

## Diagonal earlobe crease is associated with increased mean platelet volume

Diyagonal kulak memesi kırışması artmış ortalama trombosit hacmi ile ilişkilidir

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## Abstract

**Background:** Diagonal earlobe crease (DEL) is considered a sign of atherosclerosis. Platelets play an important role in the onset and subsequent complications of atherosclerotic lesions. Mean platelet volume (MPV) is an indicator of platelet activation. In this study, we aimed to evaluate MPV in DEL individuals.**Material and Methods:** Seventy-five patients with DEL (28F; mean age: 59±10 years) and 54 patients without DEL (23F; mean age: 56±11 years) were included in this study. Clinical and demographic characteristics, MPV, leukocyte counts, hemoglobin levels, platelet counts and plateletcrit levels were compared between the two groups.**Results:** Clinical and demographic characteristics were similar between the two groups. Hemoglobin levels (13.7±1.3 g/dL vs. 13.8±1.40 g/dL; p=0.782), leukocyte counts (7.01±1.57 x10<sup>3</sup>mm<sup>-3</sup> vs. 7.26±1.63 x10<sup>3</sup>mm<sup>-3</sup>; p=0.429), platelet counts (240±57 x10<sup>3</sup>mm<sup>-3</sup> vs. 246±59 x10<sup>3</sup>mm<sup>-3</sup>; p=0.617) and plateletcrit levels (0.207±0.048 % vs. 0.196±0.046%; p=0.258) were comparable between the two groups. MPV was significantly higher in the DEL group compared to non-DEL group (8.69±0.95 fL vs 7.96±0.75 fL; p<0.0001). Correlation analysis showed a significant but moderate correlation between DEL and MPV (p<0.0001; r = 0.356).**Conclusion:** MPV is elevated in patients with DEL. Considering the effects of platelets on atherosclerosis as well as their close relation to other risk factors, MPV may be an important predisposing factor for atherosclerosis in patients with DEL.**Keywords:** Diagonal earlobe crease, Platelet volume, Subclinical atherosclerosis.

## Öz.

**Giriş:** Diagonal Kulak Memesi Kırışıklığı (KMK), aterosklerozun bir işareti olarak kabul edilir. Trombositler aterosklerotik lezyonların başlamasında ve sonrasında oluşan komplikasyonlarda önemli rol oynarlar. Ortalama trombosit hacmi (OTH), trombosit aktivasyonunun bir göstergesidir. Bu çalışmada KMK'lı bireylerde OTH'nin değerlendirilmesi amaçlandı.**Materyal ve Metod:** Çalışmaya KMK olan 75 hasta (28K; ort. yaş: 59±10 yıl) ve KMK olmayan 54 hasta (23 K; yaş: 56±11 yıl) alındı. Klinik ve demografik özellikler, OTH, lökosit sayısı, hemoglobin düzeyi, trombosit sayısı ve plateletkrit düzeyi gruplar arasında karşılaştırıldı.**Bulgular:** Klinik ve demografik özellikler her iki grupta benzer bulundu. Hemoglobin (13,7±1,3 g/dL vs 13,8±1,40 g/dL; p=0,782), lökosit (7,01±1,57 x10<sup>3</sup>mm<sup>-3</sup> vs 7,26±1,63 x10<sup>3</sup>mm<sup>-3</sup>; p=0,429), trombosit (240±57 x10<sup>3</sup>mm<sup>-3</sup> vs 246±59 x10<sup>3</sup>mm<sup>-3</sup>; p=0,617) ve plateletkrit (0,207±0,048 % vs 0,196±0,046 %; p=0,258) değerleri arasında iki grup arasında istatistiksel olarak anlamlı fark saptanmadı. KMK olan grupta OTH; KMK olmayan gruba göre istatistiksel olarak anlamlı derecede daha yüksek bulundu (8,69±0,95 fL vs 7,96±0,75 fL; p<0,0001). Yapılan korelasyon analizinde KMK ile OTH arasında anlamlı ancak orta düzeyde bir ilişki saptandı (p<0,001; r = 0,356).**Sonuç:** KMK olan grupta OTH artmış olarak izlendi. Trombositlerin ateroskleroz üzerindeki etkileri ve diğer risk faktörleri ile yakın ilişkisi göz önüne alındığında, OTH, KMK'lı hastalarda ateroskleroz için önemli bir predispozan faktör olabilir.**Anahtar Kelimeler:** Kulak memesi kırışıklığı, Trombosit hacmi, Subklinik ateroskleroz.Sorumlu Yazar /  
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## Introduction

Diagonal earlobe crease (DEL) is defined as diagonal fold or wrinkle of the ear lobe skin, extending from the tragus towards the ear lobe. DEL can be seen in patients with coronary artery disease (CAD) (1). This condition was first reported by Frank in 1973 (2) and was recognized as a simple cutaneous marker to identify patients with CAD. In some studies, intima-media thickness of the carotid artery was shown to be increased in patients with DEL, and it has been suggested that DEL is closely related to atherosclerosis (3,4).

Platelets play an important role in the onset of atherosclerotic lesions and subsequent complications (5). Large platelets have higher metabolic and enzymatic potential for thrombosis compared to the small platelets, and they contain more dense granules (6). Mean platelet volume (MPV) is considered to be a marker of platelet activation, and platelet volume is suggested to be predictor of cardiovascular disease (7).

Both DEL and MPV are associated with subclinical atherosclerosis. Our literature review did not indicate any previous study investigating MPV in the individuals with DEL. The aim of the present study was to evaluate MPV in individuals with DEL.

## Materials and Methods

### Patient population

A cross-sectional study was undertaken at the Cardiology Department of Trabzon Kanuni Training and Research Hospital. Study subjects were consecutively selected among the patients referring to our outpatient clinics between July and August 2015. Patients with moderate to severe valvular disease including prosthetic valves, and patients with congenital heart disease, bacterial endocarditis, a hematological, oncological, or an inflammatory disorder; white blood cell (WBC) count  $>12000$  mm<sup>3</sup>; hemoglobin level  $<10$  g/dL; ejection fraction  $<40\%$ ; renal insufficiency; liver or thyroid dysfunction; thrombocytopenia or thrombocytosis; as well as those who had symptomatic vascular disease such as stroke, transient ischemia, coronary heart disease, congestive heart failure, or intermittent claudication, were excluded. After exclusion of patients who met above mentioned exclusion criteria, 129 patients [75 patients with DEL (28F, mean age  $59\pm 10$  years) and 54 patients without DEL (23F, mean age  $56\pm 11$  years)] were included in the study. Informed consent was obtained from each participant and the study was conducted in accordance with the Principles of Declaration of Helsinki. The study was approved by the local **Ethics Committee**.

History of hyperlipidemia (HL), arterial hypertension (HT), diabetes mellitus (DM), smoking and family history of coronary artery disease (CAD), noted down all patients. Patients with known hypertension history, antihyperten-

sive drug use history, the average measurement of systolic blood pressure  $\geq 140$  mmHg and / or diastolic blood pressure  $\geq 90$  mmHg at least twice from both arms, defined as hypertension. Patients with fasting blood glucose level of  $\geq 126$  mg/dl, history of DM and antidiabetic drug use were considered as type II DM. The patients who were on anti-hyperlipidemia therapy use and had a fasting total cholesterol level  $\geq 200$  mg/dl, a fasting low-density lipoprotein level  $\geq 160$  mg/dl, a fasting triglyceride level  $\geq 200$  mg/dl were considered as HL. History of CAD or sudden cardiac death in a first-degree relatives under the age of 55 years for men and 65 years for women were defined as family history of CAD.

### Definition of DEL

DEL is defined as diagonal fold or wrinkle on the ear lobe skin, extending from the tragus towards the ear lobe (figure 1). Patients with DEL in both ear lobes were included in the DEL group.

### Laboratory measurements

Blood samples were drawn in the morning, after 12 hours of fasting and 20 minutes of rest, into tripotassium-EDTA (ethylenediaminetetraacetic acid) based anticoagulated blood sampling tubes. The samples were stored at  $4^{\circ}\text{C}$  and assessed by Shenzhen Mindray Bio-Medical Electronics Co. Ltd, Shenzhen (CHINA) within 30 minute of sampling. Normal range of MPV was 6-10.8 fL (femtoliters).

### Statistical analysis

Data analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows 19 (SPSS Inc. Chicago, IL, USA). The continuous variables were described as mean $\pm$ SD or median (minimum–maximum), and the categorical variables were reported as frequency and percentage. Kolmogorov Smirnov test was used to evaluate normal distribution of numerical variables. Independent samples t test was used to compare normally distributed and Mann Whitney U test was used to compare non-normally distributed variables between the two groups. Quantitative data were analyzed using the Chi-square test. A correlation analysis was performed to assess the relationship between continuous variables and the analysis was interpreted using Spearman's Rank correlation coefficient. The confidence interval was at 95 % and p values of  $<0.05$  were considered statistically significant.

## Results

Clinical and demographic characteristics are shown in table 1, and hematological parameters are shown in table 2. Age, sex, HT, smoking, DM, family history for CAD, and HL were not statistically significantly different between the two groups.

**Table 1.** Clinical and demographic characteristics of subjects with and without DEL.

Variable	Without DEL (n=54)	DEL (n=75)	P
Age, years	56±11	59±10	0,126*
Female gender, n (%)	23 (42)	28 (37)	0,547**
Diabetes, n (%)	5 (9)	12 (16)	0,264**
Hypertension, n(%)	23 (42)	40 (53)	0,229**
Smoking, n (%)	10 (18)	13(17)	0,862**
Dyslipidemia, n (%)	4 (7)	9 (12)	0,393**
Family history of CAD	7 (13)	7(9)	0,513**

\*Independent Samples T test

\*\* Chi-square test

CAD, coronary artery disease

**Table 2.** Hematologic parameters of subjects with and without DEL.

Variable	Without DEL (n=54)	DEL (n=75)	P
MPV	7,96±0,75 7,93 (6,32-9,70)	8,69±0,95 8,60 (7,2-11,4)	< 0,0001 *
WBC x10 <sup>3</sup>	7,26±1,63	7,01±1,57	0,429 **
Hb	13,8±1,40	13,7±1,3	0,782 **
Plt x10 <sup>3</sup>	246±59	240±57	0,617 **
PCT	0,196±0,046	0,207±0,048	0,258 **

\*Independent Sample T test

\*\*Mann Whitney U test

Hb,Hemoglonin; MPV, mean platelet volume; PLT, platelet; PCT, platecrit; WBC, white blood cell

Hemoglobin levels (13.7±1.3 g/dL vs. 13.8±1.40 g/dL; p=0.782), leukocyte counts (7.01±1.57 x10<sup>3</sup>mm<sup>-3</sup> vs. 7.26±1.63 x10<sup>3</sup>mm<sup>-3</sup>; p=0.429), platelet counts (240±57 x10<sup>3</sup>mm<sup>-3</sup> vs. 246±59 x10<sup>3</sup>mm<sup>-3</sup>; p=0.617) and plateletcrit levels (0.207±0.048 % vs. 0.196±0.046 %; p=0.258) were not statistically different between two groups. MPV was significantly higher in the DEL group compared to the non-DEL group (8.69±0.95 fL vs. 7.96±0.75 fL; p<0.0001). Correlation analysis showed a significant but moderate correlation between DEL and MPV (p<0.0001; r = 0.356).

## Discussion

Although the clinical and demographic characteristics of the two groups were similar in our study, MPV was significantly higher in patients in the DEL group compared to the non-DEL group.

A correlation was previously demonstrated between DEL and atherosclerotic cardiovascular risk factors [8,10]. A

previous study also reported a correlation between DEL and carotid intima media thickness and epicardial fat thickness [11]. DEL was shown to be associated with vascular inflammation and oxidative stress [12], as well as CAVI, which is a subclinical marker of atherosclerosis (13). In a postmortem autopsy study of 520 patients, DEL was strongly associated with CAD in both men and women [14]. Although the association between DEL and increased ischemic heart disease has been demonstrated in several studies, the pathophysiological definition of this association is still controversial. It is assumed that the ear lobe and the myocardium share anatomical similarities, as both structures are supplied by the collateral circulation via the end arteries with the same genetic origin (15,16). The most direct pathophysiologic link between the earlobe crease and the risk of ischemic heart disease is derived from molecular biology studies investigating the earlobe collagen. Sapira described that earlobe collagen consists of peptide chains with a sequence similar to that

of the peptide chains found on the surface of macrophage scavenger receptors (17). He suggested that the ability to maintain both earlobe collagen and the macrophage receptor is reduced with aging or possibly when exposed to the other triggers. This is proposed to reduce macrophage activity, thereby decreasing the ability to phagocytose cholesterol. Theoretically, this could impair the "so-called" reverse cholesterol transport, decreasing the excretion of cholesterol into the bile, and consequently leading to the development of atherosclerosis (17). These factors play roles in the pathogenesis of increased incidence of ischemic heart disease in DEL, but the pathophysiology of coronary artery disease, which is common in patients with DEL, is not clearly explained.

MPV is an indicator of platelet activation, which is central to the pathophysiology of coronary heart disease [8,18]. MPV is one of the platelet function indices which reflects the platelet production rate and stimulation. Increased MPV values have been reported to be associated with

cardiovascular diseases [19,20]. MPV was also shown to increase in acute myocardial infarction, acute ischemic stroke, preeclampsia, and renal artery stenosis [21]. In addition, MPV was shown to be closely related to fasting glucose, DM, HT, HL, and cardiovascular risk factors [22-27]. In our study, the MPV, which is known to be associated with subclinical atherosclerosis, was found to be elevated in the DEL group. This finding suggests that increased MPV may be one of the pathophysiological mechanisms underlying the increase observed in the incidence of coronary artery disease among patients with DEL, as MPV increase reflects high platelet activity. Highly-active platelets have pronounced effects on the onset and progression of atherosclerosis. Therefore, MPV elevation in individuals with DEL may suggest that increased platelet activity plays a role in the pathogenesis and increased incidence of ischemic heart disease in DEL patients.

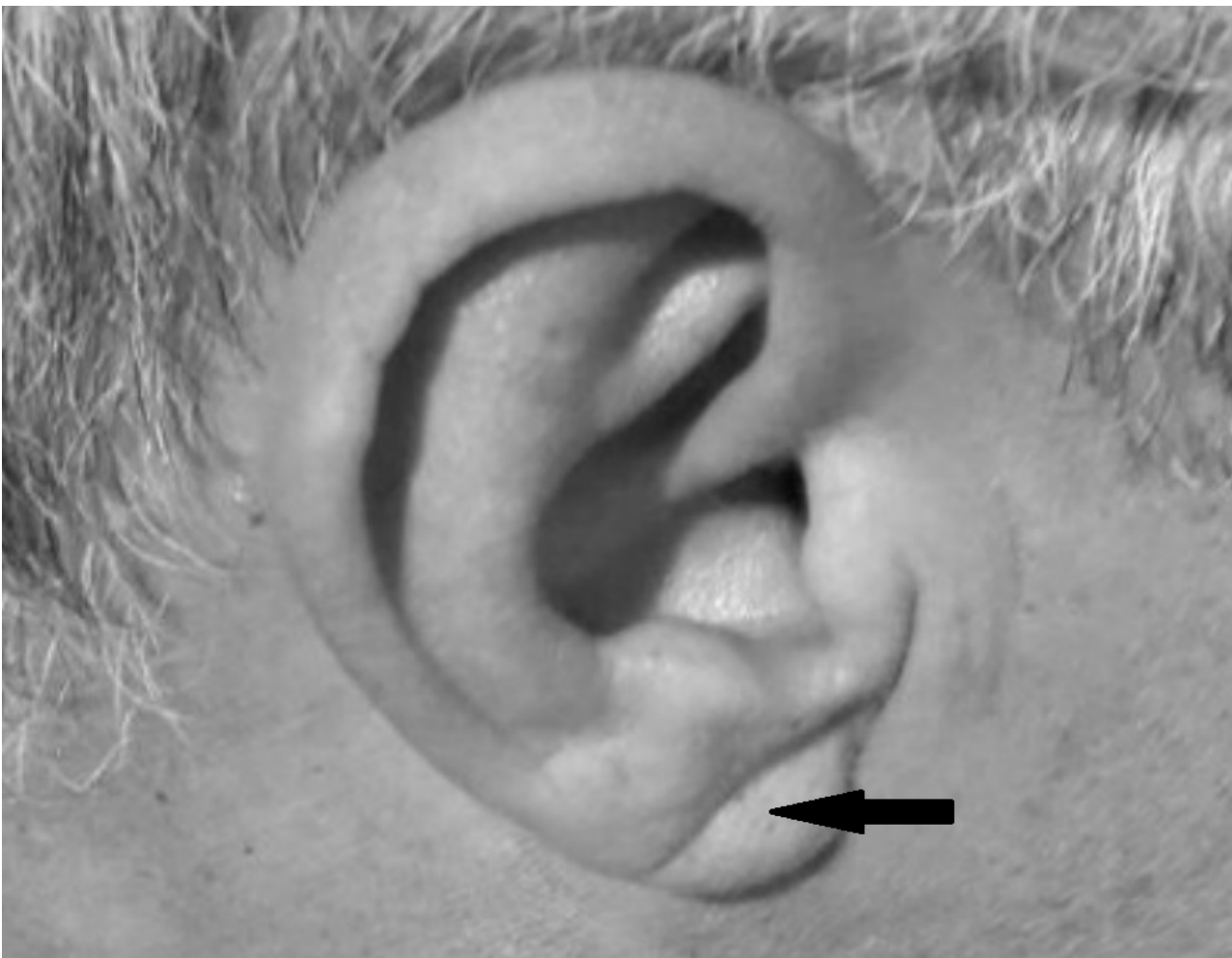


Figure 1. Arrow shows DEL. DEL; Diagonal Earlobe Crease

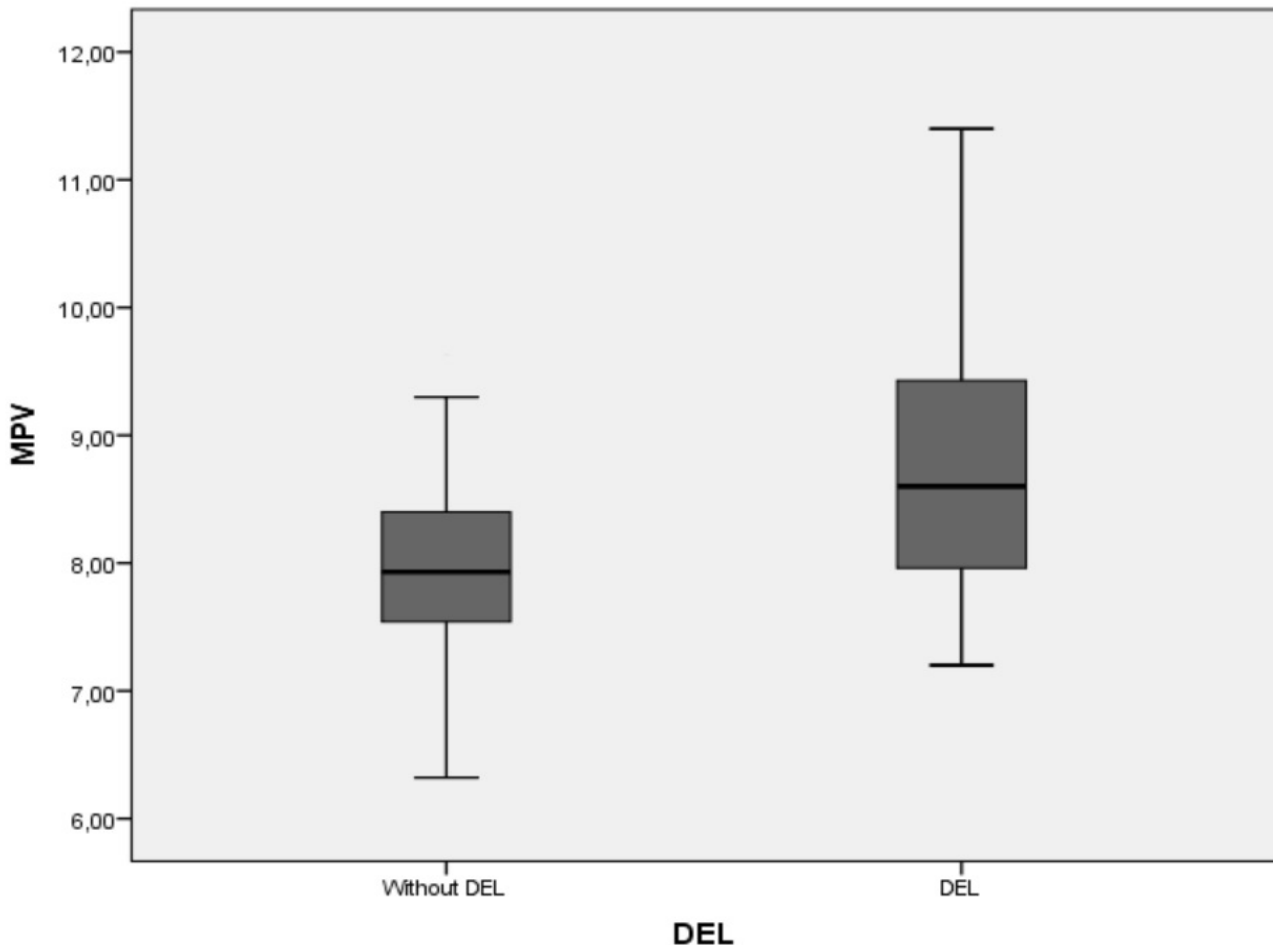


Figure 2. MPV levels DEL and without DEL subjects. DEL; Diagonal Earlobe Crease, MPV; Mean Platelet Volume

#### Study limitations:

Several limitations of this study should be addressed. First, the most important limitation of this study was the small number of patients. As the study population consisted of patients who presented to our clinic, we can speculate that it would not reflect the general population. Although we carefully assessed the patients for the presence of the cardiovascular disease, we did not use invasive methods such as coronary angiography. Thus, it is possible that our cohort might have included patients with undetected cardiovascular disease at study entry. In addition, although patients with leukocytosis were not included in the study, subclinical inflammatory status was not precisely excluded.

#### Conclusion

MPV levels are elevated in patients with DEL. Considering the effects of platelets on atherosclerosis as well as their close relation to other risk factors, MPV may be an important predisposing factor for atherosclerosis in patients with DEL.

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