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The evaluation of endothelial function and structure in hirsute patients in reproductive age

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ABSTRACT

Objective: To evaluate the endothelial function and structure in patients with hirsutism in reproductive age.

Study design: The study was conducted on 69 consecutive women admitted with complaints of hirsutism and 63 voluntary healthy women, as controls. A total of 132 subjects who applied to the Gynecology and Infertility Outpatient Clinics were included. Participants with modified Ferriman Gallway (mFG) score over 8 were considered to be hirsute. The demographic, metabolic, hormonal characteristics, risk factors of cardiovascular disease, CIMT (carotis intima media thickness) and FMD (flow-mediated dilatation) were compared between hirsute women and those in the control group. A prospective case-control study was performed.

Results: There was no statistically significant difference in CIMT (0,50 ± 0,08 vs 0,52 ± 0,08, p = 0.38) and FMD (10,80 ± 6,83 vs 9,57 ± 6,52, p = 0.34) values between the study and control groups, respectively. There was no statistically significant correleation between CIMT and FMD values with age, body mass index (BMI), waist circumference, hip circumference, waist/hip ratio, CRP (C-reactive protein), total cholesterol, LDL (low density lipoprotein), HDL (high density lipoprotein), total testosteron, FAI (free androjen index), androstenedion, SHBG (sex hormone binding globuline), DHEA-S, hirsutism score, sistolic blood pressure, diastolic blood pressure, HOMA-IR (homeostatic model of assesment insuline resistance) value.

Conclusion: The effect of the presence of hirsutism on either CIMT and FMD values, among young patients was not significant. Since endothelial dysfunction might became evident after a long period of physio-pathological process, our findings obtained from younger patients may not really show the impact of hirsutism on endothelial function in short term.

Introduction

Hirsutism, which is defined as excessive increase of terminal hair with a male pattern in regions sensitive to androgen, may affect approximately 5–10% of the women in fertile ages [1–3]. Hirsutism occurs as a result of androgenic effect on pilosebaceous unit and is usually correlated with acne and oily skin [4]. The most common causes of hyperandrogenism are polycystic ovarian syndrome, late onset adrenal hyperplasia androgen secreting tumors and idiopathic conditions [5].

Previous studies reported the association between hyperandrogenism and endothelial structure and function [6]. Dyslipidemia and atherogenic endothelial structure due to high levels of androgen in hyperandrogenic patients were reported. Hence high serum level of androgen was indicated as a risk factor for cardiovascular and metabolic disorders [7]. Furthermore hyperandrogenism was considered to increase the risk of cardiovascular events and coronary artery disease in the patients with polycystic ovarian syndrome [6,8].

The most significant changes in subclinical period of atherosclerotic disease are increased intima-media thickness (IMT) and endothelial dysfunction in whole arterial bed [9]. Preventive measures should be taken before atherosclerotic diseases become clinically evident. Thus, early detection of atherosclerotic changes is critical in order to mitigate the risk factors [9,10].

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Endothelial function can be determined with flow mediated dilatation (FMD), which is a non-invasive, easy to apply and repeatable method [11]. It was shown in previous studies that IMT correlates with FMD, which is a good indicator of endothelial function. Endothelium regulates its own tonus, thus adjusts blood flow and distribution according to local environmental changes. Most of the veins respond to the flow increase, i.e. strain stress, with dilation. This is called flow-mediated dilation [12]. Ultrasonographic assessment of carotid arterial intima-media thickness is a sensitive, specific and noninvasive diagnostic procedure in evaluation of the early pre-clinical period of systemic atherosclerosis. Increased carotid arterial intima-media wall thickness (IMT) is an important predictor for cardiovascular events that may occur in the future [9].

Many studies were performed on PCOS patients investigating the endothelial structure with CIMT and FMD. However they had different results [13–15].

In our study, our aim was to determine endothelial structure and dysfunction by using methods of carotid intima-media thickness and flow-mediated dilation measurement of the brachial artery in the patients with hirsutism.

Materials and methods

The study was carried out with a group of 132 women between the ages of 18–35 years. 69 patients was diagnosed with hirsutism, and 63 healthy subjects without hirsutism were chosen as the control group. The study was conducted at General Gynecology or Infertility outpatient clinics, University Affiliated Training and Research Hospital between September 2012 and September 2013. Sixty nine consecutive women with the complaint of hirsutism were included. The study was approved by the Institutional Review Board of Marmara University and the Local Ethics Committee. All patients gave written informed consent and their complete clinical, obstetric, and gynecologic history was taken before enrollment.

Patient selection

The study group was composed of women who applied to the clinic with excessive hair growth and diagnosed with hirsutism. The modified Ferriman–Gallway scale (mFG) was used for diagnosing hirsutism. Patients with a mFG score of $\geq$8 according to the scoring system was diagnosed as hirsutism. The control group was composed of voluntary healthy women who applied to the out-patient clinics and had mFG scores lower than 8.

Exclusion criteria

Patients with systemic diseases such as non-classical adrenal hyperplasia (21-hydroxylase deficiency), Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, androgen secreting tumor and diabetes mellitus, hypertension as well as hirsute patients who had received medical treatment within the last 6 months were excluded from the study.

Study protocol

Detailed obstetric and gynecologic, medical as well as surgical history were taken. Oligo/anovulation diagnosis was made when there was either a history of oligomenorhea (more than 6 cycles lasting over 36 days in a year [16]), amenorhhea (no menstruation during consecutive 3 cycles at a minimum [16]) or when mid-luteal phase serum progesterone level in woman with regular menstrual cycle was less than 5 ng/dl.

The height and weight of each patient was obtained with them wearing indoor clothing and without shoes. BMI was then calculated as weight (kg) divided by square of height (m). Women with BMI 19–25 were considered normal, those with BMI 25–30 were considered overweight and those with BMI $\geq$ 30 were considered obese [17]. Systolic blood pressure and diastolic BP were measured twice on both arms using a calibrated aneroid sphygmomanometer after the subject had been resting in supine position for at least 5 min; the average of two measurements was used in analysis. Age of menarche, menstrual cycle characteristics were questioned.

The modified Ferriman Gallwey scoring method was used for hirsutism scoring. Women with scores of 8 and above were accepted to have clinical hirsutism [18]. Regarding hirsutism severity, mild hirsutism was defined as having a mFG score of 16–25 and severe hirsutism by $\geq$25 [18]. Male type hair growth, acne, oily skin and alopecia are all accepted as clinical hirsutism symptoms. PCOS was diagnosed by using ASRM/ESHRE (Rotterdam) 2003 criteria [19].

Laboratory studies

Venous blood samples of the participants were taken during early follicular phase between the 3rd and the 5th days of their spontaneous or gestagen induced menstrual cycles.

Serum FSH, LH, Testosteron, DHEA-S, TSH, Prolactin and insulin levels were analyzed by electrochemiluminesence immunoassay (ECLIA) (Elecsys systems 1010/2010/modular Analytics E170 (Elecsys module), Roche Diagnostic Gmbh, D-68298, Mannheim/Germany) method; estradiol levels were analyzed with immulite chemiluminesence competitive immunoassay (DPC, Los Angeles) method. Fasting glucose, HDL, LDL, triglycerides levels were analyzed via spectrophotometric method (Roche Diagnostic Gmbh, D-68298).

Evaluation for insulin resistance was carried out by means of Homeostatic Model Assessment (HOMA—IR score, fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mg/dl)/405) [20,21]. 75 g OGTT was applied to the cases with impaired fasting glucose level (110–125 mg/dL) and the cases diagnosed with diabetes mellitus were excluded from the study. Free androgen index (FAI) was calculated with the formula ((total testosterone/SHBG) $\times$ 100) [22]

Imaging studies

Ovarian ultrasonography was assessed by using 10-Mhz vaginal or 6-Mhz abdominal probe (Mindray: DC—T6; Shenzhen Mindray Bio-Medical Electronics Co., Ltd.; Shenzhen, China). Polycystic ovary was defined according to the polycystic ovary definition stated in ESHRE/ASRM 2003 Rotterdam Convention.

Carotid artery intima media thickness (CIMT) was measured while the patient was in supine position, with the neck being in slight extension and the head being rotated contrary to the examined side. The examination was carried out by using a ultrasound device with 7.5-MHz linear probe (Mindray: DC—T6; Shenzhen Mindray Bio-Medical Electronics Co., Ltd.; Shenzhen, China). The right and left carotid artery intima media thickness were examined. A plaque-free segment in the size of 1 cm within the first 3 cm site from bilateral main carotid artery bulbus was determined and measurements were taken therefrom. In order to ensure standardization, all measurements were taken by the same physician. Intraobserver variation was determined as 10%.

In order for examination of endothelial dysfunction in brachial artery, "Flow Mediated Vasodilation (FMD)" technique was used. This technique was performed mainly on the basis of the guidelines reported by Coretti et al. [23]. In order to assess if FMD occurred after hyperemic response, the brachial artery was