Association between Insulin Resistance and Breast Parenchyma in Women with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Kadınlarda İnsülin Direnci ve Meme Paterni Arasındaki İlişki

Zeliha Fulden Sarac, Işıl Bilgen*

Ege University, Internal Medicine, İzmir, Turkey
*Ege University, Department of Radiology and Diagnostic, İzmir, Turkey

Abstract

Purpose: The aims of this study were to assess 1. whether there was an association between a polycystic ovary (PCO) and cystic breast disease based on ultrasound findings or not, 2. to evaluate the relationships between insulin resistance and breast parancime and hormone levels.

Material and Method: The study group consisted of 60 women who were diagnosed as PCOS and the control group was consisted of 45 women who had neither clinical nor ultrasound finding of PCOS. Both the groups underwent breast ultrasound (Senographe 600 T (General Electric)) examination. Breast parancim was defined as; I. fibroglandular density, II. fibroglandular, fatty breast, III. fatty breast. All subjects were evaluated for demographic and biochemical examinations. Measurements of insulin resistance were obtained using the homeostasis model assessment (HOMA-IR).

Results: At examination of breast in PCOS group, 36 fibroglandular, 18 fibroglandular/fatty and 6 fatty were found. However, 30 fibroglandular, 11 fibroglandular/fatty and 4 fatty breast were examined in control. There were 2 patients with fibrocystic breast disease and 2 patients with fibroadenoma in PCOS group. In control, 2 patients with fibrocystic breast disease were examined. In PCOS, mean levels of HOMA-IR were found 1.8±0.9, 2.0±0.1, 3.2±0.3 in patients with fibroglandular, and fibroglandular/fatty breast, and fatty breast, respectively. Mean levels of fasting blood glucose, fasting insulin and HOMA-IR were significantly higher in PCOS than control.

Discussion: Breast cystic disease does not increase in patients with polycystic ovary syndrome. However, polycystic ovary syndrome with fatty breast has high HOMA levels. *Turk Jem 2012; 16: 1-5*

Key words: Polycystic ovary syndrome, breast parancime, insulin resistance

Özet

Amaç: Çalışmamızda; 1. ultrasonografik bulgular temelinde kistik meme hastalığıyla polikistik over (PKO) arasında bir bağlantının olup olmadığı, 2. insülin direnci, meme parankimi ve hormon düzeyleri arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya, polikistik over sendromu tanısı alan 60 hasta ve klinik ve ultrasonografik olarak PKOS olmayan 45 kadın kontrol grubu olarak alındı. Her iki gruba meme ultrasonografisi (Senographe 600 T (General Electric)) yapıldı. Meme parankimi; I. fibroglandüler dansite, II. fibroglandüler, yağlı meme, III. yağlı meme olarak tanımlandı. Tüm olgular demografik ve biyokimyasal olarak değerlendirildi.İnsülin direnci; homeostasis model assessment (HOMA-IR) yöntemiyle ölçüldü.

Bulgular: PKOS grubunda memenin muayenesinde; 36 fibroglandüler, 18 fibroglandüler/yağlı ve 6 yağlı meme bulundu. Ancak, kontrolde 30 fibroglandüler, 11 fibroglandüler/yağlı ve 4 yağlı meme saptandı. PKOS grubunda, 2 hastada fibrokistik meme hastalığı ve 2 hastada fibroadenoma vardır. Kontrol grubunda, 2 hastada fibrokistik meme hastalığı saptandı. PKOS'da, ortalama HOMA-IR düzeyleri, fibroglandüler memesi olan hastalarda 1,8±0,9, fibroglandüler/yağlı memesi olan hastalarda 2,0±0,1 ve yağlı memesi olann hastalarda 3,2±0,3 olarak bulundu. Ortalama açlık glukozu, açlık insülini ve HOMA-IR düzeyleri PKOS'da kontrolden anlamlı oranda daha yüksektir.

Sonuç: Memenin kistik hastalığı polikistik over sendromlu hastalarda artmaz. Ancak, yağlı memeli polikistik over sendromunda yüksek HOMA düzeyleri mevcuttur. *Türk Jem 2012; 16: 1-5*

Anahtar kelimeler: Polikistik over sendromu, meme paterni, insülin direnci

Address for Correspondence/Yazışma Adresi: Zeliha Fulden Sarac MD, Ege University, Internal Medicine, İzmir, Turkey
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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common gynecologic, endocrine case, affects approximately 5-10% of women of reproductive age (1-3). It is known that relative hyperestrogenism and anovulation are involved in the etiology of benign breast disease (BBD), since mammary gland growth is influenced by a critical balance between estrogens and progesteron action. And also, hyperestrogenism a cause of breast disease and a significant association between PCOS and benign pathologies were reported (4). Previously, Soran et al. (5) suggested that neither fibrocystic breast disease, lump thickening, calcification, fibroadenoma, pain, redness, discharge nor hyperplasia showed a significantly higher prevalence rate in PCOS than in controls. However, in a recent study, Gumus et al. (6) showed a statistically significant association between a PCOS and fibrocystic breast disease.

Insulin resistance and elevated serum luteinizing hormone (LH) levels are common features in PCOS, and are associated with an increased risk of type 2 diabetes and cardiovascular events (7). Hyperinsulinemia from insulin resistance is an important regulatory mechanism governing ovarian hyperandrogenism. Hyperinsulinemia in hyperandrogenic anovulatory women potentiates ovarian hyperandrogenism by enhancing LH secretion (8). In many studies (9-11), a possible association between LH levels and polycystic ovary was reported. Functional hyperprolactinemia and relative hyperestrogenism are risk factors of the development concerning fibrocystic changes in the breast (12). However, there were no variations in serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) between normal subjects and women with benign breast disease (13). In many studies (14-17), glucose intolerance and insulin resistance have been defined as risk factors for breast cancer. However, there was no study related to glucose intolerance or insulin resistance in benign breast disease in PCOS.

The aims of this study were to assess 1. whether there was an association between a polycystic ovary (PCO) and cystic breast disease based on ultrasound findings or not, 2. to evaluate the relationships between insulin resistance and breast parancime and hormone levels.

Materials and Methods

Between January 2007 to September 2008, at the Medical School of Ege University, 105 women between 18 and 36 years of age, not using oral contraceptives were included into the study. The study group consisted of 60 women (mean age 25.9±2.7 years) who were diagnosed as PCOS and the control group was consisted of 45 women (mean age 24.9±4.6 years) who had neither clinical nor ultrasound finding of PCOS. PCOS patients had the following diagnostic criteria: cardinal features of hyperandrogenism: hirsutism (elevated serum total testosterone) and clinical evidence of ovarian dysfunction: oligoamenorrhea, infertility from anovulation and abnormal ultrasound finding (PCO appearance at ultrasound) (18). All subjects gave written informed concent before entering the study.

Both the groups underwent breast ultrasound examination. Breast parancim was defined as; I. fibroglandular density, II. fibroglandular, fatty breast, III. fatty breast. Fibrocystic breast disease is described as cystic lesions, anechoic with acoustic enhancehement posteriorly, round or ova, sharply marginated common benign changes involving the tissues of the breast, on breast ultrasound examination (19). Ultrasound examination was performed with Senographe 600 T (General Electric).

Body composition was determined by bioelectrical impedance analysis. All subjects were evaluated with a series of anthropometric measurements and tests for hematology and biochemistry after an overnight fast of 12- 16 hrs. Measurements of insulin resistance were obtained using the homeostasis model assessment [HOMA-IR = fasting glucose (mg/dl) x fasting insulin (µU/ml) / 22.5] (20).

Plasma glucose was measured using the glucose oxidase method. Plasma DHEA-S, 17-OH progesterone, free testosterone (FT) levels were measured by the radioimmunassay (RIA) method. Estradiol (E2), progesterone, total testosterone (TT) plasma levels were measured by Chemiluminesence method. Normal ranges of the hormones according to our laboratory are as follows: prolactin, 5-30 ng/ml; LH, 1.1-11.6 mIU/ml (follicular phase); FSH, 2.8-11.3 mIU/ml (follicular phase); DHEAS, 35-450 µg/dl; estradiol, 11-165 pg/ml (follicular phase); progesterone, 0.0-1.1 ng/ml (follicular phase); 17-OHP, 0.4-1.02 ng/ml (follicular phase); TT , 0.008-0.6 ng/ml and FT, 0.6-2 pg/ml in the morning.

Hormone determinations for each blood sample were performed in duplicate within a single assay. The mean intraassay and interassay coefficients of variation were as follows: prolactin, 5.1% and 4.9%; LH, 3.7% and 5.3%; FSH, 2.8% and 5.3%; DHEAS, 7.8% and 9.3%; E2, 3.7% and 7.9%; progesterone, 8% and 7.3%; 17-OHP, 6.7% and 8%; TT, 4.7% and 5.4%; FT, 5.2% and 5.9%.

Statistical Analysis

Data are given as mean±standard deviation (S.D.) Statistical analyses were performed using the Student's t-test and Mann-Whitney U-test. Linear relationships between variables were examined using Pearson's Correlation Analysis. Three groups were evaluated with one-way ANOVA. A p value less than 0.05 was considered statistically significant. Power analysis was performed.

Results

There was no significant differences for demographical data between the groups (Table 1). Fourty five (75%) of 60 PCOS women had anovulatuar cycles. The mean level of Ferriman Gallwey (F/G) skor was found to be 18.0±3.0 in PCOS.

At examination of breast in PCOS, 36 fibroglandular, 18 fibroglandular/ fatty and 6 fatty were found. However, 30 fibroglandular, 11 fibroglandular/fatty and 4 fatty breast were examined in control. There were 2 patients with fibrocystic breast disease and 2 patients with fibroadenoma in PCOS group. In control, 2 patients with fibrocystic breast disease were examined. In PCOS, mean levels of HOMA-IR were found to be 1.8±0.9, 2.0±0.1, 3.2±0.3 in patients with fibroglandular, and fibroglandular/fatty breast, and fatty breast, respectively. The PCOS with fatty breast had higher HOMA-IR levels than thats of subjects with other breast parancime characteristics. Mean levels of LH, E2 and prolactine levels were not different in fibroglandular, fibroglandular/ fatty breast, and fatty breast, respectively in PCOS and control.

Mean levels of triglceride, fasting blood glucose, fasting insulin, HOMA-IR, LH and FT were significantly higher in PCOS than thats of control (Table 2).

Biochemical and hormone levels were shown according to breast parancime characteristics in PCOS and control (Table 3 and 4). There were statistically significantly differences for fasting blood glucose (p=0.03) and HOMA-IR (p=0.01) and fasting insulin (p=0.01) between patents with fibroglandular and fatty breast in PCOS. However, a

Table 1. Anthropometric characteristics of PCOS and control were shown

	PCOS (n= 60)	Control (n= 45)	p
Age (year)	25.9±2.7	24.9±4.6	*0.96*
BMI (kg/m^2)	24.1±0.8	23.1±1.9	*0.96*
Weight (kg)	59.7±5.2	55.3±3.5	*0.80*
Systolic Blood Pressure (mmHg)	110.7±9.9	114.9±14.8	*0.70*
Diastolic Blood Pressure (mmHg)	50.7±8.3	59.9±11.0	*0.40*
Heart Rate	70.5±5.1	75.3±6.0	*0.90*
Waist (cm)	63.9±6.9	64.7±7.5	*0.34*
Waist / Hip	0.75±0.1	0.70±0.1	*0.80*
Percent body fat (BIA)	20.5±2.1	19.1±1.0	*0.77*
Fat mass (kg)	18.1±1.4	18.0±1.9	*0.80*
Ferriman Gallwey (F/G)	18.0±3.0		

Data are expressed as mean±SD
* p<0.05

Table 2. Biochemical and hormone tests of patients in PCOS and control were shown

	PCOS (n= 60)	Control (n= 45)	p
Triglyceride (mg/d)	155.4±40.6	106.1±31.6	*0.03**
Total-Cholesterol (mg/dl)	185.8±31.5	180.1±42.3	*0.10*
LDL-Cholesterol (mg/dl)	105.2±20.5	96.5±10.1	*0.97*
HDL-Cholesterol (mg/dl)	40.1±3.1	43.4±7.3	*0.08*
Fasting Blood Glucose (mg/dl)	96.3±15.6	89.1±8.9	*0.02**
HOMA-IR	2.4±0.7	1.77±0.3	*0.01**
Fasting insulin (µg/dl)	12.3±3.1	8.3±2.7	*0.05**
LH (mIU/ml)	7.9±1.1	4.1±1.4	*0.01**
FSH (mIU/ml)	4.5±0.4	5.6±1.8	*0.80*
E2 (pg/ml)	40.9±17.1	49.7±8.6	*0.02**
Progesterone (ng/ml)	0.9±0.3	1.0±0.7	*0.09*
TT (ng/ml)	0.3±0.01	0.4±0.03	*0.80*
FT (ng/ml)	2.0±0.01	1.1±0.31	*0.05**
Prolactin (ng/ml)	21.9±5.2	18.4±7.8	*0.40*
DHEAS (ng/ml)	271.9±53.6	280.4±45.9	*0.08*

Data are expressed as mean±SD *$p<0.05$
HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitive C-reactive protein; Luteinizing hormone (LH), follicle-stimulating hormone (FSH), Dehydroepiandrosterone sulfate (DHEAS), Estradiol (E_2), 17-OH progesterone (17-OHP), Total Testosterone (TT), and Free Testosterone (FT)

Table 3. Biochemical and hormone levels were shown according to breast parancime characteristics in PCOS

	Fibroglandular (n= 36)	Fibroglandular / fatty breast(n= 18)	Fatty breast (n= 6)	p
Triglyceride (mg/d)	150.1±35.9	149.1±38.7	159.1± 33.6	*0.09*
Total-Cholesterol (mg/dl)	200.2±45.9	180.1±41.4	199.9± 23.9	*0.15*
LDL-Cholesterol (mg/dl)	100.9±34.7	99.9±22.4	110.2± 20.5	*0.85*
HDL-Cholesterol (mg/dl)	38.7±4.8	44.1±3.9	39.9± 4.5	*0.06*
Fasting Blood Glucose (mg/dl)*	91.5±11.9*	99.1±22.3	101.3±17.9*	*0.03**
HOMA-IR*	1.8±0.9*	2.0±0.1	3.2± 0.3*	*0.01**
Fasting insulin (µg/dl)*	10.1±2.3*	10.9±3.9	17.0±2.3*	*0.01**
Prolactin (ng/ml)	18.1± 4.1	19.2±5.2	17.5±8.0	*0.75*
LH (mIU/ml)	7.8±1.1	8.0±0.5	8.2±0.3	*0.96*
FSH (mIU/ml)*	4.3±0.1	3.9±0.2*	5.0±0.9*	*0.03**
E2 (pg/ml)	40.8±5.1	42.3±5.3	45.8±4.3	*0.10*
Progesterone (ng/ml)	1.0±0.01	0.7±0.2	0.8±0.01	*0.97*
TT (ng/ml)	0.22±0.01	0.29±0.01	0.4±0.02	*0.08*
FT (ng/ml)	2.8±0.02	3.2±0.07*	2.1±0.01*	*0.02**
DHEAS (ng/ml)	278.1±26.8	300.6±41.7	260.9±27.2	*0.70*
Prolactin (ng/ml)	18.1±4.1	19.2±5.2	17.5±8.0	*0.75*

Data are expressed as mean±SD * *$p<0.05$*
(*) significance between goups
HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Luteinizing hormone (LH), follicle-stimulating hormone (FSH), Dehydroepiandrosterone sulfate (DHEAS), Estradiol (E_2), 17-OH progesterone (17-OHP), Total Testosterone (TT), Free Testosterone (FT)

Table 4. Biochemical and hormone levels were shown according to breast parancime characteristics in control

	Fibroglandular (n= 30)	Fibroglandular / fatty breast (n= 11)	Fatty breast (n= 4)	p
Triglyceride (mg/d)	100.9±42.1	101.1±44.3	90.9±37.1	*0.09*
Total-Cholesterol (mg/dl)	179.8±23.9	180.1±33.9	195.5±30.1	*0.10*
LDL-Cholesterol (mg/dl)	90.1±6.8	101.8±5.1	96.5±10.1	*0.70*
HDL-Cholesterol (mg/dl)	41.9±5.0	44.7±3.9	44.0±2.9	*0.10*
Fasting Blood Glucose mg/dl)	85.9±4.1	94.1±8.9	90.1±6.1	*0.85*
HOMA-IR	1.75±0.7	1.69±0.9	1.77±0.3	*0.07*
Fasting insulin (µg/dl)	7.6±3.0	7.9±3.3	8.0±1.1	*0.06*
Prolactin (ng/ml)	16.1±9.4	17.6±7.4	15.1±4.3	*0.75*
LH (mIU/ml)	4.0±0.5	3.7±0.1	5.1±0.1	*0.90*
FSH (mIU/ml)	5.2±1.3	5.1±2.3	4.9±1.1	*0.07*
E2 (pg/ml)	51.5±4.0	52.4±7.6	49.8±6.3	*0.10*
Progesterone (ng/ml)	1.0±0.7	1.0±0.7	0.9±0.06	*0.80*
TT (ng/ml)	0.6±0.02	0.3±0.1	0.3±0.02	*0.06*
FT (ng/ml)	1.7±0.35	0.7±0.01	0.9±0.21	*0.09*
DHEAS (ng/ml)	270.5±39.9	275.1±44.1	285.1±41.1	*0.09*

Data are expressed as mean±SD *$p<0.05$
HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitive C-reactive protein; Luteinizing hormone (LH), follicle-stimulating hormone (FSH), Dehydroepiandrosterone sulfate (DHEAS), Estradiol (E_2), 17-OH progesterone (17-OHP), Total Testosterone (TT), Free Testosterone (FT)

statistically significantly difference for FSH between patients with fibroglandular/fatty breast and fatty breast (p=0.03) was found in PCOS. And also, there was statistically difference for FT between patients with fibroglandular/fatty breast and fatty breast in PCOS (p=0.02).

Discussion

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with clinical symptoms of anovulatory infertility, hyperandrogenism, and also associated with insulin resistance and obesity (21). Several lines of evidence suggest that women with PCOS may also be at an increased risk of having a personal history of breast cancer (21, 22). However, there weren't many studies related to beast pattern in patients with PCOS. And also, no investigations about relationship between insulin resistance and breast pattern in this group were found. Recently, it was suggested that there was a significant relationship between PCOS and fibrocystic breast disease. Similarly, D Amelio et al. (4) showed a significant association between PCO and benign pathology. In the present study, 36 fibroglandular, 18 fibroglandular/fatty and 6 fatty breast pattern were found in PCOS. However, 30 fibroglandular, 11 fibroglandular/fatty and 4 fatty breast were examined in control. And also, there were 2 patients with fibrocystic breast disease and 2 patients with fibroadenoma in PCOS group. In control, 2 patients with fibrocystic breast disease were examined. To our findings, characteristics of breast parancime pattern were not different between PCOS and control. However, the limitations of this study must be taken into account. The numbers of subjects in the study and control groups were somewhat small. Future studies with large population need to establish the relationship between PCOS and breast parancime characteristics.

Adolescents and women with PCOS have menstrual disorders and physical manifestations of excessive androgen production. They are also at higher risk for insulin resistance. However there was no study related the relationship between insulin resistance and breast parancime in the PCOS patients. Obesity exacerbates insulin resistance and impaired glucose tolerance in women with PCOS (23-26). Therefore, obese patients with PCOS weren't enrolled in the study. Adipocytes made up the bulk of the human breast, with epithelial cells accounting for only approximately 10% of human breast volume. Therefore, it may be that the increased local production of such substances attriibuted insulin resistance in the breast might be part of the problem (25). In the present study, in PCOS, mean levels of HOMA-IR were found 1.8±0.9, 2.0±0.1, and 3.2±0.3 (p= 0.01) in fibroglandular, fibroglandular/fatty breast, and fatty breast, respectively. The PCOS with fatty breast had higher HOMA-IR levels than control. However, there were no differences for mean level of HOMA-IR incontrol. Insulin resistance might be associated with fatty breast pattern in PCOS, but not in control.

In previous studies, hormone levels were examined in breast cancer and PCOS (26,27). Mancini et al. (28) suggested that there was no significant difference between the groups considered and normal control subjects for any of the hormones tested; there was no significant correlation between T concentration or E2 levels in benign breast disease. However, there were no many sudies related to the relationships between hormones and breast pattern in PCOS. In the present study, mean levels of LH and E2 levels were not different in fibroglandular, fibroglandular/ fatty breast, and fatty breast, respectively in PCOS and control. However, mean level of FT in

fibroglandular/ fatty breast pattern was statistically significanly higher than thats of other breast pattern.

In summary, breast cystic disease does not increas in patients with polycystic ovary syndrome. However, polycystic ovary syndrome with fatty breast has high HOMA levels.

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