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Comparison of metabolic profile and abdominal fat distribution between karyotypically normal women with premature ovarian insufficiency and age matched controls

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ABSTRACT

Objective: We designed a prospective case-control study in order to investigate the lipid profiles, insulin sensitivity, presence of metabolic syndrome (MetS) and the abdominal fat distribution in karyotypically normal women with premature ovarian insufficiency (POI).
Methods: Anthropometric measurements, FSH, estradiol, total testosterone (T), sex hormone binding globulin (SHBG), free androgen index (FAI), fasting glucose and insulin, homeostatic model for insulin resistance (HOMA-IR), lipid profile, the prevalence of MetS and ultrasonographic abdominal fat measurements were assessed in 56 women with POI and 59 healthy controls at the same age range.
Results: Serum levels of T, SHBG and FAI were not significantly different between both groups. Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were higher in women with POI. There were no differences in glucose, insulin, HOMA-IR, low-density lipoprotein cholesterol (LDL-C), triglyceride levels between the two groups. A significant positive correlation was identified between T and TG and also between FAI and LDL-C; SHBG levels were correlated inversely with FSH, and positively with HDL-C in women with POI. The presence of MetS was significantly higher in women with POI. The subcutaneous, preperitoneal and visceral fat thicknesses were not significantly different between the groups.
Conclusions: Early cessation of ovulatory function may associated with higher levels of serum TC and HDL-C, but does not seem to cause differences in abdominal fat distribution in women with POI. POI is associated with higher risk of MetS.

1. Introduction

Cardiovascular diseases (CVD), including heart disease and cerebrovascular disease are the leading causes of mortality for women [1]. CVD is rarely seen in premenopausal women, but its incidence increases markedly after menopause [2]. Menopause is associated with increased body mass index (BMI) and redistribution of body fat in favor of abdominal adipose tissue [3]. Central distribution of body fat and menopause-induced estrogen deficiency leads to increased risk of cardiovascular and metabolic diseases [4]. Estrogen acts like an antioxidant and has vasodilating effects on cardiovascular system, it has also proven that estrogen decreases the levels of total cholesterol and low density lipoprotein cholesterol [4,5]. According to the recent studies, the rate of CVD later in life was higher among women with an earlier age at menopause [6,7]. On the contrary, no difference in CVD risk factors were identified in premenopausal women compared with postmenopausal women in some other studies [8,9]. Therefore, premature ovarian insufficiency (POI) may provide important information to disentangle the impact of menopause from that of age effects on lipid and glucose profiles.

Premature ovarian insufficiency (POI) is defined as amenorrhea of at least 4–6 months duration with elevated FSH concentrations (FSH > 40 mIU/ml) under the age of 40 years [10]. Excluding patients with abnormal chromosomal constitution, spontaneous premature ovarian insufficiency affects approximately 1% of the normal population [11]. Although, the etiology is unknown in the majority of spontaneous POI cases, it may have a variety of possible causes including infections, genetic, metabolic and autoimmune causes [12]. Since young women with premature

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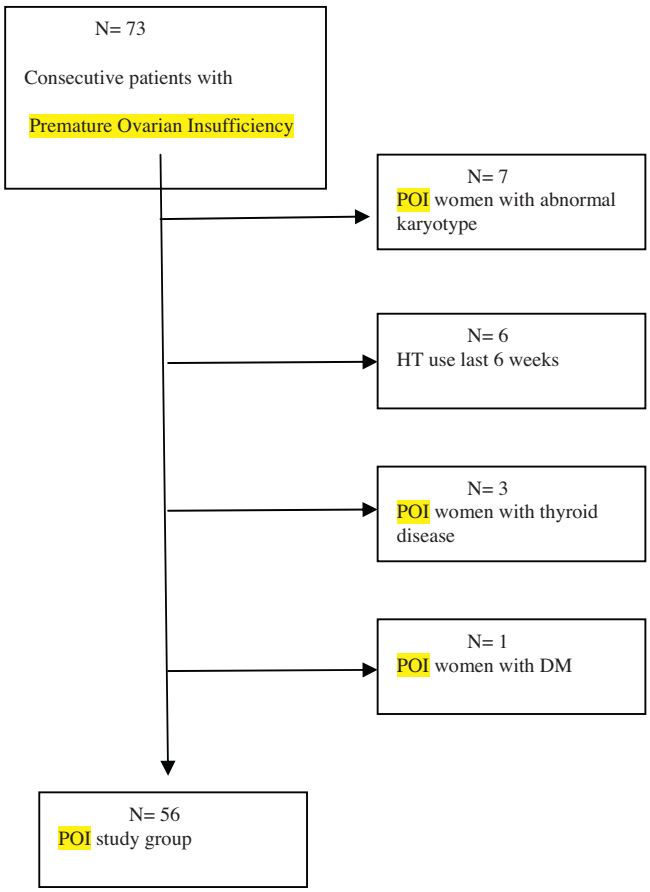

Fig. 1. Flowchart for the selection of women. POI, premature ovarian insufficiency; HT, hormone therapy; and DM, diabetes mellitus.

ovarian insufficiency have estrogen deficiency longer than naturally menopausal women, they have a higher risk of CVD and thereby premature death [2,5,12].

The purpose of the present study was to investigate the lipid profiles, insulin sensitivity, the presence of metabolic syndrome (MetS) and the abdominal fat distribution in karyotypically normal women with POI. The results were compared with a control group of regularly cycling women in the same age range.

2. Method

We studied 56 consecutive women who were newly diagnosed with POI between November 2011 and December 2013 in the outpatient clinic of Obstetrics and Gynecology, Bezmialem Vakif University, Istanbul, Turkey. The diagnosis of POI was made by the presence of at least 4 months of secondary amenorrhea, serum FSH values greater than 40 mIU/mL on two occasions at least 1 month apart before the age of 40 years. A total of 73 consecutive patients were diagnosed with POI in this prospective case-control study. Women were usually referred to the outpatient clinic for evaluation of menstrual irregularity or infertility. After excluding women who had abnormal karyotypes ($n = 7$) or received any hormonal therapy in the previous 6 weeks ($n = 6$) and women with diabetes mellitus ($n = 1$) or with thyroid disease ($n = 3$), a total of 56 women with normal 46,XX chromosomal constitution were included for further analysis (Fig. 1). We excluded POI women who had abnormal karyotypes from the study in order to provide a homogenous group. We defined POI as familial when the family history revealed at least two first or second-degree female family members affected by POI. This study was approved by the Ethics Committee of our hospital and written informed consent was obtained from all patients before entering the study.

The control group consists of 59 healthy women with regular menstrual cycle in the same age range and normal ovaries on ultrasonography and who did not take hormonal contraception or any medication were admitted to the clinic for other gynecologic disorders such as bacterial vaginosis during the study period. The smoking history was recorded but it was not a criterion for exclusion from the study. All subjects also underwent a transvaginal ultrasound or, rarely, a transabdominal ultrasound which revealed no abnormalities of the ovaries and endometrium. Antral follicules were observed in 39 patients with POI. Out of 56 patients 19 had no antral follicles. Eight patients who were virgin and undergone transabdomianl ultrasonography but the presence of antral follicles were not assessed properly.

Women were asked about their age, age at menarche, medical history, parity, education level, smoking status (yes or no), and familial history of POI and cardiovascular diseases. Anthropometric measures or indexes, such as body mass index (BMI) and waist circumference (WC), hip circumference, waist to hip ratio (WHR), body weight, height and blood pressure (BP) were evaluated in all subjects. BMI was calculated as weight (kg) divided by the square of height (m^2). Waist circumference was measured as the smallest circumference at the level of the umblicus and hip circumference was measured at the levels of the major trochanters through the pubic symphysis.

All blood samples were drawn in a fasting state for measurement of serum FSH, LH, estradiol (E2), total testosterone (T), sex hormone binding globulin (SHBG), glucose, insulin and lipid profile (Trigliserid [TG], total cholesterol [TC], high-density lipoprotein cholesterol [HDLC], low-density lipoprotein cholesterol [LDL-C]). In the control group, blood samples were taken during the early follicular phase of their menstrual cycle (days 2–5). Free androgen index (FAI) was calculated as total T/SHBG × 100 [13]. Insulin resistance was estimated by homeostasis model assessment using the following formula: HOMA-IR = [plasma glucose (mmol/l) × insulin (lU/ml)]/22.5 [14]. TG, TC, HDL-C, LDL-C and glucose were measured using enzymatic and colorimetric methods (Roche/Hitachi cobas c system). FSH, LH, E2, T, SHBG, and insulin were measured with chemiluminescent immunoassay using ADVIA Centaur XP (Siemens Healthcare Diagnostics, NY, USA). Karyotype analysis has been performed for all POI patients.

MetS was defined according to modified The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III guidelines) criteria, if at least three of the following five features were present: waist circumference >88 cm, serum HDL-C <50 mg/dl, serum triglyceride >150 mg/dl, blood pressure >130/85 mmHg or specific treatment of previously diagnosed hypertension, and fasting blood glucose >110 mg/dl [15].

The distribution of body fat was estimated by measuring subcutaneous, preperitoneal and visceral fat thickness. Ultrasound examination of the subcutaneous and preperitoneal fat areas were performed with a 5–14 MHz linear transducer and the examination of visceral fat areas with a 4–1 MHz convex transducer (Antares, Siemens, Erlangen, Germany) by a single experienced radiologist. Measurements were taken in supine position and the women were asked to hold their breath while they were scanned and special attention was given to keep the probe touching the skin lightly to avoid any compression of the fat layers. Subcutaneous fat thickness was measured on the xyphoumbilical line. Transducer was positioned perpendicularly and transversely to the body surface. The distance between the inner edge of the skin and the outer edge of the linea alba was measured. The distance between the inner edge of the linea alba and the outer edge of the visceral peritoneum was measured as the preperitoneal area. Visceral fat thickness was

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