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Correlation of Carotid Intima Media Thickness and Aortic Stiffness Index With Androgenetic Alopecia

Andogenetik Alopesililerde Karotid İntima Media Kalınlığı Ve Aortik Sertlik İndeksi İlişkisi

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Aim: Androgenetic alopecia (AGA) is a common health problem which is well associated with hair loss in both male and female subjects by the effect of androgens under the presence of genetic predisposition. Recent studies showed that there is an increased risk for coronary artery disease in AGA patients. The aortic stiffness index (ASI) and the carotid intima media thickness (CIMT) are accepted as a strong marker for the presence of atherosclerosis. The aim of this study is to determine the possible correlation of CIMT and ASI with presence of AGA.

Materials and methods: A total of 159 male asymptomatic AGA patients between 18-55 years old without any history of chronic disease enrolled to the study. Patients were classified in the means of their AGA stage as group I (stage 1-2) (n=49), group II (stage 3-5) (n=71) and group III (stage 6) (n=39) according to the Hamilton scale. Echocardiography was used to determine the elastic properties of aorta assessed by ASI and aortic distensibility (AD) parameters. CIMT was measured by color Doppler ultrasonography. ASI, AD and mean CIMT were calculated. The data including the patient's metabolic profile and anthropometric measurements were recorded.

Results: There was no significant difference between the groups in the means of age, height, body mass index, and left ventricle ejection fraction. The values of mean ASI, CIMT and systolic blood pressures were significantly higher in group III than group I and group II statistically ($p<0.001$ for all three parameters). On the other hand, AD was significantly higher in group I compared with group II and III statistically ($p<0.001$).

Conclusions: ASI and AD are parameters reflecting the aortic elastic properties. In case of an aortic elasticity deterioration, ASI value increases while AD value decrease. This study concluded that the patients at higher stages of AGA had higher CIMT and more deteriorated aortic elasticity which are indicators of atherosclerosis. Thus, we assumed that patients with advanced AGA stages may have subclinical atherosclerosis more commonly compared to the patients with beginning stages of AGA.

Key Words: **Atherosclerosis, Androgenetic alopecia, arterial stiffness index, aortic distensibility, carotid intima media thickness.**

Amaç: Androgenetik alopezi (AGA), hem erkeklerde hem de kadınlarda genetic yatkınlık varlığında androgenlerin etkisiyle saç kaybı ile giden yaygın bir sağlık sorunudur. Yeni çalışmalar AGA'lı hastalarda artmış koroner arter hastalığı riski ile ilişkili olduğunu göstermiştir. Aortik sertlik indeksi (ASİ) ve karotid intima media kalınlığı (KİMK) ateroskeroz varlığı için güçlü belirteçler olarak kabul edilir. Bu çalışmanın amacı, AGA varlığında ASİ ve KİMK arasındaki olası ilişkiyi belirlemektir.

Gereç ve Yöntem: Her hangi bir kronik hastalığı olmayan 18-55 yaş arası toplam 159 asemptomatik AGA hastası çalışmaya dahil edildi. Hastaların Hamilton skalasına göre AGA seviyeleri grup I (seviye 1 ve 2) (n=49); grup II (seviye 3-5) ve grup III (seviye 6) olarak sınıflandırıldı. ASİ ve aortik distensibilite (AD) parametreleri ile değerlendirilen aortun elastik özelliklerini belirlemek için ekokardiyografi kullanıldı. KİMK, renkli Doppler ultrasonografi kullanılarak ölçüldü. ASİ, AD ve ortalama KİMK hesaplandı. Hastaların metabolik profillerini ve antropometrik ölçümlerini içeren veriler kaydedildi.

Bulgular: Gruplar arasında yaş, boy, vücut kitle indeksi ve sol ventrikül ejeksiyon fraksiyonu açısından anlamlı fark saptanmadı. İstatiksel olarak III. grubun ortalama ASİ, KİMK ve sistolik kan basıncı değerleri I. ve II. gruba nazaran daha yüksekti (her üç parametre için $p<0.001$). Buna karşın AD değeri anlamlı olarak I. grupta, II. ve III. gruba göre daha yüksekti ($p<0.001$).

Sonuç: ASİ ve AD aortik elastik özellikleri gösteren parametrelerdir. Aortik elastisitenin bozulması durumunda, AD değeri düşerken ASİ değeri yükselir. Bu çalışma, ileri aşamada AGA'sı olan hastalarda ateroskleroz göstergesi olan daha yüksek KİMK ve daha fazla bozulmuş aortik elastisite olduğu sonucuna ulaşılmıştır. Bu nedenle, ilerlemiş AGA'li hastalar başlangıç aşamasındaki AGA'li hastalara nazaran daha yaygın olarak subklinik ateroskleroza sahip olabilirler.

Anahtar Sözcükler: **Ateroskleroz, Androgenetik Alopesi, Artepiyel sertlik indeksi, Aortik distensibilite, Karotid intima media kalınlığı**

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Androgenetic alopecia (AGA) is a common health problem which is well associated with hair loss especially in male patients. There is an increased androgenic activity in these patients (1). In the literature it is known that androgenic activity causes coronary artery disease (CAD) (2) and AGA patients can face with this health problem in rest of their life. Early diagnosis of this pathological course will solve possible problems that can disappear in future. Since aortic stiffness index ASI and aortic distensibility AD show the aortic elastic properties, our hypothesis is that evolution of ASI, AD, and carotid intima media thickness (CIMT) can show the beginning stage of CAD. The aim of this study is to determine the possible correlation of CIMT with ASI in AGA patients.

MATERIALS AND METHODS

Study population:

Subjects were collected from the male patients who were referred to dermatology department with complaints of hair loss in five months period (June-October 2014), prospectively. All patients were questioned for the presence history of chronic disease such as hypertension, CAD, diabetes mellitus, thyroid, or adrenal gland disease and chronic renal failure. To rule out the left ventricular systolic dysfunction; patients with a left ventricular ejection fraction value less than 50% excluded from the study. Any current or previous treatment for alopecia, present use of any drugs that can change the androgen profile such as anti-androgen, insulin sensitizing drugs or glucocorticoids and smokers were excluded also. After exclusion, a total of 159 male patients were included to the study. Patients' metabolic profile and anthropometric measurements such as age, height, and weight were recorded. Body mass index of all subjects were calculated. The ethical approval and patients' consent form from each patient obtained for the study and the investigation was performed with obeying the principles outlined in the Declaration of Helsinki.

Assessment of AGA

AGA was classified according to the Hamilton-Norwood baldness scale (3, 4). A well trained physician observed the participant's head from two angles (side and top), compared the natural hair pattern with series of 12 figures, and chose the best matching figure. We modified the 12 categories of the Hamilton scale into six by collapsing the consecutive categories as Doğramacı et all. (5) reported before and classified the patients in the means of their AGA stage as group I (stage 1-2) (n=49), group II (stage 3-5) (n=71), and group III (stage 6) (n=39).

Assessment of arterial stiffness and carotid intima-media thickness measurements:

Echocardiographic examination was performed on an ultrasound machine (Prosound alpha 7, IPF 1701 Model, 2009; Hitachi Aloka Medical, Ltd. Tokyo, Japan) with a 2.5-MHz transducer by a cardiologist blinded to the study. Standard 2-dimensional measurements were performed as advised by the American Society of Echocardiography (6). Following the echocardiographic examination of heart, at parasternal long axis M-mode images, the systolic (Asd) and diastolic (Add) aortic diameters of ascending aorta from anterior to posterior wall were measured 3 cm distal to the aortic valve level, differentiating diastole and systole by using simultaneous electrocardiographic recordings. The blood pressure (BP) levels were obtained from both arms of the subjects in a sitting position by one trained observer blind to the study in the echocardiography laboratory. BP was measured twice with five minutes interval. The systolic BP (SBP) and diastolic BP (DBP) were recorded at the first and fifth Korotkoff phases respectively using a mercury sphygmomanometer. The average of the four BP measurements was used for analysis. The difference of SBP and DBP was accepted as the pulse pressure (PP). Aortic stiffness index is calculated by using ASI= ln(SBP/DBP)/[(Asd-Add)/Add] while aortic distensibility is obtained by using AD [1/(10^3xmmHg)] = 2x [(Asd-Add) /Add]/PP formulas (7).

Carotid Doppler ultrasonography (US) was performed with an Aloca prosound A6 (Hitachi Aloka Medical, America) equipped with a 7.5 MHz linear array imaging probe. All measurements were performed by the same radiologist blinded with the status of the patient's clinic with the patient lying supine, the head directed away from the side of interest and the neck extended slightly. To maximize the lumen diameter, transducer located in longitudinal plane. At a location of 1 cm proximal to the carotid bifurcation the images were magnified to achieve a higher resolution of detail. CIMT of the far wall was evaluated as the distance between the lumen–intima interface and the media-adventitia interface. Measurements were obtained from five contiguous sites at 1-mm intervals bilaterally, and the average of the all measurements of the patient was used for the statistical analyses. CIMT values more than 1 mm was accepted as abnormal (8).

Statistical analysis:

All statistical analyses were carried out using the SPSS software program (ver 15.0). Continuous variables were expressed in mean± standard deviation and categorical variables were shown as frequencies (%). Except CIMT, ASI, and total cholesterol, the other continuous variables did not show normal distribution according to Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test or Fisher's exact test accordingly. Pearson or Spearman simple correlation analyses were performed to search the association between continuous parameters accordingly while Student's t test, Mann-Whitney U test, and Kruskal-Wallis tests were performed to compare groups accordingly. A p value of less than 0.05 was considered to show statistically significant result.

RESULTS

A total of 159 patients included to the study after the presided exclusion criteria. The group I with mean age of 40±7 years was composed of 49 subjects, the group II with mean age of 40±7 years included 71 subjects, and the group III with mean age of 40±5 years had 39 patients. Age, height, weight, BMI, the left ventricle ejection fraction values were statistically similar across the groups (p values 0.879, 0.298, 0.913, 0.452, and 0.299 respectively). Although SBP was the highest for the group III (p <0.001), DBP did not differ between the groups (p<0.436).

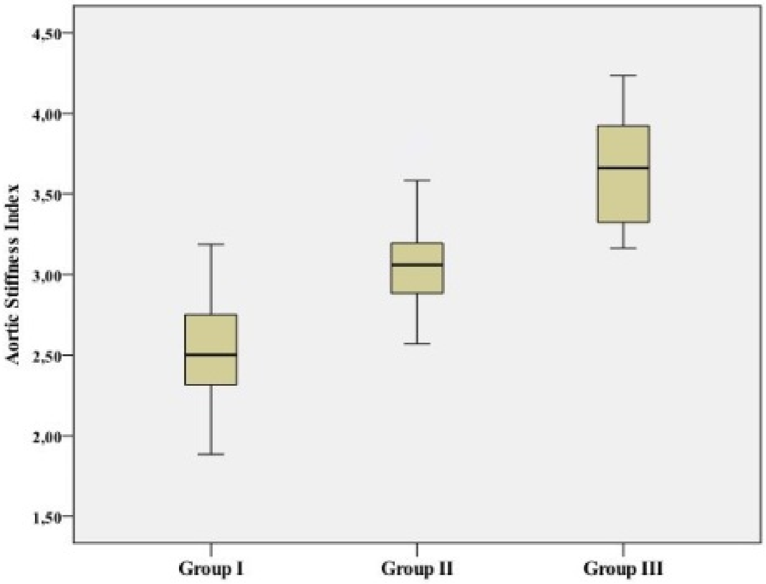

Figure 1: Comparison of the groups in respect to average aortic stiffness index

ASI values of the groups were 2.53±0.37, 3.06±0.29, and 3.67±0.32 respectively (Figure 1). Average ASI value of the group II was statistically higher than group I (p<0.001) and significantly lower than the group III (p<0.001); inversely average AD value of group II was significantly lower than group I (p<0.05 with z score= -2.362) but higher than the group III (p <0.01 with z score = -2.724).

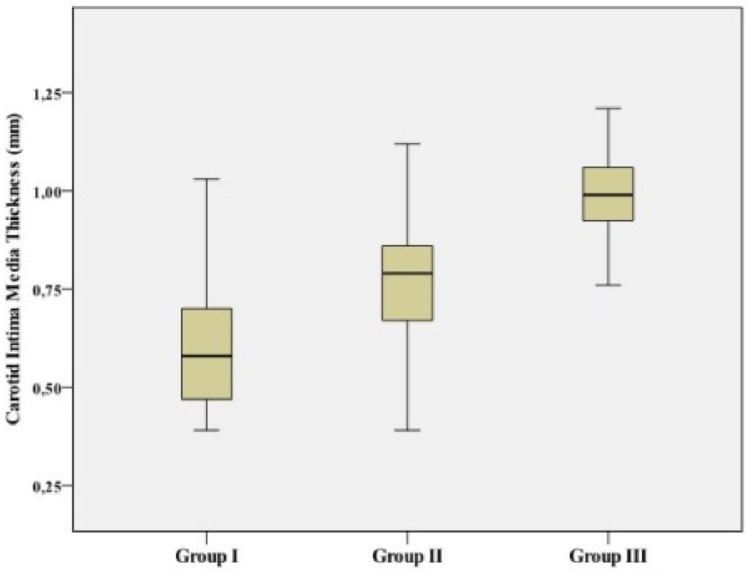

Figure 2: Comparison of the groups in respect to average carotid intima media thickness

Average CIMT values of the groups were 0.61±0.17, 0.76±0.15, and 0.98±0.14 respectively (Figure 2). Similar to the ASI values; CIMT value of the group II was statistically higher than the group I (p<0.001) but lower than the group III (p<0.001). Also frequency of abnormal CIMT values was highest in group III, then group II and the least in group I (2%, 6%, and 46% respectively). Although we could not find any significant difference between the group I and the group II in respect to frequency of abnormal CIMT, the group III had higher frequency of abnormal CIMT than both the group I (p <0.001) and the group II (p <0.001). Rest of demographic and ultrasonographic findings of the subjects was expressed in Table 1 and 2. In correlation analysis, we found significant positive correlation between ASI and CIMT (r=0.668; p <0.001) and inverse correlation between AD and CIMT (r= -0.687; p<0.001). BMI was well correlated to ASI (r= 0.156; p<0.05), CIMT (r=0.372; p<0.001), and age (r=0.283; p<0.001). In our study, age did not correlate to parameters reflecting aortic elasticity but had significant statistical correlation with CIMT (r=0.218; p<0.01). Glucose, creatinine, TSH values and lipid profile of the groups did not differ from each other as shown in Table 3.

Table 1: Demographic findings of the subjects.

	Group I (n=49)	Group II (n=71)	Group III (n=39)	p value
Age (year)	40±7	40±7	40±5	0.879
Height (cm)	174±7	173±7	172±5	0.298
Weight (kg)	85±11	85±8	85+9	0.813
BMI (kg/m²)	27.9±2.7	28.2+2.2	28.8+3.0	0.452

(BMI: Body mass index)

Table 2: Ultrasonographic findings of the subjects

	Group I (n=49)	Group II (n=71)	Group III (n=39)	p value
SBP (mmHg)	113±9	120±9	126±8	<0.001
DBP (mmHg)	75±4	76±6	76±7	0.436
LVEF (%)	63±2	63±3	62±3	0.299
Aortic Stiffness Index	2.53±0.37	3.06±0.29	3.67±0.32	<0.001
Aortic Distensibility	7.04±2.91	3.61±1.20	1.82±0.61	<0.001
CIMT (mm)	0.61±0.17	0.76±0.15	0.98±0.14	<0.001
CIMK > 1 mm (%)	1 (2)	4 (6)	18 (46)	<0.001

CIMT: Carotid intima media thickness; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; SBP: Systolic blood pressure; Aortic distensibility showed as [1/(10³xmmHg)]

Table 3: Laboratory findings of the subjects.

	Group I (n=49)	Group II (n=71)	Group III (n=39)	p value
Hemoglobin (gr/dl)	15.4±1.0	15.3±1.2	14.8±1.5	0.753
Glucose (mg/dl)	101±11	100±17	101±13	0.13
Creatinine (mg/dl)	0.94±0.14	0.94±0.11	0.99±0.14	0.516
Total Cholesterol (mg/dl)	196±40	204±41	207±72	0.336
Triglyceride (mg/dl)	192±78	189±86	201±77	0.8
HDL (mg/dl)	38±7	40±8	39±8	0.184
LDL (mg/dl)	124±34	131±32	131±26	0.154
TSH (µIU/mL)	1.58±1.07	1.32±0.54	1.39±0.98	0.749

HDL: High density lipoprotein. LDL: Low density lipoprotein. TSH: Thyroid stimulating hormone

DISCUSSION

AGA is described as recession of frontal hair line resulting as balding of the scalp cortex in which the Hamilton-Norwood baldness scale (3,4) is used to determine the classification. Several studies discussed the effect of androgens in AGA, regarding that young male AGA patients shows a higher dihydroteststerone-teststerone ratio compared with healthy population (1,9). The effects of androgens on formation of atherosclerosis is explained by the possible harmful affects combined with vasoconstriction caused by androgens (2,10). Fujimoto et al. showed that serum androgen causes increased atherosclerotic changes in rats by stimulating the proliferation of vascular smooth muscles (11). Since Cotton et al. (12) first described the association between AGA and CAD, the literature faced with efforts to find an answer to solve the effects of this possible correlation (13-16). Lesko et al (13) found a positive correlation between risks of myocardial infarction with severity of alopecia. Latufo et al (14) showed that vertex pattern AGA is a marker for increased risk for CAD. The authors proved that pathogenesis of carotid atherosclerosis are similar with coronary atherosclerosis; presence of any atheromatous plaque located in carotid arteries predicts a strongly possible coronary artery disease (17). Since the CIMT is an early predictor of CAD (18), by the postulate based on correlation of AGA with CAD, color

Doppler US can be used to determine the early effect of AGA on CAD due to its sensitivity on imaging premature atheroma. Normal value of CIMT ranges from 0,25 mm to 1 mm and values greater than 1mm accepted as abnormal (8). The correlation of AGA score with CIMT value is discussed before but results are controversial. Some authors (5, 19) found a positive correlation between AGA score compared with CIMT value; while others report no significant correlation (20). We found a significant correlation as AGA scores increase, the mean CIMT values increase in contrast with the reports of Agac et al. (20) and this discordance is due to the result of their exclusion criteria in selection of study population. They included relatively younger ages of patients who are not in the range of atherosclerotic border yet.

Aortic elasticity was measured via aortic stiffness index and aortic distensibility. Both parameters are inversely associated with each other and they are reflecting aging and atherosclerosis (21). Presence of the cardiovascular risk factors fastens atherosclerotic process; therefore reduce aortic elasticity meaning increment in ASI and reduction in AD. Also impairment in aortic elasticity was found to be related to extent of coronary artery disease (22). But mostly, the carotid-femoral pulse wave velocity (PWV) method was used to measure vascular stiffness in these studies (20-22). However the arterial stiffness was evaluated by echocardiography in our study. It is known that aorta reflects central hemodynamics better than femoral artery since femoral artery is a muscular vessel (23, 24). Additionally, the effect of atherosclerosis on muscular vessels are less than elastic great vessels such as the aorta. Difficulty in groin exposure especially in obese patients and uncorrectly estimated distance between two recording points (resulting overestimation among obese patients) are other limitations to PWV method which impairs its diagnostic accuracy (24). Echocardiography offers an easy way to assess arterial stiffness and can be alternative to PWV method in presence of these limitations.

ASI and AD shows the aortic elastic properties as mentioned before. In case of an aortic elasticity deterioration, ASI value increases with a decrement of AD value. Since the arterial stiffness may precede the early pathologic intimal changes (20).Our hypothesis is that AGA might be an indicator of arterial stiffness and early-onset of atherosclerosis when combined with CIMT values. We found that as AGA score increases; the values of aortic elastic properties are negatively affected by increment in ASI value and decrement in AD value along with increment of mean CIMT value.

To conclude; as increased androgenic activity causes atherosclerotic changes, AGA patients should alert the clinicians on the means of CAD and should be closely followed up with their CIMT and ASI values. Increment of these values in AGA patients indicating early onset atherosclerosis should induce the physician for possible CAD. This approach gives chance to prevent AGA patients from future adverse cardiovascular events.

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