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Assessment of a low ankle brachial index in young males with congenital hypogonadism

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ÖZET

Konjenital hipogonadizm bulunan genç erkek hastalarda düşük ayak bileği kol indeksinin değerlendirilmesi

Kardiyometabolik hastalık sıklığı hipogonadizmde artmıştır. Periferik arter hastalığı (PAH) sistemik aterosklerozun bir manifestasyonu olup koroner arter hastalığı ve inme açısından iyi bir öngördürücüdür. Bu çalışmada tedavi almamış genç hipogonad hastalarda PAH sıklığının artıp artmadığı ve bu hastaların sistemik ateroskleroz açısından artmış riske sahip olup olmadıkları araştırılmıştır. Çalışmaya 49 konjenital hipogonadotropik hipogonadizm (KHH) hastası (ort. yaş: 21.82 ± 2.28 yıl) ve 37 sağlıklı olgu (ort. yaş: 22.34 ± 1.20 yıl) dahil edildi. Hasta ve sağlıklı kontrollerde plazma asimetrik dimetilarjinin (ADMA) ve yüksek duyarlılıklı C-reaktif protein (hs-CRP) düzeyleri ölçüldü. İnsülin direnci, homeostatic model assessment of insulin resistance (HOMA-IR) yöntemi ile hesaplandı. PAH, Doppler tekniği kullanılarak ölçülen ayak bileği kol indeksine (ABI) göre belirlendi. KHH hastalarında, sağlıklı kontrollerle karşılaştırıldığında daha yüksek total kolesterol (p=0.038), trigliserid (p=0.047), insulin (p<0.001), HOMA-IR skoru (p<0.001) ve ADMA (p<0.001) düzeyleri ve daha düşük vücut kitle indeksi (p=0.001) ve sistolik kan basıncı (p<0.007) düzeyleri tespit edildi. Ortalama ABI değerleri hastalarda 1.05 ± 0.13 ve sağlıklı kontrollerde 1.00 ± 0.10 (NS) olarak bulundu. Düşük ABI değerleri açısından bakıldığında hastaların %12.2'sinde ve kontrollerin %13.5'inde alt ekstremite PAH tespit edildi (NS). Bununla birlikte, regresyon analizinde çalışma parametrelerinin hiçbirinin düşük ABI düzeylerini predikte etmediği bulundu. Genç ve tedavi almamış KHH hastaları sağlıklı kontrollerle karşılaştırıldığında, endotheliyal disfonksiyon ve insulin direnci gibi metabolik bozukluklar açısından artmış riske sahip oldukları tespit edilirken düşük ABI açısından anlamlı farklılık tespit edilmedi. ABI ölçümü hipogonadizm bulunan genç erkeklerde PAH tespiti açısından duyarlı bir yöntem olmayabilir.

Anahtar Kelimeler: *Hipogonadizm; Ayak bileği kol indeksi; Endoteliyal disfonksiyon; Periferik arter hastalığı.*

SUMMARY

Cardio-metabolic diseases are prevalent in hypogonadism. Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is a well-known predictor of coronary heart disease and stroke. This study investigated whether young and treatment naïve hypogonadal patients had higher frequency of PAD and were under increased risk of systemic atherosclerosis. The study included 49 patients with congenital hypogonadotrophic hypogonadism (CHH) (mean age: 21.82 ± 2.28 years) and 37 healthy control subjects (mean age: 22.34 ± 1.20 years). Blood asymmetric dimethylarginine (ADMA) and high-sensitivity C-reactive protein (hs-CRP) were measured, and insulin resistance was calculated using homeostatic model assessment of insulin resistance (HOMA-IR) score. PAD was determined by the ankle brachial index (ABI) using Doppler technique. Patients with CHH had higher total cholesterol (p=0.038), triglyceride (p=0.047), insulin (p<0.001), HOMA-IR score (p<0.001) and ADMA (p<0.001), and lower body mass index (p=0.001) and systolic blood pressure (p<0.007), compared to healthy controls. Mean ABI value was 1.05 ± 0.13 in patients and 1.00 ± 0.10 in controls (NS). Based on a low ABI, 12.2% of patients and 13.5% of controls had lower extremity PAD (NS). However, in the multivariable model none of the study parameter was a predictor of a low ABI. Young and treatment naive patients with CHH had increased dysmetabolic features such as endothelial dysfunction and insulin resistance but did not have increased frequency of a low ABI compared to controls. ABI measurement might not be a sensitive tool to detect PAD in young male patients with hypogonadism.

Key words: *Hypogonadism; Ankle brachial index; Endothelial dysfunction; Peripheral arterial disease.*

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1. Introduction

Hypogonadism is characterized by testosterone insufficiency accompanied by poor libido, loss of energy, muscle atrophy and depression. Patients with hypogonadism also have increased risk of cardiovascular diseases (CVDs) (1). The prevalence of cardiac and metabolic disorders such as type 2 diabetes mellitus, hypertension, dyslipidemia and obesity are significantly increased in hypogonadal individuals (2,3). Inflammation, insulin resistance and endothelial dysfunction are the fundamental contributors of the increased cardio-metabolic risk associated with hypogonadism (4-6).

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis (7). It is increasingly seen in advancing age and characterised by atherosclerotic occlusions in branches of aorta, classically at lower extremity arteries. PAD is associated with increased risk of cardiovascular morbidity and mortality and is a well-known predictor of coronary heart disease (CHD) and stroke (8-10). Documented risk factors for PAD are similar to CHD or stroke (i.e., age, diabetes mellitus, smoking, dyslipidemia, hypertension). Pathophysiologic mechanisms are also similar to other types of CVDs, which include inflammation and endothelial dysfunction (11,12).

Because the dysmetabolic features are present even in the very young age in patients with congenital hypogonadotrophic hypogonadism (CHH) (13,14), we designed the present study to search whether these patients had higher frequency of PAD and were at increased risk of systemic atherosclerosis. We used ankle brachial index (ABI) testing to define PAD, and determined markers of endothelial dysfunction, inflammation and insulin resistance.

2.Materials and Methods

2.1.Participant selection and basic procedures

In this single center, prospective study enrolees were selected among the outpatients attending to endocrinology clinic of the institution. The inclusion criteria were having CHH and no history of testosterone replacement or human chorionic gonadotropin (hCG) therapy. The exclusion criteria were having hypergonadotropic hypogonadism, past or current hormone replacement, and having any type of chronic diseases. The control group included age matched healthy volunteers with no chronic diseases. The study was approved by the institutional board of Kecioren Training Hospital, Ankara, Turkey, and informed consent was obtained from all participants.

The diagnosis of CHH was based on a failure to undergo spontaneous puberty, specific physical findings of hypogonadism, such as infantile genitalia (Tanner stages 1

or 2), eunuchoid proportions, high-pitched voice, and sparse male-pattern body hair; and laboratory results showing hypogonadotrophic hypogonadism (Low Testosterone, normal or low gonadotrophins and normal pituitary functions). Pubertal developments of the patients were assessed according to the Tanner stages. Pituitary hormones were evaluated in all patients to exclude panhypopituitarism. Pituitary or hypothalamic mass lesions were excluded by magnetic resonance imaging. Height and weight were measured with light indoor clothing, and body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m²). The waist circumference (WC) was taken above the iliac crest and at the natural waistline, after the patients exhaled.

2.2.Laboratory measurements

Blood samples were collected from the antecubital vein, between 08:00 and 09:00 h. after an overnight fasting. The samples were centrifuged for 15 min at 4000 rpm, aliquoted and immediately frozen at -80 C. Fasting blood glucose (FBG), total cholesterol, triglyceride (TG), and High Density Lipoprotein Cholesterol (HDL-C) levels were measured by the enzymatic colorimetric method with Olympus AU2700 auto analyzer using reagents from Olympus Diagnostics (Hamburg, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula (15). Serum basal insulin, testosterone, FSH and LH levels were measured by the electrochemiluminescence method with UnicelDXI 800 Access Immunoassay System (Miami, FL, ABD). Insulin sensitivity was calculated by using the homeostatic model assessment of insulin resistance (HOMA-IR) index by the formula, HOMA-IR= (insulin x glucose)/405 (16). High-sensitivity C-reactive protein (hs-CRP) level was determined in serum by immunoturbidimetric fixed rate method by Olympus AU-2700 autoanalyzer (Hamburg, Germany) (Minimum detectable concentration: 0.07 mg/L). Plasma Asymmetric dimethylarginine (ADMA) level was determined by ELISA (Immundiagnostik, Bensheim, Germany) (Minimum detectable concentration: 0.05 µmol/L)

2.3.Measurement and calculation of ABI

The technique described by Grenon et al. (17) was used for the ABI measurement with improved facilities (18). Armrests of 20 cm width were placed on the head of the stretcher at an angel of 30º to ensure the comfort of the arms. With the patient supine, four fully calibrated aneroid sphygmomanometers with velcro cuffs (ERKA, D-83646, Germany) were wrapped around extremities of the participant at the same time. During this process the participant was allowed to rest at least for five minutes before readings. Both of the brachial pulses in the upper extremities and tibias anterior and tibialis posterior pulses in the lower extremities were recorded. Measurements were obtained using a handheld 8-MHz Doppler instrument (Hadeco, Japan) using transducer gel. The first blood flow sound heard as the cuff was deflated was recorded. The readings were started from the right arm, followed by the right ankle, left ankle and left arm. The cycle was doubled and two values were recorded for each vessel. Mean value of the two measurements was considered as the final result for the respective vessel.

ABI was calculated based on the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) II guidelines (19). First, right and left ABIs were calculated separately by dividing the higher systolic blood pressures in each ankle (tibialis posterior or tibias anterior pulse) to the higher brachial systolic blood pressure measured in the right or left upper limbs. Then, the lower one of the right or left ABI values was considered as the final standard ABI value.

2.4.Statistical analysis

Commercially available software was used for the statistical analyses (SPSS version 23.0, SPSS Inc, Chicago, Illinois). Inter-group differences were analysed by Student's t-test and Mann–Whitney U test as appropriate. The correlations were performed by using the Pearson's or Spearman's Correlations tests. Predictors of a low ABI were examined by multiple logistic regression analysis. Differences were considered significant at $p<0.05$.

3.Results

3.1.Basic Characteristics

The clinical and laboratory characteristics of patients with CHH (n=49) and controls (n=37) are given in Table-1. The mean age of patients and healthy subjects was similar. CHH subjects had lower mean BMI but similar WC to controls. They also had lower mean SBP and higher total cholesterol and triglyceride levels. Plasma insulin level and calculated mean HOMA-IR score was higher in subjects with CHH. hsCRP levels were widely distributed in both subjects and controls and did not show any difference between the two group. CHH subjects had higher mean circulating ADMA level. Details of hormonal variables specific to hypogonadism can be found in Table-1.

3.2.ABI test results

Mean ABI value was 1.05 ± 0.13 in patients and 1.00 ± 0.10 in controls (NS). Frequency of a low ABI (≤0.9) diagnostic for lower extremity PAD was also similar in CHH patients (12.2%) and controls (13.5%) (Table-1). There was also no difference between the two groups when an ABI threshold ≤1,0 was applied but more than one quarter of participants fell in this classification.

The cross-sectional associations between presence of a low ABI and basic characteristics, hs-CRP, HOMA-IR and ADMA levels are displayed in Table-2. In the multivariable model none of the study parameter was a predictor of a low ABI value of ≤0,9.

4.Discussion

The frequency of a low ABI was similar in subjects with hypopgonadotropic hypogonadism and age matched healthy controls in this study. Compared to controls, patients with CHH had increased plasma mean ADMA level indicative of impaired endothelial functions and higher mean HOMA-IR score showing reduced insulin sensitivity.

Patients with hypogonadism have increased risk of cardiometabolic disease such as hypertension, type 2 diabetes or dyslipidemia (2,3). Although the exact mechanism of higher cardio-metabolic risk in hypogonadal patients is not clear, endothelial dysfunction, inflammation and insulin resistance are thought to be involved (4-6). In this study, increase in the level of ADMA, a condition showing endothelial dysfunction, in our group with CHH was the evidence of impaired endothelial functions (20). Moreover, endothelial dysfunction was accompanied by insulin resistance in our patients in comparison with controls. These results were not new and consistent with previ-

Table-1. Basic characteristics and ABI results.

	CHH (n=49) (Mean± SD)	Controls (n=37) (Mean± SD)	P
Age (yr)	21,82 ± 2,28	22,34 ± 1,20	0,236
BMI (kg/m²)	22,51 ± 3,90	25,00 ± 2,68	0,001
WC (cm)	85,27± 11,83	87,00 ± 7,38	0,443
SBP (mmHg)	116,36 ± 10,51	124,30 ± 10,93	0,007*
DBP (mmHg)	68,26 ± 8,30	69,61 ± 10,84	0,681
Glucose (mg/dl)	84,08 ± 10,33	88,00 ± 6,81	0,075
Total-C (mg/dl)	173,31 ± 33,71	157,06 ± 28,31	0,038
HDL-C (mg/dl)	46,63 ± 11,49	48,62 ± 9,13	0,210*
LDL-C (mg/dl)	98,39 ± 22,43	91,37 ± 25,87	0,223
Triglyceride (mg/dl)	116,06 ± 67,28	85,41 ± 36,80	0,047*
Total-Testosterone (ng/ml)	34,82 ± 28,38	478,38 ± 151,18	<0,001*
Free-Testosterone (ng/ml)	2,09 ± 1,03	16,67 ± 4,34	<0,001*
FSH (mIU/mL)	1,28 ± 2,26	2,85 ± 1,90	<0,001*
LH (mIU/mL)	0,65 ± 1,08	4,14 ± 1,60	<0,001*
Insulin (µU/ml)	18,08 ± 15,86	7,46 ± 10,02	<0,001*
HOMA-IR	3,85 ± 3,74	1,85 ± 2,54	<0,001*
hsCRP (mg/L)	3,31 ± 8,11	2,15 ± 5,48	0,506*
ADMA (µmol/L)	0,76 ± 0,15	0,49 ± 0,15	<0,001*
ABI	1,05 ± 0,13	1,00 ± 0,10	0,100
Low ABI (≤0.9) (%)	12,2	13,5	0,862**
ABI ≤1.0 (%)	26,5	37,8	0,263**

* Nonparametric test
**chi-square test
BMI: Body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Total-C: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, HOMA-IR: Homeostatic model assessment-insulin resistance, hs-CRP: High-sensitive C reactive protein, ADMA: Asymmetric dimethylarginine, ABI: Ankle brachial index

Table-2: Predictors of a low ABI (<=0.9)

Variable	Crude		Adjusted	
	OR (%95 CI)	P	OR (%95 CI)	P
Age	0,73 (0,45-1,17)	0,195	0,76 (0,46-1,25)	0,28
hsCRP	0,98 (0,87-1,10)	0,782		
Insulin	1,03 (0,99-1,06)	0,098		
HOMA-IR	1,11 (0,95-1,30)	0,173	1,11 (0,92-1,33)	0,24
BMI	1,15 (0,95-1,39)	0,142	1,03 (0,66-1,62)	0,87
WC	1,07 (0,99-1,14)	0,057	1,04 (0,90-1,22)	0,54
SBP	0,99 (0,94-1,05)	0,958		
Total-C	1,00 (0,98-1,02)	0,376		
Triglyceride	1,00 (0,99-1,01)	0,072	1,01 (0,99-1,02)	0,09
Total-Testosterone	1,00 (0,99-1,00)	0,841		
Free-Testosterone	1,00 (0,92-1,09)	0,860		
FSH	0,92 (0,65-1,31)	0,678		
LH	1,13 (0,85-1,49)	0,389		
ADMA	2,53 (0,11-58,08)	0,560	0,36 (0,003-46,002)	0,68

hs-CRP: High-sensitive C reactive protein, HOMA-IR: Homeostatic model assessment-insulin resistance, BMI: Body mass index, WC: Waist circumference, SBP: Systolic blood pressure, Total-C: Total cholesterol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, ADMA: Asymmetric dimethylarginine,

ous studies (13,21).

Frequency of a low ABI in the population of the study region was previously reported to be 5 to 20% in subjects aged 50 year or older (22,23). The patients and controls in the present study had comparable low ABI (□0.9) frequency by 12.2% and 13.5%, respectively, with no relevant signs or symptoms in their clinical evaluation. Thus, presence of a low ABI in these subjects should cautiously be considered as PAD and need to be discussed. Methodological limitations related to ABI testing were unlikely in our study due to improved measurement facilities and the guideline recommended calculation of the ABI. However, apart from possible inter-test variations in ABI values obtained at different occasions (24), ABI measurement to diagnose lower extremity PAD may itself not be completely reliable in younger people at the age of early twenties. Although the ABI testing is successful to diagnose PAD (25), its angiographically tested sensitivity was found as low as 79% in different populations (26) and 82.3% in the original population of the study region (27). Thus, even though these numbers were obtained in middle aged and older adults, false positive PAD diagnosis is not a marginal issue. In a recent study, Watanabe et al. studied the characteristics of ossilometric detection of ABI and toe-brachial index along with pulse volume recording of the ankle with brachial-ankle pulse wave velocity in healthy young adult population with the age of 20 to 25 (28). They found the frequency of ABI <1.0 as 18.1% in men and 25.6% in women. Moreover, TBI <0.7 was observed as 16.2% of the toes in men and 19.1% of the toes in women. In another previous study on people aged 20–29 years ABI <1.0 was observed in 8% of the men and in 19% of the women (29). We observed even a higher frequency of ABI 0.9 in our patients and controls probably due to use of Doppler technique. Because, ossilometric devices give higher ABI values compared with the Doppler method, particularly in the lower range readings as in the present study (30).

In older patients with PAD, impairment in endothelial functions was previously reported by measuring flow-mediated dilation (31,32) and circulating ADMA level (33). Concerning insulin resistance, age- and gender- adjusted PAD frequency was found increased in a graded fashion in increasing HOMA-IR quartiles in the National Health and Nutrition Examination Survey 1999–2004 with a mean age of 66.4 years (34). Subjects with CHH showed clues for presence of endothelial dysfunction and insulin resistance in the present study; but, in crude and adjusted multivariable regression analysis neither circulating ADMA level nor HOMA-IR score was a predictor of a low ABI value. It appears that the link between PAD and endothelial dysfunction or insulin resistance becomes evident by increasing age and is not an explanatory factor for having a low ABI value in patients with CHH.

Young patients with congenital hypogonadism having markers of endothelial dysfunction and insulin resistance were not found to have increased frequency of a low ABI in the present study. ABI might not be a sensitive tool to detect systemic atherosclerosis in young male subjects, and presence of a low ABI should not be over-interpreted in these subjects.

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