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ORIGINAL PAPER

Preoperative serum leptin levels in patients with breast cancer

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Abstract Leptin is an adipocyte-derived protein and plays an important role in the control of body weight by acting as a neurohormone regulating energy balance and food intake in the hypothalamus. The high serum leptin levels and the overexpression of leptin receptors have been documented in breast cancer patients, but the levels never checked preoperatively. In the present study, the relationship between preoperative serum leptin levels of the breast cancer patients and the healthy controls were evaluated. The serum leptin levels in 30 breast cancer patients were compared to 30 healthy female volunteers. In addition, the association of serum leptin levels and the various well-known risk factors were studied. Serum leptin levels of patients with breast cancer (28.55 + 19.7 ng/ml) were tended to be higher than those of controls (26.43 + 19.4 ng/ml), but it did not reach statistical difference ($P = 0.712$). There was significant correlation between the expression of ER, PR, and serum leptin levels ($P = 0.018$ and 0.037, respectively), but not with the HER-2/neu receptor expression ($P = 0.067$). Also association was not found between the tumor size, lymph node involvement, and the levels of serum leptin ($P = 0.235$, 0.34, and 0.86, respectively). The serum leptin level was also found to be similar in premenopausal (24.85 ± 18.14 ng/ml) and postmenopausal (30.49 ± 17.19 ng/ml) patients ($P = 0.235$). The preoperative serum leptin levels in breast cancer patients were similar to healthy controls. In subset analysis, the significant correlation between the leptin level and hormonal status was noted, but association with HER-2/neu was not detected. These findings should be confirmed with larger studies.

Keywords Leptin · Serum · Breast cancer · Body mass index

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Introduction

Leptin is an adipocyte-derived peptide hormone, has 167 amino acids with a molecular mass of 16 kDa that plays an important role in the control of body weight [1–3]. Its production depended on the size and number of lipid cells. There is a positive correlation between the plasma leptin level and the body mass index. The main role of leptin is to control satiety and energy expenditure by acting as a neurohormone regulating energy balance and food intake at the hypothalamic level [4–6]. Recently antiapoptotic and angiogenic activity of leptin has been reported [7, 8].

Obesity and obesity-related status such as type 2 diabetes mellitus (DM) and insulin resistance (IR) are also associated with high levels of leptin. The relationship between the obesity, IR, and breast cancer has been well

defined; obesity increases postmenopausal breast cancer risk up to 30–50% [9–11]. There are regulatory dysfunctions in metabolic and neuroendocrine systems in cancer. However, there have been few reports about the role of leptin in these dysfunctions [12]. Stattin et al. [13] suggested that leptin may promote the tumor growth by stimulating angiogenesis in prostate cancer.

Leptin is required for normal mammary gland development and lactation. However, it might also contribute to mammary tumorigenesis [14, 15]. The correlation between the leptin and breast cancer have been previously reported. Tessitore and Vizio suggested that the plasma leptin level and mRNA expression in adipose tissue in breast cancer patients were significantly higher than those in healthy controls. It was thought that plasma leptin levels could potentially be used as a prognostic indicator in breast cancer [16–18]. In our study, we compared the preoperative plasma leptin level in breast cancer patients and healthy controls. In addition, the association between the serum leptin level and the clinicopathological characteristics of breast cancer patients was evaluated.

Materials and methods

Thirty consecutive patients histologically confirmed with breast cancer and 30 healthy female volunteers were enrolled in this study. The body mass index (BMI) was homogenous in both groups. The patients with morbid obesity, history of secondary malignancies, metabolic diseases such as DM and hypertension, or renal and hepatic dysfunctions, were excluded.

Menopausal status, tumor size (T stage), grade, hormonal status, and lymph node involvement were recorded. Breast cancer was staged in accordance with American Joint Committee for Cancer [19]. We calculated BMI according to Quetelet's formula as the ratio of body weight to body height squared (kg/m^2). The status of estrogen receptors (ER) and progesterone receptors (PR) determined by immunohistochemical staining and HER-2/neu receptors staining was analyzed by the Standard Hercept Test procedure (Dako 5204) [20].

Blood samples for serum leptin were taken within 3 days before surgery. After 12 h of fasting, at 8 a.m., peripheral venous blood was taken. The samples were placed in tubes containing EDTA, centrifuged for 15 min at 2000 rpm, and the serum was separated. Thereafter, the samples were stored at −20°C until further analysis. Serum leptin levels were measured by radioimmunoassay using Human Leptin ELISA Kit (Linco Research Inc., Cat. EZHL-80SK). The sensitivity of the test was 0.5 ng/ml. Informed consent was obtained from each subject included in the study.

Statistical methods

Statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA) software. Descriptives of the parameters are quoted as mean ± SD and 95% confidence intervals (CI). Both groups and subgroups according to serum leptin levels were compared by non-parametric Kruskal-Wallis H test and Mann–Whitney U test. In the correlation between serum leptin levels and tumor size, bivariate Pearson correlation test was applied. *P*-values less than or equal to 0.05 were considered to be statistically significant.

Results

Thirty patients with breast cancer and thirty healthy female volunteers were analyzed; median age was 53 (range: 29–76) and 40.4 (17–69) years, respectively. There were 11 breast cancer patients (63.3%) older than 50 years. Mean BMI was 27.24 ± 4.4 kg/m^2 in breast cancer patients and 27.32 ± 4.5 kg/m^2 in the control group.

The mean serum leptin levels were 28.55 + 19.7 ng/ml for the breast cancer patients, preoperatively and 26.43 + 19.4 ng/ml for the control group. Although in patients with breast cancer the serum leptin level was tended to be higher than the controls, the difference was not statistically significant ($P = 0.712$). Also, no significant difference was found between patient and control groups with respect to BMI and serum leptin levels ($P = 0.560$ and 0.712, respectively). BMI and serum leptin levels in both groups are listed in Table 1.

In the breast cancer group, there was a significant correlation between the ER, PR status, and serum leptin levels ($P = 0.018$ and 0.037, respectively), while HER-2/neu expression was not related to the serum leptin levels ($P = 0.067$). However, the relationship between age, menopausal status, tumor size, lymph node involvement and the serum leptin level was not found ($P = 561$, 0.235, 0.710, and $p = 0.864$, respectively). The relationship between clinicopathological features and the serum leptin levels are shown in Table 2.

Table 1 BMI and serum leptin levels in patient and control groups

	Patient group	Control group	*P*
BMI (kg/m^2—mean ± SD)	27.24 ± 4.4	27.32 ± 4.5	0.560
Serum leptin level (ng/dl—mean ± SD)	28.55 ± 19.7	26.43 ± 19.4	0.712

BMI Body mass index

Table 2 The relationships between serum leptin levels and histopathological/demographical features in breast cancer group

Patient characteristics	Number of patients (%)	Serum leptin level (ng/dl)	*P*
Age			0.561
≤50	11 (36.7)	28.82	
>50	19 (63.3)	28.39	
Menopausal status			0.235
Premenopause	10 (33.3)	24.85	
Postmenopause	20 (66.7)	30.40	
T stage			0.710
T1	3 (10.0)	19.65	
T2	23 (79.7)	29.93	
T3	4 (13.3)	27.28	
N stage			0.864
N0	10 (33.3)	30.71	
N1	17 (56.7)	28.04	
N2	3 (10.0)	24.22	
C-erb-B2			0.067
Positive	11 (36.7)	33.79	
Negative	19 (63.3)	25.52	
ER status			0.018*
Positive	17 (56.7)	23.89	
Negative	13 (43.3)	34.65	
PR status			0.037*
Positive	11 (36.7)	23.43	
Negative	13 (63.3)	31.51	

ER Estrogen receptor, *PR* progesterone receptor

* $P < 0.05$

Discussion

The relationship between obesity and breast cancer has been previously documented and obesity may increase postmenopausal breast cancer risk up to 30–50% [9–11, 21, 22]. Recent reports also indicate that leptin receptor (OBR) expression is elevated in overweight and obese subjects. Leptin is an adipocyte-derived hormone, involved in the regulation of body weight and sexual maturation. It may play a pivotal role in the development and/or progression of different cancers. Furthermore, leptin also can stimulate cell growth, counteract apoptosis, induce expression and migration of matrix degrading enzymes and angiogenic factors in different cancer [1–3, 7, 8, 15].

The leptin levels have been detected to be significantly increased in breast cancer patients [17, 18, 23]. Tessitore and Vizio reported that the serum leptin levels and mRNA expression were significantly increased in breast cancer patients in comparison to healthy controls, and the plasma leptin level might be used as a prognostic factor in patients with breast cancer [17]. In addition, they also reported that ER and PR levels were higher than in the control group, but this observation was not elaborated upon in the text.

In our study, the plasma leptin levels were tended to be higher in breast cancer patients than control. However, this difference was not statistically significant. The reason may be the small sample size of our study.

Mantzoros et al. [24] studied serum leptin levels in 83 patients with premenopausal in situ breast cancer and in 69 control groups. They reported that no significant difference was found between the groups. Authors concluded that serum leptin level did not increase in premenopausal in situ cancer. Our findings are compatible with their results.

In the study carried out by Ozet et al. [23], the serum leptin levels were higher in breast cancer patients than in the control group, and this increase was more prominent in tamoxifen-receiving patients. However, the leptin levels were measured after surgery. We also detected a significant relationship between the ER, PR status, and the serum leptin levels. It may be that the serum leptin level is increased in breast cancer patients with positive hormone receptor and receiving hormone therapy.

In our study, HER-2/neu receptor and lymph node involvement status were not correlated with the serum leptin level, and they did not influence the serum leptin levels as well. Moreover, there were no relationship between serum leptin levels and tumor size. Miyoshi et al. [25] suggested that leptin mRNA levels were significantly higher in ER-positive breast tumors than ER-negative tumors, but did not found correlation among tumor size, menopausal status, histological grade, and lymph node status. In contrast, Ishikawa et al. [26] showed that the expression levels of both leptin and leptin receptor (OBR) tended to increase with tumor size, although the relation was not statistically significant.

Marttunen et al. [27] showed that the serum leptin concentrations were increased significantly in patients with postmenopausal breast cancer receiving both tamoxifen and toremifene after 6 months of treatment. It was suggested that the antiestrogens may stimulate the synthesis and release of leptin in the adipocyte.

There was no significant difference in the serum leptin levels between premenopausal and postmenopausal women in our study. The previous reports found that the serum leptin levels were higher in postmenopausal breast cancer patients than in the control group [18, 23]. These differences also could be due to the small sample size in our study.

In conclusion, no significant difference was found according to preoperative serum leptin levels in the breast cancer patients in comparison with those in healthy female volunteers. However, there were significant correlation between the ER, PR status, and serum leptin levels. These findings need to be confirmed by a prospective study

including the analysis of leptin and its receptors in blood and tissue samples of breast cancer patients.

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