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Original Scientific Paper

SERUM LEPTIN LEVEL IN BREAST CANCER

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SUMMARY – Leptin is a polypeptide which is mostly produced in white fat tissue and is an important proinflammatory, proangiogenic, proinvasive and mitotic factor. There is ever more evidence suggesting the key role of leptin in the occurrence of breast cancer. The aim of the study was to investigate serum leptin levels in patients with benign breast tumors, as well as in various breast cancer phenotypes, taking into account leptin levels connected to menopausal status and body mass index (BMI). The study included 97 patients having their breast tumor surgically removed. Serum leptin level was determined by ELISA method in all study patients. Study results showed that significantly more women, regardless of having malignant or benign tumors, were postmenopausal and had a significantly higher level of leptin compared to the premenopausal group. The highest level of leptin was recorded in the group of postmenopausal obese women compared to other postmenopausal women but also compared to premenopausal women. According to BMI alone, obese women had a significantly higher level of leptin regardless of the type of tumor. The most significant differences in leptin levels observed through BMI were found in the Luminal B1 group. In conclusion, serum leptin level was shown to be a good diagnostic parameter suggesting a higher possibility of breast cancer development.

Key words: *Breast cancer; Leptin; Malignant tumor; Menopause; Obesity*

Introduction

Breast cancer is the most common malignancy among women. It is a heterogeneous disease which is dependent on many factors such as age, higher hormone expression, early onset, late menopause, hormone therapy, and family history of breast cancer[1,2]. Development of cancer disease is dependent on many prognostic factors such as tumor size, lymph node status, hormone receptor activity, histologic grade, Ki-67 proliferation index expression, and invasion in lymphatic and vascular tissue[3,4]. According to St. Gallen Breast Cancer Conference, they are divided into 5 subgroups: Luminal A, Luminal B HER2 negative (LUM B1), Luminal B HER2 positive (LUM B2), HER2 positive (HER2 pos) and triple negative subtype. This division is based on estrogen (ER) and progesterone (PR) receptor and human epithelial growth factor expression[5,6]. This classification includes all breast cancer types regardless of their histopathologic group. For this reason, it would be very useful to develop and find new biomarkers that would help us better understand and heal breast cancer[7,8]. Also, our previous study showed that breast carcinoma in women under age 40 was different from breast carcinoma occurring in older

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women (>60 years of age). The differences are manifested in ER status, multicentricity, histologic grade and Ki-67 index[9].

Leptin is a polypeptide made of 167 amino acids. It is mostly produced in fat tissue, but it is also synthesized in placenta, ovaries, skeletal muscles, epithelial breast cells, bone marrow, hypophysis and liver[10]. It is a product of genes connected with overweight and obesity[11], and it acts on other tissues through leptin receptor on those tissues[12]. Leptin has an important role in body weight regulation and metabolism[13]. An unbreakable connection has been proven between serum leptin level and body mass index (BMI)[14,15]. Leptin and its receptors are exceedingly expressed in breast cancer, especially high grade tumors, and absent in healthy breast tissue[16,17]. In obese patients, high serum leptin level is connected to higher fat tissue content and insulin resistance development[18,19]. These data refer to possible interaction of hormones, fat tissue distribution, and breast cancer.

The aim of this research was to determine serum leptin levels in the groups of patients with benign breast tumors and different phenotypes of breast cancer, to assess whether serum leptin level is correlated with reproductive age and BMI, and to determine whether serum leptin level causes occurrence of a specific breast cancer subtype or occurrence of breast cancer in general.

Materials and Methods

This 30-month prospective study comprised 97 patients with breast tumors who were operated on at the Department of Surgery, Osijek University Hospital Center. Twenty patients had benign breast tumor, whereas 77 patients had breast cancer. Patients with diabetes mellitus type 2 and patients with any other cancer were excluded. Informed consent was obtained from all patients included in the study. Serum leptin level was determined in all study patients. Blood samples were collected in tubes without anticoagulant, centrifuged at 3500 rpm for 10 minutes, and serum samples were stored at -80 °C. Leptin was evaluated using the commercially available enzyme immunoassay kits (BioVendor, Brno, Czech Republic) at the Laboratory of Molecular and Clinical Immunology, Department of Physiology and Immunology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek. Histologic classification was based on the World Health Organization criteria, while carcinoma phenotypes were set according to St. Gallen Breast Cancer Conference 2015 and were divided based on immunohistochemical determination of estrogen (ER) and progesterone (PR) receptors, HER 2 antibodies and Ki67 proliferation index into 5 subtypes, as follows: Luminal A, Luminal B HER2 negative (LUM B1), Luminal B HER2 positive (LUM B2), HER2 positive (HER2 pos) and triple negative subtype. Immunohistochemical procedures were conducted using Ventana BenchMark Ultra (Roche Diagnostics, Rotkreuz, Switzerland).

Statement of ethics

The study was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and approval obtained from the Ethics Committee of the Osijek University Hospital Center (25-1:8554-10/2013) and Ethics Committee of the Faculty of Medicine, Josip Juraj Strossmayer University in Osijek (2158/61-07-13-33).

Statistical analysis

Depending on the normality distribution of data tested with Shapiro Wilk test, data on leptin concentration in the two groups were analyzed using the one-way ANOVA (SigmaPlot version 11.2, Systat Software, Inc., Chicago, IL, USA). Differences in the normally distributed numerical variables between the two groups were tested with Student's t-test, and in case of deviations from normal distribution with Mann-Whitney U test. All data were expressed as mean ± standard deviation (SD). The level of statistical significance was set at $p<0.05$.

Results

The study included 97 women aged 21-91; 20 of them had benign tumor and 77 malignant breast tumor. Out of the total number of malignant tumors, 17 patients had Luminal A, 40 LUM B1, 10 LUM B2, 7 triple-negative and 3 women had HER 2 positive breast tumor. Out of the total number of patients, information on reproductive status was collected for 94 women, which showed that 70 patients were premenopausal and 24 postmenopausal. Furthermore, BMI value was calculated in 66 women, which revealed that 27 women had normal weight, 23 were overweight, and 16 were obese.

Serum level of leptin between benign and malignant breast tumors

Serum leptin levels were significantly increased in malignant tumors (22.24±22.58) compared with benign tumors (11.21±9.46, p=0.013) (Fig. 1A). Comparison of the malignant tumor subgroups with benign fibroadenoma showed that triple-negative tumors (36.11±17.95) had a statistically higher level of leptin compared to fibroadenoma (11.21±9.46, p=0.003), Luminal A (16.25±10.03, p=0.013) and LUM B1 (21.73±27.86, p=0.022). Also, LUM B1 had a significantly higher level of leptin compared to benign tumors (11.21±9.46, p=0.041) (Fig. 1B). Comparison of the malignant tumor subgroups showed that triple-negative tumor (36.11±17.95) had significantly higher levels of leptin compared with Luminal A (16.25±10.03, p=0.020) and LUM B1 (21.73±27.86, p=0.025) (Fig. 1C).

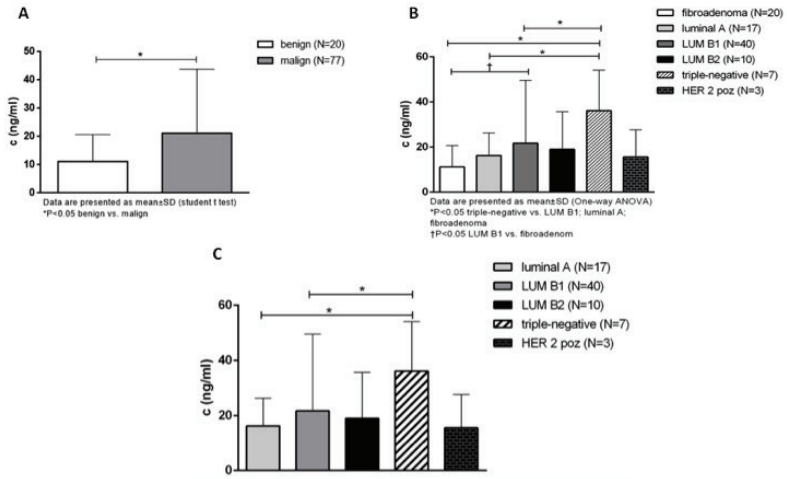

Fig. 1. Difference in serum level of leptin between benign and malignant breast tumors.

Groups were compared with one-way ANOVA test and p<0.05 was considered statistically significant; data were expressed as mean ± standard deviation (SD).

Leptin concentration depending on reproductive status

Postmenopausal patients with either malignant or benign tumor had significantly higher levels of leptin compared to premenopausal patients (19.76±14.07 *vs.* 12.01±10.33, p=0.008) (Fig. 2A). Observation of all subjects in premenopausal and postmenopausal groups and divided according to BMI revealed that obese postmenopausal women (n=2) had significantly higher levels of leptin (40.76±14.32) compared with other groups (p<0.05), except for obese postmenopausal women. The group of obese premenopausal women had a higher level of leptin compared with other premenopausal groups and postmenopausal women with normal body weight (29.006±14.23 *vs.* 9.30±6.71) (Fig. 2B).

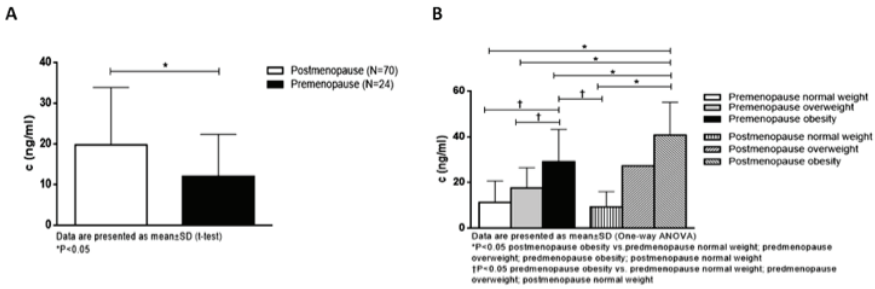

Fig. 2. Serum leptin level depending on reproductive status (A) and body mass index (B).

Groups were compared with Student's t-test (2A) and one-way ANOVA test (2B); p<0.05 was considered statistically significant; data were expressed as mean ± standard deviation (SD).

Leptin levels in malignant breast tumors depending on BMI

In the malignant tumor group, obese women had a significantly higher level of leptin (29.00±14.23) than those with normal weight (11.95±9.12, p<0.001) or overweight (17.56±8.87, p=0.003) (Fig. 3A). Upon dividing each malignant tumor according to BMI, the same differences were recorded within LUM B1, where obese women (33.74±11.174) had significantly higher levels of leptin compared to normal weight (9.53±9.33, p<0.001) and overweight women (18.48±9.08, p=0.002), as well as overweight women in relation to those with normal weight (p=0.011) (Fig. 3B).

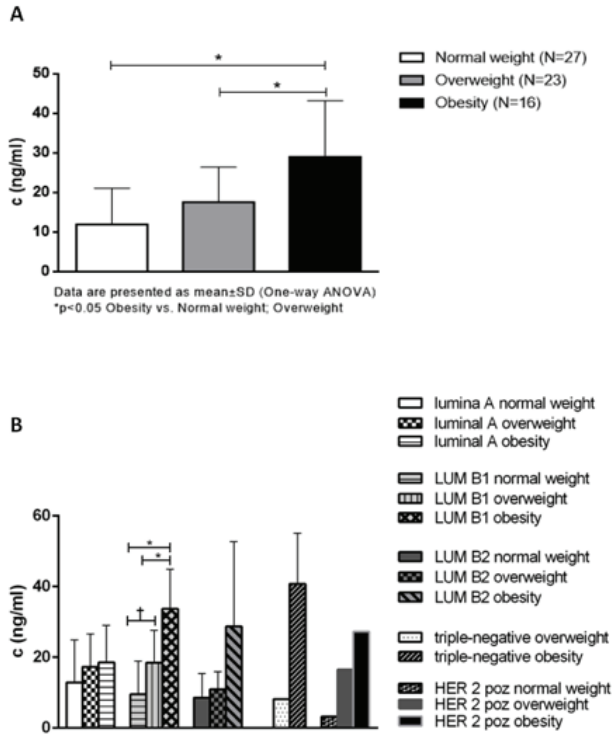

Fig. 3. Serum leptin levels in malignant breast tumors depending on body mass index.

Groups were compared with one-way ANOVA test; p<0.05 was considered statistically significant; data were expressed as mean ± standard deviation (SD).

Discussion

We researched serum leptin levels in benign breast tumor and different breast cancer phenotypes. The research included 97 women, 20 of which had benign and 77 malignant breast tumor. Out of the total number of malignant tumors, 17 patients had Luminal A, 40 LUM B1, 10 LUM B2, 7 triple-negative and 3 women had HER 2 positive breast tumor.

The main study findings were as follows: (1) LUM B1 type of malignant breast tumor was established in the majority of patients; (2) serum leptin level was significantly highest in the triple-negative group; (3) significantly more women, regardless of having malignant or benign tumors, were postmenopausal and they had the significantly highest level of leptin compared to premenopausal group; (4) postmenopausal obese women had the highest level of leptin in comparison to other postmenopausal, as well as premenopausal women; (5) according to BMI alone, obese women had a significantly higher level of leptin regardless of the type of tumor; and (6) the most significant differences in leptin levels, observed through BMI, were recorded in LUM B1 group.

Leptin is an adipokine hormone produced by metabolically active white adipose tissue[20]. It exerts its effects through lacking functional leptin receptor LEPR-B-mediated downstream pathways[21] and it is necessary for appropriate functioning of mammary gland[22]. It has been shown that leptin has mitogenic effects on epithelial cells, and in breast cancer cell lines it affects their proliferation and migration[23]. Studies on colon cancer cell cultures showed it to inhibit apoptosis and exert mitogenic effects[24,25]. Other studies showed that serum leptin levels, irrespective of BMI, were significantly higher in papillary thyroid cancer patients as compared with control subjects; also, in the same type of tumor, increase in one of the antiapoptotic proteins occurred secondary to increase in leptin receptor expression[26,27]. In cases of higher serum leptin level in breast tumor, intratumoral leptin and leptin receptor (ObR) isoform mRNA levels are predictors of poor prognosis. It has also been found that increased expression of leptin receptor mRNA predicts poor prognosis in patients with high serum leptin levels[28]. Animal studies on mice with hypothalamus lacking functional leptin receptor (LEPR-B) reconstitution suggest that an LEPR-B-mediated signal promotes tumor growth and metastasis[29]. Our results that showed increased serum leptin concentrations in malignant tumors are consistent with the above previous studies. A more detailed division and comparison among all types of malignant breast tumors has not been reported in the literature so far. Most studies covered only a

single segment/group of malignant tumors. Therefore, our results are the first to compare differences in leptin concentration among all malignant groups of breast tumors, and showed significant differences in serum leptin concentration between the examined groups. Further research should determine in detail the cause of such differences in serum leptin concentrations.

Different animal studies showed correlation between obesity and cancer. A study on obese mice showed that mammary tumors grew faster under high-fat diet conditions and showed increased leptin levels[30]. Furthermore, breast cancer cells transplanted into diet-induced obese mice, which maintained high levels of circulating leptin, grew faster[31]. Especially in obese individuals, leptin induces production of inflammatory cytokines (TNF-α and IL-6) by macrophages, which increases the risk of obesity related diseases and cancer[32,33]. It has been shown that obesity through LEPR-B-mediated signaling pathways, at various stages, promotes breast tumor growth, and that leptin is involved in cancer cell survival at early stages[34].

Serum leptin level is connected to adiposity and BMI. A link between obesity and certain forms of breast cancer suggests the role of leptin in breast cancer development but the relation between circulating leptin and breast cancer or breast cancer risk is still unclear[14,15,35]. Overweight breast cancer patients have higher leptin level than normal weight women with breast cancer. Serum leptin level is positively related with BMI and is higher in patients with breast cancer than in control group[35,36]. Obese patients with breast cancer have 2.5 times greater chance of dying within 5 years of diagnosis than women with normal weight[37]. Our research supported the studies published so far, with the additional fact that all malignant forms of breast tumors, and not just certain types of malignant tumors, were included in our research.

Results of studies on the interdependence of reproductive status and leptin level are controversial, reporting that serum leptin level was related with breast cancer independently of menopausal status[38,39]. Furthermore, some studies report that circulating leptin is not associated with breast cancer or risk of being affected by the same type of tumor, independently of the reproductive status[40,41]. Petridou *et al*. showed negative correlation between leptin and breast cancer only in premenopausal women[42] but different studies have also shown that there is a higher risk of breast cancer in postmenopausal obese women[43-45]. Our study and results are consistent with the fact that serum concentration of leptin depends on menstrual status, to grow significantly in the postmenopausal period, and that this is a very important parameter in addition to BMI, as another risk factor for developing breast tumors.

In the literature, we found no specific data on how the level of serum leptin is altered in all subgroups of malignant breast tumors taken together. So, we can conclude that our results are representative and that further research should be carried out on these facts (leptin serum dependence on reproductive status and BMI) to give a real picture and insight into the importance of determining leptin in the occurrence of breast tumors. Considering all these results, leptin appears to be a therapeutic target for breast cancer, in obese breast cancer patients in particular.

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Sažetak

RAZINA LEPTINA U SERUMU KOD RAKA DOJKE

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Leptin je polipeptid koji se uglavnom proizvodi u bijelom masnom tkivu te predstavlja važan proupalni, proangiogeni, proinvazivni i mitotički čimbenik. Sve je više dokaza koji ukazuju na ključnu ulogu leptina u nastanku tumora dojke. Istraživali smo serumsku razinu leptina u bolesnica s benignim tumorima dojke, kao i kod različitih fenotipova malignih tumora dojke te ovisnost razine leptina o reproduktivnom statusu i indeksu tjelesne mase (ITM). Istraživanje je obuhvatilo 97 bolesnica kojima je tumor uklonjen kirurškim zahvatom. Serumska koncentracija leptina utvrđena je metodom ELISA u svih bolesnica uključenih u istraživanje. Znatno više žena, bez obzira na to jesu li imale zloćudni ili dobroćudni tumor, bilo je u postmenopauzi te su imale značajno više razine leptina u usporedbi s premenopauzalnim skupinama. Najviša razina leptina utvrđena je kod pretilih žena u postmenopauzi u usporedbi s drugim ženama u postmenopauzi, ali i u usporedbi sa ženama u premenopauzi. Prema ITM, pretile ispitanice su imale značajno više razine leptina bez obzira na vrstu tumora. Najznačajnije razlike u razinama leptina, promatrane kroz ITM, utvrđene se u skupini Luminal B1. Razina leptina u serumu je dobar dijagnostički parametar koji govori u prilog većoj predispoziciji za nastanak karcinoma dojke.

Ključne riječi: *Tumor dojke; Leptin; Zloćudni tumor; Menopauza; Pretilost*