ORIGINAL ARTICLE

Diagonal earlobe crease associated with increased epicardial adipose tissue and carotid intima media thickness in subjects free of clinical cardiovascular disease

Klinik olarak kardiovasküler hastalığı olmayan kişilerde diyagonal kulak memesi kıvrımı varlığı epikardiyal yağ dokusu ve karotis intima medya kalınlığında artış ile ilişkilidir

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ABSTRACT

Objective: Atherosclerotic coronary artery disease is a leading cause of death, worldwide. Diagonal earlobe crease (DELC) has been suggested as a simple, noninvasive marker of cardiovascular disease. Although epicardial adipose tissue (EAT) thickness and carotid intima media thickness (CIMT) are closely related to atherosclerosis, the relation between EAT, CIMT, and DELC had yet to be studied. The present objective was to analyze this association.

Methods: Subjects were apparently healthy individuals referred to the cardiology outpatient clinic. A total of 65 subjects with DELC and 65 age- and sex-matched controls without DELC were enrolled. EAT thickness and CIMT were measured and analyzed.

Results: Epicardial adipose tissue thickness was significantly higher in the DELC group (0.57±0.12 *vs.* 0.35±0.05; p<0.0001). CIMT was also significantly higher in DELC group (0.85±0.16 *vs.* 0.60±0.15; p<0.0001). Correlation analysis showed that CIMT was significantly correlated with EAT thickness (r: 0.594; p<0.0001). Linear regression analysis showed that presence of DELC was independently associated with CIMT and EAT thickness.

Conclusion: A significant and independent association between the presence of DELC and increased CIMT and EAT thickness was presently determined, for the first time, in subjects free of clinical cardiovascular disease.

ÖZET

Amaç: Aterosklerotik koroner arter hastalığı, tüm dünyada önde gelen ölüm nedenlerinden birisidir. Diyagonal kulak memesi kıvrımı (DKMK) kardiyovasküler hastalıkların basit, noninvaziv bir belirtecidir. Epikardiyal yağ dokusu kalınlığı (EYDK) ve karotis intima medya kalınlığının (KIMK) ateroskleroz ile ilişkisi oldukça iyi araştırılmış olmasına rağmen DKMK ile EYDK ve KIMK arasındaki ilişkiyi gösteren bir veri yoktur. Bu çalışmada biz bu ilişkiyi incelemeyi amaçladık.

Yöntemler: Çalışmaya dahil edilen olgular kardiyoloji kliniğine ayaktan tedavi için başvuran sağlıklı yetişkinler arasından seçildi. Diyagonal kulak memesi kıvrımı olan 65 olgu ile yaş-cinsiyet eşleştirilmiş ve DKMK olmayan 65 kontrol olgusu çalışmaya alındı. Tüm olgularda EYDK ve KIMK ölçüldü ve sonuçlar değerlendirildi.

Bulgular: Epikardiyal yağ dokusu kalınlığı DKMK grubunda anlamlı derecede daha fazla idi (0.57±0.12 ve 0.35±0.05; p<0.0001). Bunun yanında, KIMK da DKMK grubunda anlamlı derecede fazla idi (0.85±0.16 ve 0.60±0.15; p<0.0001). Karotis intima medya kalınlığı ile EYDK arasında anlamlı pozitif korelasyon saptandı (r=0.594; p<0.0001). Regresyon analizleri ile DKMK varlığının EYDK ve KIMK ile bağımsız olarak ilişkili olduğu saptandı.

Sonuç: Bu çalışma ile, literatürde ilk kez klinik olarak kardiyovasküler hastalığı olmayan olgularda DKMK ile EYDK ve KIMK arasında anlamlı, bağımsız bir ilişki olduğu gösterilmiştir.

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Diagonal earlobe crease (DELC) is defined as a fold or crease in the skin of the earlobe[1] (Figure 1). Since DELC was first described, various studies have demonstrated the relationship between it and coronary artery disease (CAD).[2–5]

Atherosclerosis is a chronic inflammatory disease that can affect the vast majority of the arterial tree. Furthermore, atherosclerotic changes of the carotid arteries are closely related to increased cardiovascular morbidity and mortality.[6] Carotid intima media thickness (CIMT) is an indication of atherosclerosis. Assessment of CIMT is a confirmed method of atherosclerosis progression assessment, and has been shown to be highly predictive of future cardiovascular events and death.[7,8]

Epicardial adipose tissue (EAT) is a visceral fat depot, present on the surface of the heart under the visceral layer of the pericardium. It is usually concentrated in the atrioventricular and interventricular grooves, and along the major branches of the coronary arteries, as well as, to a lesser extent, around the atria, over the free wall of the right ventricle, and over the apex of the left ventricle.[9] EAT is composed of adipocytes, and inflammatory and immune system cells.[10] In various studies, it has been shown to directly effect vasomotor function of coronary arteries via diffusion of bioactive molecules synthesized in EAT.[11,12] As cardiovascular disease is the most common cause of death in the world, and CAD is the most common cardiovascular disease, considerable effort has been put into investigating the precursors of CAD.[13] Thus, the present aim was to investigate the correlation of DELC with CIMT and EAT thickness in subjects free of clinical cardiovascular disease.

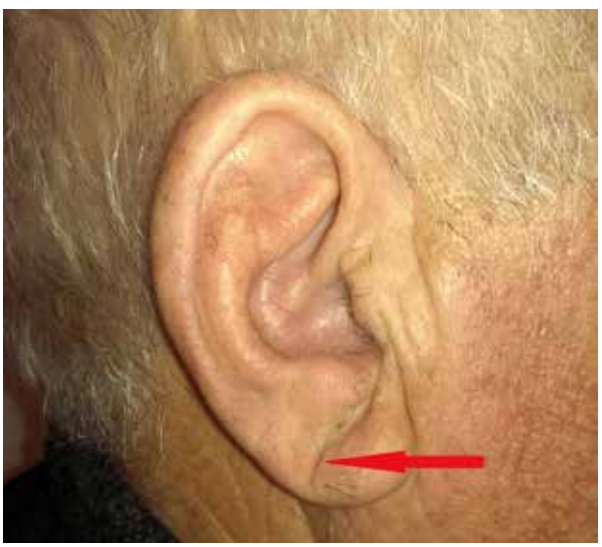

Figure 1. Arrow indicates diagonal earlobe crease.

Abbreviations:

CAD	*Coronary artery disease*
CIMT	*Carotid intima media thickness*
DELC	*Diagonal earlobe crease*
EAT	*Epicardial adipose tissue*
HDL	*High-density lipoprotein*
LDL	*Low-density lipoprotein*
TG	*Triglyceride*

METHODS

Study population

In the present observational cross-sectional study, subjects were admitted to the cardiology outpatient clinic between January 2011 and May 2012. Excluded were patients with known or suspected CAD on clinical history or laboratory evaluation (electrocardiography, echocardiography, treadmill stress test, or myocardial perfusion scintigraphy), or poor acoustic window. A total of 65 subjects with unilateral or bilateral DELC comprised the DELC group, and 65 age- and sex-matched subjects without DELC comprised the control group. Approval was obtained from the local ethics committee.

Study protocol

Clinical and demographic features of all subjects were obtained. Venous blood samples for biochemical analysis were drawn following overnight fasting. Triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and fasting plasma glucose levels were analyzed. Later, all subjects underwent ultrasonographic examination, and EAT and CIMT were evaluated.

Measurement of epicardial adipose tissue thickness

Each subject underwent detailed transthoracic 2-dimensional, M-mode, Doppler, and tissue Doppler echocardiography using standardized techniques. Echocardiogram was performed by an experienced physician. Each subject underwent transthoracic 2-dimensional, guided M-mode echocardiography using commercially available equipment (Vivid-e; General Electric Vingmed Ultrasound AS, Horten, Norway). Standard parasternal and apical views were obtained in the left lateral decubitus position. EAT was identified as echocardiographic free space between the outer wall of the myocardium and the visceral layer of the pericardium. EAT thickness was perpendicu-

larly measured on the free wall of the right ventricle at end diastole in 3 cardiac cycles (Figure 2). Parasternal long- and short-axis views provided the most accurate measurement of EAT in the right ventricle, with optimal cursor beam orientation in each view. Maximum EAT thickness was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, and was used as an anatomic landmark. For midventricular, parasternal short-axis assessment, maximum EAT thickness was measured as an anatomic landmark on the right ventricular free wall along the midline of the ultrasound beam, perpendicular to the ventricular septum at the midchorda and the level of the tip of the papillary muscle. The average value of 3 cardiac cycles from each echocardiographic view was considered.

Longitudinal images of the common carotid artery were obtained 1-cm proximal to the bifurcation in which the far wall intima-media interface was clearly defined, before being magnified and recorded for further analysis. The distance between the leading edge of the intima and the media-adventitia interface was measured. Three measurements were obtained from the right and left common carotid arteries, and mean CIMT was calculated.

Statistical analysis

Statistical analysis was performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Fitness and normal distribution of continuous variables were analyzed with the Kolmogorov-Smirnov test. Inter-observer agreement between 2 cardiologists was calculated using Cohen's kappa coefficient.

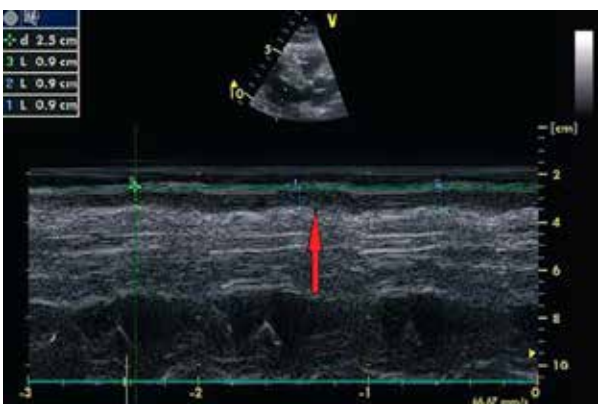

Figure 2. Echocardiographic measurement of epicardial adipose tissue thickness. Arrow indicates epicardial adipose tissue.

A kappa coefficient (κ)<0 indicated no agreement, 0.0–0.20 indicated none to slight, 0.21–0.40 indicated fair, 0.41–0.60 indicated moderate, 0.61–0.80 indicated substantial, and 0.80 indicated almost perfect agreement. Chi-square and independent-samples t-test were performed to compare clinical and laboratory characteristics of patients and control subjects. Correlation of continuous variables was evaluated using Spearman's correlation analysis. Age-adjusted linear regression analyses were performed to explore independent factors associated with DELC presence. Data were expressed as mean±SD for continuous variables and as percentage for categorical variables. Differences of $p<0.05$ were considered statistically significant.

RESULTS

Clinical and demographic characteristics of the DELC and control groups are presented in Table 1. Interobserver agreement of 2 cardiologists regarding EAT thickness and CIMT, using Cohen's kappa coefficient, is shown in Table 2. Substantial agreement of EAT thickness and CIMT was determined.

Each group included 65 patients. Mean age was 57.9±6.28 years in the DELC group and 56.2±8.32 years in the control group. Males comprised 42 of the 65 (64.6%) DELC patients and 43 of the 65 (67.7%) control patients. No statistically significant differences regarding clinical, demographic, and laboratory characteristics were found between the DELC and control groups. EAT was significantly higher in DELC group, compared to the control group (0.57±0.12 vs 0.35±0.05; $p<0.0001$), as was CIMT (0.85±0.16 vs 0.60±0.15; $p<0.0001$) (Figure 3).

Moderate positive correlation between EAT thickness and CIMT ($r=0.671$; $p<0.0001$), and weak positive correlation between EAT thickness and age ($r=0.219$; $p<0.05$) were determined. In addition, moderate positive correlation was determined between CIMT and age ($r=0.346$; $p<0.0001$) (Figure 4). No significant correlation was found between EAT thickness and BMI ($r=-0.042$; $p=0.63$), CIMT and BMI ($r=-0.080$; $p=0.36$), EAT and HDL ($r=-0.078$; $p=0.37$), CIMT and HDL ($r=-0.042$; $p=0.64$), EAT and TG level ($r=0.48$; $p=0.59$), CIMT and TG level ($r=-0.005$; $p=0.95$), EAT thickness and LDL level ($r=0.121$; $p=0.17$), or CIMT and LDL level

Table 1. Demographic, biochemical, and clinical characteristics of diagonal earlobe crease and control groups

Parameter	Diagonal ear lobe crease		Control		*p*
	%	Mean±SD	%	Mean±SD	
Age (year)		57.9±6.28		56.2±8.32	0.200
Gender (male)	64.6		67.7		0.710
Hypertension	38.5		36.5		0.850
Diabetes mellitus	9.2		6.2		0.740
Smoking	24.6		20.0		0.670
Family history	28.5		20.0		0.820
Body mass index (kg/m^2)		27.7±5.11		28.2±3.74	0.560
Low density lipoprotein (mg/dl)		120.5±29.93		113.7±25.87	0.170
High density lipoprotein (mg/dl)		43.1±4.55		44.6±5.34	0.310
Triglyceride (mg/dl)		149.6±39.78		155.6±46.61	0.610
Fasting blood glucose (mg/dl)		101.6±11.48		97.4±14.76	0.520

Data are presented as mean±standard deviation and number (percentage).

Table 2. Interobserver agreement data of two cardiologists

Parameter	Kappa coefficient (□)
Epicardial adipose tissue thickness	0.71 (95% CI [0.62–0.78])
Carotid intima media thickness	0.77 (95% CI [0.69–0.87])

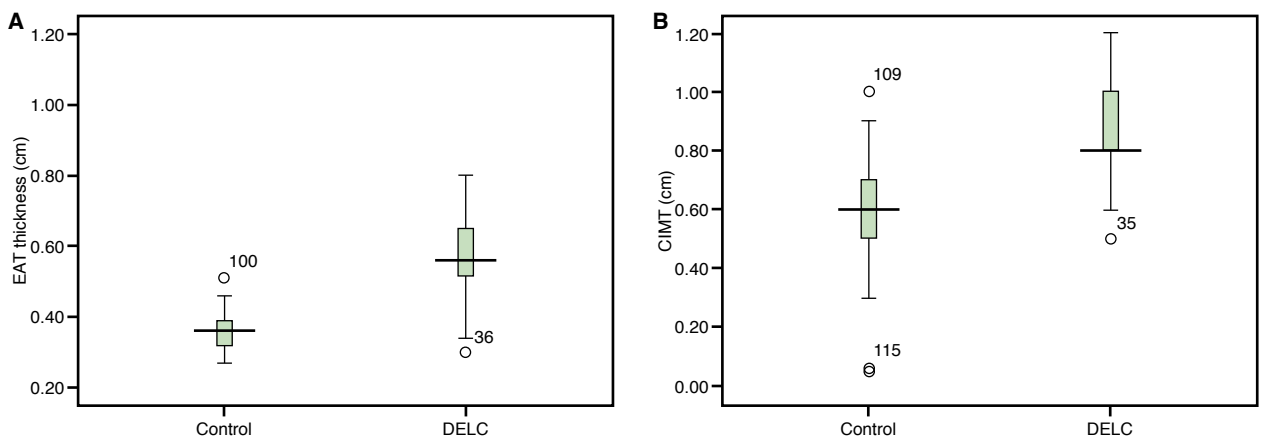

Figure 3. Box plot graphs showing **(A)** distribution of epicardial adipose tissue thickness values of diagonal earlobe crease and control groups, and (B) distribution of carotid intima media thickness values of both groups. (Box plot explanation: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Circles represent outliers.)

(r=0.124; p=0.15). Age-adjusted simple linear regression analysis revealed that presence of DELC was an independent risk factor for increased EAT thickness (β=0.582; p<0.0001) and CIMT (β=0.272; p<0.0001).

DISCUSSION

Relation between DELC and atherosclerosis was first described in 1973 by Frank et al.[1] Although the underlying mechanism is still unclear, several studies

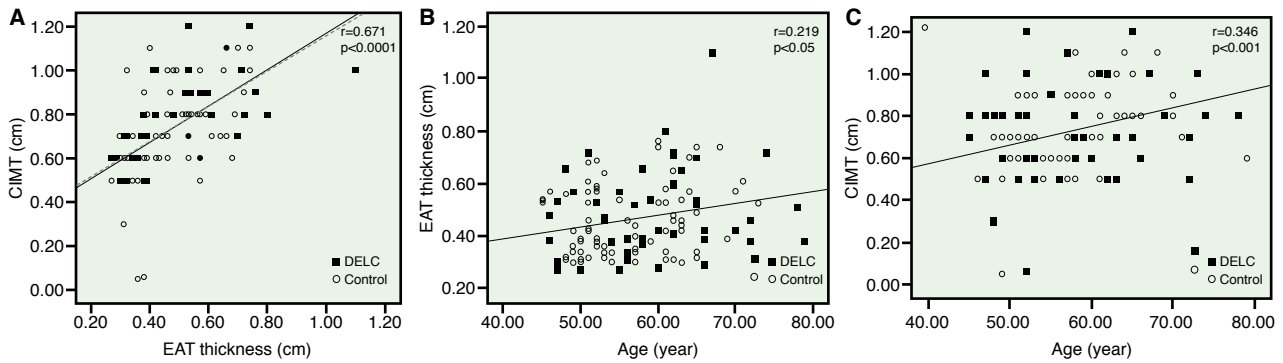

Figure 4. Graphs showing the correlation between **(A)** epicardial adipose tissue thickness and carotid intima media thickness, **(B)** epicardial adipose tissue thickness and age, and **(C)** carotid intima media thickness and age.

have found varying degrees of association between DELC and CAD,[14] and various mechanisms were postulated. It was initially proposed that both the earlobe and heart are supplied by end arteries, without the possibility of collateral circulation, which could cause simultaneous rise in both DELC and CAD. Some researchers found degeneration of the elastin, tear in elastic fibers, and pre-arteriolar wall thickening in cases of DELC.[15] Although atherosclerotic changes in the arterial wall could include smooth muscle cell proliferation and accumulation of collagen and proteoglycans, degeneration caused by changes in the collagen:elastin ratio may be the final common pathophysiological pathway of both atherosclerosis and DLEC.[16] In a recent Japanese study, Higuchi et al.[17] showed that males with DELC have shortened telomeres, correlating with accelerated cell turnover and premature aging, and leading to atherosclerosis.

Increased adipose tissue mass has long been associated with cardiovascular disease.[18] Many acceptable mechanisms may account for this, including changes in blood pressure, glucose and lipid metabolism disorders, and exocrine-paracrine secretion of adipokines.[19] Although distribution and amount of adipose tissue changes throughout the body, visceral fat tissue is essential to cardiometabolic risk, and could therefore be a marker and target of therapy in cardiometabolic diseases.[20] As a visceral fat depot, EAT, which is in direct contact with the coronary vasculature, has the same embryologic origin as mesenteric and omental adipose tissue.[21] Direct contact of EAT and coronary arteries creates an environment for close physical interaction and possibly effects locally secreted adipokines, which is worth investigating. The effect of EAT on atherosclerosis has become a challenging issue. Adipokines, secreted from EAT, could have endocrine and paracrine functions, effecting development of CAD.[22] Previous studies have shown that EAT thickness is positively correlated with atherosclerotic burden.[23] Furthermore, Bettencourt et al.[24] found that increased EAT thickness was associated with increased coronary calcification, a surrogate marker of atherosclerosis.

The present study is the first to investigate the relationship between EAT thickness and DELC. Results demonstrate that EAT thickness was significantly higher in the DELC group. Although exact mechanisms are unclear, close correlation of atherosclerosis with both EAT and DELC has been shown. However, pathophysiological data could not be supplied. The effect of lipid profile on EAT thickness has been analyzed; Liu et al.[25] showed that volume of intrathoracic fat, which is composed of epicardial and pericardial fat, is significantly correlated with high TG and low HDL cholesterol levels. In a more recent study, Aydın et al.[26] showed that EAT thickness is significantly correlated with total cholesterol level and BMI. In the present study, although all lipid parameters were analyzed, no statistically significant correlations were found between EAT thickness and lipid parameters. High prevalence of low HDL[27] and high TG levels[28] in the Turkish population may have been the cause of the lack of significance. Neither was a significant correlation found between EAT thickness and BMI. Both groups had similar HDL, TG, and BMI levels, all of which are CAD risk factors. DELC is a marker of atherosclerosis, as has been mentioned. Because the control group also had

high values, differences between groups were less statistically significant. Small sample size may also have influenced these results, causing the lack of statistical significance.

CIMT is a surrogate marker of early atherosclerosis, and correlation with future cardiovascular events has been shown.[29] It has also been demonstrated that patients with CAD had significantly increased CIMT, compared to patients without.[30] Furthermore, Polak et al.[31] demonstrated the significant association between CIMT and cardiovascular risk factors. The relationship between CIMT and DELC has also been investigated. Celik et al.[32] showed that subjects with DELC had significantly higher CIMT, compared to age- and gender-matched controls. In a similar study, Shrestha et al.[33] demonstrated an independent correlation between DELC and CIMT in multivariate regression analysis after adjusting for age, sex, and hypertension. Hong et al.[34] concluded that subclinical atherosclerosis, diagnosed by presence of plaque and/or increased CIMT, is more prevalent among individuals with both diabetes and hyperlipidemia than in diabetic patients without additional cardiovascular risk factors. It was presently demonstrated that CIMT was significantly higher in the DELC group. Moreover, CIMT was significantly correlated with LDL level. Close correlation between DELC, CIMT, and atherosclerosis makes these results predictable.

The primary present limitation was small sample size. The study may also have been affected by cross-sectional, single-center design, as well as other limitations.

Conclusion

It was presently demonstrated that EAT thickness and CIMT were significantly higher in subjects with DELC. Due to close correlation of atherosclerosis with CIMT and EAT thickness, DELC may be a marker of atherosclerosis. Further studies on a larger scale are necessary.

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

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Keywords: Atherosclerosis; diagonal ear lobe crease; epicardial adipose tissue; intima media thickness.

Anahtar sözcükler: Ateroskleroz; diyagonal kulak memesi kıvrımı; epikardiyal yağ doku; intima media kalınlığı.