The Significance of Insulin Resistance in Nondiabetic Breast Cancer Patients

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Abstract

Background: The relationship between insulin resistance (IR) and prognostic factors in breast cancer (BC) in premenopausal (pre-M) and postmenopausal (post-M) women is still controversial. We evaluated the potential association between hemoglobin A1c (HbA1c), fasting blood glucose (FBG), fasting insulin levels (FILs), the homeostasis model assessment index (HOMA), and the prognostic factors of BC in nondiabetic patients with pre-M and post-M breast tumors.

Methods: We compared 80 nondiabetic patients with pre-M and post-M breast tumors to 60 women with normal mammography as a control.

Results: Age, body mass index (BMI), FBG, and HbA1c did not differ between the groups. FIL (P < 0.001) and HOMA-IR (P < 0.001) of the BC group were significantly higher than in the control group. FIL (P < 0.001) and HOMA-IR (P < 0.001) of the BC group were significantly higher than in the control group, for both pre- and post-M patients. FIL and HOMA-IR values were found to be significantly higher in the patients with stage IV BC than in other stages of BC. FIL and HOMA-IR are highly specific and sensitive parameters in their ability to diagnose BC.

Conclusions: FIL and HOMA-IR are associated with BC risk in nondiabetic patients with pre-M and post-M breast tumors. When BC risk was evaluated according to the stage of menopause, no difference was observed; only the disease stage was significant. FIL and IR may function as potential biomarkers and therapeutic targets for human cancers.

Keywords: Breast cancer; HbA1c; Fasting blood glucose; Fasting insulin; Insulin resistance

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer among women. It is also in the second place among female cancer patients in cancer-related deaths; and mortality rates are expected to increase further in the next decade [1].

Insulin resistance (IR) is a pathologic clinical condition progressing with hyperinsulinemia. Hyperinsulinemia doubles the risk of BC in postmenopausal (post-M) women [2, 3]. IR takes a role in the pathogenesis of type 2 diabetes mellitus (T2DM), obesity, and cancer. Women with IR syndrome characteristics such as obesity, high insulin levels, diabetes, and physical inactivity are at increased risk of BC [4, 5]. It should be noted that insulin is not a parameter indicating the future incidence of BC. However, it is thought that there may be a weak relationship between BC and T2DM [5].

The mechanical relationship between overweight and negative BC is linked to IR and fasting insulin level (FIL)-related pathways. Obesity poses different BC risks in premenopausal (pre-M) and post-M women, depending on estrogen receptor (ER) status [6]. Genetic variants related to IR can affect the risk of BC [7].

Our goal in this research was to clarify the potential relationship between hemoglobin A1c (HbA1c), fasting blood glucose (FBG), FILs, and IR, and the prognostic factors of BC in nondiabetic patients with pre-M and post-M breast tumors.

Materials and Methods

This was a retrospective case-control study conducted at the Department of General Surgery and the Department of Internal Medicine, approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty. Eighty con-
secutive nondiabetic patients with pre-M and post-M breast tumors and 60 consecutive age-matched, pre-M and post-M healthy control subjects were enrolled in this research.

All subjects were selected from people of Turkish origin. Pregnant women, patients with renal, hepatic, rheumatic or endocrine diseases were not included in the study. In addition, smokers, those with a history of chronic alcohol consumption, and subjects taking oral antidiabetics such as metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, hepatotoxic drugs (antituberculosis), and subjects taking antiepileptic or oral contraceptive pills were also excluded from the study. For cancer staging, the tumor-node-metastasis (TNM) classification established by the American Joint Cancer Committee (AJCC) was used [8].

Healthy subjects without any endocrine, vascular, cardiac or inflammatory diseases were selected as the control group. None of the subjects has a family history of diabetes. None of the subjects had diabetes or glucose intolerance as confirmed by the oral glucose tolerance test (OGTT).

Anthropometric characteristics (weight, height) of the individuals were recorded. Body mass index (BMI) of the subjects was calculated using the formula: BMI (kg/m2) = weight (kg)/(height (m))2 [9].

Demographic (age, gender) and clinical characteristics of individuals (comorbid conditions, primary tumor size, histological subtype, axillary lymph node involvement, TNM stage, ER or progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) status and histological grade) were obtained from the medical records of individuals.

The dilution was 1/100 for ER (Novocastra, Leica Biosystems, Nussloch, Germany; clone 6F11), 1/75 for PR (Novocastra, Leica Biosystems; clone 312), and 1/80 for HER-2 (Novocastra, Leica Biosystems; clone CB11).

Blood samples were taken from the participants before surgery. After an overnight fasting, they were taken into tubes containing anticoagulant (ethylenediamine tetraacetic acid (EDTA)) and tubes without anticoagulant. Immediately after venous blood collection, blood samples were centrifuged at 4 °C for 10 min (3,000 g) and plasma and serum were obtained. Glucose levels were determined by enzymatic methods (Abbott Diagnostics, Abbott Park, IL, USA). FIL was measured by an electrochemiluminescence immunoassay (ECLIA) method on a Roche-Hitachi E170. HbA1c levels were assessed by high performance liquid chromatography (HPLC) (Bio-Rad Variant 2 Turbo). All biochemical parameters were obtained from the patients’ medical records.

FBG and FIL were measured in subjects, and these values were used to determine the degree of IR in conjunction with homeostasis model assessment (HOMA). HOMA-IR was calculated using the following formula: HOMA-IR = (FBG (mg/dL) × FIL (µU/mL))/405 [10].

Statistical analysis

Distribution was tested using the single sample Kolmogorov-Smirnov test. Categorical variables were presented as the frequency and percentage and analyzed by using Chi-square test. Numerical variables were expressed as mean ± standard deviation and analyzed by using two-sided Student’s *t*-test. Receiver operating characteristic (ROC) curve analysis was performed. Statistical significance limit was accepted as 0.05. Analyzes were performed using SPSS 20.0 software for Windows (SPSS, Chicago, IL, USA).

Results

The demographic data and laboratory findings of the studied groups are shown in Table 1. Age, BMI, FBG, and HbA1c did not differ among the groups. FIL (P < 0.001) and HOMA-IR (P < 0.001) levels of the BC group were significantly higher than controls. In addition, Table 1 displays also the frequency of BC patients belonging to TNM, ER status, PR status, HER-2/neu status, and molecular subtype’s classification.

In Table 2, each of the BC and control groups is divided into pre-M and post-M subgroups. When the demographic and biochemical data for these subgroups were compared, age difference was found between pre-M and pre-M control individuals (P < 0.001). The age of post-M BC patients was significantly higher than that of the pre-M BC group (P < 0.001). FIL and HOMA-IR values of pre-M BC patients were statistically significantly higher than those of pre-M control individuals (each P < 0.001); likewise, FIL and HOMA-IR values of post-M BC patients were found to be statistically significantly higher than those of post-M control individuals (each P < 0.001).

The ROC analysis results of FIL, FBG, HbA1c, and HOMA-IR levels for BC versus control are compared in Table 3. FIL and HOMA-IR had AUC values of 0.987 (sensitivity 98.8%, specificity 82.7%, and cutoff 8.5) and 0.998 (sensitivity 97.5%, specificity 96.7%, and cutoff 2.4), respectively, which demonstrates their sufficiency in distinguishing BC from control.

FIL (P < 0.001) and HOMA-IR (P < 0.001) levels of BC group according to TNM stage were significantly higher in the stage IV group (Table 4). A re-analysis of the biochemical parameters of ER, PR, and HER-2 in the BC subgroups revealed no change in the statistical significance of FIL and HOMA-IR (Table 5).

Discussion

IR is often overlooked because it is not classified as a disease. This study provides evidence that FIL and IR estimated using the HOMA were increased in nondiabetic patients with pre-M and post-M breast tumors. When FIL and IR were evaluated according to the stage of menopause, no difference was found; it was the disease stage that was significant. FIL and HOMA-IR had a sensitivity of 98.8% and specificity of 82.7%, and a sensitivity of 97.5% and specificity of 96.7%, respectively, which demonstrates their sufficiency in distinguishing BC from healthy subjects. IR plays an important role in HOMA homeostasis related to cancer.

It is known that IR, which is considered as the primary factor in metabolic syndrome mechanisms, also increases the risk of cardiovascular disease (CVD). IR is a key player in the pathogenesis of metabolic diseases and can be observed in...
several clinical conditions such as BC [11, 12]. The causative association between BC and IR is also controversial [13]. Ferroni et al [14] reported that it showed increased pretreatment FBG and FIL in nondiabetic women with BC; although the higher pretreatment levels were not pathological, they resulted in higher HOMA indexes. In a meta-analysis, Hernandez et al [15] reported that they could not find any change in IR markers in BC patients. Since both factors are directly related to IR and

| Table 1. Demographic and Biochemical Parameters of the Groups |
|---------------------------------------------------------------|
| Control group (n = 60)            | Breast cancer (n = 80) | P         |
| Age (years)                      | 49.8 ± 11.5            | 50.4 ± 12.5 | 0.750                     |
| BMI (kg/m²)                      | 25.67 ± 1.43           | 25.79 ± 1.48 | 0.567                     |
| FIL (mIU/L)                      | 7.1 ± 1.7              | 16.5 ± 3.7  | < 0.001                   |
| FBG (mg/dL)                      | 89.9 ± 8.5             | 93.8 ± 10.3 | 0.099                     |
| HbA1c (%)                        | 5.3 ± 0.4              | 5.2 ± 0.3   | 0.815                     |
| HOMA-IR                           | 1.57 ± 0.45            | 4.81 ± 1.19 | < 0.001                   |
| TNM                              |                         |            |                          |
| 1                                | 8 (10)                 |            |                          |
| 2                                | 23 (28.7)              |            |                          |
| 3                                | 22 (27.5)              |            |                          |
| 4                                | 27 (33.8)              |            |                          |
| ER                               |                         |            |                          |
| Negative                         | 28 (35)                |            |                          |
| Positive                         | 52 (65)                |            |                          |
| PR                               |                         |            |                          |
| Negative                         | 44 (55)                |            |                          |
| Positive                         | 36 (45)                |            |                          |
| HER-2                             |                         |            |                          |
| Negative                         | 61 (76.3)              |            |                          |
| Positive                         | 19 (23.8)              |            |                          |
| Classification                    |                         |            |                          |
| Triple (-)                       | 3 (3.8)                |            |                          |
| Luminal                          | 46 (57.5)              |            |                          |
| HER-2 (+)                        | 19 (23.8)              |            |                          |
| Triple (+)                       | 12 (15)                |            |                          |

BMI: body mass index; FBG: fasting blood glucose; FIL: fasting insulin level; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment-insulin resistance; TNM: tumor-node-metastasis; ER: estrogen receptor; PR: progesterone receptor; HER-2/neu: human epidermal growth factor receptor-2.

| Table 2. Demographic and Biochemical Parameters of the Groups for Menopause |
|---------------------------------------------------------------|
| Control group                                                | Breast cancer                      |
| Premenopause (n = 30)                                         | Menopause (n = 30)                    | Premenopause (n = 40)                  | Menopause (n = 40)                    |
| Age (years)                                                  | 39.1 ± 3.1                          | 60.5 ± 4.5                            | 38.9 ± 4.0                            | 61.9 ± 5.4                            |
| BMI (kg/m²)                                                  | 25.46 ± 1.24                         | 25.88 ± 1.57                          | 25.76 ± 1.46                         | 25.82 ± 1.50                         |
| FIL (mIU/L)                                                  | 7.1 ± 1.5                            | 7 ± 1.8                               | 16.8 ± 3.9*                           | 16.2 ± 3.4*                           |
| FBG (mg/dL)                                                  | 88.3 ± 18.6                          | 91.7 ± 8.5                            | 90.2 ± 9.8                            | 95.6 ± 11.2                           |
| HbA1c (%)                                                    | 5.2 ± 0.4                            | 5.4 ± 0.3                             | 5.1 ± 0.4                            | 5.3 ± 0.3                             |
| HOMA-IR                                                      | 1.54 ± 0.48                          | 1.59 ± 0.43                           | 4.81 ± 1.18*                          | 4.82 ± 1.21*                          |

Comparison with control group, *P < 0.001. BMI: body mass index; FBG: fasting blood glucose; FIL: fasting insulin level; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment-insulin resistance.
In our study, BMI, FBG, and HbA1c concentrations did not differ between patients and control subjects, nor did FIL, FBG, HbA1c, or HOMA-IR differ between the pre-M and post-M BC groups. No relation was found between FIL and IR and prognostic factors, such as ER, PR, and HER-2, in nondiabetic patients with pre-M and post-M breast tumors. Brown et al [16] showed that FBG levels and HOMA-IR scores were higher in post-M women than in pre-M women. Luque et al [13] found that BC presence is associated with IR in overweight or obese pre-M women but not in pre-M or post-M women of normal weight. Tumor and IR markers are associated with impaired glucose/insulin metabolism in overweight or obese pre-M BC patients. This indicates a bidirectional relationship between irregular or unbalanced glucose/insulin metabolism data and BC. Yadav et al [17] noted significant differences in the HbA1c level, FIL, and C-peptide concentration of pre-M women between cases and controls. Insignificant results were found for FBG and BMI. Similarly, significant differences in FBG, FIL, C-peptide concentration, and HbA1c level were observed in post-M patients and controls. Similarly to our study, Manjer et al [18] found no significant differences in BC risk for perimenopausal (peri-M) and post-M women from different BMI quartiles and FBG levels. The association between BC presence and IR was independently influenced by BMI, ER, PR, and HER-2 in nondiabetic peri-M and post-M women. The role of FIL, FBG, and IR as markers for the diagnosis of BC in peri-M and post-M women must be widely evaluated.

Insulin has been shown to stimulate cell proliferation in normal breast tissue and human BC cell lines [19, 20], and to enhance breast tumor growth in animal models [21, 22]. Insulin growth factors (IGF) and IGF binding proteins (IGFBP) are valuable factors for work as well as FIL. It is emphasized that IGF1 and IGF1/IGFBP3 ratios may be parameters associated with mammographic density and the risk of BC development [23, 24]. IGF1, released by adipocytes and regulated by glucose and fatty acids, has been reported to play a role in the control of cancer cell growth in obese individuals [25]. IGF1 concentrations and sex steroids and plasma sex hormone binding globulin (SHBG) concentrations are thought to be factors that may explain this association between cancer and obesity [26]. Clinical studies have also shown an association between hyperinsulinemia, IR and SHBG [27-29]. Insulin and IGF1 inhibit the hepatic synthesis of SHBG. By reducing SHBG levels, insulin exerts a positive effect on estrogen bioavailability, thereby increasing BC risk [30]. In our study, FIL and HOMA-IR of the BC group were significantly higher than those of the control group. FIL and HOMA-IR of the BC group according to TNM stage were significantly higher in the stage IV group.

Table 3. Sensitivity, Specificity, AUC, Cutoff, and Asymptotic Significance of Parameters in Study Groups (Control vs. Breast Cancer)

| Parameter | Sensitivity (%) | Specificity (%) | AUC   | Cutoff | P      |
|-----------|----------------|----------------|-------|--------|--------|
| FIL (mIU/L) | 98.8           | 82.7           | 0.987 | 8.5    | < 0.001|
| HOMA-IR    | 97.5           | 96.7           | 0.998 | 2.4    | < 0.001|

FIL: fasting insulin level; HOMA-IR: homeostasis model assessment-insulin resistance; AUC: area under the curve.

Table 4. Biochemical Parameters of the Breast Cancer Group for TNM Stage

| Parameter | TNM | P      |
|-----------|-----|--------|
|          | 1   | 2   | 3   | 4   |
| FIL (mIU/L) | 10.3 ± 1.4 | 14.9 ± 3.4 | 17.4 ± 2.2 | 19 ± 2.2 | < 0.001 |
| HOMA-IR    | 2.7 ± 0.4 | 4.1 ± 0.7 | 5.1 ± 0.7 | 5.9 ± 0.6 | < 0.001 |

FIL: fasting insulin level; HOMA-IR: homeostasis model assessment-insulin resistance; TNM: tumor-node-metastasis.

Table 5. Biochemical Parameters of the Breast Cancer Group for ER, PR and HER-2

| Parameter | PR (-), (n = 44) | PR (+), (n = 36) | P      |
|-----------|-----------------|-----------------|--------|
| FIL (mIU/L) | 16.3 ± 3.9 | 16.7 ± 3.4 | 0.645 |
| HOMA-IR    | 4.8 ± 1.3 | 4.9 ± 1.1 | 0.616 |
| ER (-), (n = 28) | 16.7 ± 3.8 | 16.4 ± 3.6 | 0.767 |
| HOMA-IR    | 4.9 ± 1.2 | 4.8 ± 1.2 | 0.556 |
| HER-2 (-), (n = 61) | 16.2 ± 3.6 | 17.6 ± 3.8 | 0.127 |
| HOMA-IR    | 4.7 ± 1.2 | 5.2 ± 1.1 | 0.115 |

FIL: fasting insulin level; HOMA-IR: homeostasis model assessment-insulin resistance; ER: estrogen receptor; PR: progesterone receptor; HER-2/neu: human epidermal growth factor receptor-2.
than in the other stages. FIL and HOMA-IR had a sensitivity of 98.8% and specificity of 82.7%, and a sensitivity of 97.5% and specificity of 96.7%, respectively, which demonstrates their sufficiency in distinguishing BC from control. The results of our study were consistent with some other studies [2, 3, 31-33]. However, some results in the literature are contradictory. No consistent association was found between FIL and BC [5, 34-35]. Del Giudice et al [31] found that FIL and IGFBP-3 levels were elevated in women with pre-M BC, regardless of diet and other known risk factors for BC. This finding may indicate the presence of an underlying IR syndrome independent of obesity. Gunter et al [3] stated that hyperinsulinemia is an independent risk factor for BC and may be the basis for explaining the relationship between obesity and BC. Jernstrom et al [34] reported that proinsulin, FIL and C-peptide levels were positively correlated with current weight and weight gain, but these hormones and IGF1 levels did not differ between women with and without BC. Past estrogen replacement therapy (ERT) was more common among women with BC and the duration of use was longer. It has been emphasized that the risk of BC increases significantly in women who gain weight or use hormone replacement therapy (HRT), but this increased risk is not related to circulating levels of IGF1, FIL, proinsulin or C-peptide. Kaaks et al [35] reported that there was no clear relationship between BC risk and FIL. Mink et al [5] reported that FIL do not predict future incidence of BC, but may be weakly associated with T2DM, perhaps modulated through increased adiposity. Given these conflicting results, the effects of insulin on BC need to be further investigated [36].

In one study conducted in 2020, Pan et al [37] found that increased IR in post-M women is associated with higher BC incidence and higher all-cause mortality after BC. Another study found that IR may have a negative effect on pathological complete response following neoadjuvant therapy particularly with hormone-positive and HER-2-negative cases of non-diabetic BC [38]. Despite all speculation, Yee et al [39] recommended that oncologists care about insulin because of “Given the important role insulin signaling plays in driving signaling pathways that promote aggressive cancer biology, more attention should be paid by cancer physicians to screening and treating IR.”

The outcomes of this research suggest that insulin may be one of the contributing factors (excluding obesity) to the development of BC. A high FIL is a potential risk factor for BC development in non-diabetic women. IR is an interrupted state in the biological response to insulin in non-diabetic patients with pre-M and post-M breast tumors. Because insulin may affect BC risk and prognosis, it is important to control IR. Considering that the insulin signal activates the signaling pathways in cancer biology, the treatment of IR with medical and integrative approaches may be useful in cancer treatment. FIL and IR may function as potential biomarkers and therapeutic targets for human cancers, and their role should be further studied to improve our understanding of BC pathogenesis and progression.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Written informed consent was obtained from each subject after they were informed about the study.

Author Contributions

BPK, CP, RG, and HU contributed to the conception and interpretation of the data. SD, MC, and VS performed the statistical analysis. BPK, SD, FOK, CP, RG, and HU were involved in writing, reviewing, and editing the manuscript. All the authors read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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