Patterns of plasma leptin and insulin concentrations in hospitalized patients after the initiation of total parenteral nutrition[1,2]

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ABSTRACT

Background: The regulation of leptin in patients with critical illness is poorly understood. Sex, diet, body mass, and cytokines may all play a role.

Objective: The aims of this study were to determine the factors influencing leptin concentrations in hospitalized patients beginning total parenteral nutrition (TPN) and whether a 3-d regimen of TPN would further increase plasma leptin concentrations above baseline.

Design: Twenty-six patients requiring TPN were enrolled in this prospective, nonintervention study. Only 20 (11 women and 9 men) completed all 3 d of TPN.

Results: Baseline plasma leptin in the TPN patients ranged from 62.5 to 1625 pmol/L ($\bar{x}$ ± SD: 419 ± 387; n = 26) and was not significantly different between men (444 ± 494 pmol/L) and women (363 ± 244 pmol/L). Baseline plasma insulin ranged from 76 to 695 pmol/L (271 ± 188; n = 26) and was not correlated with plasma leptin. Leptin concentrations increased after 3 d of TPN, from 356 ± 300 to 794 ± 600 pmol/L ($P < 0.05$) in parallel with an increase in insulin from 257 ± 187 to 979 ± 917 pmol/L ($P < 0.01$) in the 20 patients who completed the study; however, the changes were not correlated when expressed as percentages. Although the men and women had insulin responses to feeding that were not significantly different, leptin concentrations did not increase significantly in men but increased 3-fold in women (to 1094 ± 638 pmol/L; $P < 0.01$).

Conclusions: Leptin regulation in patients with a critical illness differs substantially from that in healthy persons. The importance of glucose and insulin in leptin secretion remains unclear, especially in men. *Am J Clin Nutr* 2002;75:931–5.

KEY WORDS Total parenteral nutrition, TPN, leptin, insulin, fasting, critical illness, cytokines, sex differences, body mass

INTRODUCTION

Leptin is a hormone secreted by adipose tissue that has a critical role in determining food intake and food-seeking behavior in multiple species, including humans (1). Various studies have shown that the plasma leptin concentration in most individuals is proportional to fat mass and that a decrease in body weight through diet or exercise is associated with lowered leptin concentrations (2). Hypoleptinemia generally stimulates an increase in food intake and reduces physical activity—a homeostatic mechanism designed to return fat mass to baseline and maintain the status quo. Insulin, glucocorticoids, and cytokines have all been implicated in modulating plasma leptin concentrations, although most of the studies that showed these mediators to be important were conducted in animals or cultured cells (3, 4).

In humans, the role of insulin in stimulating the release of leptin is unclear. Unlike in rodents, food intake and acute insulin administration in humans had little immediate effect on leptin concentrations in most (5–7) but not all (8) studies. Sustained increases in plasma insulin (via hyperinsulinemic, euglycemic clamp) (9) or overfeeding (10) provoke elevations in leptin after several hours. In a report of a single patient with insulinoma and elevated plasma insulin and leptin concentrations, surgical removal of the tumor normalized concentrations of both of these hormones (7). Although plasma insulin concentrations rose rapidly after a mixed meal in one study in healthy volunteers, no changes in leptin were found 240 min postprandially (11).

An additional factor potentially influencing plasma leptin concentrations is a systemic elevation in cytokines, as might occur in inflammatory states and critical illness. Leptin is recognized as having a possible role in immunologic challenge (12). Many studies have shown that the administration of endotoxin, tumor necrosis factor α, or other cytokines to laboratory animals or humans results in a significant elevation in plasma leptin concentrations despite ongoing fasting and intercurrent catabolic illness (13–15).

The circulating plasma leptin concentration is not clearly related to fat stores in elderly hospitalized patients, suggesting the superimposition of additional mediators (16). In a small study of ill, undernourished patients, baseline leptin was correlated with body mass index (BMI), and intervention with total parenteral nutrition (TPN) produced further elevations in plasma leptin concentrations (17). High circulating leptin concentrations, normally a signal of nutritional sufficiency, may contribute to the anorexia that is so prominent in inflammatory conditions. In a cohort of critically ill patients receiving continuous enteral or parenteral

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TABLE 1
Underlying diagnoses or reasons for initiation of total parenteral nutrition

Diagnosis	Number of patients
Postoperative ileus	9
Acute pancreatitis	5
Medical illness with ileus	5
Bowel perforation with or without abscess	3
Small-bowel obstruction	2
Gastrointestinal bleeding	1
Ischemic bowel with ileus	1

nutrition, leptin was higher than in healthy control subjects but was unrelated to BMI and plasma cortisol and insulin (18). However, in a series of patients with major trauma, who were not receiving nutritional support, leptin was significantly lower than in healthy control subjects postabsorptively, whereas TPN restored leptin to a normal range (19). The goal of the present study was to investigate the effects of initiation of TPN on plasma leptin and insulin concentrations in a large and diverse group of hospitalized patients in whom enteral feeding was unsuitable.

SUBJECTS AND METHODS

Subjects

Twenty-six sequential patients (14 women and 12 men) who were to begin TPN at Beth Israel Deaconess Medical Center (Boston) were enrolled in the study. The mean (±SD) age of the subjects was 64 ± 19 y (range: 26–91 y). The mean body mass of the subjects was 74 ± 20 kg, whereas ideal body weight was 63 ± 8 kg. The underlying diagnoses of the subjects or the reasons for TPN initiation are listed in **Table 1**. Energy intake during the 3 d before entry was required to be <840 kJ/d, although many patients had fasted for ≤5 d before entry. This criterion was based on the previous finding that higher (>1400 kJ/d) energy intakes restore basal leptin concentrations in fasting healthy persons (20).

Data on height, weight, pre-TPN energy intake, serum chemistries, and medical history were abstracted from the patients' records. The severity of underlying illness was scored before TPN began; temperature (>38 or <36°C) and white blood cell count (>12 × 10^9/L, >10% band forms, or both) were used as markers of the systemic inflammatory response syndrome (SIRS) (21). Because many of the patients were being ventilated or were in the early postoperative phase, pulse and respiratory rate were deemed unsuitable markers of SIRS.

Seven subjects were known to have diabetes and received insulin throughout the 3 d of TPN administration. Three additional patients required an insulin admixture with TPN for stress hyperglycemia. The study was approved by the hospital's Institutional Review Board, and patients or a health care proxy gave signed, informed consent to participate.

Hormone assays

Plasma leptin and insulin concentrations were measured just before TPN began and again after 3 d of TPN administration in those subjects who completed the protocol. Both measurements were performed at 1600. Plasma leptin was measured with a commercial radioimmunoassay kit (Linco Diagnostics, St Louis). The antibody used in the kit is 100% specific for human leptin, and [^{125}I]leptin is used as a tracer. Plasma insulin was measured with a commercial radioimmunoassay kit (Ventrex Laboratories, Portland, ME), with [^{125}I]porcine insulin used as a tracer.

Total parenteral nutrition

The TPN orders were written exclusively by the nutrition support team. The formula was based on a goal of 105 kJ/kg dry wt. In obese subjects, ideal body weight was adjusted upward by 25%, and this weight was used to calculate the dose of TPN. The protein goal was 1.5 g/kg body wt (with the use of ideal body weight in obesity) and was included in the calculation for energy. The remainder of the energy was either from dextrose alone or from a mixture of dextrose and lipid—the latter accounting for ≤30% of the total energy. On the first day of TPN, dextrose was limited to 150 g to assess glucose tolerance. Subcutaneous regular human insulin was administered by algorithm every 6 h in patients with finger-stick blood glucose concentrations >11.1 mmol/L. If required, insulin was added to the TPN solution in appropriate amounts for the subsequent days. The amount of dextrose was increased toward the goal as glycemia permitted. TPN was given continuously over 24 h/d as a 3-in-1 solution.

Statistical methods

Two-way analysis of variance (ANOVA) was performed to assess the effect of sex and 3 d of treatment with TPN on plasma leptin concentrations in the 20 patients who completed the study. Different groups were compared by using Fisher's least-significant-difference test with the software program SIGMASTAT (version 2.0; SSPS Inc, Chicago). The baseline data for the 26 patients enrolled in the study were analyzed by using an unpaired *t* test (for group comparisons) or Spearman's rank-order test (for continuous data). Significance was defined by the 95% CI and data are presented as means ± SDs unless otherwise specified.

RESULTS

Thirteen patients had features of SIRS. Only 20 patients completed the 3-d TPN protocol; data from the 6 other subjects were included in the analysis of the baseline data but not in the analysis of the longitudinal follow-up data.

At study entry (baseline), leptin concentrations varied widely (range: 62.5–1625 pmol/L; $\bar{x}$ ± SD: 419 ± 387 pmol/L) and did not correlate with BMI or with plasma insulin concentrations in the entire group of 26 patients (**Figure 1**). Exclusion of data from the patients who received exogenous insulin did not alter this finding significantly (data not shown). Plasma leptin concentrations were not significantly different between men (444 ± 494 pmol/L) and women (363 ± 244 pmol/L). Patients without evidence of SIRS had a somewhat lower plasma leptin concentration (300 ± 313 pmol/L) than did the group with SIRS (506 ± 394 pmol/L), but the difference was not significant by *t* test.

Sex and initiation of TPN both contributed to the significant increase in plasma leptin after 3 d, whereas only initiation of TPN contributed to the increase in plasma insulin concentrations (**Figure 2**). Leptin concentrations increased significantly from 356 ± 300 to 794 ± 600 pmol/L in the 20 patients receiving TPN for ≥3 d, in parallel with the significant increase in insulin concentrations from 257 ± 187 to 979 ± 917 pmol/L. When the data were grouped by sex, only women showed a significant increase in leptin (from 363 ± 244 to 1094 ± 638 pmol/L) in response to TPN. However, both men and women had significant (by the least-significant-difference method) insulin responses to TPN.

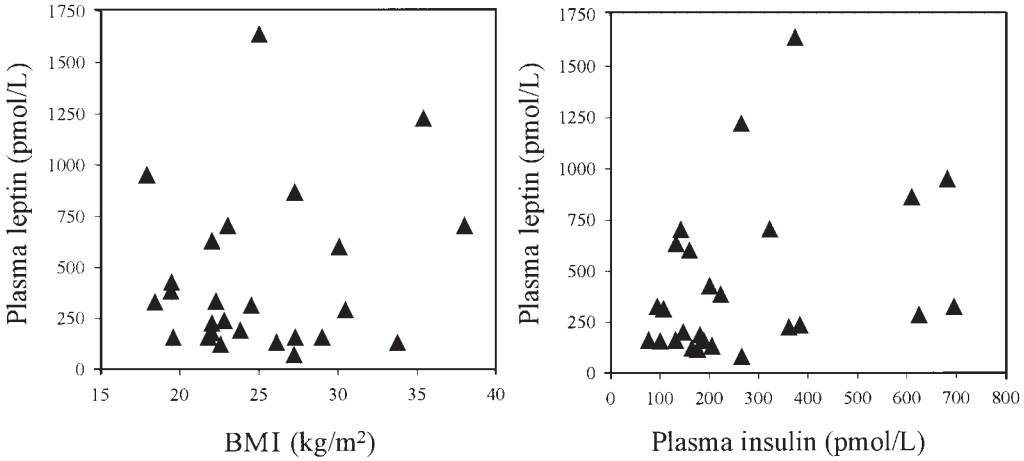

FIGURE 1. Correlation between plasma leptin concentrations (n = 26) and BMI (r = 0.26, NS) and plasma insulin concentrations (r = 0.3, NS) at baseline in patients with prior trivial energy intakes.

The percentage increases in insulin and leptin after TPN were not significantly correlated in the group as a whole (**Figure 3**), nor when divided by sex. The leptin concentrations 3 d after TPN were not significantly correlated with the amount of dextrose administered over the 24 h before leptin measurement (**Figure 4**).

DISCUSSION

Despite trivial energy intakes in the subjects at baseline, plasma leptin concentrations varied widely and were not correlated with BMI or plasma insulin. In addition, no significant sex differences in leptin concentrations were found before the initiation of TPN. In contrast, clear influences of sex and BMI on plasma leptin are evident in healthy persons (1). A positive correlation between BMI and plasma leptin concentrations was noted in some studies of hospitalized patients (17, 19). This finding is surprising when the multiplicity of potential overriding influences is considered and is in contrast with the findings of other studies (16, 18).

Baseline plasma insulin concentrations also varied widely in subjects, despite their trivial energy intakes. Hyperinsulinemia in patients with minimal energy intakes probably reflects the presence of insulin resistance related to catabolic illness. The nature of the relation between leptin and insulin is controversial and may not be direct. Several studies show correlations between insulin and leptin, even after correction for confounding factors such as BMI (2, 20, 22). Feeding studies clearly indicate that, whereas insulin increases sharply in response to meals or glucose infusions, several hours elapse before leptin also increases.

Our primary goal in performing these studies was to determine whether, despite the multiplicity of influences on leptin, administration of hypertonic dextrose as a component of TPN would result in further stimulation of leptin. TPN administration resulted in a significant 2-fold increase in leptin concentrations and a significant 3-fold increase in insulin compared with baseline. Interestingly, in isolated adipocytes, insulin causes leptin release in the presence of glucose but not in the presence of the 2-deoxyglucose analogue, suggesting that cellular uptake and metabolism of glucose is somehow coupled to leptin secretion (23). The critical steps mediating the effects of insulin and glucose on leptin production or release remain unknown.

A major sex effect was found. The TPN-related increase in leptin occurred only in women, despite the finding that TPN-related increases in insulin were not significantly different between the sexes: 3-fold in men and 4-fold in women. However, even in women, the percentage changes in insulin and leptin were not correlated. In rodents, a clear sex difference in fed and fasted leptin concentrations (higher in females) is present, although leptin is more closely related to food consumption in rats than in humans (24). Most studies in humans that addressed sex differences in plasma leptin concentrations were performed in healthy volunteers and indicate, as in the present study, that sex differences may be abolished with fasting (25, 26). In general, leptin is correlated positively with estradiol concentrations in both men and women and negatively with testosterone in men (22, 27, 28). Women generally have a higher percentage of body

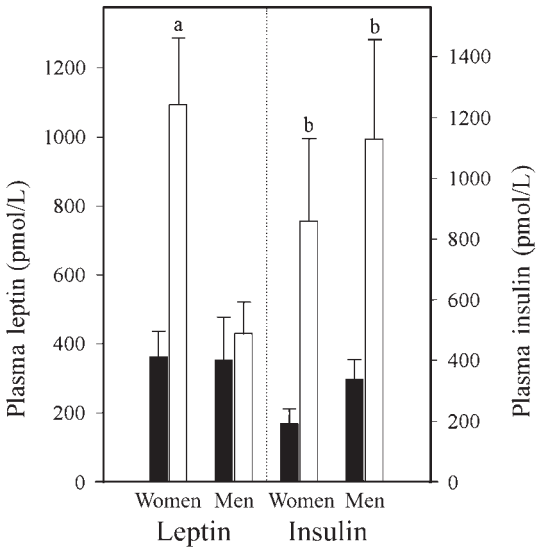

FIGURE 2. Mean (±SEM) plasma leptin and plasma insulin concentrations at baseline (■) and 3 d after the initiation of total parental nutrition (□) for men (n = 9) and women (n = 11) separately. The sex × time interaction was significant for leptin (P = 0.02, two-way ANOVA) but not for insulin. [a,b]Significantly different from baseline (Fisher's least-significant-difference test): [a]$P < 0.01$, [b]$P < 0.05$.

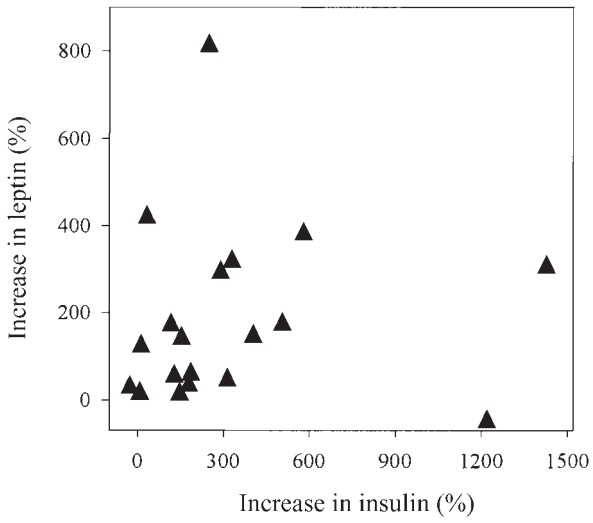

FIGURE 3. Correlation (r = 0.07, NS) between the percentage increase in plasma insulin and the percentage increase in plasma leptin 3 d after the initiation of total parenteral nutrition (n = 20).

fat than do men, even when their BMIs are similar; in studies that address this difference, correction for body fat does not usually explain the difference found in leptin between the sexes (29, 30). In one study of adipocytes from obese persons examined ex vivo, dexamethasone stimulated leptin production only in women (31). Although we did not measure plasma cortisol in the present study, our TPN patients probably had hypercortisolemia, which may have contributed to the observed sex differences in leptin concentrations. Interestingly, diurnal patterns of cortisol and leptin are directly opposed in healthy persons. Shifting mealtimes by 6 h in one study in humans showed that, whereas cortisol exhibits a true circadian pattern, leptin is diurnally released and entrained to meals, confirming differential regulation under normal circumstances (32). In critical illness, both hormones lose their diurnal rhythmicity (33). However, the present study was not designed to examine this issue further.

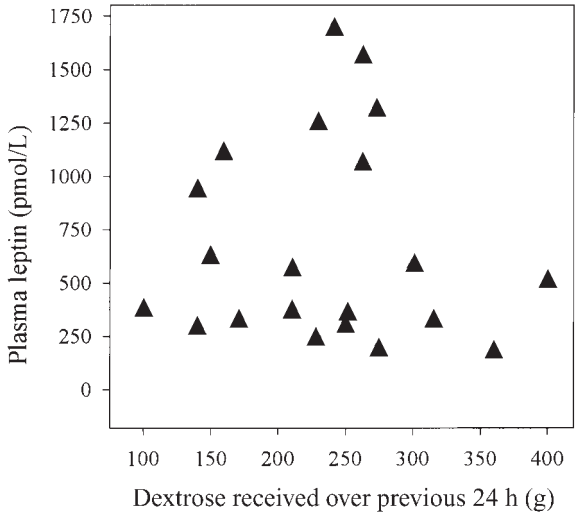

FIGURE 4. Correlation (r = −0.1, NS) between plasma leptin concentrations after 3 d of total parenteral nutrition and the amount of dextrose received over the 24 h before leptin was measured in hospitalized patients (n = 20).

Many studies of leptin in critical illness and feeding have not considered men and women separately (17, 33). In one study, women showed a greater leptin responsiveness to feeding than did men, although clear differences existed at baseline (19), unlike in our patients. However, only trauma patients had been enrolled in that study; no trauma patients participated in our study. Although the trauma patients were severely injured and had biochemical evidence of stress on the basis of elevated plasma cortisol concentrations, their mean plasma insulin concentration was 63 pmol/L. In contrast, the average plasma insulin concentration in our patients was 271 pmol/L. This difference suggests far greater catabolic stress in our study participants and may reflect greater circulating concentrations of cytokines and counterregulatory hormones. The trauma patients were probably in the "ebb" phase of injury, whereas our patients were in an established phase of catabolism, having been ill for >48 h. In addition, the patients in our study probably had sick hypogonadal syndrome (34), but there is no published information about whether circulating sex steroids are preserved in trauma patients shortly after injury. If gonadal steroids do play an important role in sex differences in baseline (fasting) plasma leptin concentrations, it might explain a large measure of the difference between the trauma study and our own. In the trauma study, the goals for energy intake were higher than in our study, although we were unable to determine the feeding rates of the trauma patients at the onset of that study or how quickly their energy goals were met. It is possible that the female trauma patients were provided substantially more energy and received more insulin than did the male patients or that the plasma glucose concentrations were significantly different between the sexes; however, these details were not provided in Jeevanandam et al's (19) study.

In critically ill or catabolic patients, diverse factors probably play a role in mediating leptin production, leptin clearance, or both. Tumor necrosis factor α and other cytokines may be important in this regard (13). Patients with fever and elevated white blood cells in the present study generally had higher plasma leptin concentrations at baseline than did trauma patients without SIR. This difference was not significant, not surprisingly given that these factors are imperfect indicators of intercurrent infection and severity of inflammation.

In conclusion, considering all of the published literature on this topic, the typical medical-surgical intensive care unit patient population regulates plasma leptin differently than do healthy persons and young trauma patients. Future research in this area should include measurements of cortisol and sex steroids and must consider males and females separately.

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