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Serum leptin concentration and advanced gastrointestinal cancers: a case controlled study

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Published: 24 June 2004

Received: 16 March 2004

BMC Cancer 2004, 4:29 doi:10.1186/1471-2407-4-29

Accepted: 24 June 2004

This article is available from: <http://www.biomedcentral.com/1471-2407/4/29>

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Abstract

Background: Serum leptin level is associated with appetite and energy expenditure in healthy individuals. We aimed to evaluate the serum leptin concentration and the other factors which may be associated with weight loss in patients with advanced gastrointestinal cancer.

Methods: Forty-four patients with advanced gastrointestinal cancer (25 gastric and 19 colorectal cancer) and 25 healthy controls were enrolled. Serum leptin levels were measured as ng/ml via enzyme linked immuno-sorbent assay (ELISA) method in all subjects. The difference in serum leptin concentration between cancer and control group, the factor associated with its serum level and the relationship between serum leptin concentration and weight loss was evaluated.

Results: Serum leptin concentration of cancer group was significantly lower than controls ($p = 0.002$). Female subjects had significantly higher serum leptin concentration than male subjects in control group ($p = 0.01$), while not in cancer group ($p > 0.05$). Serum leptin concentration was significantly related with gender in controls ($p = 0.023$, $\beta = 0.479$), while no gender difference was observed in cancer group ($p > 0.05$). No relationship was found between serum leptin concentration and weight loss percentage in cancer group in linear regression analysis ($p > 0.05$). No significant difference was observed in serum leptin concentrations between colon and gastric cancer sub-groups ($p > 0.05$).

Conclusion: Independently from the site of gastrointestinal tract, serum leptin concentration in advanced gastrointestinal cancer is lower than controls and it is not a determinant factor in weight loss. In contrast to healthy subjects, gender does not effect the serum leptin concentration in patients with advanced gastrointestinal cancer.

Background

Leptin, a 16-kilodalton protein, is involved in the regulation of food intake and body composition, as discovered

by Friedman et al [1,2]. It is a member of the cytokine family, most closely related to ciliary neurotropic factor and to leukemia inhibitory factor [2]. Plasma leptin level

is correlated with body fat percentages, suggesting that leptin is an important signal of fat stores [3,4]. In healthy individuals, decrease in leptin increases neuropeptide Y production in the hypothalamus, which in turn increases appetite and decreases energy expenditure. As a result, fat storage increases [5].

Weight loss in cancer patients remains a major clinical problem because it contributes to loss of independence and compromises the quality of life [6,7]. There is increasing evidence in the literature that the inflammatory response plays an important role in such alterations in gastrointestinal cancer patients [8,9]. Several inflammatory cytokines, especially tumour necrosis factor (TNF), interleukin 1 (IL-1), interleukin 6 (IL-6), and ciliary neurotrophic factor (CNTF), induce anorexia and cachexia [10,11]. The serum leptin level and its role in the weight loss of patients with advanced cancer are still controversial. In one study which was conducted in patients with colorectal cancer, serum leptin level has been found to be similar with controls [12]. In contrast, in other studies, low or undetectable circulating leptin concentrations have been observed in patients with lung and gastrointestinal cancer [13,14]. The net effect of these various observations on cancer patients is largely unknown.

The aim of the present study was to evaluate the serum leptin concentration in patients with advanced gastrointestinal cancer and to determine the factors such as gender, age and body mass index (BMI) which may be related with this peptide in this subjects. In addition, we aimed to find out the relationship of leptin with weight loss and to compare the serum leptin concentrations in distinct type of gastrointestinal cancers.

Methods

Forty-four cancer patients with histologically confirmed stage IV gastrointestinal malignancy with more than 5% weight loss in previous six months who had life expectancy of at least two months (25 gastric and 19 colorectal cancers) and 25 healthy controls were enrolled in this study. Patient group was composed from outpatients of Oncology Department. Control group was selected from completely healthy subjects with stable weight. Patients with diabetes mellitus, hypertension, renal and hepatic insufficiency, and major depression, active problem to interfere with oral intake and who were under active chemotherapy were excluded from the study. The study was approved by the local human institutional review committee and written consents were received from all participants.

Body weight of subjects with wearing standard clothes and no shoes in two groups was determined using a calibrated beam scale. A Harpenden Stadiometer was used in

height measurement. Body mass index (BMI) was determined as the actual body weight divided by the square of height (kg/m^2). Body weight and BMI which were assessed six months earlier and obtained from the outpatient data records were accepted as baseline values. After obtaining baseline and actual values, the percentage of lost in body weight and BMI was calculated.

Blood samples were obtained in the morning after 12 hours of fasting period following anthropometric measurements. Routine blood tests were performed in all subjects using auto-analyser. Serum leptin levels were measured as ng/ml via enzyme linked immuno-sorbent assay (ELISA) method by using Kat./cat: DX-EIA-1863, Test:96 Wells 11/0 (DRG International Inc., New Jersey, USA) in all subject. Reported leptin concentrations were the mean of two determinations of the same sample. Sensitivity of the test was 0.10 ng/ml.

Statistical analysis

Data were reported as median and range. Continuous variables were compared using Mann-Whitney U or Kruskal-Wallis H test. A linear regression analysis was used to determine the variables related with the serum leptin levels. The statistical significance was defined as a $p < 0.05$. Statistical analyses were performed using the SPSS 9.0 for windows.

Results

Clinical and demographic characteristics of malignant and control group were shown in table 1. Median BMI values were significantly higher in control group ($p = 0.008$), while median age in cancer group ($p < 0.001$). No statistically significant differences were observed in male and female number of the groups ($P > 0.05$). In each group, male and female subjects had similar age and BMI (both, $p > 0.05$). Median weight loss was 9.1% and 8.8% in female and male subjects of cancer group, respectively ($p > 0.05$). (Table 2)

Serum leptin concentration of cancer group was significantly lower than controls ($p = 0.002$). Female subjects had significantly higher serum leptin concentration than male subjects in control group ($p = 0.01$), while not in cancer group ($p > 0.05$). (Table 2)

Linear regression analysis showed that serum leptin concentration was significantly related with gender in controls ($p = 0.023$, $\beta = 0.479$), while no gender difference was observed in cancer group ($p > 0.05$). Serum leptin concentration was not related to age and BMI in both groups (both, $p > 0.05$). No relationship was found between serum leptin concentration and weight loss percentage in cancer group in linear regression analysis ($p > 0.05$).

Table 1: Characteristics of control and study groups.

	Gastric cancer group	Colorectal cancer group	Malignant group	Control group
n	25	19	44	25
Sex m/f	16/9	13/6	29/15	12/13
Age (year)	58 (34–80)	59 (33–80)	58 (33–80)*	38 (22–67)*
Body mass index (kg/m ²)	22 (17–24)	23 (16–25)	22 (16–25)**	25 (21–28)**
Weight loss percentage (%)	7.8 (5.3–23.8)	8.4 (5.2–19)	8.1 (5.2–23.8)	-----
Leptin (ng/ml)	1.8 (0.1–12)	1.9 (0.2–11)	1.8 (0.1–12)***	3 (2.5–13)***

Data were reported as median and range. *p < 0.001 **p = 0.008 ***p = 0.002

Table 2: Comparison of cancer and control groups based on gender

	Cancer group (n = 44)		Control group (n = 25)	
	female (n = 15)	male (n = 29)	female (n = 13)	male (n = 12)
Leptin (ng/ml)	1.8 (0.2–12)	1.8 (0.1–10)	5.7 (2.3–13)*	2.5 (2–11.2)*
Body mass index (kg/m²)	22 (19–24)	21 (16–25)	24 (21–28)	25 (22–28)
Weight loss (kg)	9.1 (5.2–21)	8.8 (5.6–23.8)	----	----

Data were reported as median and range. *p = 0.01

When the cancer group was sub-grouped according to type of cancer (e.g. colon and gastric), control subjects had significantly higher serum leptin concentration than two cancer sub-groups (both, $p < 0.016$). No significant difference was observed in serum leptin concentrations between colon and gastric cancer sub-group ($p > 0.05$). (Table 1)

Discussion

Primary aim of the present study was to evaluate the serum leptin concentration in advanced gastrointestinal cancer patients. We have found a significant decrease in serum leptin concentrations of cancer group compared to controls. Although it is still controversial, serum leptin concentration has been reported to be lower than controls, especially in the lung and colorectal cancer, in the literature. It has been suggested that low serum leptin concentration may be related to decreased body fat mass in this subjects [13,14]. Tessitore et al [12] reported that patients with breast cancer had higher serum leptin concentration than controls. However, they did not observed any increase in serum leptin concentration in patients with colorectal cancer compared to controls. No mechanism related to these results has been suggested by this author [12]. Median weight loss has reached up to 8% in our cancer patients. Therefore decrease in leptin concentration may be related to decreased body fat mass which was developed secondary to weight loss in our patients.

It has been reported that healthy women have more adipose tissue and consequently have higher leptin concentrations than men with equivalent BMI [14,15]. Similarly, in the present study, serum leptin concentrations were higher in women than in men in controls, while not in cancer group. Linear regression analysis has shown that serum leptin concentration was only related with gender in controls, however, there was no relationship between gender and serum leptin concentration in cancer group. This observation may indicate that gender factor is not a determinant for serum leptin level in patients with advanced gastrointestinal cancer. As reported previously [14,16], other parameters such as BMI and age were not related with serum leptin concentration neither in controls nor in cancer patients. Inflammatory cytokines have been suggested to influence serum leptin concentrations [17], whereas conflicting results have been reported in the literature [18]. The influence of these cytokines on serum leptin concentrations couldn't be investigated in the present study.

In our study, body weight loss percentage was not related with leptin concentration in cancer group in linear regression analysis. This finding was consistent with the literature [13,14,19]. In the healthy subjects a decrease in serum leptin concentration appears to stimulate an increase in neuropeptide Y from the hypothalamus and this, in turn, results in increased appetite and decreased

energy utilization [5]. Although decrease in serum leptin concentration in cancer patients has been reported in previous studies, no increase in appetite and decrease in energy expenditure have been observed in these subjects. This finding has been suggested to be due to a block in the hypothalamic response to low circulating leptin concentrations in such cancer patients [13,14,20]. In the present study, the lack of relationship between serum leptin concentration and body weight loss percentage, and decrease in serum leptin concentration suggested that leptin level is not a causative factor in weight loss in patients with gastrointestinal cancer.

In addition to findings mentioned above, we have also found no difference between patients with advanced gastric and colorectal cancer in regarding to serum leptin concentrations. This finding has not been reported in previous studies. This suggested that serum leptin concentration is not affected from the site of advanced stage cancer of gastrointestinal tract and it is constantly low in these subjects.

Conclusion

Independently from the involved site of the gastrointestinal tract, serum leptin concentration in advanced gastrointestinal cancer is lower than controls and it is not a determinant factor in weight loss. In contrast to healthy subjects, gender does not effect the serum leptin concentration in patients with advanced gastrointestinal cancer.

Abbreviations

TNF, tumor necrosis factor; IL-1, interleukin 1; IL-6, interleukin 6; CNTF, ciliary neurotropic factor; BMI, body mass index; ELISA, enzyme linked immuno-sorbent assay;

Competing interest

None declared.

Authors' contributions

FFB conceived of the study, and participated in its design and coordination. HK collected the samples and carried out the laboratory analysis. CB conceived of the study and participated in the sequence alignment and drafted the manuscript. MG collected the clinical data performed the statistical analysis. MH participated in the design of the study, participated in the sequence alignment and drafted the manuscript. NST drafted the manuscript and revised it critically for important intellectual content. BK participated in study design and coordination and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1471-2407/4/29/prepub>