Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2023; 40(4): 692-696
doi: 10.52142/omujecm.40.4.5

Does insulin resistance increase the probability of fibrocystic breast disease in women with polycystic ovary syndrome

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Received: 20.02.2023 • **Accepted/Published Online:** 29.08.2023 • **Final Version:** 29.10.2023

Abstract

The aim of this study was to investigate if higher insulin resistance (IR) levels among polycystic ovary syndrome (PCOS) patients are the predictor of the fibrocystic breast disease risk in women aged 30-40 years. This case-control retrospective observational study was carried out on 180 patients admitted between September 2020 and June 2022. Women aged 18-36 years diagnosed with PCOS included the study. Women who were diagnosed with PCOS but not fibrocystic breasts formed the control group. Women were divided according to their IR levels into four groups. The optimal insulin (23.6% vs. 54.65), the insulin sensitivity (22.7% vs. 28.6), early IR (29.1% vs. 18.6), and significant IR (24.5% vs. 25.7) were similar between women with fibrocystic breasts and normal breasts, respectively. This study showed no statistically significant difference between women with fibrocystic breasts and normal breasts in study parameters (p-value > 0.05). There was no statistically difference between two groups in terms of IR levels. The results show that IR levels cannot be used to assess fibrocystic breast disease in PCOS women.

Keywords: insulin resistance, polycystic ovarian syndrome, benign breast disease, fibrocystic breast changes

1. Introduction

Polycystic ovary syndrome (PCOS) as the most common endocrine disorder affects 5%-10% of women of reproductive age (1). Based on the Rotterdam consensus, the presence of at least two of the abnormalities below shows the PCOS: biological and/or clinical hyperandrogenism, oligo- and/or anovulation, and polycystic ovaries (2). PCOS is important due to the severity of the related complications: Reproductive complications including menstrual dysfunction, hyperandrogenism, and higher pregnancy and metabolic complications including higher risk factors for type 2 Diabetes mellitus (DM) and cardiovascular disease (CVD) and insulin resistance (IR), oncological complications including ovarian, endometrial, and breast cancers (3). Almost 35%-80% of PCOS women show IR as the most prevalent metabolic feature independently of body fat distribution and body mass index (BMI) (4, 5). Today, researchers believe that PCOS is due to different genetic and environmental factors, all involved in pathophysiology of this syndrome (6,7).

IR refers to the condition where a given amount of insulin decreases the amount of glucose below normal (8). First, beta cells in the pancreas compensate for this resistance by increasing insulin production and keeping blood glucose levels within a normal range (7). At this time, the patient has only IR with a high hormone rate. A patient with IR reaches high and abnormal glucose levels from the high amount of this hormone with normal limits and eventually, the patient will suffer from diabetes. High levels of insulin stimulate ovaries and type 2 DM produces high amounts of androgens. In addition, high levels of insulin decrease globulin binding to sex hormones, resulting in the increasing power of androgens (9).

Several health problems of women with a prevalence rate of 16-50% as shown in different reports are related to breast complaints (10). According to the studies, about half of those visiting clinics due to breast-related symptoms show benign breast disorders including fibrocystic changes occurring in 50% of patients aged above 30 years (11). As the most common benign breast changes, fibrocystic breast changes are found in 90% of women undergoing histopathological examination, and 50% of women undergoing clinical examination. Women aged 20-50 years show fibrocystic breast changes with symptoms such as discharge and nipple pain adversely affecting the premenopausal women's life quality (12,13). Some previous reports show a significant relationship between PCOS and fibrocystic breast changes while others have not found any association (11,14). The risk of breast cancer increases due to fibrocystic breast disease. The risk of fibrocystic breast disease will be doubled because of the proliferative changes and will increase fourfold due to lack of typical hyperplasia resulting from more changes in the tissue (15). The clinical characteristics of fibrocystic breast disease include fibrocystic plaques, axillary pain or tenderness in response to the progress of nodularity, macrocysts, and fibrocystic lumps. The women aged 40 will show more prevalent disease with increasing premenopausal age (16).

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The aim of this study was to investigate if higher in IR levels among PCOS patients are the predictor of the fibrocystic breast disease risk in women aged 25-40 years.

2. Materials and Methods

Patients who were followed up with the diagnosis of PCOS in İstanbul Medipol University Hospital Gynecology and Obsterrics Clinic and Medistate Hospital General Surgery Clinic between September 2020 and June 2022 and had breast ultrasonography (USG) for any reason were not screened retrospectively. For different reasons, patients who had previously undergone Homeostasis Model Assesment index (HOMA) and breast USG were included in the study. Patients will be selected as PCOS and control groups according to the same mean age.

The HOMA index is also used to evaluate IR. This index was calculated from the following formula using fasting serum glucose and insulin levels:

HOMA-IR = [Fasting Glucose (mg/dl) x Fasting Insulin (uU/ml)/405]

Patients were divided into four subgroups according to their HOMA-IR levels. HOMA-IR <1 optimal insulin level, HOMA-IR=1-1.9 insulin sensitivity, and HOMA-IR=1.9-2.5 early IR will be determined as significant IR above HOMA-IR>2.5. The groups of patients are shown in Table 1.

Table 1. Groups of patients

Groups	Description
Group I	HOMA-IR <1 ; optimal insulin level
Group II	HOMA-IR=1-1.9 ; insulin sensitivity
Group III	HOMA-IR=1.9-2.5 ; early insulin resistance
Group IV	HOMA-IR>2.5 ; significant insulin resistance

HOMA, Homeostasis Model Assesment index

In the present study, PCOS was diagnosed based on the Rotterdam (Rott) criteria. Rott's diagnostic criterion for PCOS is the presence of at least two of the following three symptoms:

1) Menstrual disorders (Oligoovulation); 2) clinical/laboratory hyperandrogenism; 3) Ovaries containing multiple cysts in ultrasound (PCO).

2.1. Statistical Analysis

The Kolmogorov-Smirnov test was conducted to study the normality. SPSS v26 was used for statistical analyses. Median, minimum, maximum, mean, and standard deviations (SD) were measured to check each continuous variable. According to the Kolmogorov-Smirnov test results, the Mann-Whitney U test was performed to study the difference between women with fibrocystic breasts and normal breasts. A value of $p<0.05$ was accepted as statistically significant.

The G Power 3.1 program was used to calculate the sample size. Two groups' total mean was measured based on the Mann-Whitney test with a power of 94%, effect size of 50%, and 0.05 type 1 error for at least 174 patients (17).

3. Results

This study included 180 women aged 28 to 39 diagnosed with polycystic ovaries divided into four groups. The descriptive statistics of participants are shown in Table 2. This study included age-matched (33.11±2.06) and body mass index (BMI)-matched (25.47±1.59) women. The minority of study participants were smoker (23.9%). Only 19 (10.6%) of the participants had a family history of breast cancer.

Table 2. Descriptive statistics of study parameters in women

	Study parameters	median (range) mean ± SD
Maternal characteristics	Age	33(28-39)33.11±2.06
	BMI	25(20-29)25.47±1.59
	Age of menarche	11(10-14)11.44±0.93
Laboratory values	AMH	5.17(1.03-15.72)5.14±1.92
	FSH	7(3-9.86)6.36±1.78
	LH	10.2(3.52-22.8)10.2±3.15
	E2	44(30-54)42.25±6.5
	FT4	1.11(0.31-2.75)1.12±0.26
	TSH	2(0.46-7.98)2.14±1.26
	Prolactin	16.3(5.05-74.29)17.19±7.32
	FBS	88(26-121)87.44±11.56
	Fasting Insulin	10.8(3.99-81.42)12.41±8.62
	HbA1c	5.53(4-6.56)5.46±0.54
Main parameter	HOMA-IR	1.88(0.3-5.7)1.94±1.12

SD,standard deviation; BMI, body mass index; AMH, Anti-Mullerian hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; FT4, Free T4; TSH, thyroid-stimulating hormone; FBS, Fasting blood sugar, HbA1c, Hemoglobin A1C, glycosylated hemoglobin, HOMA, Homeostasis Model Assesment index

We assessed the capability of those parameters to differentiate between women with fibrocystic breasts and normal breasts. Table 3 shows the comparison of the study parameters of the two groups. As stated in Table 3, a Mann-Whitney test did not find a statistically significant association between the two groups regarding AMH, FSH, LH, E2, FT4, TSH, Prolactin, FBS, Fasting Insulin, and HbA1c ($p>0.05$).

There was no statistically significant difference between groups in terms of HOMA-IR (*p value* >0.05). HOMA-IR of women with fibrocystic breasts (Mean±SD = 2±1.16) was similar to the women with normal breasts (Mean±SD = 1.86±1.05).

The relationship between women (with fibrocystic and normal breasts) and groups classified by HOMA-IR rates is shown in Table 4.

Table 3. Comparison of women with fibrocystic and normal breasts regarding study parameters

Study parameters	Women with fibrocystic breasts (n=110) median (range) mean ± SD	Women with normal breasts (n=70) median (range) mean ± SD	*p*-value
Age	33(30-39)33.18±2	33(28-38)32.99±2.17	0.60
BMI	25(20-29)25.48±1.6	25(22.8-29)25.44±1.6	0.59
Age of menarche	11(10-14)11.37±0.9	11(10-14)11.56±0.99	0.28
AMH	5.17(1.03-9.5)4.92±1.66	5.17(1.13-15.72)5.48±2.23	0.46
FSH	7(3-9)6.37±1.76	7(3-9.86)6.33±1.82	0.91
LH	10.35(3.52-18)10.14±3.29	10.06(4.65-22.8)10.28±2.96	0.88
E2	44(30-54)42.22±6.48	44(30-54)42.28±6.6	0.99
FT4	1.13(0.31-2.75)1.14±0.29	1.08(0.53-1.62)1.08±0.21	0.06
TSH	2(0.54-6.7)2.1±1.18	2(0.46-7.98)2.2±1.39	0.73
Prolactin	16.3(5.05-74.29)17.63±8.44	16.15(6.34-25.82)16.5±5.07	0.69
FBS	88(26-121)86.52±12.35	88(56-116)88.9±10.1	0.31
Fasting Insulin	11.35(3.99-33.32)11.95±5.49	10.18(4.12-81.42)13.14±12	0.23
HbA1c	5.6(4-6.56)5.44±0.6	5.5(4.5-6.25)5.49±0.41	0.93
HOMA-IR	1.91(0.4-5.7)2±1.16	1.8(0.3-3.75)1.86±1.05	0.41

*All parameters was test by the Mann-Whitney U test

As presented in Table 4, a chi-square test found no statistically significant association between women (with fibrocystic and normal breasts) and the four groups (p>0.05). 23.6%, 22.7%, 29.1%, and 24.5% of the group I, II, III, and IV were women with fibrocystic breasts, respectively. 27.1%, 28.6%, 18.6%, and 25.7% of the group I, II, III, and IV were women with normal breasts, respectively.

Table 4. The relationship between women (with fibrocystic and normal breasts) and the four groups

		Women with fibrocystic breasts (n=110) n(%)	Women with normal breasts (n=70) n(%)	*p*-value
Groups	I	26(23.6)	19(27.1)	0.438*
	II	25(22.7)	20(28.6)	
	III	32(29.1)	13(18.6)	
	IV	27(24.5)	18(25.7)	

*A Chi-square test

As presented in Figure 1, the rate of women (with fibrocystic and normal breasts) in four groups were similar.

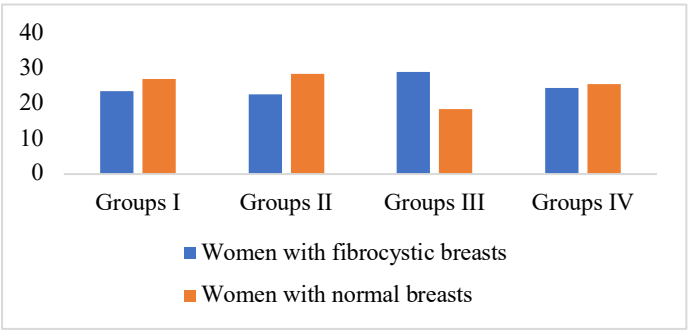

Fig. 1. The rate of women (with fibrocystic and normal breasts) in four groups

4. Discussion

In this study, we investigated the effect of HOMA-IR on the risks of fibrocystic breasts in women. The results showed that the HOMA-IR level in the four groups was not significantly higher or lower in women with fibrocystic and normal breasts. In group III, classified as early IR, the percentage of women with fibrocystic is more than women with normal breasts (29.1% vs. 18.6%). However, in group IV, classified as having significant IR, this issue does not continue. In group IV, the percentage of women with normal breasts is higher than those with fibrocystic breasts (25.7% vs. 24.5%). These results show that increasing IR has no significant effect. All study parameters were similar in women with fibrocystic breasts and women with normal breasts.

The most frequent breast changes are observed in women older than 30 (18). Several factors are influential in forming breast cysts, including micro and macro cysts (12, 19). In studies, family history, prolactin, growth factors, hormonal disturbances, thyroid hormone, dietary fat consumption, caffeine intake, smoking, PCOS, and insulin have been reported to influence breast changes (20-22). However, these studies' results are inconsistent, and no definite conclusion can be reached (12).

It is difficult to express a significant relationship between PCOS and fibrocystic breast disease, and there are conflicting

results in the literature. We found that many studies investigated the relationship between PCOS and fibrocystic breast disease in the literature. However, studies that have studied women with PCOS are limited. Some of the studies (23,24) have documented no significant differences between PCOS and fibrocystic breast disease, and some studies (11,25,26) have indicated that significant differences between PCOS and fibrocystic breast disease. In an updated review, Kunicki et al. (12) showed no clear association between PCOS and fibrocystic breast disease.

The female breast appears to be influenced by DM in numerous ways (27). Previous studies have shown the possible relationship between DM and breast cancer (28-30). In a comprehensive meta-analysis, Hardefeldt et al. (31) reported a significantly increased risk of breast cancer in diabetic females compared to non-diabetic women. Wang et al. (32) in a prospective case-control study with 492 women, showed an association between DM and female breast cancer. In a systematic review and meta-analysis, Anothaisintawee et al. (33) presented DM as a risk factor for breast cancer. Boyle et al. (34) examined premenopausal and postmenopausal women and reported no significant relationship between breast cancer and DM in postmenopausal women. Scholars believe that the effect of DM on breast cancer differs in the two groups.

The effect of DM on cancer and the probability of success in cancer treatment have been reported in many studies. However, it is currently early to conclude that IR would confer an effect on fibrocystic breast disease in PCOS women. This study's motivation was to investigate the effect of IR on fibrocystic breast disease. According to the results, there was no significant difference between women with fibrocystic breasts and normal breasts in terms of IR.

This study also had limitations. The main limitations are the biased potential of medical records and the retrospective study design. The number of women participating in the study could be higher. The fact that the data is from a single center is another study limitation. It is recommended to collect data from several centers in future studies.

The current study concluded that the PCOS group did not show a significant difference between IR levels and fibrocystic breast disease. The current study indicates that IR levels cannot be used to assess fibrocystic breast disease in PCOS women. The association between IR and fibrocystic breast disease should be further confirmed with larger sample sizes, and further study is eagerly awaited.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: Ş.Ö., A.Ş.K. Design: A.Ş.K. Data Collection or Processing: Ş.Ö., A.Ş.K, Analysis or Interpretation: Ş.Ö., A.Ş.K., Literature Search: Ş.Ö., A.Ş.K Writing: Ş.Ö., A.Ş.K

Ethical Statement

Approval was obtained from İstanbul Medipol University Noninvasive Clinical Research Ethics Committee, the study started. The ethics committee decision date is 10/11/2022 and the number of ethical committee decisions is 930.

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