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BÜYÜME HORMONU YETERSİZLİĞİ OLAN HASTALARDA ERKEN ATEROSKLEROTİK DEĞİŞİKLİKLER

EARLY ATHEROSCLEROTIC CHANGES IN HIPOPITUITARY PATIENTS WITH GROWTH HORMONE DEFICIENCY

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ABSTRACT

Objective: Cardiovascular diseases have been implicated in excess mortality in adult hypopituitary patients (HP) who do not receive growth hormone (GH) replacement. GH deficiency induces a proatherogenic state. In this study we aimed to investigate endothelial function and early atherosclerotic changes in GH-deficient HP.

Material and methods: Endothelial function was assessed by flow mediated dilation (FMD) of the brachial artery. Demographic, anthropometric, endocrine and biochemical findings, brachial artery FMD and carotid artery intima-media thickness (IMT) were recorded.

Results: Nineteen HP not receiving GH (9 women, age: 42±16 years) and 19 healthy controls (6 women, age: 39±16 years) were enrolled. In HP, the waist circumference (94.5±13.2 cm vs. 86.8±8.7 cm, p=0.04), and the body fat mass (%) were found higher(30.9±9.1 vs. 23.8±8.6, p=0.02), the lean body mass (%) was found lower (69.0±9.1 vs. 76.1±8.6, p=0.01). The carotid artery IMT was higher (0.80±0.22 vs. 0.56±0.25, p=0.01) and the brachial artery FMD was lower (8.8±6.06 vs. 13.5±4.6, p=0.02) in HP compared to healthy controls. There was a significant correlation between patient age and carotid artery IMT in both groups; the association was more prominent in the patient group (r=0.8624 p<0.001 for patients, r=0.7859 p=0.001 for controls).

Conclusion: The decreased FMD in the GH-deficient HP established the endothelial dysfunction. The relationship between carotid artery IMT and age was more prominent in the hypopituitary group. Our findings suggest that endothelial function is impaired in HP and the effects of aging on atherosclerosis appear in a more pronounced way in HP.

Key words: Hipopituitarism, growth hormone deficiency, endothelial function

ÖZET

Amaç: Kalp ve damar hastalıklarının büyüme hormonu (BH) replasmanı almayan erişkin hipopitüiter (HP) hastalarda mortaliteye ek katkıda bulunduğu bildirilmektedir. BH eksikliği proaterojenik bir duruma neden olmaktadır. Bu çalışmada BH eksikliği olan HP hastalarda endotel fonksiyonu ve erken aterosklerotik değişiklikleri incelemeyi amaçladık.

Gereç ve yöntem: Endotel fonksiyonu brakiyal arterin akıma bağlı dilatasyonu (FMD) ile değerlendirildi. Demografik, antropometrik, endokrin ve biyokimyasal bulgular ile brakiyal arter FMD ve karotis intima-media kalınlığı (İMK) ölçümleri kaydedildi.

Bulgular: Çalışmaya 19 BH almayan HP hasta (9 kadın, 42±16 yaş) ile 19 sağlıklı kontrol (6 kadın, 39±16 yaş) alındı. HP hastalarda kontrollere göre kalça çevresi (94,5±13,2 cm vs. 86,8±8,7 cm, p=0,04), vücut yağ kütlesi (%) daha yüksek bulundu (30,9±9,1 vs. 23,8±8,6, p=0,02). HP hastalarda yağsız vücut kütlesi (%) daha düşüktü (69,0±9,1 vs. 76,1±8,6, p=0,01). Karotis İMK'sı hastalarda kontrollere oranla daha yüksek (0,80±0,22 vs. 0,56±0,25, p=0,01), brakiyal arter FMD'si ise daha düşüktü (8,8±6,06 vs. 13,5±4,6, p=0,02). Her iki gruptada hasta yaşı ile karotis İMK'sı arasında anlamlı bir korelasyon mevcuttu ancak ilişki hasta grubunda daha belirgindi (hastalar için r=0,8624 p<0,001, kontroller için r=0,7859 p=0,001).

Sonuç: BH eksikliği olan HP hastalardaki düşük FMD endotel disfonksiyonunu ortaya koymuştur. Hipopitüiter grupta karotis İMK'sı ile yaş arasındaki ilişki daha belirgindi. Bulgularımız HP hastalarda endotel fonksiyonunun bozulduğuna ve yaşlanmanın ateroskleroz üzerine etkilerinin daha belirgin hal aldığına işaret etmektedir.

Anahtar kelimeler: Hipopitüitarizm, büyüme hormonu yetersizliği, endotel fonksiyonu

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INTRODUCTION

Life expectancy of hypopituitary patients (HP) is decreased despite adequate replacement therapy (adrenal, gonadal and thyroid hormones) without growth hormone (1). Growth hormone deficiency (GHD) has been implicated in this observation. The excess mortality was not due to the primary disease itself but to cardiovascular diseases. Metabolic changes accompanying GHD are the main causes of increased vascular mortality in HP (2).

Tomlinson and colleagues demonstrated that standard mortality rate was significantly higher than healthy controls in a cohort of 1014 HP (3). The excess mortality was attributed to cardiovascular, cerebrovascular and respiratory diseases. Another recent study compared the risk of death due to cerebrovascular accidents in HP and healthy controls. An increased standard mortality ratio was determined especially in women. The authors established a relatively higher risk in patients who became hypopituitary at younger ages (4).

Epidemiological studies demonstrated the increased incidences of ischemic heart disease and cardiac failure in HP receiving conventional replacement therapy. This increase in mortality may be related with increased cardiovascular risk factors such as truncal obesity, insulin resistance, dyslipidemia, endothelial dysfunction and hypertension due to GHD in HP (5, 6). Although GH treatment was shown to improve body composition and the lipid profile, whether the mortality risk is decreased or not remains to be elucidated (7).

Endothelial dysfunction due to decreased nitric oxide (NO) has been recently identified as an early marker of atherosclerosis (8,9). Endothelial dysfunction has a predictive role for future coronary events even before atherosclerotic changes develop (10,11). Therefore, assessment of endothelial function may help early identification of individuals at risk. Flow mediated dilation (FMD) which reflects the dilation response of the arterial diameter to reactive hyperemia, is an endothelium-dependent phenomenon. The increased flow causes dilation via increased NO synthesis in arteries with a healthy endothelium. FMD which can be assessed non-invasively by ultrasonography is a parameter that reflects endothelial function in large vessels (8,12). Another method for the assessment of early atherosclerotic changes is the measurement of the intima media thickness (IMT) in the carotid artery. Ultrasonographic measurement of IMT in the extracranial segments of the carotid arteries revealed a correlation between increased thickness and increased prevalence of coronary heart disease. In populations without hypopituitarism, well-known risk factors for atherosclerosis were found to be associated with carotid artery IMT (13, 14).

The aims of this study were to investigate early atherosclerotic parameters (carotid artery IMT and endothelial dysfunction) in HP and healthy controls, to identify the relationships between these parameters and demographic, anthropometric and metabolic findings.

MATERIAL and METHODS

The study was conducted in accordance with the Helsinki Declaration on biomedical investigations on human subjects. All the subjects gave informed consent before participation. Nineteen patients with the diagnosis of adult onset hypopituitarism and 19 healthy controls were enrolled in the study. The patients were stable for at least 6 months under conventional replacement therapy (glucocorticoid, thyroid hormone, sex hormone and when needed, desmopressin). Nineteen healthy people selected from hospital workers and patient relatives formed the control group. Nonfunctional pituitary adenoma was the most frequent cause of hypopituitarism (Table 1).

Table 1. Causes of hypopituitarism in the patient group

Causes	No. of patients
Non-secreting pituitary adenoma	8 (42%)
Craniopharyngioma	3 (15%)
Prolactinoma	2 (10%)
Sheehan syndrome	2 (10%)
Primary empty sella	2 (10%)
Suprasellar dysplasia	1 (5%)
Pinealoma	1 (5%)

Patients with known cardiovascular diseases, chronic conditions that may affect endothelial function or symptoms suggestive of cardiovascular diseases were excluded from both groups.

GH deficiency was diagnosed by the absence of at least 3 pituitary hormones and an IGF-1 level lower than 86 ng/mL (>2 standard deviations lower than the mean of the control group) and/or a maximal GH level less than 3 ng/mL in the glucagon stimulation test.

The doses of conventional replacement were optimized according to clinical findings, biochemical results and serum hormone levels. All patients were receiving their usual regimes when they were enrolled in the study. Venous blood samples were collected for biochemical parameters (glucose, total cholesterol, triglycerides) and hormone tests (free T4 and lGF-1). Serum IGF-1 level was measured by the immunoradiometric assay (IRMA) using a DSL 5600 ActiveTM IGF-1 with extraction kit (Diagnostic Systems Laboratories, Inc., Webster, Texas, USA-2000). Free T4 level was measured by chemiluminescence technique with the 'Immunolite 2000' device.

In both groups, after 10-12 hours of fasting (between 08:00-08:30 AM) physical examination and arterial blood pressure measurement were performed in the resting supine position. The body weight, height, waist and hip circumferences were also measured. Body composition was assessed by bioelectric impedance analysis in the morning with the 'Bodystat 1500' apparatus (Bodystat Ltd., Douglas Isle of Man, British Isles, Great Britain). The body fat mass, body water content and lean body mass were calculated with the aid of the apparatus.

Endothelial function and carotid artery IMT measurements were performed in the morning after 10-12 hours of fasting following anthropometric measurements and withdrawal of blood samples. The patients abstained from smoking for 12 hours and did not consume caffeine-rich drinks.

Brachial artery FMD measurement was performed on the dominant arm with the 'Vingmed System Five' (General Electric, Hortan, Norway) via a 10 MHz linear probe. The basal and hyperemic brachial artery diameters were determined as previously described (9). FMD was obtained with the following formula:

FMD= % mean diameter after hyperemic flow-basal diameter / Basal diameter

At end of the study, the data were analyzed by two specialists independently. Inter-observer and intra-observer variability for measurements of brachial artery diameter were 4.1 and 3.7 %, respectively.

The carotid arteries were also evaluated with the 'Vingmed System Five'. The IMT of the carotid arteries were measured in the proximal segment of the carotid bulb. Three measurements were made for each side of the body; separate means were calculated and recorded as the right and left IMT. None of the patients had stenosis, atheroma plaque or local thickening >2 mm in the carotid arteries. The intra-observer coefficient of variation for carotid IMT was %2.9.

STATISTICAL ANALYSIS

Statistical analyses were performed with the 'Statgraphics/PCV 5.0' program (Statistical Graphics Corporation, USA). The patient and control groups were compared with the unpaired t-test. The relationship between various parameters was assessed by the regression analysis. 'Pearson correlation coefficient' (r) was calculated. A p value of < 0.05 was considered significant.

RESULTS

The mean duration of sickness was 84.2 ± 42.2 months. One woman in each group was in the postmenopausal stage; these patients did not receive sex hormone replacement. None of the study group patients received GH replacement. The patient and control groups were similar with respect to gender, age, BMI. The findings of resting electrocardiograms (ECGs) of all subjects were within normal limits. The frequencies of smokers in the two groups were the same (4/19, 21%). The two groups did not differ significantly with respect to total cigarette consumption (8.7 ± 4.9 pack-years *versus* 9.0 ± 7.5 pack-years in the study and control groups respectively).

The demographic and anthropometric data are shown in Table 2. There were no significant differences between the groups with respect to gender, age, BMI, hip circumference, waist/hip ratio (WHR), systolic and diastolic blood pressures ($p > 0.05$). The waist circumference ($p=0.04$) and body fat mass (expressed as % of body weight and kg; $p=0.02$ and $p=0.01$ respectively) were significantly higher in the patient group. There was no significant difference between the groups in lean body mass expressed in kg; the result was significantly lower in the patients when it was expressed as % of body weight ($p=0.01$).

Table 2. Demographic and anthropometric data of the patients and controls

	Hypopituitary patients	Control group	p
Gender(woman/man)	9/10	6/13	0.54
Age (years)	42.57±16.28	39.57±16.10	0.57
Weight (kg)	73.0±12.43	69.34±8.86	0.30
Height (cm)	163.78±11.83	165.78±8.50	0.55
BMI (kg/m^2)	27.33±4.73	25.23±2.77	0.10
Waist (cm)	94.55±13.24	86.84±8.70	**0.04**
Hip (cm)	106.33±9.62	101.78±13.30	0.06
WHR	0.8838±0.083	0.8489±0.079	0.19
Systolic pressure (mmHg)	119.21±15.47	114.21±10.70	0.25
Diastolic pressure (mmHg)	80.0±9.27	76.05±8.09	0.17
Body fat mass* (%)	30.95±9.19	23.89±8.69	**0.02**
Body fat mass* (kg)	22.84±8.76	16.38±5.76	**0.01**
Lean body mass* (%)	69.04±9.19	76.15±8.68	**0.01**
Lean body mass* (kg)	50.15±9.69	53.20±10.95	0.36

BMI; body mass index, WHR; waist/hip ratio
* determined by bioelectric impedance analysis

Table 3. Biochemical and endocrinological data of the patients and controls

	Hypopituitary patients	Control group	p
Glucose (mg/dL)	75.66±16.12	86.83±10.21	**0.01**
Cholesterol(mg/dL)	213.72±41.65	180.89±41.97	**0.02**
Triglycerides(mg/dL)	119.88±63.58	120.78±52.57	0.96
HDL-cholesterol (mg/dL)	46.16±13.33	43.57±8.13	0.47
LDL- cholesterol (mg/dL)	137.72±31.40	111.0±31.66	**0.01**
VLDL-cholesterol (mg/dL)	27.83±19.41	29.94±15.10	0.71
FreeT4 (pmol/L)	15.46±3.32	14.67±1.81	0.38
IGF-I (ng/ml)	71.28±48.33	294.63±104.51	<**0.001**

Although the serum glucose levels of the HP were significantly lower ($p=0.01$), the levels of all patients were

within normal limits. The total cholesterol and LDL cholesterol levels were significantly higher in the patient group (p=0.02 and p=0.01 respectively). The triglyceride, HDL cholesterol and VLDL cholesterol levels were similar. There was no significant difference between the serum T4 levels of the HP receiving conventional replacement and healthy controls whereas IGF-1 levels were significantly lower in the HP group (p< 0.001) (Table 3).

Table 4. Carotid artery IMT and brachial artery measurement in relation to endothelial function in hypopituitary patients and healthy controls

	Hypopituitary patients	Control group	p
IMT (mm)	0.80±0.22	0.56±0.25	**0.01**
Basal diameter (mm)	3.16±0.48	3.52±0.38	**0.03**
FMD (%)	8.8±6.06	13.5±4.6	**0.02**

The carotid artery IMT was significantly higher in HP (p=0.01). The basal brachial artery diameter in HP was significantly lower than those of controls (p=0.03). Hyperemic FMD results were significantly lower in the patient group (p=0.02). The carotid artery IMT and brachial artery FMD results of the patients and controls are shown in Table 4.

Table 5. Carotid artery IMT and brachial artery FMD in hypopituitary and healthy women and men

	Hypopituitary women	Control group	p
IMT (mm)	0.73±0.18	0.46±0.15	**0.02**
FMD %	8.8±6.5	13.8±6.07	0.24

	Hypopituitary men	Control group	p
IMT (mm)	0.85±0.25	0.63±0.28	0.11
FMD %	7.8±5.4	13.3±4.5	**0.03**

In women, the carotid IMT of HP was higher than the IMT in controls (p=0.02). The brachial artery FMD values of the hypopituitary men were lower than those of healthy controls (p=0.03). The FMD in hypopituitary women and carotid IMT in men did not differ significantly from corresponding values in controls (Table 5).

There was a statistically significant correlation between the FMD and hip circumference (r=0.52, p=0.03) in HP. In both groups, there was a negative association (significant in HP) between the FMD and brachial artery basal diameter (r=-0.59, p=0.01 and r=-0.50, p=0.07).

There was a significant correlation between carotid artery IMT and age in both HP (r=0.86, p<0.001) and healthy controls (r=0.78, p= 0.001). The association was stronger in the patient group. Carotid artery IMT showed significant positive correlations with body weight (r=0.67, p=0.001), height (r=0.51, p=0.02) and body fat mass in kg (r=0.51, p=0.02) in the patient group. In the patient group, a positive correlation between the IGF-1 and serum glucose level was present (r=0.59, p= 0.01). In the control group, IGF-1 showed negative correlations with age (r=-0.75 p<0.001), waist circumference (r=-0.56 p=0.01), WHR (r=-0.60 p<0.01), serum total cholesterol (r=-0.46 p=0.04) and body fat mass (r=-0.49 p=0.03). A positive correlation was also present between the lean body mass and IGF-1 level (r=0.48 p=0.04).

DISCUSSION

Epidemiological studies revealed an increased incidence of ischemic cardiovascular disease in HP receiving conventional replacement therapy. Current data suggest a cause-effect relationship between the GH deficiency and increased cardiovascular morbidity and mortality (2, 5).

Early signs of atherosclerosis have been detected in the peripheral arteries and aortas of asymptomatic HP (15). Carotid artery ultrasonography in these patients revealed increased IMT, intimal plaque formation and decreased arterial flexibility (15, 17). Currently, increased IMT is considered as a precursor lesion of asymptomatic atherosclerosis. Increased IMT in the extracranial parts of the carotid arteries was found to be associated with an increased prevalence of coronary heart disease (13). Prolonged GH deficiency in adults sets the stage for early development of atherosclerosis. In the present study, the increased fat mass and waist circumference and decreased lean body mass in HP were found to be the body composition changes brought about by GH deficiency. The increased cholesterol and LDL cholesterol in HP reflect the effects of GH deficiency on lipid composition and are in accordance with the results of the previous studies (18). Although these changes may cause early atherosclerosis, IMT showed significant positive associations with age, weight, height and body fat mass only. We determined a strong correlation between age and IMT. This observation suggests that the effects of aging on atherosclerosis are more pronounced in this patient group.

To investigate the natural history and clinical implications of partial GHD, Colao A et al. have studied 27 HP (19). Severe GHD has been accompanied by other alterations such as impairment of lipid profile, with increase of insulin resistance, and increased IMT at common carotid arteries, indicating early atherosclerosis. Slight increase of IMT has been found in the control population as well as in the patients who normalized GH secretion, but the magnitude of the effect has been found greater in patients who has developed GHD and in those showing persistent partial GHD (19).

In accordance with the present results, studies on endothelial function in HP revealed signs of endothelial dysfunction and early atherosclerosis. In a study by Evans et al (20), FMD showed significant negative correlations with the total cholesterol level in both hypopituitary and control patients. In another study by Evans et al (21), 8 patients with hypopituitarism were examined and it was emphasized that endothelial dysfunction was a part of the clinical picture of GHD. The authors suggested also that GH replacement restored endothelial dysfunction (20, 22). In our study, there was no significant relationship between the FMD and clinical, anthropometric or biochemical parameters.

Pfeiffer and colleagues reported a resolution of endothelial dysfunction and a decrease in carotid artery IMT after 3 months of GH replacement in HP (7). However, in their study, no

association between plasma lipid levels, endothelial function and IMT were detected. This observation may be explained in part by the plasma lipid concentrations are inadequate for reflecting early atherosclerotic changes which starts with LDL oxidation in the arterial wall. Oliveira et al. showed the presence of increased abdominal obesity, higher total and LDL cholesterol levels in GHD patients than controls (23). No increase in carotid IMT, and no evidence of premature atherosclerosis as evaluated by exercise echocardiography have been found in untreated severe isolated GHD patients (23).

The concentrations of NO metabolites are increased in HP with GHD (24). Decreased NO activity results with decreased endothelium-dependent vasodilation, increased platelet aggregation, increased leukocyte adhesion to the endothelium and intimal thickening (25, 26). IGF-1 may directly stimulate NO synthesis (27). Decreased IGF-1 levels in GHD were implicated in decreased NO production in GHD (28). GHD may cause endothelial dysfunction through decreased NO production or increased inactivation of NO by free radicals.

In our study, the brachial artery diameter of HP was significantly lower than the controls'. A significant negative correlation between the basal diameter of the brachial artery and FMD was also present in HP. This finding corroborates the observations on endothelial dysfunction in HP. The carotid IMT was significantly increased in female HP when compared to healthy controls but we did not determine a statistically significant increase in male HP, although they had an increasing trend. In our study, FMD was found to be similar between HP and healthy controls among women while it was significantly reduced among HP men. These differences may be partially associated with small number of subjects in each subgroup.

Our results revealed that FMD was significantly and positively correlated with hip circumference in HP. This finding supports the observation that regional fat deposition at the femoro-gluteal region may have protective effects against atherosclerosis.

In the control group, IGF-1 showed significant correlations with anthropometric and metabolic parameters. This may be taken to suggest that IGF-1 exerts anti-atherogenic effects in healthy adults. There are IGF-1 receptors on endothelial cells. IGF-1 stimulates NO release (28). The positive correlation between IGF-1 and lean body mass was compatible with the association between body fat content and distribution and unfavorable cardiovascular risk factors. In our study, the negative correlations between the IGF-1 level and total cholesterol, waist, and waist/hip ratio were striking.

The basal glucose level of the patient group was significantly lower than that of the control group. This may attributed to the secondary hypocortisolemia in these patients. The positive correlation between the IGF-1 and basal glucose level in HP, may be explained by the counter-insulin effects of the growth hormone.

The atherosclerosis changes seen in HP may not be related to conventional cardiovascular risk factors. The change in the body fat composition, development of central obesity, insulin resistance, peptides such as endothelin-1 and angiotensinogen released from fat tissue, plasma oxidant/antioxidant status may accelerate atherosclerosis in GHD. Further studies are needed to investigate the possible beneficial effects of GH replacement against accelerated atherosclerosis. Surveys and epidemiological studies suggest that there is need to develop new criteria or modify existing ones to elucidate the management of increased atherosclerosis risk in HP.

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