood cell (RBC) and platelet count using Beckman Coulter LH 750 hematology analyzer (Beckman-Coulter, Miami, FL, USA). RDW was calculated from the coefficient of variability of the red blood cell volume distribution. The reference range for RDW in the laboratory of our hospital was 11.5-14.5%. Fasting glucose, serum creatinine, total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured by standard techniques after centrifugation of blood samples and

Table 1. Baseline characteristics, spirometric and echocardiographic parameters of the study population

	Smokers (n=220)			Non-smokers (n=230)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age, years			40.5±11.1			40.4±10.9	0.92
Gender, female %	112	50.9		116	50.4		0.92
BMI (kg/m^2)			25.4±2.3			25.8±2.5	0.16
Habitual exercise (n, %)	158	71.8		175	76.1		0.3
FVC (%pred)			96.3±5.3			97.0±5.8	0.19
FEV_1 (%pred)			91.8±4.4			92.3±5.4	0.22
FEV_1/FVC (%)			95.1±3.2			95.2±2.3	0.73
Ejection fraction (%)			61.2±5.9			61.8±6.7	0.31
LVEDD (mm)			47.1±3.3			46.7±3.1	0.16
LVESD (mm)			31.9±4.5			31.3±3.1	0.09
IVST (mm)			9.5±0.76			9.6±0.8	0.19
PWT (mm)			9.3±0.7			9.4±0.6	0.15
Left atrium (mm)			32.1±3.1			31.6±3.0	0.79
LVMI (kg/m^2)			110.7±13.3			108.8±17.1	0.19
sPAP (mmHg)			22.1±2.0			21.8±1.9	0.09
E (cm/s)			72±17			75±20	0.1
A (cm/s)			63±19			60±17	0.06
E_m (cm/s)			11.4±2.5			11.9±2.2	0.07
A_m (cm/s)			9.3±2.3			8.9±2.2	0.09
E/A			1.20±0.43			1.26±0.45	0.2
E/E_m			6.4±2.5			6.3±2.1	0.47
E_m/A_m			1.38±0.58			1.47±0.53	0.07
Number of cigarettes/day			18.8±9.7			–	**<0.0001**
Packyears			20±16			–	**<0.0001**

SD: Standard deviation; A: Peak late mitral velocity; A_m: Peak late mitral annular velocity; BMI: Body mass index; E: Peak early mitral velocity; E_m: Peak early mitral annular velocity; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; IVST: Interventricular septal thickness; LVMI: Left ventricular mass index; sPAP: Peak systolic pulmonary artery pressure; PWT: Left ventricular posterior wall thickness.

expressed as milligrams per deciliter. High-sensitive C-reactive protein (hs-CRP) levels were calculated by the nephelometric method (Behring Nephelometer Analyzer, Germany) and expressed as milligrams per liter.

Exclusion criteria were any of the following: anemia, recent transfusion within the past 3 months, obesity, chronic obstructive pulmonary disease, asthma, systemic or pulmonary hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, systolic or diastolic heart failure, arrhythmia, renal insufficiency, cancer, peripheral arterial disease, thyroid disorders, pregnancy, chronic liver disease, inflammatory and autoimmune disorders, alcohol consumption and any medication use.

Statistical analysis

All statistical analyses were made using SPSS version 17.0 (SPSS, Chicago, IL). The normality of the data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using chi-square test or Fisher's exact test whenever appropriate and reported as numbers and percentages. Continuous variables were compared using Student's t-test and reported as means and standard deviations. Correlations between RDW and smoking amount per day and duration of smoking were analyzed with the Pearson's correlation method. All *p* values were two-tailed and a level of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics, spirometric and echocardiographic parameters of the study population are presented in Table 1. There were no statistically significant differences between smokers and non-smokers with regard to age, sex, BMI and habitual exercise. Two-dimensional, pulsed- and tissue-Doppler echocardiographic parameters as well as results of spirometry tests were also not different between groups. Results of hematological testing and plasma biochemical analysis are presented in Table 2. The mean RDW values were significantly higher in smokers as compared to non-smokers (13.9%±1.2% *vs.* 13.1%±0.8%, $p<0.0001$) (Figure 1). Total leukocyte counts were within the normal range in both groups, but the mean total leukocyte count was significantly

Table 2. Results of hematologic testing and plasma biochemical analysis of the study population

	Smokers (n=220)	Non-smokers (n=230)
	Mean±SD	Mean±SD
WBC count ($10^3/\mu L$)	8.44±1.75	7.09±1.55
RBC count ($10^6/\mu L$)	4.92±0.43	4.87±0.41
Platelet count ($10^3/\mu L$)	263±47	271±58
Hemoglobin (g/dL)	14.6±1.6	14.4±1.3
Hematocrit (%)	42.3±4.3	41.9±3.7
MCV (fL)	85.9±7.3	86±4
MPV (fL)	8.7±0.8	8.3±0.6
RDW (%)	13.9±1.2	13.1±0.8
Fasting glucose (mg/dL)	83±7	81±8
Creatinine (mg/dL)	0.82±0.13	0.80±0.16
Total cholesterol (mg/dL)	191.2±34.3	186.1±30.9
Trigliserides (mg/dL)	131.8±57.4	124.2±58.3
HDL-cholesterol (mg/dL)	45.1±8.9	46.2±10.5
LDL-cholesterol (mg/dL)	113.1±31.9	109.1±26.9
Hs-CRP (mg/dL)	2.42±0.53	1.46±0.52

SD: Standard deviation; HDL: High-density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; LDL: Low-density lipoprotein; MCV: Mean corpuscular volume; MPV: Mean platelet volume; RBC: Red blood cell; RDW: Red bood cell distribution width; WBC: White blood cell.

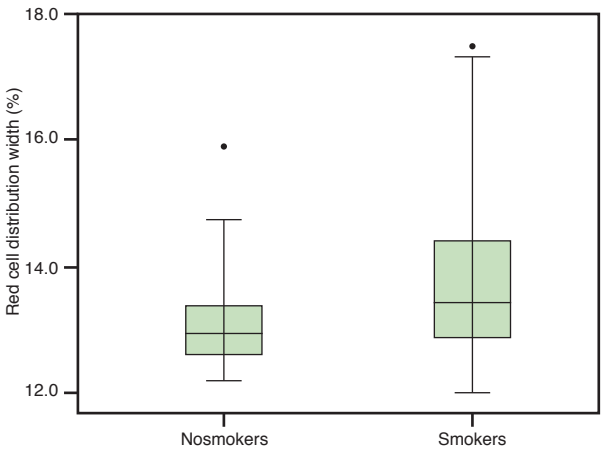

Figure 1. Red blood cell distribution width (RDW) values in nonsmokers and smokers.

greater in smokers than in non-smokers (8440±1750 *vs.* 7090±1550, p<0.0001). MPV values trended higher in smokers as compared with non-smokers (8.7±0.8 fL *vs.* 8.3±0.6 fL, p<0001). In addition, the levels of hs-CRP in smokers were significantly higher than those in nonsmokers (2.42±0.53 mg/L *vs.* 1.46±0.52 mg/L, p<0.0001). Hemoglobin, hematocrit, mean corpuscular volume, RBC and platelet count, serum glucose, creatinine and lipid profile did not differ between smokers and non-smokers.

We also examined smokers by numbers of cigarettes smoked per day and duration of smoking, evaluated as pack years, to determine whether there existed a relationship between RDW and the amount of smoking. As presented in Figure 2, RDW had a moderate and significant degree of correlation with amount of smoking and a mild but still significant correlation with duration of smoking (r=0.565, p<0.0001; r=0.305, p<0.0001, respectively).

DISCUSSION

The important findings of our study include the following: (1) RDW values were significantly higher in smokers compared to non-smokers, (2) a moderate degree of a positive correlation existed between increasing RDW and smoking amount, whereas a weak but significant correlation existed for duration of smoking, (3) smoking is associated with an increase in the WBC count and hs-CRP levels.

RDW is a widely available and inexpensive test routinely performed as part of the complete blood cell count (CBC) and is equivalent to anisocytosis.[5] It is widely used as a guide for the differential diagnosis of anemia, with high values found in increased RBC destruction (hemolytic anemias) or defective erythropoiesis (e.g., nutritional deficiencies of iron, folic acid, vitamin B12) or blood transfusion.[20,21] It has been shown that RDW are elevated in cardiovascular and pulmonary diseases.[7-14] Increased RDW has also been noted in a variety of noncardiovascular disease states including pregnancy,[22] liver disease,[23] inflammatory bowel disease,[24] occult colon cancer[25] and neoplastic metastases to the bone marrow.[26] More recently, population studies have identified RDW as a predictor of all-cause and cardiac mortality.[11,13,16] Presently the mechanistic relationship between RDW

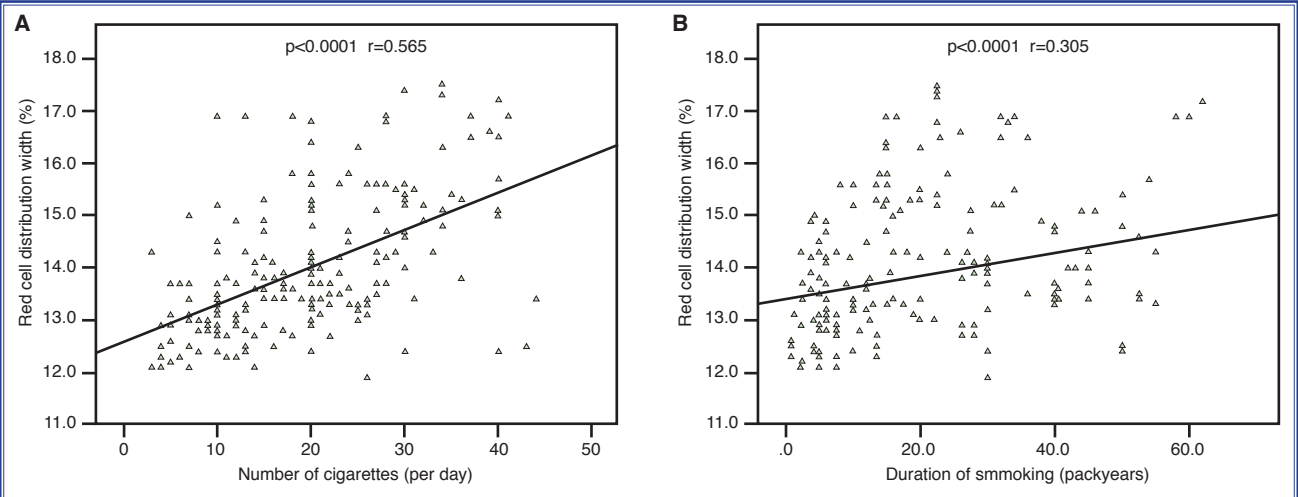

Figure 2. Correlations between RDW and number of cigarettes per day **(A)** and duration of smoking **(B)** in smokers.

and morbidity or mortality remains unknown and the relationship is simply an association.

RDW values were found to be higher among smokers in the present study, from which the most common causes of an elevated RDW were excluded. Although the putative pathophysiologic mechanisms explaining RDW's association with smoking are yet to be elucidated, chronic subclinical inflammation appears to be the driving factor. hs-CRP levels, a well-established surrogate marker of inflammation, as well as numerous other inflammatory markers such as interleukin-6 and soluble tumor necrosis factor alpha, VCAM-1, ICAM-1 and E-selectin have been independently associated with smoking.[17] It has been also demonstrated that RDW values have been associated with inflammatory markers.[27] Thus, elevated RDW may also be a surrogate measure of the chronic inflammatory process in smokers, which results in ineffective erythropoiesis causing immature RBCs to enter the circulation and in turn results in heterogeneity in the size of RBCs causing anisocytosis. Exposure to greater oxidative stress may be yet another potential contributing pathophysiologic mechanism linking higher RDW with smoking. A relationship between smoking and higher oxidative stress has been established.[28] It has been shown that oxidized RBCs lose their flexibility owing to a loss of lipid asymmetry and cytoskeleton rearrangement, causing them to be more rigid and thus develop anisocytosis.[29] Adrenergic activation caused by smoking may also affect bone marrow response, thus resulting anisocytosis.[30]

Chronic cigarette smoking results in a decrease in platelet function while smoking cessation improves platelet function.[31,32] The platelet function can be evaluated easily by MPV which does not require advanced or expensive technology.[33] In the present study, we found elevated MPV values in smokers than those of controls and this finding is consistent with previous data.[34] Possible explanation for why smoking leads to increment in MPV may be related to chemicals such as nicotine and carbon monoxide in cigarette smoke, which increase platelet activity.

Several studies have indicated that cigarette smoking causes about a 20% to 25% increase in the peripheral blood leukocyte count.[35] The mechanism by which cigarette smoking induces changes in WBC count is not clear. However, a positive association between smoking and presence of higher WBC and hs-CRP levels may well reflect an acute or chronic inflammatory response induced by particulates of cigarette smoke.[36] Indeed, inflammatory stimulation to bronchial tract, which can lead to chronic bronchitis, may be related to increase in inflammatory indicators in blood.[37] In addition, alterations of immune function and glycoprotein from tobacco leaf may stimulate lymphocyte proliferation and differentiation.[38]

Lipid profile analysis in our study groups did not significantly correlate between different between groups and this finding is inconsistent with previous findings that showed higher serum levels of cholesterol and triglyceride concentrations and lower plasma concentrations of HDL-cholesterol in smokers.[39] This may be due to dietary differences between smokers and non-smokers in our study and exclusion of dyslipidemic subjects from the study.

Chronic cigarette smoking causes some alterations in diastolic myocardial function parameters in healthy young subjects as assessed by color tissue Doppler imaging.[40] RDW values tend to be higher in this group of patients with diastolic dysfunction and a normal ejection fraction.[41] Moreover, these patients had similar RDW levels similar to what is observed in systolic heart failure.[41] We, therefore, chose to exclude both systolic and diastolic heart failure subjects from the present study because of their confounding effects on RDW levels. Similar pulsed- and tissue-Doppler diastolic parameters observed between subjects with and without smoking in our study groups may be due to exclusion of these clinical entities.

The negative effects of cigarette smoking on lung function in the general population is well known.[42] However, we found similar spirometric parameters and peak systolic pulmonary artery pressure as assessed by echocardiography between smokers and nonsmokers. This may be seem to be conflicting at first. But possible explanations for these findings may include; the relatively younger population of our study, exclusion of patients with obesity, chronic obstructive pulmonary disease, asthma, pulmonary hypertension and those with a BMI over 30 kg/m^2.

Limitations

The present study was limited to smokers without a known disease in the community, and these findings cannot necessarily be generalized to those with other comorbidities and or the geriatric population. The

cross-sectional design of the study limits interpretation of the causal relationship between RDW, WBC, hs-CRP and smoking. Measurement of erythropoietin, reticulocyte count or markers for iron availability, proinflammatory cytokines and HbA1c were not available in our study. We also did not evaluate right ventricular function. Lastly, vitamin B12 and folate levels were not measured in this study, however severe vitamin B12 or folate deficiency in this study population is unlikely since subjects with macrocytosis were excluded from the study.

In conclusion, we found RDW values tended to increase in healthy smokers and found an association between RDW values and numbers of cigarettes/day and smoking pack years. Cigarette smoking may contribute to the initiation and progression of many pathophysiologic processes in otherwise healthy and clinically asymptomatic smokers. RDW, which is routinely measured with CBC in virtually every medically-evaluated patient, may be indicator of these silent processes in smokers. Large prospective studies are needed to validate the association between RDW and smoking.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Biological markers; blood flow velocity; C-reactive protein; coronary circulation; erythrocyte indices; inflammation; smoking, cigar.

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