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Research

The role of leptin in gynecological oncology

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Abstract

Introduction: Leptin is a hormone which is related with body weight control and sexual maturation. The role of leptin in gynecological diseases is still unclear. The aim of this study was to evaluate levels of leptin in women with benign and malignant tumors of the genital system and to investigate leptin as a potential diagnostic or prognostic marker for the disease course.

Material and methods: Ninety - four women aged 24 - 70 years were studied; sixty - three of them were diagnosed with a genital tumor, whereas 31 were healthy controls. The 63 patients were divided in two groups: the first group comprised of 33 women with benign genital tumors and the second group comprised of 30 patients with malignant tumors of ovaries and endometrium. In all participants, serum leptin levels, weight, body mass index (BMI), leptin/BMI ratio, abdominal circumference, and femoral circumference were measured, preoperatively, and 7 days and 2 months postoperatively.

Results: Serum leptin levels were statistically significantly increased among women with malignant tumors, in comparison with women with benign tumors and controls, and this difference remained significant 2 months after surgical treatment.

Conclusion: Our results indicate that serum leptin levels in women with benign tumors are low, compared with patients with malignant tumors as well as controls. Leptin could be used as a potential diagnostic as well as a prognostic marker in gynecological oncology after further research.

Keywords: leptin; cancer; gynecological oncology

The prevalence of obesity has risen dramatically, reaching epidemic proportions in the developed world with serious public health consequences, and has led to intensive research on new methods and factors affecting body weight[1]. Leptin is the protein product of ob gene[2]. Its discovery confirmed the lipostatic theory, according to which, adipose tissue produces and secrets hormones which affects feeding and satiety centers, regulating body weight[1]. The initial observation of leptin and its role in the regulation of food intake and metabolism was suggested after experiments in mice[1,3,4]. Further clinical studies linked leptin with a number of hormonal, immunological and inflammatory functions in humans, as well as energy balance, eating disorders and cachexia[5-7]. Furthermore, there is solid evidence that leptin plays a major role in human reproduction and carcinogenesis[8-10].

The aim of our study was to investigate serum leptin levels in women with benign and malignant tum-

ors of the genital system, the changes in body weight in these women during the disease course, as well as before and after therapy, and the possible correlation of leptin levels with weight loss in cases of malignancy.

Material and methods

This was a prospective study conducted in the first department of obstetrics and gynecology of the Aristotle university of Thessaloniki at Hippokratio hospital, from February 2000 to June 2004, and included 94 women who presented in our clinic either for their routine annual gynecological examination or after a referral for further investigation for malignancy[11].

The participants were divided in three groups. The first group (group 1) included 33 women with benign genital tumors (age range: 24 - 70 years, mean: 48.5 ± 22.2 years). The second group (group 2) included 30 women with malignant genital tumors, diagnosed pre- or postoperatively (ovarian and endometrial cancer) (age range: 24 - 74 years, mean: 51.0 ± 31.6 years). The third group (group 3) included 31 healthy women (controls) (age range: 24 - 72 years, mean: 47.4 ± 24.6 years). In all women of groups 1 and 2, serum leptin levels were measured 3 times: preoperatively, 7 days and 2 months postoperatively. Similarly, in healthy controls serum leptin levels were measured at admission, and 7 days and 2 months after admission.

A detailed personal and family history was obtained from all participants. The gynecological examination of all participants included examination of the vulva, vagina, cervix, uterus, and ovaries by bimanual examination and with a sterile vaginal speculum. Papanikolaou samples were also obtained from every participant. The clinical examination of all participants also included bilateral breast palpation, measurement of body weight and height, body mass index (BMI) as well as the measurement of the smallest waist circumference (abdominal circumference, AC) and the largest femoral circumference (FC). Additionally, a pregnancy test was performed in all participants of reproductive age. Finally, all women underwent urine, hematological and biochemical control. Uterus and ovaries were meticulously examined by ultrasound scanning and Doppler was used for evaluation of blood supply of the tumors. Those with a benign or a malignant tumor in their genital system were admitted to the hospital for further surgical treatment.

The samples were collected in a cone - shaped phial without anticoagulant and were centrifuged for 15 minutes at 2,500 spins per minute and were kept in -20°C). All the blood samples were collected between 08:00 - 09:00 am after overnight fasting. Enzyme - linked immunosorbent assay (ELISA) was used for the quantitative determination of leptin in human serum (Biosource International Inc.). The minimum detectable value of leptin was 3.5 pg/ml. The intra - and inter- assay coefficients of variation were 3.8% and 4.6% for leptin. Student's t-test, analysis of variance (ANOVA), chi square test and Fisher exact test were used for the statistical analysis. Two - tailed p - value of less than 0.05 was considered significant.

Results

In the group of women with benign genital tumors (group 1), there was no significant difference preoperatively, 7 days and 2 months postoperatively, in weight (p= 0.485), BMI (p= 0.408), leptin serum levels (p= 0.417), leptin/BMI ratio (p= 0.283), and AC (p= 0.151) (Table 1). Similarly, there was no significant difference preoperatively, and 7 days and 2 months after surgery in weight (p= 0.800), BMI (p= 0.580), leptin serum levels (p= 0.216), and leptin/BMI ratio (p= 0.151) in the group of women with malignant genital tumors (group 2). However, mean AC of women in this group was significantly higher preoperatively, compared with 7 days and 2 months after surgery (94.7cm vs 86.6cm and 89.9cm, respectively, p= 0.044) (Table 2). Moreover, mean serum leptin levels as well as mean leptin/BMI ratio increased significantly from 7 days to 2 months after surgery in women with malignant genital tumors (leptin: 287.8 vs 199.0 pg/ml, respectively, p= 0.037, leptin/BMI: 10.88 vs 7.32, respectively, p= 0.018). Furthermore, among controls (group 3), the mean

weight (p= 0.940), BMI (p= 0.984), serum leptin levels (p= 0.867), leptin/BMI ratio (p= 0.897), and AC (p= 1) were similar before and after surgery.

Preoperatively (or at admission for controls), women of the three groups did not differ regarding age (p= 0.421), weight (p= 0.905), height (p= 0.313), BMI (p= 0.571) and FC (p= 0.450). However, the mean AC of women with malignant tumors (group 2) was significantly higher than those of the two other groups (94.7cm vs 84.9cm and 84.1cm, respectively, p= 0.032) (Table 4).

At seven days after surgery (or after admission for controls), there was also no significant difference regarding weight (p= 0.619), BMI (p= 0.685), AC (p= 0.264), and FC (p= 0.573) among the three groups (Table 5). However, women with malignant and benign tumors had a higher mean AC, compared with controls (86.6cm and 84.4cm vs 79.3cm, respectively, p= 0.016).

At 2 months postoperatively (or after admission for controls), there was no significant difference regarding weight (p= 0.821), BMI (p= 0.719), AC (p= 0.319), and FC (p= 0.573) among the three groups (Table 6).

Levels of serum leptin among women with benign tumors at admission were lower than the other two groups, although the difference was of marginal statistical significance (198.5 pg/ml vs 259.3 pg/ml and 251.0 pg/ml, respectively, p= 0.053). Moreover, 7 days later, mean level of serum leptin was significantly lower among women with benign and malignant genital tumors, compared with controls (171.2 pg/ml and 199.0 pg/ml vs 245.0 pg/ml, respectively, p= 0.013). Furthermore, 2 months later, controls had lower mean serum leptin level than groups 2 and 3 (202.2 pg/ml vs 287.8 pg/ml and 242.0 pg/ml, respectively, p= 0.036) (Table 7).

Finally, at admission, leptin/BMI ratio was significantly lower among women with benign tumors, in comparison with women with malignant tumors and controls, at admission (6.78 vs 8.86 and 8.78, respectively, p= 0.030) and 7 days later (6.19 vs 7.32 and 8.68, respectively, p= 0.001), although leptin/BMI ratio did not differ among the three groups 2 months postoperatively (group 1: 7.30, group 2: 10.88, group 3: 8.54, p= 0.080).

Discussion

In this study, weight, BMI, AC, FC, and serum leptin levels were determined in women with benign and malignant tumors of the genital tract who underwent surgical therapy. Although, no significant differences were identified among the three groups, as well as before and after surgery, regarding weight, BMI, and FC, we found that women with gynecological cancer had increased abdominal fat (expressed as AC), compared with those with benign tumors and controls. This finding is in accordance with literature reporting a strong relation between obesity and the development of malignancy, especially with hormone - dependent cancer[12]. Petridou et al reported that obese women are at higher risk of developing endometrial cancer[13,14].

We also found that in our sample, levels of circulating leptin among women with gynecological cancer were statistically significantly higher at admission, in comparison with subjects with benign genital tumors. This finding confirms previous reports of leptin levels rise in patients with ovarian, endometrial and breast cancer. Tessitore et al[15] analyzed levels of leptin in premenopausal and postmenopausal women with gynecological cancer and noted an association between high levels of leptin and the simultaneously increase of follicle - stimulating hormone (FSH) in cases of ovarian cancer as well as the increase in estrogen and progesterone receptors in the endometrium in cases of endometrial cancer. Moreover, in cases of ovarian cancer, high levels of leptin correlated with the increases of FSH and luteinizing hormone (LH).

Current evidence suggest an association between high serum leptin levels and cytokines in inflammation as well as in cancer, leading to the development of anorexia, cachexia and weight loss[16-19]. However, in our sample, we found that increased levels of leptin do not seem to correlate with cachexia or weight loss, since women in our study did not show a significant weight loss after therapy. On the other hand,

Table 1. Comparison of weight, body mass index (BMI), leptin levels, leptin/BMI ratio, and abdominal circumference (AC), preoperatively, 7 days and 2 months after surgery, respectively. Group of women with benign tumors (group 1)

Mean	Preoperatively	7 days postoperatively	2 months postoperatively	P - value
Weight (kgr)	70.0	66.6	69.1	0.485
BMI (kgr/m²)	28.51	26.42	26.57	0.408
Leptin (pg/ml)	198.5	171.2	202.0	0.417
Leptin/BMI	6.78	6.19	7.30	0.283
AC (cm)	89.4	79.3	83.2	0.151

Table 2. Comparison of weight, body mass index (BMI), leptin levels, leptin/BMI ratio, and abdominal circumference (AC), preoperatively, 7 days and 2 months after surgery, respectively. Group of women with malignant tumors (group 2)

Mean	Preoperatively	7 days postoperatively	2 months postoperatively	P - value
Weight (kgr)	69.4	68.1	68.2	0.800
BMI (kgr/m²)	27.64	26.83	26.38	0.580
Leptin (pg/ml)	259.3	199.0	287.8	0.216
Leptin/BMI	8.86	7.32	10.88	0.151
AC (cm)	94.7	86.6	89.9	0.044

Table 3. Comparison of weight, body mass index (BMI), leptin levels, leptin/BMI ratio, and abdominal circumference (AC), preoperatively, 7 days and 2 months after surgery, respectively. Control group (group 3)

Mean	Preoperatively	7 days postoperatively	2 months postoperatively	P - value
Weight (kgr)	69.5	69.1	69.3	0.940
BMI (kgr/m²)	27.07	27.01	27.08	0.984
Leptin (pg/ml)	251.0	241.0	242.0	0.867
Leptin/BMI	8.78	8.68	8.59	0.897
AC (cm)	84.9	84.9	84.9	1.000

Table 4. Comparison of age and height among the three groups. Comparison of body mass index (BMI), abdominal circumference (AC), and femoral circumference (FC) among the three groups preoperatively (at admission for control group)

Mean	Benign tumors group (group 1)	Malignant tumors group (group 2)	Control group (group 3)	P - value
Age (years)	48.5	51.0	47.4	0.521
Weight (kgr)	70.0	69.4	69.5	0.905
Height (m)	1.57	1.58	1.60	0.313
BMI (kgr/m²)	28.54	27.64	27.07	0.571
AC (cm)	84.1	94.7	84.9	0.032
FC (cm)	78.1	76.2	75.1	0.450

Table 5. Comparison of weight, body mass index (BMI), abdominal circumference (AC), and femoral circumference (FC) among the three groups 7 days postoperatively (or after admission for controls)

Mean	Benign tumors group (group 1)	Malignant tumors group (group 2)	Control group (group 3)	P - value
Weight (kgr)	66.6	68.1	69.1	0.619
BMI (kgr/m²)	27.42	26.83	27.1	0.685
AC (cm)	79.3	86.6	84.4	0.264
FC (cm)	78.1	76.7	75.1	0.573

Table 6. Comparison of weight, body mass index (BMI), abdominal circumference (AC), and femoral circumference (FC) among the three groups 2 months postoperatively (or after admission for controls)

Mean	Benign tumors group (group 1)	Malignant tumors group (group 2)	Control group (group 3)	P - value
Weight (kgr)	69.1	68.2	69.3	0.821
BMI (kgr/m²)	26.57	26.38	27.08	0.719
AC (cm)	83.15	89.05	84.90	0.319
FC (cm)	78.00	76.39	75.05	0.573

Table 7. Comparison of levels of leptin preoperatively, and 7 days and 2 months postoperatively, in the three groups

Leptin, mean (pg/ml)	Benign tumors group (group 1)	Malignant tumors group (group 2)	Control group (group 3)	P - value
Preoperatively	198.5	259.3	251.0	0.53
7 days postoperatively	171.2	199.0	245.0	0.013
2 months postoperatively	202.2	287.8	242.0	0.036

Table 8. Comparison of leptin/BMI ratio preoperatively, and 7 days and 2 months postoperatively, in the three groups

Leptin/BMI	Benign tumors group (group 1)	Malignant tumors group (group 2)	Control group (group 3)	P - value
Preoperatively	6.79	8.86	8.79	0.030
7 days postoperatively	6.19	7.32	8.68	0.001
2 months postoperatively	7.30	10.88	8.54	0.080

our subjects had high serum leptin levels 2 months after surgery, an observation that agrees with the study of Bomstein et al, who reported that high levels of serum leptin in critically ill patients are associated with better prognosis, whereas lower leptin levels were found in those with poor outcome[20].

In our study, we found low serum leptin levels in women with benign genital tumors preoperatively and 2 months after surgery. Moreover, women with benign tumors were found with lower leptin levels than controls at admission. In agreement with our findings, Chan et al reported decreased serum leptin levels in women with urerine leiomyomas[21]. In another study, Abramov et al found low serum levels of leptin in a patient with a large ovarian tumor, which increased after surgery[22]. Moreover, the group of women with benign tumors had significantly lower levels of serum leptin before surgery and even 7 days after surgical treatment, whereas serum leptin levels increased 2 months after surgery. Serum leptin levels among women with benign tumors remained lower than those with cancer in all three measurement periods.

Conclusion

Our results indicate that no significant correlation exists between levels of circulating leptin and loss of weight and cachexia that occurs in gynecological oncology. However, serum leptin levels among women with benign tumors of the genital tract were significantly lower, in comparison with women with malignancy as well as healthy controls. Consequently, leptin could be used as a potential diagnostic marker before surgery in women with a tumor of genital system. Furthermore, leptin could be included in the markers of prognosis of malignancy, especially in endometrial and ovarian cancer, after further research.

Conflict of interest

All authors declare no conflict of interest.

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