Effect of Weight Loss and the Inflammatory Response on Leptin Concentrations in Gastrointestinal Cancer Patients

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ABSTRACT
Animal research suggests that leptin may have an important role in the regulation of energy balance. The role of leptin in the progressive involuntary weight loss associated with cancer in humans is of considerable interest. However, such studies are limited. In this study, we compared circulating leptin concentrations in gastrointestinal cancer patients and weight loss (n = 27) with those of healthy subjects (n = 27). The effect of the presence of an inflammatory response on leptin concentrations was also examined. There were significantly lower leptin concentrations in male (median, 2.4 μg/liter; range, <0.5–6.0 μg/liter) and female (median, 3.4 μg/liter; range, <0.5–9.8 μg/liter) cancer patients than there were in male (median, 6.5 μg/liter; range, 3.1–10.9 μg/liter) and female (median, 18.7 μg/liter; range, 8.0–31.5 μg/liter) healthy subjects (P < 0.001). However, the leptin concentrations in both patients and normal subjects were related to the predicted percentage of body fat (r = 0.731; P < 0.001). Circulating leptin concentrations in the cancer patients were not altered by the presence of an inflammatory response. These results suggest that cancer anorexia/cachexia is not due to a simple dysregulation of leptin production.

INTRODUCTION
After the discovery that the adipocyte ob gene encodes leptin, a secreted protein that regulates body weight in mice (1, 2), there has been considerable interest in its role in humans. It has been reported that circulating leptin concentrations increase with obesity (3–5) and correlate with the percentage of body fat (3, 4) and with adipocyte ob mRNA expression (3) in humans. Such associations have led to the proposal that the circulating leptin concentrations accurately reflect adipose mass and regulate adiposity and energy status through a control feedback loop involving neuropeptide Y (6).

Weight loss in cancer patients remains a major clinical problem because it results in a loss of independence and reduces the quality of life (7, 8). Although little is known about the mechanisms involved, there is evidence that energy intake is decreased and energy expenditure increased (9, 10) such that there is a reduction of both fat and fat-free mass (11). There is increasing evidence that the inflammatory response plays an important role in such alterations in gastrointestinal cancer patients (12, 13).

Recent studies in the hamster (14), mouse (15), and human (16, 17) have demonstrated that leptin is increased by the administration of endotoxin or cytokines, and, through its action on decreasing appetite and increasing energy expenditure, leptin has been implicated in the anorexia of infection. However, information on the role of leptin in cancer-associated cachexia in humans is limited. Recently, Simons et al. (18) reported low or undetectable circulating leptin concentrations in patients with lung cancer and weight loss. However, these investigators did not report the leptin concentrations in normal subjects and did not examine the relationship with the inflammatory response.

MATERIALS AND METHODS
Patients with histologically proven locally advanced or metastatic gastrointestinal cancer with more than 5% weight loss in the previous 6 months who were receiving supportive care only and had a life expectancy of at least 2 months were studied. No patient complained of moderate or severe dysphagia, and none had an obvious functional obstruction to food intake. No patient had grossly abnormal liver function tests.

After an overnight fast, measurements of height and weight were carried out, and circulating concentrations of leptin and C-reactive protein were analyzed. Similarly, these measurements were performed in healthy weight-stable subjects for comparison. The study was approved by the local ethical committee. All patients were informed of the purpose of the study, and all gave written consent.

Serum leptin was measured by radioimmunoassay as described previously (5) using commercial kits (Human Leptin RIA kit; Linco Research Inc., St. Charles, MO). The limit of sensitivity was 0.5 μg/liter, and the intra- and interassay coefficients of variation were 5.8 and 6.5%, respectively, over the sample concentration range.

Circulating C-reactive protein concentrations were measured on an Olympus AU5200 analyzer (Olympus Diagnostic Systems, Eastleigh, United Kingdom) by turbimetry after binding to a specific antibody. The limit of sensitivity was 5 mg/liter, and the intra- and interassay coefficients of variation were 5 and 7%, respectively, over the sample concentration range.

To adjust for variations in body fat, the predicted percentage of body fat was calculated from fat-free mass as follows: percentage of body fat = [(weight fat-free mass)/weight] × 100.

Fat-free mass was derived from the predicted total body water based on the sex, age (years), height (centimeters), and weight (kilograms) equations of Watson et al. (19). For female...
patients, the predicted total body water (liters) = 0.1069height + 0.2466weight. For male patients, the predicted

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\text{fat-free mass (kilograms)} = -2.097 + 0.1069\text{height} + 0.2466\text{weight.}
\]

Fat-free mass was determined using the following formulae: fat-free mass (kilograms) = total body water + 0.73.

Data are presented as the median and range, and, where appropriate, group differences were examined using the Mann-Whitney U test. Correlations between two variables (using the logarithm of leptin concentration where appropriate) were calculated by using Spearman’s rank correlation test (Minitab Inc., State College, PA).

**RESULTS**

The characteristics of the healthy subjects (n = 27) and cancer patients (n = 27) are given in Table 1. The median weight loss of the patients was 13.2% and was similar in both male and female cancer patient groups. The healthy subjects had significantly higher BMIs and leptin concentrations than did the cancer patients (P < 0.001). In healthy male and female subjects with similar BMIs, there were significant higher circulating leptin concentrations in the latter group (P < 0.001). This difference was not seen in the cancer patients.

Because leptin concentrations are related primarily to fat mass (3, 4), the percentage of body fat was derived in healthy subjects and cancer patients and compared with the leptin concentrations (Fig. 1). There was a significant positive correlation between the percentage of body fat and the log circulating leptin concentrations of healthy subjects and cancer patients (r = 0.731; P < 0.001).

The cancer patients were grouped on the basis of the presence (C-reactive protein concentration > 10 mg/liter) or absence (C-reactive protein concentration < 10 mg/liter) of an inflammatory response (Table 2). The groups were similar in terms of sex distribution, BMI, and the percentage of weight loss. Leptin concentrations were not significantly different between these groups.

**DISCUSSION**

The results of the present study demonstrate that weight loss in patients with gastrointestinal cancer is associated with a decrease in circulating leptin concentrations. These results are consistent with the findings of Simons et al. (18) in lung cancer patients. However, in the present study of gastrointestinal cancer patients, a significantly lower proportion of patients had undetectable leptin concentrations (14 versus 71%; P < 0.001). Because the amount of weight loss was similar in the two studies, and there was no control group in the latter study, this difference may be due to methodological differences.

By also examining healthy subjects in the present study, it would appear that the circulating leptin concentrations in cancer subjects were lower than would be predicted from the difference in BMI. However, when circulating leptin concentrations were related to the percentage of predicted body fat, the relationship appeared similar in both normal subjects and gastrointestinal cancer patients.

It has been reported that healthy women have more adipose tissue and consequently have higher leptin concentrations than men with equivalent BMIs (5). This was confirmed in the healthy subjects of the present study; however, there was no significant difference in the leptin concentrations of male and female cancer patients, despite similar BMI ranges. The basis of these observations is unclear; however, it may indicate that as body fat is lost, such sex differences in leptin concentrations no longer apply.

![Fig. 1](image-url) The relationship between circulating leptin concentrations and the predicted percentage of body fat in healthy subjects (○) and weight-losing gastrointestinal cancer patients (●).
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From what is known about the mechanism of action, a decrease in leptin concentration appears to stimulate an increase in neuropeptide Y from the hypothalamus (6), and this, in turn, results in increased appetite and decreased energy utilization. In the normal subject, such changes will subsequently result in increased fat stores, and these, in turn, lead to an increase in leptin production. In the present study, there were lower circulating leptin concentrations in the weight-losing gastrointestinal cancer patients; however, previous studies of similar patients indicate that appetite is not increased and energy expenditure is not reduced (10). Therefore, this may suggest a block in the hypothalamic response to low circulating leptin concentrations in such cancer patients.

A number of recent studies show that leptin concentrations are increased during an acute cytokine-induced inflammatory response in animals (14, 15), and humans (16, 17) and suggest that elevated leptin may account for the associated anorexia. Therefore, it is of interest that in the present study, the presence of an inflammatory response, as evidenced by an increase in the circulating concentrations of C-reactive protein (20), was not associated with an increase in leptin concentration. The reasons for this are as yet unclear, but it may be that the effects of acute inflammation reported in the previous studies differ from that of the chronic inflammation seen in advanced gastrointestinal cancer patients (21). Our findings, however, are similar to those found in patients with AIDS. AIDS, like gastrointestinal cancer, is associated with anorexia, weight loss, and secondary infection, and circulating leptin concentrations are not elevated but are appropriate for the amount of body fat (22).

Further evidence from experiments performed on the administration of endotoxin to leptin receptor-deficient (db/db) and leptin-deficient (ob/ob) mice indicates that leptin is not essential for endotoxin-induced anorexia in animals (23).

In summary, it is clear that circulating leptin concentrations are not elevated in weight-losing cancer patients and are not related to the magnitude of the inflammatory response. Moreover, from our results, it would appear that the concentrations of leptin are appropriate for the amount of body fat in gastrointestinal cancer patients with weight loss. Therefore, it would appear that cancer anorexia/cachexia is not brought about by the dysregulation of leptin production.

ACKNOWLEDGMENTS

We gratefully acknowledge Patricia O’Gorman for assistance and Prof. C. S. McArthur for advice and support.

REFERENCES


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