Serum Chemerin Level in Breast Cancer

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ABSTRACT

Breast cancer is the most commonly diagnosed cancer in women, and obesity is a causative factor via estrogen exposure. Chemerin is a novel adipokine associated with obesity, metabolic syndrome, and polycystic ovary syndrome. We aimed to investigate serum chemerin levels in breast cancer and to correlate chemerin levels with clinicopathologic parameters of patients with newly diagnosed breast cancer. A total of 117 patients were enrolled the study. Serum chemerin levels were measured using an enzyme-linked immunosorbent assay. Ethical approval and informed consents were attained. Thirty-seven of the study population was metastatic and 80 were non-metastatic at the time of diagnosis. The mean chemerin levels were 257.3 ± 68.7 ng/mL (148.1-526.0 ng/mL). Serum chemerin levels were significantly higher in post-menopausal women and patients with diabetes, hypertension, body mass index (BMI) ≥30 kg/m² and age ≥50 years. Chemerin levels were not different in either group (p= 0.435). Multivariate analyses of parameters showed that CA15.3 and CEA levels were associated with metastatic disease. Our results propose that serum chemerin levels are not associated with breast cancer stage. However, further studies need to evaluate its role in carcinogenesis.

Keywords: Breast cancer, Chemerin, Body mass index.

ÖZET

Meme Kanserinde Serum Chemerin Düzeyi

Meme kanseri kadınlarda en sık görülen kanserdir. Obezite, östrojen fazlalığı nedeniyle meme kanserinin etiyolojik faktörleri arasında yer almaktadır. Chemerin; obezite, metabolik sendrom ve polikistik over ile ilişkilendirilmiş yeni bir adipokin olarak bilinmektedir. Bu çalışmada meme kanserinde serum chemerin düzeyini ve yeni tanı hastalarda serum chemerin düzeyinin klinik ve patolojik parametreler ile korelasyonunu araştırdık. Çalışmaya toplam 117 bayan hasta alındı. Serum chemerin düzeyi enzyme-linked immunosorbent assay (ELİSA) metodu ile ölçüldü. Etik kurul onayı alındı. Çalışmaya alınan hastalardan onam formu alındı. Çalışmaya alınan yeni tanı almış meme kanserli hastalardan 37'si metastatik iken, kalan 80 hasta ise metastatik değildi. Ortalama serum chemerin düzeyi 257.3 ± 68.7 ng/mL (148.1-526.0 ng/mL) olarak bulundu. Serum chemerin düzeyi post-menapozal kadınlarda, diyabeti ve hipertansiyonu olanlarda, vücut kitle indeksi(VKİ) ≥30 kg/m² ve yaş≥50 olan hastalarda istatistik olarak anlamlı oranda daha yüksek bulundu. Hastalar metastatik ve metastatik olmayan diye gruplandırıldığında serum CA15.3 düzeyi dışında diğer parametrelerde anlamlı fark gözlenmedi. Serum chemerin düzeyleri her iki grupta benzerdi (p= 0.435). Çok değişkenli analizlerde serum CA15.3 ve CEA düzeyleri metastatik hastalık ile ilişkili bulundu. Çalışmamızda serum chemerin düzeyinin meme kanseri evresi ile ilişkili olmadığını bulduk. Meme kanseri etiyopatogenezinde chemerinin rolü olduğunu anlamak için kontrol grubu içeren geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Meme kanseri, Chemerin, Vücut kitle indeksi

INTRODUCTION

Breast cancer is the most common cancer in women, affecting 1 in 8 women during their lives. Extended estrogen exposure is one of the most important risk factors for breast cancer. Post-menopausal obesity, which is also an estrogen excess condition, increases the risk of breast cancer by more than 63%.[1] Moreover, overweight women have higher blood insulin levels and increased insulin activation of tyrosine kinase growth receptor pathways.[2] Thus, it is another causative factor for breast cancer in obese women.

Chemerin is a recently identified adipokine that regulates adipogenesis and is associated with obesity, metabolic syndrome, and polycystic ovary syndrome. Many obesity-related parameters such as BMI, blood pressure, and insulin levels have been correlated with chemerin.[3] Besides its autocrine effects, chemerin is related to inflammation via its paracrine effect. Tumor necrosis factor-alpha (TNF-α) triggers the production of chemerin from adipocytes.[4] Chemerin is a chemoattractant protein that acts as a ligand for the G protein-coupled receptor CMKLR1.[5] This receptor, also called ChemR23, is the major receptor for chemerin and mainly expressed in adipocytes and immune cells, additionally in breast tissue.[6] The association of chemerin and cancer is not yet fully understood. Chemerin has been shown to have a potential role in immunoreactivity by acting as chemotactic for antigen presenting cells in inflammatory tissue.[6] Thus, researchers may hypothesize that chemerin could have an antitumor role. Otherwise, chemerin also promotes angiogenesis via inducing matrix metalloproteinase secretion and activity.[7] Therefore, it is thought that high levels of chemerin may have an initiating role in a further process; carcinogenesis, then metastasis.

Chemerin has been detected in breast cancer tissues.[8] Chemerin expressions of tumor tissues were assessed in many studies. Serum chemerin levels were also investigated in a few studies in such cancers, gastric and colon cancer. The aim of our study was to investigate serum chemerin levels in breast cancer and to correlate chemerin levels with clinicopathologic parameters of patients with newly diagnosed breast cancer.

PATIENTS AND METHODS

Patients and Methods

One hundred seventeen female patients with newly diagnosed breast cancer were evaluated in a cross-sectional observational study. All subjects were evaluated using a standardized form that included medical history and physical examination findings. Weight and height were measured. The patients' BMI (weight (kilograms)/height (meters)^2) was calculated. Basal blood samples of subjects were tested for fasting glucose, hemoglobin A1C (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). Glucose was measured using a spectrophotometer assay (Human Gesellschaft, Wiesbaden, Germany), HbA1c was assessed using high-pressure liquid chromatography with a Primus CLC330 Ghb analyzer (Prismus, Kansas City, MO). Triglyceride, total and HDL cholesterol were measured using an enzymatic calorimetric test (Roche Diagnostics GmbH, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald formula. Chemerin level measurement was performed according to the manufacturer's protocol (Biovendor Human Chemerin ELISA Kit). Research ethics committee approval was obtained from Hacettepe University Ethics Board and Commissions. Written informed consent was obtained from all participants.

Statistical Analysis

The statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Data on normal distribution are expressed as mean± SD and were compared using a t- test. Categorical variables are expressed as percentage and were compared using the Chi-square test or Fisher's exact test, as appropriate. Non-parametric variables were analyzed using the Mann-Whitney U test. Correlation analyses were performed using Spearman's and Pearson correlation tests. For the multivariate analysis, the possible factors(serum chemerin level, age at diagnosis, BMI, CEA and CA15-3) identified with univariate analyses were further entered into the logistic regression model to determine independent predictors of metastatic

Table 1. Clinical characteristics of the patients

| Variables (n= 117)	
Age at diagnosis (mean ±SD)	51.9 ± 12.2
Body mass index (kg/m²)	28.7 ± 5.1
Menopause [n, (%)]	
Premenopausal	56 (47.9)
Postmenopausal	61 (52.1)
Histopathology [n, (%)]	
Invasive ductal carcinoma	83 (70.9)
Invasive lobular carcinoma	8 (6.8)
Others*	26 (22.2)
Estrogen receptor [n, (%)]	
Positive	92 (78.6)
Negative	25 (21.4)
Progesterone receptor [n, (%)]	
Positive	81 (69.2)
Negative	36 (30.8)
Her2 status [n, (%)]	
Positive	36 (30.8)
Negative	81 (69.2)
Stage [n, (%)]	
Metastatic	37 (31.6)
Non-metastatic	80 (68.4)
Chemerin (ng/mL)	257.3 ± 68.7

* The remaining 26 patients had rare histological types of breast cancer: 19 mixed ductal-lobular carcinoma, 2 neuroendocrine carcinoma, 2 mucinous carcinoma, 1 cribriform carcinoma, 1 metaplastic carcinoma and 1 tubular carcinoma.

disease. In the statistical analyses, $p < 0.05$ value was considered significant.

RESULTS

The study population included 117 female patients with newly diagnosed breast cancer. Thirty-seven of which were metastatic and 80 were non-metastatic at the time of diagnosis. The mean age at diagnosis was 51.9 ± 12.2 years (range, 27-84 years). The mean chemerin levels were 257.3 ± 68.7 ng/mL (range, 148.1- 526.0 ng/mL). Table 1 lists the demographic characteristics of the study population.

Serum chemerin levels were significantly higher in patients with diabetes. Similarly, serum chemerin levels were significantly higher in patients with older age, BMI ≥30 kg/m², hypertension, and in post-menopausal women (Figure 1). Serum chemerin levels were positively correlated with age at diagnosis, BMI, presence of diabetes mellitus, presence of hypertension, and post-menopausal status (r= 0.26, p= 0.005; r= 0.30, p= 0.001; r= 0.26, p= 0.005; r= 0.317, p< 0.001 and r= 0.21, p= 0.018, respectively). We also examined the as-
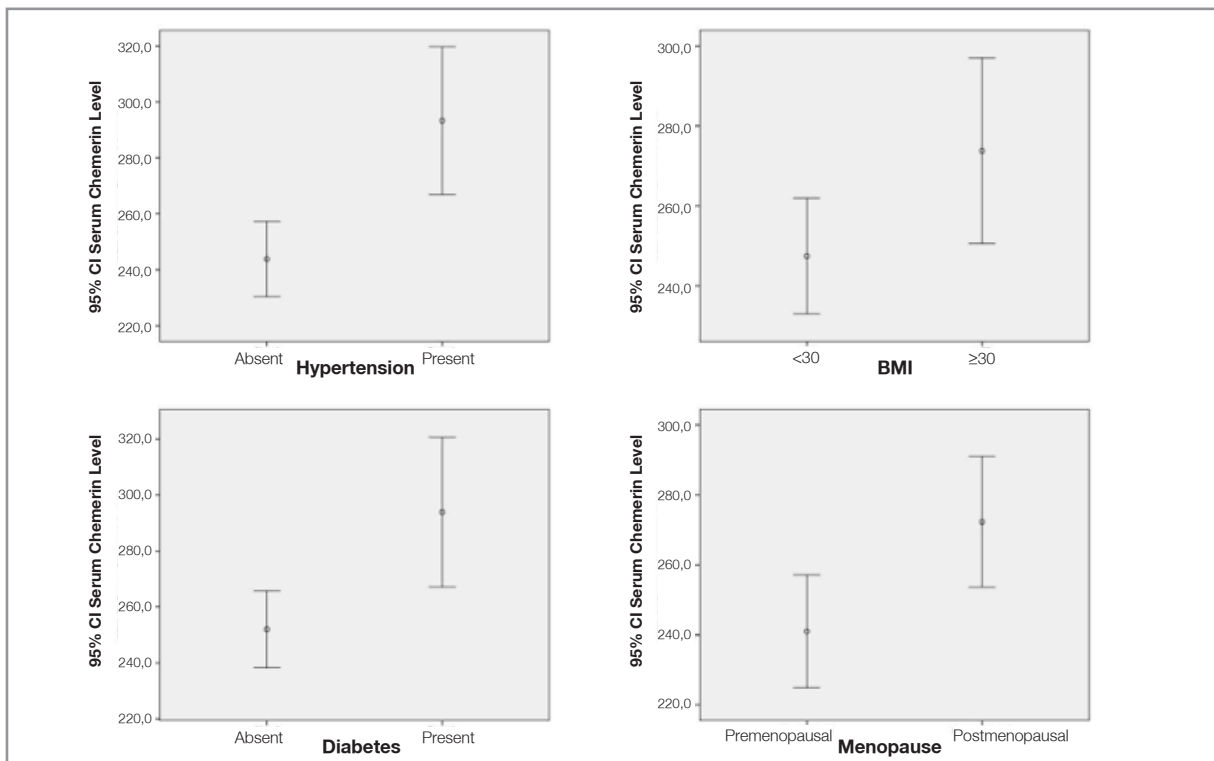
Figure 1. Serum Chemerin Levels in Different Clinical Parameters. Significant differences were observed in hypertensive, diabetic, obese and postmenopausal patients compared with normotensive, non-diabetic, normal weight and premenopausal patients (p< 0.001, p= 0.027, p= 0.025, p= 0.013, respectively). BMI= body mass index

Table 2. Clinical and laboratory variables according to the metastatic status

	Metastatic disease	Non-metastatic disease	p
No. of patients	37	80	
Age, year	52.3± 11.8	51.7 ± 12.5	0.824
BMI, kg/m²	29.1 ± 5.5	28.6 ± 4.9	0.682
Fasting plasma glucose, mg/dL	104.4 ± 47.1	95.4 ± 16.3	0.265
HbA1c, %	5.6 ± 1.07	5.5 ± 0.7	0.508
CEA (U/mL)	0.8-3401 (2.5)	0.6-5.6 (1.3)	0.236
CA15.3 (U/mL)	4.7-719.0 (22.7)	3.6-54.2 (12.1)	0.017
Presence of diabetes [n, (%)]	4 (10.8)	11 (13.8)	0.658
Presence of hypertension [n, (%)]	7 (18.9)	25 (31.3)	0.164
Menopause [n, (%)]			
Premenopausal	15 (40.5)	41 (51.3)	0.281
Postmenopausal	22 (59.5)	39 (48.8)	
Presence of estrogen receptor [n, (%)]	27 (73.0)	65 (81.3)	0.310
Presence of progesterone receptor [n, (%)]	23 (62.2)	58 (72.5)	0.260
Presence of HER2 [n, (%)]	10 (27.0)	26 (32.5)	0.551

Table 3. Multivariate analyses of the clinical and laboratory parameters associated with the presence of metastatic breast cancer

	RR (95% CI)	p
Chemerin	0.99 (0.99-1.00)	0.832
Age at diagnosis	0.95 (0.87-1.03)	0.266
BMI	1.00 (0.88-1.14)	0.930
CEA	1.32 (1.06-1.66)	0.012
CA15.3	1.08 (1.03-1.14)	0.004

sociation of serum chemerin levels with fasting plasma glucose, HbA1c, LDL-cholesterol, HDL-cholesterol, triglyceride, CA15.3 and CEA, but no association was observed.

Patients were divided into subgroups according to metastatic status: metastatic and non-metastatic disease. The results were as follows: in 37 women who had metastatic breast cancer and 80 women who had non-metastatic breast cancer, chemerin levels were 250.0 ± 58.9 ng/mL and 260.7 ± 72.9 ng/mL, respectively. When clinical characteristics were compared according to the metastatic and non-metastatic disease, with the exception of serum CA15.3 levels, there were no significant differences in most parameters (Table 2). Chemerin levels were not different in either group (p=0.435). Multivariate analyses of parameters also showed that CA15.3 and CEA levels were associated with metastatic disease (Table 3).

DISCUSSION

To our knowledge, this study is the first study of chemerin in patients with breast cancer. In this study, we found that there was no difference in plasma chemerin levels between patients with metastatic and non-metastatic breast cancer. Similar to the literature, BMI and diabetes mellitus was found strongly correlated with chemerin levels. In addition, chemerin levels were affected by age of disease onset and menopausal status.

Several adipokines have been implied in cancer development, mainly through insulin resistance, inflammation, and production of sex hormones. An increased level of most of these adipokines such as leptin, resistin, apelin, and visfatin, has played a pro-carcinogenic role.[9] On the other hand, some adipokines such as adiponectin are known to be anti-carcinogenic. Chemerin is a recently identified adipokine that regulates adipocyte development and metabolic functions, as well as immunity.[10,11] There are conflicting data about the link between chemerin and cancer. This novel adipokine may have tumorigenic or anti-tumor effects. Chemerin may have an antitumor role via recruitment of natural killer (NK) cells. Thus, the immune system recognizes cancer cells and fights them in the event of high levels of chemerin.[12] Down regulation of chemerin expression was revealed in non-small cell lung cancer, melanoma, hepatocellular carci-

noma, and squamous cell carcinoma of the skin.[13-16] On the other hand, in gastric cancer and oral squamous cell cancer of the tongue, high chemerin levels were associated with aggressive features such as advanced stage and increased tumor angiogenesis.[17,18] Chemerin promotes angiogenesis by triggering the production and activity of matrix metalloproteinase, which plays a crucial role in angiogenesis. In this study, chemerin levels of patients with early or advanced-stage breast cancer were similar.

As with many adipokines, increased serum chemerin levels show a correlation with BMI, obesity, and metabolic syndrome through its local inflammatory response via chemokine-like receptor-1.[19] Moreover, other metabolic indices, for instance plasma triglyceride levels and systolic blood pressure, have been shown to be correlated with serum chemerin levels.[20] Serum chemerin levels were found significantly different between individuals with normal glucose tolerance and individuals with type II diabetes and their first-degree relatives in a small study.[21] In our study, chemerin levels were correlated with age of diagnosis, BMI, presence of diabetes mellitus, presence of hypertension, and post-menopausal status. These findings are consistent with the literature.

Limitations of our study include the lack of a control group without breast cancer. Controlled cross-sectional studies necessitate examining whether chemerin is involved in the development of breast cancer. There are some factors that influence other adiponectin levels, such as diet and exercise.[22] Therefore, measurement of serum chemerin may be altered by other factors. In some previous studies, chemerin expression was immunocytochemically investigated in tumor and non-tumor tissues. Serum chemerin levels and tissue chemerin expressions should be analyzed together. Another limitation of our study was the small number of patients.

In conclusion, we demonstrated that serum chemerin level is not associated with the stage of breast cancer Further studies with control groups should investigate the role of chemerin in the carcinogenesis and development of breast cancer in postmenopausal women.

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