**Plasma leptin, energy intake and hunger following total hip replacement surgery**

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1. This study aimed to investigate the possible role of leptin in post-traumatic anorexia by making pre- and post-operative (0–8 days) measurements of circulating leptin concentrations in six patients undergoing elective total hip replacement for osteoarthritis.

2. Mean daily hunger rating (four categories) and food intake (assessed by food record charts) were measured pre-operatively, as well as post-operatively for the first 5 days (days 0–5). Leptin concentrations, circulating metabolites [glucose, non-esterified fatty acids, glutamine and 3-hydroxybutyrate] and insulin and cortisol concentrations were measured pre-operatively (day 0) and post-operatively (days 1, 2, 3, 5 and 8).

3. Mean leptin concentrations were significantly increased only on day 1 (56% increase compared with pre-operative values, $P < 0.009$), whereas food intake (only 0.6 MJ on day 0) and hunger (5/6 patients 'not hungry' on day 0) only gradually improved over the next few days. (The energy intake over the first 5 days was 56% of the pre-operative value.)

4. Circulating insulin and cortisol concentrations were elevated on day 1 compared with pre-operative values on day 0 ($P < 0.005$). Of the measured metabolites implicated in the control of food intake, circulating non-esterified fatty acids and 3-hydroxybutyrate were not significantly altered in the post-operative period, but significant hyperglycaemia was noted on day 1 compared with day 0 pre-operatively (8.8 compared with 6.4 mmol/l glucose; $P < 0.01$).

5. It is concluded that circulating leptin is involved in the early (<24 h) acute-phase response after moderately severe surgical trauma (characterized biochemically by a substantial acute-phase protein response, hypoalbuminaemia, hyperglycaemia and hyperglocotaminemia). Therefore, leptin may be implicated in post-traumatic anorexia, although other factors are likely to be involved, especially after the first 24 h when circulating leptin concentrations are no longer elevated.

**INTRODUCTION**

Many mediators are implicated in the anorexia of disease, including cytokines [1], hormones and various substrates [2], such as glucose, non-esterified fatty acids and ketone bodies. Leptin (from the Greek *Leptos* meaning thin), the 16 kDa protein product of the *obese (ob)* gene [3], has been implicated as an important factor involved in the regulation of body weight, food intake and energy expenditure. Mutations in the *ob* gene, leading to a failure of expression of this protein, account for the over-eating and subsequent obesity in *ob/ob* mice [3], while injections of leptin in these animals reduce food intake, increase physical activity and thermogenesis, and decrease body weight [4, 5, 6]. Adipose tissue produces leptin, and the hypothalamus is the central nervous system target [7] where leptin acts by inhibiting the synthesis and release of neuropeptide Y, a peptide which stimulates food ingestion and increases thermogenesis.

Most human studies with leptin have been undertaken in healthy subjects and in obesity (over-nutrition). Little work has investigated the possible role of leptin in the anorexia of inflammatory or traumatic disease which contributes to under-nutrition. Recent work suggests that endotoxin administration to fasted hamsters increases the expression of leptin mRNA in adipose tissue to levels found in fed control animals, and that this expression is inversely and strongly correlated to subsequent food intake [8]. In addition, pharmacological doses of corticosteroids [9, 10] and cytokines [8] stimulate leptin mRNA expression and/or increase the circulating leptin concentration, whereas administration of catecholamines (noradrenaline) reduce *ob* gene expression [11]. These findings suggest that leptin may be involved in the anorexia of infective or traumatic conditions. How-

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**Key words:** Energy intake, hunger, leptin, total hip replacement surgery.

**Abbreviations:** ACT, alpha-1-antichymotrypsin; CRP, C-reactive protein.

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ever, data in humans is lacking and therefore this study was undertaken to investigate the possible role of leptin in mediating the anorexia that follows surgical trauma. Total hip replacement was chosen as a surgical model that does not directly involve the gastrointestinal tract and its function, in contrast to abdominal surgery which affects food and fluid intake for 'mechanical' reasons (e.g. ileus).

METHODS

Six patients (three male, three female), undergoing total hip replacement, were recruited for the study. Mean age was 65.4 years (SD 9.4), pre-operative weight 72.3 kg (SD 14.1), height 1.73 m (SD 0.13), body mass index 24.0 kg/m² (SD 2.4) and pre-operative percentage body fat 29.9% (SD 5.4).

All subjects were studied during their in-patient admission to the Cambridge Lea Hospital. All the patients had uncomplicated total hip replacements for osteoarthritis. The operations were undertaken by the same surgeon without pre-medication and with the anaesthetics propofol and isoflurane. The patients were bed-bound on the day of surgery (day 0) and gradually mobilized thereafter. They received antibiotics (flucloxacillin or cefotaxime on day 0) and analgesics (morphine, diamorphine on day 0 and coproxamol or paracetamol subsequently). Two subjects received antiemetics (metoclopramide) on the day of surgery (day 0) and one subject was treated with warfarin.

The protocol was approved by the Local Research Ethics Committee, and written informed consent was obtained from all the subjects before entry into the study.

Dietary assessment

Pre-operative food intake was assessed by a dietitian using 24 h dietary recall. Post-operatively, daily dietary intake was assessed using food record charts, on the day of surgery and for five subsequent days.

Hunger

At the end of each day, the patients were asked to summarize their overall hunger experienced during the day, by choosing one of four categories: 'not at all hungry', 'slightly hungry', 'moderately hungry', and 'very hungry'. This was carried out pre-operatively, on the day of surgery, and for 5 days after surgery.

Bloods

Venous blood was taken at 7.30 hours after an overnight fast (10 to 12 h) on day 0 (pre-operatively) and on days 1, 2, 3, 5 and 8 after surgery. Blood was kept on ice until centrifugation at 4°C and the plasma was stored at −80°C until analysis for the following: leptin (human leptin RIA kit, Linco Research Inc, St. Louis, MO, U.S.A., within assay coefficient of variation 3.4–8.3%, between assay coefficient of variation 3.0–6.2%); albumin (immunoturbimetric kit, Dako, High Wycombe, U.K.); C-reactive protein (CRP) (ELISA kit, Dako); alpha-1-antichymotrypsin (ACT) (immunoturbimetric kit; Dako); creatinine (Jaffé reaction); cortisol (Incstar, Wokingham, U.K.), insulin (Incstar); metabolites glucose, 3-hydroxybutyrate and glutamine, following the methodology of Khan et al. [12]; and non-esterified fatty acids (Wako NEFA-C kit, Alpha Laboratories, Eastleigh, Hants., U.K.).

Anthropometry

Apart from weight and height, measurements of four skin-fold thicknesses (triceps, biceps, suprailiac and subscapular) were obtained, using the method of Durnin and Womersley [13] to calculate percentage body fat.

Statistical analysis

Analysis of variance and Student's paired t-test were applied to normally distributed data, which in the case of leptin and CRP required log transformation to normalize a positively skewed frequency distribution. Values for leptin are presented as geometric means+SEM (the antilog of the 'mean of logged data +1 SE of logged data') as well as the measured ranges of leptin concentrations. CRP concentrations are presented as geometric means+SD (the antilog of the 'mean of logged data +1 SD of logged data') in Table 1.

Food intake data analysis

Food intake data was analysed using the Dunn Nutrition Laboratory's nutritional analysis programme, based on McCance and Widdowson's The Composition of Foods [14].

RESULTS

Figure 1 (top) shows the changes in leptin concentrations from pre-operative levels (day 0) to those after hip surgery. The highest leptin concentrations were observed on day 1 [9.16 ng/ml+4.34 ng/ml (geometric mean+SEM), measured range 2.67–37.1 ng/ml], 56% higher than those observed before surgery on day 0 (6.07 ng/ml+2.44 ng/ml, measured range 1.87–23.8 ng/ml, P<0.009). The extent to which the circu-
Leptin, energy intake and hunger post-surgery

Table 1. Pre- (day 0) and post-operative (days 1–8) circulating concentrations (means ± SD; n = 6) of glucose, glutamine, non-esterified fatty acids (NEFA), 3-hydroxybutyrate, albumin, CRP, ACT, creatinine, insulin and cortisol. Statistically significant by *analysis of variance (all values P < 0.01) and †paired t-test (day 0 and day 1) (all values P < 0.05). ‡CRP geometric mean ± SD (see text), n = 5.

<table>
<thead>
<tr>
<th>Analyte (reference range)</th>
<th>Day 0 (before surgery)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (4–7 mmol/l)†</td>
<td>6.4±0.3</td>
<td>8.8±0.9</td>
<td>7.8±2.0</td>
<td>7.1±0.8</td>
<td>6.6±0.3</td>
<td>6.4±0.4</td>
</tr>
<tr>
<td>Glutamine (450–700 µmol/l)††</td>
<td>484±38</td>
<td>324±155</td>
<td>362±50</td>
<td>387±48</td>
<td>422±53</td>
<td>433±24</td>
</tr>
<tr>
<td>NEFA (150–890 µmol/l)</td>
<td>579±138</td>
<td>693±284</td>
<td>632±124</td>
<td>596±170</td>
<td>501±150</td>
<td>377±137</td>
</tr>
<tr>
<td>3-Hydroxybutyrate (&lt;200 µmol/l)†</td>
<td>115±70</td>
<td>116±30</td>
<td>161±34</td>
<td>121±113</td>
<td>69±49</td>
<td>65±31</td>
</tr>
<tr>
<td>Albumin (30–50 g/l)†</td>
<td>34.9±3.9</td>
<td>29.3±1.4</td>
<td>27.5±2.5</td>
<td>26.5±2.8</td>
<td>27.2±1.7</td>
<td>28.1±1.7</td>
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<tr>
<td>CRP (&lt;6 mg/l)††</td>
<td>1.6±1.4</td>
<td>33.5±11.7</td>
<td>79.4±35.6</td>
<td>83.2±67.8</td>
<td>45.7±43.4</td>
<td>20.0±37.5</td>
</tr>
<tr>
<td>ACT (&lt;0.6 g/l)†††</td>
<td>0.4±0.2</td>
<td>0.5±0.2</td>
<td>0.7±0.2</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Creatinine (&lt;0.125 mmol/l)</td>
<td>0.10±0.01</td>
<td>0.10±0.01</td>
<td>0.10±0.02</td>
<td>0.10±0.02</td>
<td>0.10±0.02</td>
<td>0.11±0.02</td>
</tr>
<tr>
<td>Insulin (&lt;25 units/ml)†</td>
<td>8.55±3.6</td>
<td>21.0±8.5</td>
<td>12.8±3.2</td>
<td>15.8±5.3</td>
<td>13.3±3.8</td>
<td>14.2±4.4</td>
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<tr>
<td>Cortisol (193–690 nmol/l)†††</td>
<td>479±101</td>
<td>686±171</td>
<td>487±224</td>
<td>619±157</td>
<td>490±204</td>
<td>468±81</td>
</tr>
</tbody>
</table>

Fig. 1. Pre- and post-operative changes in: plasma leptin concentrations (geometric means ± SEM) (top); daily energy intakes (MJ/day) (means ± SEM) (middle); hunger (absence of hunger) (bottom). Leptin concentrations were obtained at the beginning of each day (values on day 0 are pre-operative), and energy intakes and hunger represent values for the whole day.

Circulating leptin concentrations (log-transformed data) increased after surgery (day 1) tended to relate to basal leptin concentrations, but this was not significant. For the remainder of the post-operative period leptin concentrations were not significantly elevated above baseline (P = 0.36). No significant relationship was demonstrated between pre-operative leptin concentrations and percentage body fat.

Patients were fasted before hip surgery and ate virtually no food during the first 24 h after surgery [mean intake 0.62 MJ ± 0.6 MJ (mean ± SEM), n = 6]. Mean energy intake gradually increased thereafter, but overall the post-operative intake did not exceed 56% of the pre-operative intake (P < 0.01). (Fig. 1, middle). Furthermore, the mean intake during the first five post-operative days was not even sufficient to meet basal energy expenditure (predicted basal metabolic rate based on weight and height [15], plus 10% following total hip replacement [16]).

The reduction in post-operative energy intake is reflected by the changes in the subjective feelings of hunger. The numbers of patients with 'no hunger' progressively decreased during the post-operative recovery period (Fig. 1, bottom).

Circulating glucose concentrations increased (P < 0.01) and glutamine concentrations decreased (P < 0.01) significantly after surgery. Changes in non-esterified fatty acids and 3-hydroxybutyrate were variable and not significant, presumably because the effect of starvation in increasing their concentrations was counteracted by the effect of injury [17]. Creatinine concentrations were essentially unchanged throughout the study. After surgery there was a substantial positive acute-phase protein response [increased CRP (P < 0.001) and ACT (P < 0.02)], associated with hypoalbuminaemia (P < 0.01), and significant elevation in insulin and cortisol concentrations (P < 0.05) on day 1 compared with pre-operative values on day 0 (see Table 1). The increments in leptin concentration (log-transformed data) between day 0 (pre-operative) and day 1 (post-operative) were significantly related to the increase in insulin concentrations (r = 0.82, P < 0.05)
observed over the same period, but not to the increase in cortisol concentrations.

**DISCUSSION**

As far as we are aware, this is the first study reporting longitudinal measurements of circulating leptin concentrations in relation to food intake and hunger sensations in patients undergoing elective surgical trauma. The surgery produced a positive acute-phase protein response (elevated CRP and ACT), hypoalbuminemia, hyperglycaemia and reduced circulating glutamine concentrations, typical of moderately severe surgical trauma. This study provides new information that suggests that leptin is involved in the acute-phase response, but the changes are short-lived. The highest recorded value (and the only mean value higher than the pre-operative value) was on day 1, but since multiple measurements were not made during the first 24 h it is not possible to identify the exact time of the peak. At this time plasma creatinine levels did not suggest any impairment in the excretory function of the kidneys, a major site of leptin removal in animals [18]. The short-lived nature of the leptin response is probably partly due to the confounding effects of reduced food intake (virtually total starvation during the first 24 h). In a study involving 24 h starvation, the total circulating leptin concentration decreased by more than half in lean subjects and by a little less than half in the obese [19]. Another study reported a 64% decline in leptin levels in normal-weight subjects after 24 h of fasting [20]. Since our subjects starved almost completely during the first 24 h after surgery, they would also be expected to reduce their circulating leptin concentration. Therefore, the significant increase observed on day zero underestimates the effect of surgery on the circulating leptin concentration.

Typically, if the hypothalamus senses the total circulating leptin concentration and responds by altering food intake, this would suggest that other factors are likely to be involved in the post-operative anorexia, since energy intake remained low after the first 24 hours when the mean leptin concentrations were not elevated above pre-operative values. However, the magnitude and duration of any anorectic effects produced by acute elevations in leptin concentration similar to those observed in the present study, are unknown.

Concentrations of metabolites, such as glucose, non-esterified fatty acids and 3-hydroxybutyrate [2], as well as cytokines and hormones, have been suggested to influence food intake, but of the metabolites measured only glucose was significantly elevated in the first 24 h. Cortisol (which responds to pain and stress) and insulin concentrations were elevated on day one after surgery, and may have contributed to the rise in circulating leptin which also occurred at this time. However, many of the studies suggesting stimulatory effects were undertaken with supraphysiological doses of hormones [21–23], and in the case of insulin, prolonged administration (up to 72 h) was necessary to demonstrate an effect [21]. Therefore the significance of these observations to our findings is uncertain. In addition, glucocorticoids [24] and insulin [2] have been suggested to stimulate appetite, in contrast to leptin which is implicated in appetite suppression.

The conclusion that circulating leptin concentrations are only transiently elevated during the first 24 h after ‘injury’, whereas anorexia persists on subsequent days, is supported by an animal model of ‘injury’ which involves formation of aseptic abscesses (G. Jennings and M. Elia, unpublished work). However, other human studies have been unable to demonstrate a change in leptin concentration during an acute-phase response. Grunfeld et al. [25] compared single cross-sectional measurements of leptin in patients with acquired immunodeficiency syndrome suffering from acute secondary infections. However, the exact timing of blood sampling during the phase of the infection was not defined, and the variation in leptin concentration and body composition was so large in both the patient and control groups of subjects that possible changes due to infection could be difficult to identify. Our findings suggest a possible role for leptin early in post-operative anorexia, although other mediators are likely to be involved. However, to elucidate the role of leptin more fully it is necessary to undertake further studies in patients with different types and severity of ‘injury’ and demonstrate the extent to which increments in leptin concentration, similar to those observed after injury, reproduce the post-traumatic anorexia.

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**REFERENCES**


