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Adipokine Omentin-1: A Diagnostic Tool in Breast Cancer

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Abstract

Introduction: Breast cancer is the most frequent solid malignancy in women. Omentin-1 is synthesized by visceral adipose tissue, placenta, and ovary and its production is altered in some cancers. The aim of this study was to assess omentin-1 as a diagnostic marker in patients with breast cancer.

Methods: The participants of the study included 90 women (45 patients with breast cancer and 45 healthy women as control group). In addition to anthropometric and blood parameters analysis, omentin-1 serum levels were measured by enzyme-linked immunosorbent assays method. Receiver operator characteristic curve and positive and negative predictive values (PPV and NPV) were calculated to define diagnostic accuracy.

Results: Serum omentin-1 level in breast cancer patients (157 ng/L ± 66 ng/L, mean ± SD) was significantly lower than that of the control group (217 ng/L ± 75 ng/L, mean ± SD). There was no significant correlation between omentin-1 levels and anthropometric and blood parameters. The best cut-off point for the diagnosis of breast cancer was at 146 ng/L. The sensitivity and specificity for omentin-1 with 95% CI (0.611 to 0.837) were 60% and 85%, respectively. Calculated PPV and NPV at the 146 ng/L cut-off point were 88.8% and 51.5%, respectively.

Conclusion: Breast cancer patients had significantly lower serum level of omentin-1 than healthy women. Omentin-1 may be beneficial as a screening test along with the early-approved methods in the diagnosis of patients with breast cancer.

Keywords: Adipokine, Breast cancer, Omentin-1

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Introduction

Breast cancer is the most frequent neoplasm in women and the second leading cause of cancer-related mortality in the world. Currently, breast cancer prevalence is rising and early diagnosis is critical to the higher survival rate.[1]

In this respect, omentin-1, as an adipokine that was identified by Yang and colleagues for the first time, is secreted from fat tissue visceral, ovary, and placenta in human and rhesus monkey.[2,3] Adipokines are considered as different classes of pro- and anti-inflammatory factors.[4,5]

The expression of omentin-1 is reduced in obesity, inadequate glucose balance, diabetes mellitus type-2, and insulin-resistance obese women with polycystic ovary syndrome (PCOS). However, in addition to anti-inflammatory effects of omentin-1 in vascular smooth muscle cells, there are conflicting results regarding its increased or decreased concentration in different cancers.[6-9]

Since breast cancer prevalence is increasing and early diagnosis plays an important role in the treatment and prognosis of the disease, finding a potential diagnostic tool is critical for early cancer detection. Despite introducing new screening tests including Her2/neu or CA 15-3 antigens, mammography is the gold standard screening method for breast cancer diagnosis.[10,11] Hence, emerging screening laboratory tests along with the early-approved methods can provide an

accurate diagnosis. A far as is known and due to reported conflicting results in the omentin-1 level in cancers, the serum level of omentin-1 was measured in women with breast cancer.[6,7,12]

Materials and Methods

Patient Selection

Forty-five patients with breast cancers (within the age range of 18-60 years) from Vali-Asr hospital (Arak, Iran) and 45 healthy unrelated subjects (with the age range of 22-56 years) from healthy blood donors referring to Arak Blood Transfusion Organization during August 2015 to May 2016 were included in this age-matched case-controlled study. Selected patients were confirmed in terms of clinical and para-clinical signs of breast cancer. Women were included in case they were newly diagnosed and histologically proven to have stage I-III breast cancers. Patients underwent standard breast magnetic resonance imaging (MRI) or dedicated axillary MRI prior to the surgery. Since body mass index (BMI) may influence omentin-1 levels, the selected groups were managed to have BMI within the range of 18.5–25 kg/m^2. Women who had undergone any type of neo-adjuvant chemo-, immune- or endocrine therapy were excluded from the study. Similarly, patients with a history of breast surgery or treatment, liver dysfunction, obesity, and diabetes mellitus were excluded from this study as well.

Anthropometric and Blood Parameters Analysis

Anthropometric measures including height, weight, and BMI were recorded. BMI was calculated as body weight divided by height squared (kg/m^2).[6] Blood parameters including blood sugar (BS), red blood cell (RBC), white blood cell (WBC), as well as platelet (PLT) and hemoglobin (Hb) concentration were measured in duplicates in venous blood samples taken after at least 10 hours fast. For this purpose, 10 mL of peripheral blood was taken from both groups (patient and healthy women) and were poured into clot and ethylenediaminetetraacetic acid (EDTA)-contained tubes separately and transferred to the laboratory, immediately. Clot tubes were centrifuged for 10 minutes at 2000 × g, serum samples were separated and the BS of all tubes were measured by the enzymatic colorimetric method (Pars Azmun, Tehran, Iran). EDTA-contained tubes were assessed for cell blood counting using Sysmex automated hematology analyzer KX-21 (Sysmex, Milton Keynes, UK).

ELISA Assay

The serum samples were stored at -80°C until omentin-1 measurement. Omentin-1 serum level was measured in duplicates using enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, Hangzhou, China) based on the manufacture's instruction. All specimens were measured with the microplate reader (Stat Fax 2100) at wavelengths of 450 nm.

Statistical Analysis

Kolmogorov–Smirnov test was used for assessing normal distribution of the data. The *t* test was performed for comparison within and between the normally-distributed groups. Spearman rank correlation coefficient analyses were performed to show a correlation between omentin-1 concentration and anthropometric and blood parameters analysis. Data were analyzed using SPSS software version 16.0 (SPSS Inc., Chicago, USA) and were represented as mean ± standard deviation (SD). *P* values less than 0.05 were considered to be statistically significant. Receiver operator characteristic (ROC) curves and positive and negative predictive values (PPV and NPV) were calculated using MedCalc Statistical software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) to define the diagnostic accuracy as determined by the area under the ROC curve (AUC) of omentin-1.

Results

Comparison of Anthropometric and Blood Parameters

This study was conducted on 45 women with stage I-III breast cancers and 45 healthy women as the control group. In patients and healthy control groups, BMI anthropometric parameter as well as serum levels of blood parameters including BS, Hb, RBC, WBC, and PLT were measured (Table 1). Except for WBC count (*P*=0.03), there were no significant differences between blood parameters and BMI analysis of patients and healthy control groups.

Comparison of Omentin-1 Concentration

The results of omentin-1 concentration showed that its serum levels were significantly lower in patients (157 ± 66 ng/L) compared to healthy control group (217 ±75 ng/L, *P*=002) (Figure 1). Furthermore, there was no significant correlation between omentin-1 levels and BMI and blood parameters analysis including, BS, Hb, RBC, WBC, and PLT.

Diagnostic Value of the Omentin-1 Level

The diagnostic value of omentin-1 level was investigated through calculating ROC curve (Figure 2). The best cut-off point for the diagnosis of breast cancer was at 146 ng/L. The sensitivity and specificity for omentin-1 with 95% CI (0.611 to 0.837) were 60% and 85%, respectively. Calculated PPV and NPV as predictive values at 146 ng/L cut-off point were 88.8% (CI: 79.2 to 94.3) and 51.5% (CI: 42.2 to 60.8), respectively.

Discussion

Adipokines are white adipose tissue-derived peptides. As previously mentioned, omentin-1, which was defined by Yang et al, is a new adipokine and is known to have anti-inflammatory roles in vascular smooth muscle cells and synovial fluid of patients with rheumatoid arthritis.[13,14] A far as is known, due to reported conflicting results in

Table 1. Comparison of Anthropometric and Blood Parameters in Patients With Breast Cancer and Healthy Control Groups

Variables	Patients Group Mean ± SD, n=45	Control Group Mean ± SD, n=45	*P* Value
Number, average age (y)	39 ± 11	35 ± 7	0.25
BMI (kg/m^2)	26 ± 3.4	24.2 ± 6	0.85
BS (mg/dL)	100 ± 9	97 ± 13	0.36
WBC (× 10^3/μL)	(7.11 ± 1.8)	(5.11 ± 1.5)	0.02
RBC (× 10^3/μL)	(4.6 ± 0.5)	(5.3 ± 0.9)	0.5
PLT (× 10^3/μL)	(259 ± 105)	(311 ± 75) × 10^3	0.85
Hb (g/dL)	12.9 ± 0.4	13.3 ± 0.35	0.28

Abbreviations: BMI, body mass index; BS, blood sugar; WBC, white blood cell; RBC, red blood cell; PLT, platelet; Hb, hemoglobin.

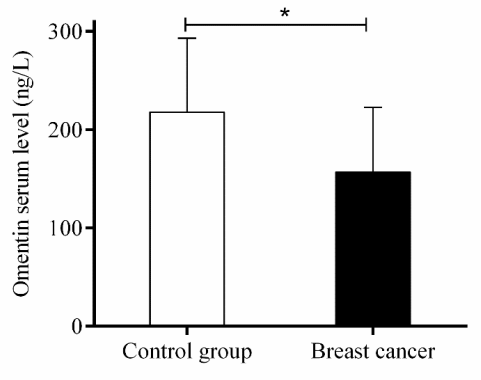

Figure 1. The bar graph shows omentin-1 serum levels in patients with breast cancer compared to those of control group. *P value < 0.05.

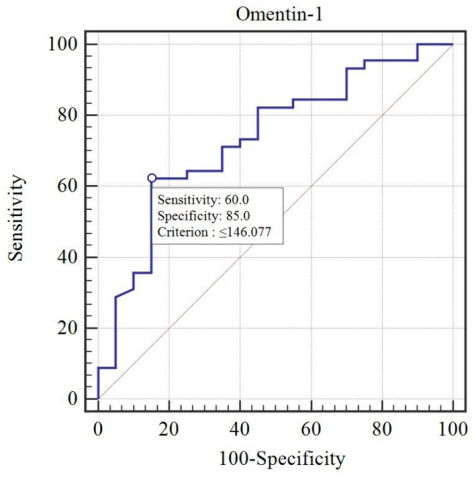

Figure 2. Receiver-Operator Characteristics (ROC) for Serum Omentin-1 in Women With Breast Cancer. Sensitivity: 60%, Specificity: 85%, and Values ≤ 146 ng/L are considered positive (Criterion ≤ 146 ng/L).

the omentin-1 concentration in the previously studied, cancers' serum level of omentin-1 were measured in patients with breast cancer.[6,7,12]

Despite introducing new screening tests including Her2/neu or CA 15-3 antigens, mammography is the gold standard screening method for breast cancer diagnosis. As a result, emerging screening laboratory tests together with early-approved methods can provide an accurate diagnosis.[11] The present study demonstrated that serum levels of omentin-1 in patients with stage I-III breast cancers, as early breast cancer stages, were significantly lower than the serum levels in healthy control group. A cut-off value was assessed for omentin-1 to test its diagnostic performance as 146 ng/L. At this cut off value, omentin-1 had a sensitivity of 60% and specificity of 85% with PPV and NPV of 88.8% and 51.5%, respectively. In this study, in order to match the groups, BMI anthropometric parameter and serum levels of blood parameters including, BS, Hb, RBC, WBC, and PLT were measured and the results revealed that except for WBC count, there were no significant differences between blood parameters and BMI analysis of patients and healthy control groups.

Fazeli et al indicated that concentrations of omentin-1, visfatin, and vaspin in the serum of patients with colorectal cancer (CRC) were significantly higher than those of healthy control subjects. Based on this study, these adipokines may play potential roles in the development of colorectal cancer by mechanisms unrelated to obesity through Akt signaling pathway as Akt signaling can play important roles in cell proliferation and apoptosis prevention.[12] In another study, omentin-1 in the serum of 81 women, 41 leans, and 40 obese individuals with PCOS and 61 healthy subjects were measured. The results showed that the amounts of omentin-1 in all patients with PCOS were significantly higher compared to the control group. Similarly, the average concentration of omentin-1 in obese patients with PCOS was significantly higher compared to the obese subjects in the control group.[15]

Results of a study on 45 patients with third stage colon cancer treated with surgery and 35 healthy subjects showed that omentin-1 values in patients were higher compared to the control group.[7] Zhang et al demonstrated that the omentin-1 considerably inhibits 2 types of liver cancer cell lines (HepG2 and Huh7) proliferation. Omentin-1 positively regulates p53 protein levels by reducing deacetylation of p53 and increases the stability of P53. The data from this study indicate that omentin-1 may contribute to the treatment of hepatocellular carcinoma.[16]

In addition, Uyeturk et al found that level of omentin-1 in

patients with prostate cancer was higher than its level in people with benign prostatic hyperplasia.[6]

Conversely, however, the results of this study reporting lower concentration of omentin-1 in patients with breast cancer, the above mentioned studies showed higher levels of omentin-1 in CRC, PCOS, prostate cancer, and liver cancer cell lines. Therefore, the only difference between our study and the other findings might be the result of the different study population, type of cancer tissues and treatment.

Omentin-1 serum levels in some cancers were studied; however, so far there is only one study on the measurement of serum levels of omentin-1 in patients with breast cancer. In this regard, Alaee and colleagues have recently measured serum omentin-1 level in patients with breast cancer. Similar to the results of the current study, they reported reduced amounts of omentin-1 in patients; however, unlike our study, there was no evaluation of omentin-1 potential as a diagnostic tool.[17] In the other study, Shen and colleagues confirmed the lower concentration of omentin-1 in patients with renal cell cancer.[8] In consistent with the results of the present study, Mogal and colleagues showed reduced omentin-1 in patients with RCC.[18]

Omentin-1 was involved in colorectal-tumor development through Akt phosphorylation/activation.[19] There are some documents showing that omentin-1 plays a role in apoptosis induction in hepatocellular carcinoma cells via p53 and p21 upregulation or activation of caspase-3 signaling pathway through increasing bax/bcl2 ratio.[16] Reducing levels of omentin-1 in patients with breast cancer could be for defense strategies of the patients or escape routes of cancers that remains to be investigated in the future studies.

One of the limitation of the study was the small sample size (only 45 patients residing in Arak were included in the study).

Furthermore, omentin-1 gene expression could be useful for better evaluating the results. Therefore, studies with higher samples and gene expression are recommended.

Conclusion

In summary, finding a potential diagnostic tool is critical in early cancer detection. Since the serum level of omentin-1 was significantly lower than its level in healthy group, thus, it can be used as a screening test along with the early-approved methods in diagnosis of patients with stage I-III of breast cancers, as early breast cancer stages.

Ethical Approval

Informed consent was obtained from all individual participants prior to their inclusion in the study. The experimental protocol for blood collection was approved by Human Ethics Committee of Arak University of Medical Sciences, Arak, Iran (code number: ARAK.RAC.1394.147) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

Competing Interests

The authors declare that they have no conflict of interests.

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