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Comparison of Serum Leptin Levels among Patients with Benign or Malignant Breast Lesions

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ABSTRACT

Background: Studies have shown that obese individuals are at increased risk of breast cancer development and poorer prognosis. Leptin, an adipose tissue-derived hormone, has pro-inflammatory and proliferative effects and a well-established association with several comorbidities of obesity. This study was designed and conducted to compare the serum levels of leptin in patients with malignant and benign breast lesions.

Methods: A cross-sectional study was conducted in Research Center of Cancer Institute, Tehran, Iran between 2010 and 2011. Sixty-five patients with breast cancer and 65 BMI-matched patients with benign breast lesions were enrolled in this study. The serum leptin level was measured by the ELISA method and compared between the two groups.

Results: A total of 130 patients were collected. The mean BMI in benign and malignant groups was 25.2±3.2 and 25.8±3.8 (kg/m^2), respectively. Circulating levels of leptin were 20.05±14.69 vs. 14.74±10.16 mL in malignant and benign groups, respectively (P=0.011). A positive correlation was observed between BMI and leptin concentration (r = 0.431, P < 0.001). Leptins levels were not associated with the patients' age (P = 0.108), menstrual status (P = 0.214), and history of OCP use (P = 0.269).

Conclusions: Our findings suggest that patients with breast cancer have significantly higher levels of leptin compared to those with benign lesions.

Introduction

Breast cancer is one of the most common malignancies among women, and the leading cause of cancer-related death around the world. It has been shown that not only obese individuals are at increased risk of breast cancer development; but, they also have poorer disease-free and overall survival.[1-4] The pro-inflammatory condition due to adipose-derived hormones, hyperinsulinemia, and increased levels of estrogen are hypothesized to be the underlying causes of the mentioned association.[2]

Although the adipose tissue was initially assumed as fat-storing cells, further studies proved that adipose cells were part of the endocrine system and had complex interactions in human physiologic and pathologic processes. Secreted by the adipose tissue, leptin is a cytokine that reduces appetite and increases energy expenditure by affecting hypothalamic centers.[5] The leptin concentration is positively correlated with the amount of body fat.[6]

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Corroborating in vitro evidence suggests that leptin is carcinogenic and induces cellular proliferation.[7-9] Studies that compared the leptin level in patients with breast malignancy and healthy subjects have reported conterversial results.[10-12]

The aim of the current study was to investigate the serum leptin level in patients with benign and malignant breast lesions.

Methods

A study was conducted in Research Center of Cancer Institute affiliated with Tehran University of Medical Sciences between 2010 and 2011 in Tehran, Iran. Two groups of patients with a final diagnosis of benign or malignant breast lesions who were BMI matched were enrolled. After obtaining written consent, a questionnaire was filled by all patients regarding their demographic information. The collected data included age, marital status, menstrual status, family history of breast cancer, and history of oral contraceptive pill (OCP) consumption. The height and weight of the patients were measured in light clothing using a stadiometer and calibrated digital scale, and BMI was calculated by dividing the patients' weight (kg) to the square of height (m). The patients were asked to fast overnight for at least 10 hours before test. Five milliliters of venous blood was drawn and sent to the central laboratory of our research center. Quantitative determination of serum leptin was performed using ELISA assay with inter- and intra-assay coefficient variations of 7.7-8.3% and 5.5-6.9%, respectively (Leptin ELISA E07, Mediagnost, Reutlingen, Germany).

Statistical analysis was performed using SPSS software version 20.0 (IBM Corp., NY, USA). Categorical variables are presented as percentages and continuous variables are reported as mean and standard deviation. The serum leptin distribution violated the assumption of normality; therefore, the Mann-Whitney U test was used to compare the results between study groups. The association between two continuous variables was assessed by Pearson correlation coefficient. P values less than 0.05 were considered statistically significant.

Results

A total of 130 patients with benign and malignant breast lesions were enrolled. The details of histopathological classification of the lesions are summarized in Table 1. The mean age of the patients in benign and malignant groups was 41.68±12.15 and 49.74±12.69 years, respectively. The majority of the patients were married (87.7%) and pre-menopausal (60%). Among patients with malignant breast lesions, a family history of breast cancer was positive in 22 (33.84%) participants. A total of 33 (25.4%) subjects reported a history of OCP consumption. The patients with breast cancer had higher serum leptin concentrations compared with those with benign lesions (20.05±14.69 vs. 14.74±10.16, respectively) (Table 2). The observed difference between two groups was statistically significant (P = 0.033). No significant association was detected between leptin values and age (P = 0.108), menstruation status (P = 0.214), family history of breast cancer (P = 0.481), and history of OCP use (P = 0.269) (Table 2). An increase in BMI was associated with an increasing trend in the leptin concentration ($r = 0.431$, $P < 0.001$).

Table 1 . Histopathological classification of the lesions in benign and malignant groups

	N (%)
Benign lesions	Total = 65
Fibrocystic change	40 (61.5%)
Fibroadenoma	22 (33.8%)
Complex fibroadenoma	3 (4.7%)
Malignant lesions	Total = 65
Ductal carcinoma in situ	8 (12.3%)
Invasive lobular carcinoma	4 (6.2%)
Invasive ductal carcinoma	53 (81.5%)

Table 2. Association between serum leptin and participants' characteristics

	Leptin value	P-value
Type of lesion		0.033
Benign	14.74±10.16	
Malignant	20.05±14.69	
Menstruation status		0.214
Postmenopausal	19.90±15.54	
Premenopausal	15.72±10.49	
OCP consumption		0.269
Yes	18.36±11.45	
No	17.06±13.35	
Family history		0.481
Positive	15.05±9.65	
Negative	17.87±13.41	

Discussion

In the current study, serum leptin concentrations were compared between patients with benign and malignant lesions. Leptin is an adipose tissue-derived hormone; therefore obesity is accompanied by higher serum leptin. In our study, the group-matching method was employed to eliminate the mentioned effect. Patients with breast cancer had a higher leptin concentration, while a history of OCP consumption, patients' age, family history, and menstruation status were not associated with higher leptin values.

Studies have shown that leptin has a pro-inflammatory role and induces the secretion of C-reactive protein and interlukin-6.[13] The systemic inflammation caused by leptin secretion in obese patients increases the risk of metabolic syndrome, diabetes, and coronary disease.[14-16] In addition to the pro-inflammatory activity of leptin, its role in cell

proliferation has been the subject of several studies. Recent in-vitro studies have suggested that leptin induces the proliferation of human breast cancer cell lines, and inhibiting its signaling pathways through receptor blocking agents can suppress cell proliferation and secretion of pro-proliferative molecules.[7,9] Moreover, the proliferation of normal breast cells can also be affected and triggered by leptin.[17] In contrast to leptin which has a positive association with the body fat mass, adiponectin is another protein with decreased levels in obese patients that has a well-established association with obesity and its comorbidities. A study conducted by Jarde *et al.* revealed that leptin and adiponectin had opposite effects on breast cell growth and proliferation.[8] This paradoxical effect is more important considering the 37-fold higher levels of leptin mRNA expression compared to adiponectin in breast cancer cells.[8] Therefore, in vitro studies suggest that a complex interaction between decreased levels of adiponectin and increased levels of leptin in obese patients can play an important role in breast carcinogenesis.

Our findings were in accordance with results of similar case-control studies that showed higher levels of leptin in patients with breast cancer compared to healthy subjects or patients with benign breast disease.[10,11,18] However, a study with smaller sample size (90 patients) did not find any associations between breast cancer and high leptin levels.[12] The impact of leptin on breast cancer survival was assessed by Miyoshi *et al.* and Snoussi *et al*.[19,20] Their results indicated that higher expression of leptin mRNA in tumor cells and leptin and its receptor gene polymorphism were associated with a poorer survival.[19,20]

In conclusion, according to our results, serum leptin is higher in patients with breast cancer compared to patients with breast benign lesions. Further prospective studies should be conducted to confirm the causal relationship between higher leptin levels and breast cancer.

References

1. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, *et al.* Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000; 152(6): 514-27.
2. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4(8): 579-91.
3. Kaviani A, Neishaboury M, Mohammadzadeh N, Ansari-Damavandi M, Jamei K. Effects of obesity on presentation of breast cancer, lymph node metastasis and patient survival: a retrospective review. Asian Pac J Cancer Prev 2013; 14(4): 2225-9.
4. Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, *et al.* Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002; 13(8): 741-51.
5. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 2010; 152(2): 93-100.
6. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, *et al.* Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334(5): 292-5.
7. Chen C, Chang YC, Liu CL, Chang KJ, Guo IC. Leptin-induced growth of human ZR-75-1 breast cancer cells is associated with up-regulation of cyclin D1 and c-Myc and down-regulation of tumor suppressor p53 and p21WAF1/CIP1. Breast Cancer Res Treat 2006; 98(2): 121-32.
8. Jarde T, Caldefie-Chezet F, Goncalves-Mendes N, Mishellany F, Buechler C, Penault-Llorca F, *et al.* Involvement of adiponectin and leptin in breast cancer: clinical and in vitro studies. Endocr Relat Cancer 2009; 16(4): 1197-210.
9. Rene Gonzalez R, Watters A, Xu Y, Singh UP, Mann DR, Rueda BR, *et al.* Leptin-signaling inhibition results in efficient anti-tumor activity in estrogen receptor positive or negative breast cancer. Breast Cancer Res 2009; 11(3): R36.
10. Chen DC, Chung YF, Yeh YT, Chaung HC, Kuo FC, Fu OY, *et al.* Serum adiponectin and leptin levels in Taiwanese breast cancer patients. Cancer Lett 2006; 237(1): 109-14.
11. Han C, Zhang HT, Du L, Liu X, Jing J, Zhao X, *et al.* Serum levels of leptin, insulin, and lipids in relation to breast cancer in china. Endocrine 2005; 26(1): 19-24.
12. Woo HY, Park H, Ki CS, Park YL, Bae WG. Relationships among serum leptin, leptin receptor gene polymorphisms, and breast cancer in Korea. Cancer Lett 2006; 237(1): 137-42.
13. Bullo M, Garcia-Lorda P, Megias I, Salas-Salvado J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. Obes Res 2003; 11(4): 525-31.
14. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama 2001; 286(3): 327-34.
15. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 2000; 148(2): 209-14.
16. Esteghamati A, Noshad S, Khalilzadeh O, Morteza A, Nazeri A, Meysamie A, *et al.* Contribution of serum leptin to metabolic syndrome in obese and nonobese subjects. Arch

Arch Med Res 2011; 42(3): 244-51.
17. Hu X, Juneja SC, Maihle NJ, Cleary MP. Leptin--a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst 2002; 94(22): 1704-11.
18. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, *et al.* Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003; 9(15): 5699-704.
19. Miyoshi Y, Funahashi T, Tanaka S, Taguchi T, Tamaki Y, Shimomura I, *et al.* High expression of leptin receptor mRNA in breast cancer tissue predicts poor prognosis for patients with high, but not low, serum leptin levels. Int J Cancer 2006; 118(6): 1414-9.
20. Snoussi K, Strosberg AD, Bouaouina N, Ben Ahmed S, Helal AN, Chouchane L. Leptin and leptin receptor polymorphisms are associated with increased risk and poor prognosis of breast carcinoma. BMC Cancer 2006; 6: 38.