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ORIGINAL ARTICLE

The relationship of insulin resistance and metabolic syndrome with known breast cancer prognostic factors in postmenopausal breast cancer patients

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Summary

Purpose: *The aim of this study was to investigate the effect of metabolic syndrome and insulin resistance at the time of diagnosis on the known prognostic factors of breast cancer in postmenopausal breast cancer patients.*

Methods: *The study included 71 patients with a recent diagnosis of postmenopausal breast cancer, admitted at the Medical Oncology outpatient clinic of the Izmir Ataturk Training and Research Hospital between June 2010 and June 2011. We determined whether the patients had metabolic syndrome and insulin resistance at diagnosis, and recorded known prognostic factors, such as tumor size, axillary lymph node involvement, presence of distant metastasis, tumor grade, estrogen receptor (ER), progesterone receptor (PR), and CerbB-2 status.*

Results: *Among 71 patients, 25 (35%) had metabolic syndrome at the time of diagnosis, and 33 (46%) had insulin resistance with Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR)>2.7. No statistically significant difference was found in the prognostic values of breast cancer, i.e. tumor size, axillary lymph node involvement, distant metastasis, tumor grade, ER, PR, and CerbB-2 status between the patients with and without metabolic syndrome. There was no statistically significant difference in the prognostic factors of breast cancer at the time of diagnosis between 33 patients with insulin resistance and 38 patients without insulin resistance.*

Conclusion: *Several previous studies showed a negative relationship between metabolic syndrome and insulin resistance and prognostic factors of breast cancer in postmenopausal breast cancer patients. However, our study failed to show such a relationship. The relationship between metabolic syndrome and insulin resistance and postmenopausal breast cancer was not well demonstrated due to the small number of patients, unknown duration of the metabolic syndrome and insulin resistance, and shorter follow-up period. Further studies are required to demonstrate the effect of metabolic syndrome and insulin resistance on the prognosis of breast cancer, including larger number of patients and longer follow-up periods.*

Key words: *breast cancer, insulin resistance, metabolic syndrome, postmenopausal breast cancer*

Introduction

Recent studies have demonstrated a negative relationship between metabolic syndrome and insulin resistance and overall survival in postmenopausal breast cancer patients [1]. In postmenopausal women, estrogen is largely synthesized in adipose tissue by aromatization due to reduced synthesis of estradiol. Increased estrogen levels may represent a risk for breast cancer, as the majority of patients with metabolic syndrome is obese, and adipose tissue is increased in obese patients [1]. A negative relationship was found between insulin resistance and hyperinsulinemia and postmenopausal breast cancer patients [2]. Hyperinsulinemia, the key factor in insulin resistance, may exert mitotic activity via insulin-like growth factor-1 (IGF-1), leading to poor prognosis

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for all neoplasms. Hyperinsulinemia also reduces sex hormone- binding globulin (SHBG) levels in women, which is associated with increased free estrogen levels [3]. Increased free estrogen levels have negative effects on postmenopausal breast cancer patients [4-6]. In a study by Malin et al., which is one of the studies carried out on insulin resistance and breast cancer, it has been shown that insulin resistance is associated with 2 to 3-fold increase in the risk of developing breast cancer [7]. A study by Patrizia et al. with 110 postmenopausal breast cancer patients indicated that metabolic syndrome had a negative effect on their prognosis [8]. A study completed in 2010 by Tone et al. with the largest cohort of patients (Metabolic Syndrome and Breast Cancer/Me-Can) enrolled 287,320 women between 1974 and 2005. After a mean follow-up of 11 years, 4,862 women were diagnosed with breast cancer. It was concluded that metabolic syndrome was associated with poor prognosis in breast cancer [9].

The objective of this study was to determine the relationship between insulin resistance and metabolic syndrome and known prognostic factors of breast cancer, and also the frequency of these conditions in postmenopausal breast cancer patients.

Methods

Patient selection

A total of 71 postmenopausal patients with a recent diagnosis of breast cancer at the Izmir Ataturk Training and Research Hospital between June 2010 and June 2011 were enrolled. We excluded patients with diabetes mellitus. Included were postmenopausal patients with histologically confirmed breast cancer and TNM stages II-IV, who applied to our medical oncology outpatient clinic prior to chemotherapy.

Study design

Fasting serum insulin, glucose and lipid profile were assessed in all included patients. Waist circumference, body weight and height and blood pressure were measured.

Any patient with a waist circumference >80 cm and two of the other diagnostic criteria (triglycerides >150 mg/dl, HDL <50 mg/dl, blood pressure >130/85 mm/Hg, and fasting blood glucose >100mg/dl) was characterized as having metabolic syndrome.

Any patient with a HOMA-IR value >2.7 was considered to have insulin resistance. HOMA-IR was calculated using the following equation: HOMA–IR=Fasting insulin (μU/mL) x Fasting glucose (mg/dL) /405.

Laboratory examinations

For laboratory tests, venous blood samples were collected into vacuum tubes and gel tubes from patients after overnight fasting. They were centrifuged at 4000 rpm/min after being kept at room temperature for 30 min, and then routine biochemical tests were performed. Routine serum total cholesterol, HDL, LDL glucose and insulin were measured with Olympus 2700 autoanalyzer using kits of the same manufacturer.

Statistics

Descriptive statistics were used for the studied variables (characteristics) and presented as frequencies and percents. Chi-square test was used to determine relationships between categorical variables. In addition, odds ratio was also computed to indicate risk factors for the metabolic syndrome and HOMA-IR. Statistical significance level was set at $p<0.05$. SPSS (version13) statistical program was used for all statistical computations.

Results

The patient mean age was 62.44±9.7 years. Twenty-five (35.2%) had metabolic syndrome and 33 (46%) had a HOMA –IR value >2.7. Fifteen (21%) patients developed new metastases or showed progression of existing metastases during a 2-year follow-up. The majority of the patients (71.8%) had T2 tumors, and most of them (66.2%) had positive axillary lymph nodes. Only 8 (11%) patients had distant metastasis at the time of diagnosis. ER was positive in 52 (73%) patients and 48 (68%) patients had well and moderately well differentiated disease.

No statistically significant difference was found in tumor size when 25 patients with metabolic syndrome were compared to 46 patients without metabolic syndrome (Table 1). Also, there was no statistically significant difference between positive or negative axillary lymph nodes and metabolic syndrome (Table 2). Presence of distant metastasis was not correlated with metabolic syndrome (Table 3). Also, metabolic syndrome and tumor grade showed no statistically significant difference (Table 4).

Among 71 patients, 33 (46%) had insulin resistance. No statistically significant difference was found between patients with and without insulin resistance in relation to tumor size (Table 5). Also, no statistically significant difference was noticed between insulin resistance and axillary lymph node involvement (Table 6), presence of distant metastasis (Table 7) as well as tumor grade (Table 8).

Table 1. Metabolic syndrome and tumor size in breast cancer patients

Metabolic syndrome	*T1* *N (%)*	*T2* *N (%)*	*T3* *N (%)*	*T4* *N (%)*	*Total* *N(%)*
Yes	8 (17.4)	33 (71.7)	2 (4.3)	3 (6.5)	46 (100)
No	3 (12)	18 (72)	4 (16)	0 (0)	25 (100)
Total	11 (15.5)	51 (71.8)	6 (8.5)	3 (4.2)	71 (100)

x^2, p=0.535

Table 2. Metabolic syndrome and lymph node involvement in breast cancer patients

Metabolic syndrome	*N0* *N (%)*	*N1* *N (%)*	*N2* *N (%)*	*N3* *N (%)*	*Total* *N(%)*
No	17 (37)	16 (34.8)	7 (15.2)	6 (13)	46 (100)
Yes	7 (28)	8 (32)	6 (24)	4 (16)	25 (100)
Total	24 (33.8)	24 (33.8)	13 (18.3)	10 (14.1)	71 (100)

x^2, p=0.446

Table 3. Metabolic syndrome and distant metastasis in breast cancer patients

Metabolic syndrome	*M0* *N (%)*	*M1* *N (%)*	*Total* *N (%)*
No	43 (93.5)	3 (6.5)	46 (100)
Yes	20 (80.0)	5 (20)	25 (100)
Total	63 (88.7)	8 (11.3)	71 (100)

x^2, p=0.086

Table 4. Metabolic syndrome and tumor grades in breast cancer patients

Metabolic syndrome	*G1* *N (%)*	*G2* *N (%)*	*G3* *N (%)*	*Total* *N(%)*
No	3 (6.5)	30 (65.2)	13 (28.3)	46 (100)
Yes	3 (12)	12 (48)	10 (40)	25 (100)
Total	6 (8.5)	42 (59.2)	23 (32.4)	71 (100)

x^2, p=0.428

Table 5. Insulin resistance and tumor size in breast cancer patients

HOMA-IR	*T1* *N (%)*	*T2* *N (%)*	*T3* *N (%)*	*T4* *N (%)*	*Total* *N(%)*
< 2.7	5 (13.2)	28 (73.7)	2 (5.2)	3 (8)	38 (100)
≥ 2.7	6 (18.2)	23 (69.7)	4 (12.1)	0 (0)	33 (100)
Total	11 (15.5)	51 (71.8)	6 (8.5)	3 (4.2)	71 (100)

HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance
x^2, p=0.896

Table 6. Insulin resistance and axillary lymph node involvement in breast cancer patients

HOMA-IR	*N0* *N (%)*	*N+* *N (%)*	*Total* *N (%)*
< 2.7	15 (39.5)	23 (60.5)	38 (100)
≥ 2.7	9 (27.3)	24 (72.7)	33 (100)
Total	24 (33.8)	47 (66.2)	71 (100)

HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance
x^2, p=0.278

Table 7. Insulin resistance and distant metastasis in breast cancer patients

HOMA-IR	*M0* *N (%)*	*M1* *N (%)*	*Total* *N (%)*
< 2.7	34 (89.5)	4(10.5)	38 (100)
≥ 2.7	29 (87.9)	4 (12.1)	33 (100)
Total	63 (88.7)	8 (11.3)	71 (100)

HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance
x^2, p=0.832

Table 8. Insulin resistance and tumor grade in breast cancer patients

HOMA-IR	*G1* *N (%)*	*G2* *N (%)*	*G3* *N (%)*	*Total* *N(%)*
< 2.7	3 (7.9)	25 (65.7)	10 (26.3)	38 (100)
≥ 2.7	3 (9)	17 (51.5)	13 (39.5)	33 (100)
Total	6 (8.5)	42 (59.2)	23 (32.4)	71 (100)

HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance
x^2, p=0.857

No significant relationship was found between 25 patients with and 46 without metabolic syndrome and ER, PR and CerbB-2 status. Also, no significant difference was found between patients with HOMA-IR less (N=38) or more (N=33) 2.7 in relation to ER,PR and CerbB-2 status. Similarly, no statistically significant difference was found between insulin resistance and ER, PR, CerbB-2 status. A statistical analysis performed between 15 patients who developed disease progression at 2 years and 56 patients who didn't, showed no statistically significant difference in ER, PR and CerbB-2 status.

Discussion

Our objective was to determine whether there was a relationship between metabolic syndrome and insulin resistance and the known prognostic factors of breast cancer in postmenopausal breast cancer patients. At the end of the study, we found no statistically significant difference between patients with and without metabolic syndrome and known prognostic factors (tumor size, lymph node involvement, distant metastasis, tumor grade, ER, PR, and CerbB-2 status) at the time of diagnosis. Patients with a HOMA-IR value >2.7 at the time of diagnosis were considered to have insulin resistance. No statistically significant difference was found between patients with and without insulin resistance and the previously described prognostic factors. Fifteen of 71 patients developed disease progression within 2 years. Although the number of patients who developed progression is very small and the follow-up period is very short, no statistically significant difference was found in patients with and without disease progression in relation with the presence of metabolic syndrome and insulin resistance.

In the Western world, the incidence of breast cancer increases in parallel to the major components of the insulin resistance syndrome - hyperinsulinemia, dyslipidemia, hypertension and atherosclerosis. Studies show that breast cancer development is facilitated by specific dietary fatty acids, visceral fat accumulation and inadequate physical exercise, all of which are believed to contribute to the development of the insulin resistance syndrome [10].

Obesity is a well established risk factor for postmenopausal breast cancer, being explained by biochemical parameters. In premenopausal women, the predominant estrogen is estradiol, while in postmenopausal women the source of estrogen is estrone, which is a product of aromatization of androstenedione, formed by aromatase. Furthermore, biologically there is an increase in active hormone levels due to decreased SHBG levels in all obese people. Since obesity is a component of the metabolic syndrome, hyperinsulinemia can exert a mitogenic activity on the tumor cells. Another fact is that obesity and hypercholesterolemia are frequently concomitant. As already known, cholesterol is a precursor of all steroid hormones, and estrogen is also synthesized from cholesterol. Breast cancer is also estrogen-dependent. Also data from several studies indicate that breast cancer mortality is higher in obese patients [11-13].

The association between insulin resistance and breast cancer has been attempted to be clarified in different ways. Cancer cell lines need insulin for optimal growth. Insulin receptor (IR) provides proliferation and differentiation of normal and neoplastic hematopoietic cells. Insulin has been shown to play a direct role in cancer growth in animal models. In a study with human MCF-7 breast cancer cells, no tumor growth was observed in diabetic mice, whereas tumor growth was 100% in diabetic mice treated with insulin. DMBA (7,12 dimethylbenz(a) anthracene)-induced breast tumors in rats regressed after induction of alloxan diabetes in these rats [14]. Using ELISA it has been shown that the level of IR is higher in breast cancer tissue than in normal breast tissue. Immunohistochemically, IR is mainly expressed in neoplastic cells [15]. The 5-year survival rate of patients (all cancers included) with higher IR is lower compared to those with moderate IR. Multivariate analyses showed that IR content is the strongest independent factor for 5-year survival and increased IR content was also found in colon, lung, ovary and thyroid cancers [15-18].

IR has two isoforms: IR-A and IR-B. Of these isoforms, IR-A is expressed in fetal tissues and upregulated in type-2 diabetes, cancer and myotonic dystrophy. IR-B is expressed in tissues which are targeted for metabolic insulin action. IR-A sends mitogenic and anti-apoptotic signals, while IR-B prefers differentiation signals. Non-breast malignancies such as colon cancer, lung cancer, ovarian cancer, thyroid cancer and myosarcoma mainly express IR-A. In thyroid cancer, overexpression of IR-A is associated with tumor progression and cancer de-differentiation. Proliferative effects of IGF-II can be inhibited by specific antibodies. Both IR and IGF-IR are increased in tumor progression, but only IR expression is increased in poorly differentiated and anaplastic thyroid cancers [19]. Most malignant cells express insulin and IGF-

1 receptors. IR is capable of stimulating cancer cell proliferation and metastasis in addition to its metabolic functions. Glucose uptake is consistently high in cancer cells, and it is independent of insulin binding to its receptor; IR activation on neoplastic cells is associated with cell survival and mitogenesis rather than glucose uptake [19]. Multiple signalling pathways are activated by respective ligands following interaction with IR or IGF-1 receptors (IGF-IR). Once activated, these signalling pathways may stimulate proliferation, protection from apoptosis, invasion and metastasis. Hyperglycemia allows IGF-1 to stimulate vascular smooth muscle cell proliferation and migration. Although this process is associated with the pathophysiology of atherosclerosis, abnormal vascular growth is the most remarkable indicator of cancer [20]. Increased circulating insulin also has many indirect effects. Insulin reduces the hepatic synthesis and level of sex hormone-binding globulin (SHBG) and increases estrogen bioavailability in both men and women, and testosterone bioavailability only in women, not in men. Androgen synthesis is increased with hyperinsulinemia in the ovaries and probably in the adrenal glands in premenopausal women. Increased endogenous sex steroid levels are associated with increased risk of postmenopausal breast, endometrial and, probably, other cancers. Insulin suppresses hepatic IGF binding protein (IGFBP) production, increasing free IGF-1 levels in the circulation [21].

Components of the metabolic syndrome, i.e. type-2 diabetes, hypertension, dyslipidemia, hyperuricemia, hypercoagulability also represent general characteristics of the insulin resistance syndrome [22]. Clinical and epidemiological evidence suggests that breast cancer and metabolic disorders including insulin resistance are polygenic and multifactorial in origin [10]. Experimental evidence suggests that hyperinsulinemia and its characteristics can increase mammary carcinogenesis, and it is likely that the mechanism is related to the increased bioactivity of IGF-1 [10]. Lawlor et al. performed a large cross-sectional study of 3837 postmenopausal women without diabetes in England. This study measured fasting serum insulin levels. Of them 147 (3.7%) subjects developed breast cancer with high concentrations of insulin. In this study, the risk of developing breast cancer was significantly higher in women with higher insulin concentration (p=0.03) [23]. Goodwin et al. showed that there was high fasting plasma insulin concentration in high-grade tumors, positive axillary lymph nodes, increased relapse rate and reduced overall survival both in post and pre-menopausal patients with breast cancer [24].

Body mass index (BMI) can be a potential risk factor for breast cancer, and it is mediated by both insulin resistance and estrogen metabolism [25]. A study by Geoffrey et al. highlights that elevated glucose level is not a risk factor, but elevated insulin levels may be a risk factor for postmenopausal breast cancer [26].

Although a negative relationship was found between metabolic syndrome and insulin resitance and breast cancer, several studies have failed to demonstrate it. In a study by Cust et al. BMI and C-peptide were not risk factors for development and progression of breast cancer [27]. Lersson et al. indicated that diabetes was not associated with risk of developing breast cancer and increased breast cancer mortality [28].

In the present study, there was no association between obesity and fat distribution in the upper body and breast cancer. This may be attributed to the fact that our patients had different pathologies of breast cancer and to the small number of patients.

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