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CARDIOVASCULAR RISK FACTORS CAN AFFECT ENDOTHELIAL DYSFUNCTION IN ESSENTIAL HYPERTENSIVES: A CROSS SECTIONAL CASE-CONTROL STUDY

ESANSİYEL HİPERTANSİYONLU HASTALARDA KARDİYOVASKÜLER RİSK FAKTÖRLERİNİN ENDOTEL DİSFONKSİYONUNA ETKİSİ: KESİTSEL VAKA KONTROLLÜ BİR ÇALIŞMA

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ABSTRACT

Objective: Endothelial dysfunction is now recognized as an early, perhaps initiating event in the pathogenesis of cardiovascular diseases. The purpose of the present study was to examine the influence of cardiac risk factors on endothelial function in essential hypertension (EH).

Material and methods: Young 129 (53 males, mean age 45.0±6.4) mild hypertensive patients and same number of healthy controls were selected. All patients were under antihypertensive treatment for a mean duration of 44±63 months, and were at the targeted blood pressure. Major risk factors for cardiovascular diseases according to the National Cholesterol Education Program criteria and some other risk factors were evaluated. Seventy-eight EH patients and 78 age and sex matched control subjects were assessed for endothelial function using brachial artery ultrasound. Endothelium dependent (EDD) and independent (EID) vasodilation were evaluated.

Results: Patients with EH were older with female dominance, had higher frequency of diabetes, obesity, higher cholesterol, triglycerides, and fibrinogen levels. EH patients had significantly impaired EDD (17.4±7.2% vs 20.7±5.8%, p=0.002) and EID (20.9±8.2% vs 24.4±6.8%, p=0.004) compared with controls. In multiple regression test only uric acid levels, presence of EH, and body mass index (BMI) were retained as significant for EDD. Only uric acid, hemoglobin levels, presence of EH, and BMI were significantly associated with EID.

Conclusion: It was concluded that endothelial dysfunction was present in EH group despite optimal medical therapy. The factors analyzed in the study explain only a fraction of the variability in EDD but were intimately related to metabolic syndrome which may be one of the reasons why endothelial dysfunction was present in EH despite medical therapy.

Key words: Endothelial dysfunction, cardiac risk factors, essential hypertension, metabolic syndrome

ÖZET

Amaç: Endotel disfonksiyonu, patogenezinde erken dönemde saptandığı kardiyovasküler hastalıkları belki de başlatan bir olaydır. Bu çalışmanın amacı, kardiyovasküler risk faktörlerinin esansiyel hipertansiyon (EH) hastalarında endotel fonksiyona etkisini değerlendirmekti.

Gereç ve yöntem: Evre I 129 (53 erkek, ortalama yaş 45,0±6,4) hipertansif hasta ve aynı sayıda sağlıklı kontrol çalışmaya alındı. Hastalar ortalama 44±63 aydır tedavi altındaydı ve hedef kan basıncına ulaşılmıştı. Ulusal kolesterol eğitim programı kriterlerine göre major risk faktörleri ve bazı diğer risk faktörleri değerlendirildi. Brakiyel arter ultrasonografisi ile 78 yaş ve cinsiyeti eşleştirilmiş kontrol ve EH hastasının endotel fonksiyonu incelendi. Endotele bağımlı (EDD) ve endotelden bağımsız (EID) vazodilatasyon değerlendirildi.

Bulgular: Hastalar daha yaşlı idi, kadın hastalar çoğunluktaydı, hasta grubunda diabetes, obezite, yüksek kolesterol, trigliserid ve fibrinojen düzeyleri daha sık idi. Hipertansiflerde EDD (%17,4±7,2 karşın %20,7±5,8, p=0,002) ve EID (%20,9 ± 8,2 karşın %24,4 ± 6,8, p=0,004) kontrol grubuna göre anlamlı olarak azalmıştı.. Multipl regresyon analizinde EDD için ürik asit, EH varlığı, vücut kitle indeksi (VKİ), EID için ise ürik asit, hemoglobin düzeyi, EH varlığı ve VKİ öngördürücü bulundu.

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Sonuç: Optimal tıbbi tedaviye rağmen EH grubunda endotel disfonksiyonu saptandı. Çalışmamızda değerlendirilen faktörler EDD'ki değişkenliğin ancak küçük bir bölümünü açıklayabildi, bu faktörlerin bazıları metabolik sendromun komponentleri idi. Bu durum EH'da optimal tıbbi tedaviye rağmen süregelen endotel disfonksiyonun nedenlerinden birisi olabilir.
Anahtar kelimeler: Endotel disfonksiyonu, kardiyak risk faktörleri, esansiyel hipertansiyon, metabolik sendrom

INTRODUCTION

Endothelial dysfunction is now recognized as an early, perhaps initiating event in the pathogenesis of cardiovascular diseases and has been shown to be present in patients with essential hypertension (EH), heart failure, and other risk factors for coronary heart disease (4, 8, 10, 11, 13, 15, 16, 17, 18). The purpose of the present study was to examine the influence of cardiac risk factors on endothelial function in EH.

MATERIALS and METHODS

Study population

A total of 129 (53 males, mean age 45.0±6.4) hypertensive patients were selected according to the following criteria: age between 20 and 50 years, onset of EH at <50 years of age, mild-established EH according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) (12), absence of secondary forms of hypertension, family history of EH occurring before 60 years of age, with at least one parent or one sibling affected. All patients were under antihypertensive treatment for a mean duration of 44±63 months, and were at the targeted blood pressure (<140/90 mmHg) during the last two visits 3 months apart in the outpatient clinic. The antihypertensive treatment included angiotensin converting enzyme inhibitors in 50% of the patients, angiotensin II type 1 receptor blockers in 30%, beta blockers in 15%, statins in 35%, aspirin in 57%, calcium channel blockers in 21%, and diuretics in 24%, respectively. About 72% of the patients were on monotherapy, 28% were on combination therapy.

One hundred and twenty-nine healthy control subjects (70 males, mean age 35.6±6.8) were selected according to the following criteria: age between 20 and 50 years, blood pressure <140/90 mm Hg, absence of other concomitant diseases, and drug intake. Informed consent was obtained from each subject and the Declaration of Helsinki on biomedical research on humans was followed for the study (6).

Laboratory analysis

Major risk factors for cardiovascular diseases according to the National Cholesterol Education Program (9) criteria (age, sex, smoking, high total cholesterol and low density lipoprotein cholesterol, low high density lipoprotein cholesterol, diabetes mellitus, hypertension, and positive family history) as given in Table 1 and the following risk factors were evaluated: triglycerides >2.26mmol/L (200mg/dl), uric acid >446µmol/L (7.5 mg/dl), obesity (BMI >27kg/m2), fibrinogen >4g/L (400 mg/dl). Hemograms, electrolytes, renal and liver functions

Table 1. Cardiovascular risk factors of the hypertensives and controls

	Controls n=129	Hypertension n=129	P value
Age (Years)	35.6 ±6.8	45.0 ±6.4	<0.001
Sex (M/F)	70/59	53/76	0.046
Sex (M/F)*	9/0	34/1	NS
Smoking	52	40	NS
Diabetes mellitus*	0	14	<0.001
High TC*	3	53	<0.001
High LDL*	7	42	<0.001
Low HDL*	25	29	NS
High TG *	11	32	0.001
High UA*	1	3	NS
High fibrinogen*	10	41	<0.001
Positive family history*	30	26	NS
BMI>27kg/m2	31	68	<0.001

*Men>45, women>55 years of age
Glucose>7mmol/L (126mg/dl), TC (Total cholesterol>5.17 mmol/L (200mg/dl),
LDL (Low density lipoprotein cholesterol>3.36 mmol/L (130mg/dl)
HDL (High density lipoprotein cholesterol<0.9 mmol/L (35mg/dl)
TG (Triglycerid>2.26 mmol/L (200mg/dl), UA (Uric acid>446mmol/L (7.5mg/dl)
Fibrinogen>4g/L (400mg/dl)
Myocardial infarction or sudden death in first degree consanguity in men before 55, in women before 65 years of age.

Table 2. Comparison of endothelial-dependent (EDD) and independent (EID) vasodilation between patients and controls

	Controls (n=78)	Hypertensives (n=78)	P value
Age (years)	41.2 ± 4.1	44.9 ± 6.2	NS
Males/Females	45/33	33/45	NS
EDD* (%)	20.7 ± 5.8	17.4 ± 7.2	0.002
EID* (%)	24.4 ± 6.8	20.9 ± 8.2	0.004

**EDD: endothelial dependent vasodilation, EID: endothelial independent vasodilation*

were recorded. Biochemical analysis was measured by standard methods in the clinical laboratory department of the University Hospital.

Endothelial function assessment

The endothelial function of the brachial artery was assessed by Echo-Doppler using a Vingmed Technology, System Five, Norway with a 10.0 MHz linear phased-array ultrasound transducer longitudinally just above the antecubital fossa as previously described (1, 2). Seventy-eight EH patients and 78 control subjects were assessed for endothelial function (Table 2). Blood pressure cuff was wrapped around the upper arm (1), inflated to 250 mmHg and held for 5 minutes to induce ischemia. The cuff was released and brachial artery diameter was measured every minute for 5 minutes to assess maximal EDD in response to reactive hyperemia. After vessel diameter returned to baseline values (~ 7-10 minutes), endothelium independent vasodilation (EID) was assessed after 0.5 mg sublingual nitroglycerine, every minute for 5 minutes. Vessel diameters were measured at the end diastole coincident with the onset of the R-wave of the simultaneously obtained ECG trace. During the measurements particular attention was paid to the age, temperature of the laboratory, menstrual cycle, exercise, drugs, food, and sympathetic stimuli as recommended by the guideline (3). The percent vasodilation was calculated with the following formula:

Percent EDD or EID = 100*(pBAD- bBAD)/(bBAD)

pBAD: Peak brachial artery diameter after intervention.

bBAD: Baseline brachial artery diameter

The intra and inter-observer variability of the measurements in our laboratory was 1-3%.

Statistical analysis

The statistical analysis was done using the Statistical Package for Social Sciences for Windows Ver. 10.0 (SPSS Inc, Chicago, Illinois, USA). Student's t test, χ^2 test, and Fisher's exact test were used. Correlation between two numerical variables with normal distribution was sought with Pearson's bivariate correlation test, else correlation was performed using Spearman's correlation test. Factors that affect EDD and EID were examined with multiple regression test. A P value of <0.05 was accepted as significant.

RESULTS

Cardiovascular risk factors of patients and controls are shown in Table 1. The patients and controls were not similar with respect to distribution of age, sex, and cardiac risk factors as expected. Patients with EH were older with female dominance, had higher frequency of diabetics, obese, and had higher cholesterol, triglycerides, and fibrinogen levels.

EH patients had significantly impaired EDD (17.4±7.2% vs 20.7±5.8%, p=0.002) and EID (20.9±8.2% vs 24.4±6.8%, p=0.004) compared with their age-matched controls (Table 2). EDD and EID in controls were significantly correlated with body mass index (BMI) (r=-0.23, p=0.008; r=-0.25, p=0.004, respectively), hemoglobin levels (r=-0.25, p=0.005; r=-0.31 p< 0.001, respectively), high density lipoprotein (HDL)-cholesterol (r=0.20, p=0.026; r=0.17 p= 0.048, respectively), uric acid (r=-0.25, p=0.004; r=-0.28, p=0.001, respectively). EDD and EID in EH patients was significantly correlated to uric acid levels (r=-0.26, p=0.022; r=-0.28, p=0.014).

When factors found significant for EDD were included in multiple regression test (hemoglobin level, presence of EH, BMI, uric acid and HDL-cholesterol levels) only uric acid levels, presence of EH, and BMI were retained as significant (Multiple R = 0.399, adjusted R2=0.14, F=9.57, p<0.001). Only uric acid, hemoglobin levels, presence of EH, and BMI were significantly associated with EID in multiple regression test (Multiple R=0.404, adjusted R2=0.15, F=9.89, p<0.001).

DISCUSSION

Endothelial dysfunction has been reported to appear early in the cardiovascular disease continuum, in which we found EH at the very early stage (7).

In the present study, EH patients had severe endothelial dysfunction discernible despite optimal medical treatment. It was also seen that EDD and EID were impaired together.

In our study, only 14% of the variability of EDD was explained by the parameters collected in the study. The main factors found were uric acid levels, BMI, and the presence of EH. This implies that, firstly, the greater part of variability in EDD remained unexplained; secondly, the factors found related are intimately related to a clinical entity called metabolic syndrome (MS). These findings are especially relevant to the population studied because MS prevalence in Turkey is high (14). Onat et al showed that MS prevalence rates in Turkish population above 30 years of age were 28% for men, and 45% for women (14).

Also, in this study group no relations between genetic markers and the presence of EH or between endothelial dysfunction and genetic markers were established (5).

It was concluded that endothelial dysfunction was present in EH group despite optimal medical therapy. The factors analyzed in the study explain only a fraction of the variability in EDD but were intimately related to MS which may be one of the reasons why endothelial dysfunction was present in EH despite optimal medical treatment. Whatever the reason might be, these findings do raise the questions that should be further investigated in future trials.

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