

# Serum leptin levels and their response during laparoscopic and open cholecystectomy

Anastasios J. Karayiannakis<sup>1</sup>, Byron Asimakopoulos<sup>2</sup>, Anna Efthimiadou<sup>2</sup>,  
Alexandra K. Tsaroucha<sup>1</sup>, Alexandros Polychronidis<sup>1</sup>, Constantinos Simopoulos<sup>1</sup>

<sup>1</sup> Second Department of Surgery, Democritus University of Thrace, Medical School, 6 I. Kaviri Street, 68100 Alexandroupolis, Greece

<sup>2</sup> Department of Physiology, Democritus University of Thrace, Medical School, Alexandroupolis, Greece

**Correspondence :** Anastasios J. Karayiannakis  
<akarayan@usa.net>

**ABSTRACT.** We compared serum leptin responses during and after laparoscopic and open cholecystectomy, and assessed their correlation with the responses of inflammatory cytokines. Serum levels of leptin, interleukin-1 $\alpha$  (IL-1 $\alpha$ ), interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured by an enzyme-linked immunoassay in 31 patients who underwent laparoscopic cholecystectomy and in 24 patients who underwent open cholecystectomy. Serum samples were obtained preoperatively, at 10 and 30 min after the commencement of surgery, and at 6 and 24 h after the operation. The cumulative responses of leptin, IL-1 $\alpha$ , IL-6 and TNF- $\alpha$  to surgery were calculated and the associations between them were evaluated. Serum leptin levels were significantly increased at 24 h after both procedures. The serum leptin concentration at this time point and the cumulative leptin response were significantly lower after laparoscopic cholecystectomy than after open cholecystectomy. Changes in serum IL-1 $\alpha$ , TNF- $\alpha$  and IL-6 concentrations showed similar kinetics in both groups, with postoperative IL-6 levels being consistently lower in the laparoscopic cholecystectomy group. Cumulative IL-6 and TNF- $\alpha$  responses were significantly lower after laparoscopic cholecystectomy than after open cholecystectomy. The cumulative responses of leptin, IL-1 $\alpha$  and IL-6 correlated significantly with each other. Leptin may be involved in the systemic inflammatory response to surgical injury, and the postoperative leptin elevation and cumulative leptin response are significantly lower after laparoscopic cholecystectomy than after open cholecystectomy.

**Keywords:** leptin, laparoscopic cholecystectomy, stress response, inflammatory response, surgery

Human leptin, the product of the *ob* gene, is a non-glycosylated polypeptide containing a 146 amino-acid residue [1, 2]. Leptin is produced mainly in the adipose tissue. It was initially thought to play an important role in appetite control and in the regulation of body weight by targeting the central nervous system, particularly the hypothalamus. Subsequent studies, however, have demonstrated that its effects must be more complicated than simple appetite regulation, and have assigned a role for leptin as a multi-potent cytokine implicated in the regulation of systemic inflammatory and immune responses. Exogenous administration of leptin upregulates both phagocytosis and the expression of proinflammatory cytokines in intact, genetically obese rodents [3]. Conversely, administration of interleukin-1 (IL-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and bacterial endotoxin has been shown to increase leptin gene expression in the adipose tissue and circulating leptin levels in fasted mice and hamsters [4, 5]. In addition, elevated serum levels of leptin have been demonstrated during surgical stress [6-9] and acute sepsis [10] and after the administration of interleukin-1 $\alpha$  (IL-1 $\alpha$ ) and TNF- $\alpha$  in humans [11, 12], thus providing evidence that leptin is implicated in the acute-phase or stress response. Laparoscopic cholecystectomy has nowadays replaced the open procedure for the treatment of symptomatic

cholelithiasis. The laparoscopic procedure is both standardized and reproducible, and is associated with a minimal impact on human physiology and a better clinical outcome than the open procedure. In addition, previous studies have shown that the systemic inflammatory and neuroendocrine stress responses, as measured by the cytokine, cortisol and catecholamine responses, are significantly lower after laparoscopic cholecystectomy than after open cholecystectomy [13-15].

In this study, we evaluated serum leptin levels and their response during and after laparoscopic and conventional open cholecystectomy. Serum levels of a range of inflammatory cytokines including IL-1 $\alpha$ , interleukin-6 (IL-6), and TNF- $\alpha$  during and after surgery were also measured, and their responses correlated with the cumulative leptin response.

## PATIENTS AND METHODS

### Patients

This study involved 31 patients with uncomplicated, symptomatic cholelithiasis, who underwent elective laparoscopic cholecystectomy, and 24 patients who underwent open cholecystectomy and who served as the control

group. Twelve of the control patients underwent open surgery directly because it was considered either technically impossible or too dangerous to attempt laparoscopy due to previous major gastric surgery ( $n = 3$ ), previous surgery for abdominal aortic aneurysm ( $n = 4$ ), or previous mesh repair of ventral hernias ( $n = 5$ ). The remaining 12 control patients were initially scheduled for laparoscopic cholecystectomy. However, after the creation of the pneumoperitoneum and the insertion of the laparoscope, evaluation of the abdominal cavity revealed adhesions that either prevented adequate visualization or provided inadequate access to the operative field, and hence performing laparoscopic cholecystectomy was considered unsafe. In these cases, the pneumoperitoneum was released soon after its initiation (less than 5 min in all cases) and an open procedure was performed. The time of skin incision for the open procedure served as a baseline time point for subsequent intraoperative serum sampling. None of these patients was suffering from acute cholecystitis (confirmed histologically). Patients with endocrine, metabolic, hepatic, or renal disease, morbid obesity (body mass index greater than  $40 \text{ kg/m}^2$ ), and those receiving medications known to interfere with hormonal responses to stress (such as corticosteroids, immunosuppressive and nonsteroidal anti-inflammatory drugs, and drugs affecting the sympathetic nervous system) were excluded from the study. The study was performed in accordance with the Helsinki Declaration and all patients gave their consent for blood sampling after the aim of the study was fully explained to them.

All patients were operated on a standardized regime of general anesthesia at the same time of day (09:00 hours), after an overnight fast. Anesthesia was induced with fentanyl ( $2 \mu\text{g/kg}$ ) and thiopentone ( $5 \text{ mg/kg}$ ), and was maintained with isoflurane (1%) in a mixture of nitrous oxide (60%) and oxygen (40%), fentanyl, and pancuronium. Laparoscopic cholecystectomy was performed using a typical four-trocar technique. Carbon dioxide was used for peritoneal insufflation with the intraabdominal pressure maintained at 12 mmHg. During the study period, all patients received only intravenous Ringer's solution for fluid replacement, antibiotic prophylaxis (cefotaxime), and low-molecular-weight heparin (nadroparine). Patients were started on clear liquids at 24 h postoperatively after serum sampling.

#### **Blood samples and assays**

Blood samples were taken through an indwelling catheter inserted into a forearm vein at 08:00 hours on the day of surgery before premedication, at 10 and 30 min after the start of surgery, and at 6 and 24 h after surgery (08:00 hours). Blood samples were centrifuged and serum was stored at  $-70^\circ\text{C}$  until assayed.

Serum leptin levels were determined using a commercial available enzyme-linked immunoassay (ELISA) designed to measure soluble human leptin concentrations in cell culture supernatant, serum, and plasma (Quantikine, R&D Systems, Minneapolis, MN, USA). This assay has a threshold sensitivity of less than  $7.8 \text{ pg/mL}$ . Serum IL-1 $\alpha$ , IL-6 and TNF- $\alpha$  concentrations were also measured by commercial ELISA kits (Quantikine), whose sensitivities

were  $1 \text{ pg/mL}$ ,  $0.7 \text{ pg/mL}$  and  $0.18 \text{ pg/mL}$ , respectively. Optical densities were measured at 450 nm, with wavelength correction set to 540 nm using a microtiter plate reader (MR 5000, Dynatech Laboratories, Chantilly, VA, USA). Standard curves were generated, from which protein concentrations were calculated.

All assays were run in the same batch. All samples were assayed in duplicate, and the average value was used for the calculation of results. An investigator, who was blinded to the nature of the study and clinical details, performed all assays.

#### **Statistical analysis**

Statistical analysis was performed using the SPSS statistical software package. The distributions of the data were found to be not normally distributed, and hence all data values are presented as medians and interquartile ranges, with nonparametric analyses being employed to assess statistically significant differences. Within-group differences were evaluated using the Friedman related-samples analysis of variance, followed by the Wilcoxon signed test for paired data. Differences between groups were evaluated by the Mann-Whitney test. The area under the curve (AUC; calculated by the trapezoidal rule) was used to quantify the cumulative response to surgery, as suggested by Altman [16]. Correlations were evaluated using the Spearman rank test. All tests were two-tailed with statistical significance set at  $P < 0.05$ .

## **RESULTS**

Patient characteristics, preoperative serum leptin, IL-1 $\alpha$ , IL-6 and TNF- $\alpha$  levels, anesthesia and operating time were similar between the two study groups (*table 1*). Preoperative routine laboratory tests (hemoglobin, hematocrit, leukocytes, platelets, glucose, urea, creatinine, sodium, potassium, direct and total bilirubin, aspartate and alanine aminotransferases, gamma-glutamyl transpeptidase, alkaline phosphatase, and amylase) were all normal and did not differ significantly between the two groups, and are not reported here. There were no postoperative complications during the study period. Blood loss was minimal in both groups, with no transfusions being required. None of the patients had a postoperative temperature  $> 37.8^\circ\text{C}$  during the observation period.

Serum leptin levels progressively increased to reach peak values at 24 h after both laparoscopic ( $7.91 (4.53-18.93) \text{ ng/mL}$ ) and open ( $18.93 (10.19-52.61) \text{ ng/mL}$ ) cholecystectomy, with the levels being significantly higher than their corresponding preoperative values (*figure 1A*). Serum leptin concentrations at 24 h were significantly lower ( $P = 0.001$ ) after laparoscopic cholecystectomy than after open cholecystectomy.

Serum IL-1 $\alpha$  concentrations showed similar kinetics in both groups. The highest values were observed at 30 min after the beginning of surgery ( $0.21 (0.08-1.03) \text{ pg/mL}$  for laparoscopic and  $0.3 (0.081-1.01) \text{ pg/mL}$  for open cholecystectomy), and these were significantly higher than the preoperative values (*figure 1B*). Thereafter they fell progressively and returned to preoperative values on the first postoperative day in both groups. There was no significant difference between the two groups at any time point.

**Table 1**  
Preoperative clinical details of patients undergoing laparoscopic or open cholecystectomy

	LC (n = 31)	OC (n = 24)	P Value*
Age (years)	53 (43-61)	60 (49-73)	0.11
Gender (M/F)	17/14	13/11	1.0†
BMI (kg/m <sup>2</sup> )	25.88 (23.14-27.77)	23.85 (21.12-26.90)	0.07
Leptin (ng/mL)	5.29 (2.22-8.18)	4.92 (2.19-10.23)	0.91
IL-1 $\alpha$ (pg/mL)	0.14 (0.02-0.52)	0.09 (0.02-0.36)	0.83
IL-6 (pg/mL)	2.88 (1.90-7.72)	5.02 (3.37-6.80)	0.11
TNF- $\alpha$ (pg/mL)	2.90 (2.76-3.27)	2.89 (2.41-3.28)	0.66
Operative time (min)	60 (45-80)	65 (45-79)	0.91
Anesthesia time (min)	70 (60-90)	78 (56-90)	0.74

Values are median (interquartile range). LC: laparoscopic cholecystectomy; OC: open cholecystectomy; BMI: body mass index; IL-1 $\alpha$ : interleukin-1 $\alpha$ ; IL-6: interleukin-6; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ . \* Mann-Whitney test except as noted. † Fisher's exact test.

The serum IL-6 level had increased significantly at 30 min after the commencement of surgery and remained elevated throughout the study period in both groups (figure 1C). During the postoperative period, serum IL-6 levels were significantly lower after laparoscopic cholecystectomy than after open cholecystectomy.

The serum TNF- $\alpha$  level had increased significantly compared to preoperative values at 6 h after surgery in both groups (figure 1D). There was no statistically significant difference ( $P = 0.095$ ) in TNF- $\alpha$  levels at this time point between laparoscopic cholecystectomy (3.67 (3.15-4.85) pg/mL) and open cholecystectomy (4.68 (3.56-6.30) pg/mL).

The cumulative responses (as estimated by the AUC determinations) of leptin, IL-6, and TNF- $\alpha$  were significantly lower after laparoscopic cholecystectomy than after open cholecystectomy (5.89 (3.68-14.21) ng/mL versus 13.63 (7.42-23.08) ng/mL, 30.14 (26.9-35.13) pg/mL versus 54.38 (35.52-70.55) pg/mL, and 3.34 (2.64-4.14) pg/mL versus 3.89 (3.19-4.51) pg/mL, respectively). There was no significant difference in the cumulative IL-1 $\alpha$  response between laparoscopic and open cholecystectomy (0.10 (0.05-0.54) pg/mL versus 0.12 (0.04-0.49) pg/mL, respectively;  $P = 0.95$ ). The cumulative response of leptin correlated significantly with both IL-1 $\alpha$  and IL-6 responses. There was also a significant association between IL-1 $\alpha$  and IL-6 responses (table 2). These associations were evident when correlation analysis was applied to the entire study population, and remained valid in both laparoscopic and open cholecystectomy subgroups.

## DISCUSSION

This report describes perioperative changes in serum leptin levels after laparoscopic cholecystectomy and after open cholecystectomy. The serum leptin concentration was significantly elevated at 24 h after both procedures, but was lower after laparoscopic cholecystectomy than after open cholecystectomy. The cumulative response of leptin to surgery correlated significantly with both IL-1 $\alpha$  and IL-6 responses, and was significantly lower after laparoscopic cholecystectomy than after open cholecystectomy.

Leptin is produced by adipose tissue, and circulating leptin levels have a diurnal pattern with the lowest values observed in the morning (around 09:00-10:00 hours) and with a peak occurring around midnight [17, 18]. These levels are also influenced by food intake, with short-term (24-72 h) fasting resulting in a large reduction in plasma

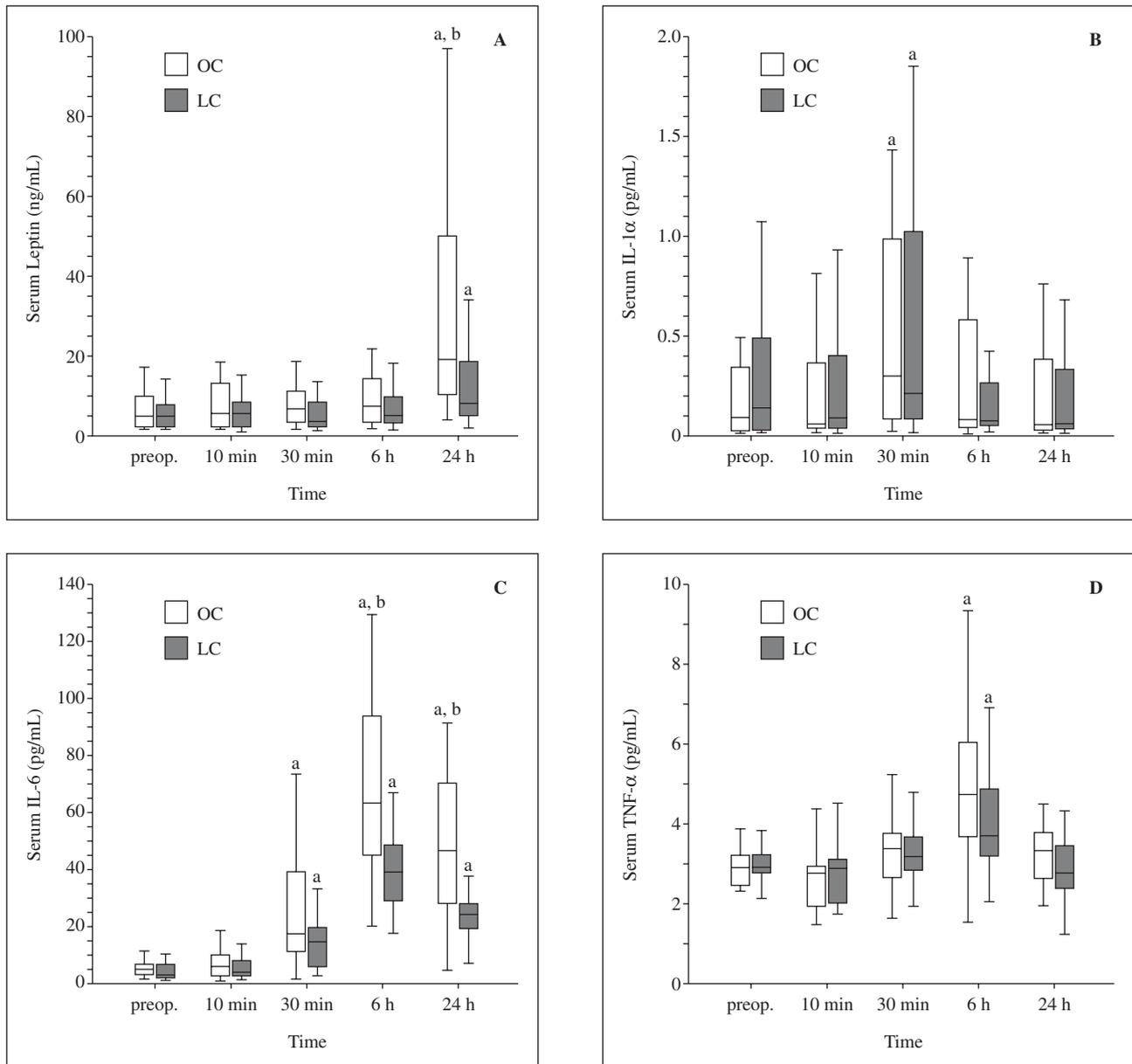
leptin concentrations in both normal-weight and obese subjects [18, 19]. Our study was limited to a 24-h follow-up period because of the early discharge of patients undergoing laparoscopic cholecystectomy. All patients were fasting for this period and receiving only intravenous fluid replacement whereas baseline and end-point serum samplings were taken at the same time of the day (08:00 hours). The highest serum leptin levels were reached in the morning of the first postoperative day, when reduced levels would have been expected. Thus, the significant increase observed at that sampling point might underestimate the impact of surgery on circulating levels of leptin, although disturbance of diurnal leptin rhythmicity during and/or after surgery cannot be excluded. Nevertheless, serum leptin concentrations at 24 h postoperatively as well as the cumulative leptin response to surgery were significantly lower after laparoscopic cholecystectomy than after open cholecystectomy. This finding provides further evidence that laparoscopic cholecystectomy has a reduced impact on human physiology compared with open cholecystectomy.

Previous studies have shown similar changes to ours in circulating leptin levels after different types of surgery. Stratton *et al.* [8] measured circulating leptin concentrations up to the eighth postoperative day in six patients undergoing elective total hip replacement, and detected significantly increased leptin concentrations only on the first postoperative day (a 56% increase compared with preoperative values). Kain *et al.* [6] measured plasma leptin levels in 21 women before, during, and after total abdominal hysterectomy. They reported that leptin levels were maximally decreased at 2 h after surgery, which was

**Table 2**  
Associations between cumulative responses (AUC) of leptin, IL-1 $\alpha$ , IL-6 and TNF- $\alpha$  in the entire study population

	Leptin	IL-1 $\alpha$	IL-6
IL-1 $\alpha$	$r = 0.80$ $P < 0.001$		
IL-6	$r = 0.81$ $P < 0.001$	$r = 0.52$ $P < 0.001$	
TNF- $\alpha$	$r = 0.20$ $P = 0.14$	$r = 0.029$ $P = 0.83$	$r = 0.23$ $P = 0.09$

AUC: area under curve; IL-1 $\alpha$ : interleukin-1 $\alpha$ ; IL-6: interleukin-6; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ .  $r$  Spearman's rank correlation coefficients.



**Figure 1**

Changes in serum concentrations of **A)** leptin, **B)** IL-1α, **C)** IL-6, **D)** TNF-α during and after laparoscopic and open cholecystectomy. LC: laparoscopic cholecystectomy; OC: open cholecystectomy. The data represent the median value, the interquartile range (box plots) and the absolute range (whiskers) of values. <sup>a</sup> Statistically significant differences vs. preoperative values. <sup>b</sup> Statistically significant differences, laparoscopic vs. open cholecystectomy.

followed by an increase to just above preoperative values at 24 h postoperatively. Wallace *et al.* [9] studied serum leptin changes in nine patients receiving an elective mini-laparotomy cholecystectomy, and detected that leptin levels peaked at 18 h after surgery. These discrepancies in the peak leptin levels may be related to differences in study populations and methods of leptin evaluation, different grades of surgical injury, and different sampling times. Laparoscopic cholecystectomy has nowadays replaced the open procedure for the treatment of cholelithiasis. Hence, ethical considerations make it impossible to perform a randomized study. In the present study, the control group consisted of patients in whom open cholecystectomy was undertaken for safety-related reasons or in whom laparoscopic cholecystectomy was converted early to an open procedure again for safety reasons. Consequently, statistical analysis was performed on a treatment-received basis

rather than on an intention-to-treat basis. In the laparoscopic cholecystectomy group, the first sampling point (10 min after skin incision) reflected in fact, the creation of the pneumoperitoneum, whereas the second sampling point (at 30 min) corresponded in most cases to the dissection of the cystic pedicle. Serum leptin levels at the 30-min time point showed a mild decrease compared with preoperative values (3.62 (2.21-8.84) ng/mL *versus* 5.29 (2.22-8.18) ng/mL, respectively) although the difference was not statistically significant. Pneumoperitoneum-related abdominal distention has been suggested to be a stimulus for the sympathetic stress response [15], but the effect of pneumoperitoneum (if any) on leptin release is currently unknown. Despite these methodological constraints, this study still demonstrates that the postoperative increase in serum leptin levels and its cumulative response were

smaller after laparoscopic cholecystectomy than after open cholecystectomy.

In our study, the changes in serum IL-1 $\alpha$ , TNF- $\alpha$  and IL-6 concentrations showed similar kinetics in both groups, with postoperative IL-6 levels being consistently lower after laparoscopic than after open cholecystectomy. The cumulative IL-6 and TNF- $\alpha$  responses to laparoscopic cholecystectomy were also significantly lower compared to those after open cholecystectomy. IL-6 is the major mediator of the systemic stress response, with serum IL-6 levels reflecting the grade of surgical injury and the severity of the acute phase response [20, 21]. Several cytokines, including IL-1 $\alpha$ , IL-6, and TNF- $\alpha$  have been shown to induce leptin expression and to increase circulating leptin levels in rodents [4, 5] and humans [11, 12]. A positive association between the circulating levels of leptin and soluble TNF- $\alpha$  receptor, which has been validated as a sensitive indicator of activation of the TNF- $\alpha$  system, has been reported in both diabetics and healthy subjects [22]. In our study, the peaks in IL-1 $\alpha$ , IL-6, and TNF- $\alpha$  levels preceded the leptin peak by approximately 18 h. Furthermore, the cumulative responses of leptin, IL-1 $\alpha$ , and IL-6 correlated significantly with one another. These findings suggest that elevations in leptin and cytokine are coordinated during the systemic inflammatory stress response. However, since the mechanism of the induction of leptin release by cytokines is at present unclear, a potential role of individual cytokines in modifying leptin secretion and its circulating level is speculative, at best. Experimental studies have provided evidence of a direct action of cytokines on fat cells, resulting in leptin release from an existing pool [23, 24]. However, the existence of a paracrine or autocrine mechanism for cytokine-stimulated leptin secretion cannot be excluded. Alternatively, cytokines can act indirectly through activation of the hypothalamic-pituitary-adrenal axis and subsequent elevation of serum glucocorticosteroid levels, which are capable of stimulating leptin expression, and secretion as has been shown in both animal models and humans [25-27]. In this context, the reduced neuroendocrine stress response after laparoscopic cholecystectomy [13-15] may explain our findings of lower serum leptin concentrations at 24 h and a lower cumulative leptin response after laparoscopic cholecystectomy than after open cholecystectomy.

In conclusion, this study has revealed that the serum leptin concentration is significantly elevated at 24 h after both laparoscopic and open cholecystectomy. The leptin level at this time point and its cumulative response was lower after laparoscopic cholecystectomy than after open cholecystectomy. The cumulative responses of leptin, IL-1 $\alpha$ , and IL-6 to surgery correlated significantly with each other, which suggests a role for leptin in the systemic inflammatory response to surgical injury.

## REFERENCES

1. Cohen SL, Halaas JL, Friedman JM, *et al.* Human leptin characterization. *Nature* 1996; 382: 589.
2. Green ED, Maffei M, Braden VV, *et al.* The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome 7. *Genome Res* 1995; 5: 5.
3. Loffreda S, Yang SQ, Lin HZ, *et al.* Leptin regulates proinflammatory immune responses. *FASEB J* 1998; 12: 57.

4. Grunfeld C, Zhao C, Fuller J, *et al.* Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *J Clin Invest* 1996; 97: 2152.
5. Sarraf P, Frederick RC, Turner EM, *et al.* Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *J Exp Med* 1997; 185: 171.
6. Kain ZN, Zimolo Z, Heninger G. Leptin and the perioperative neuroendocrinological stress response. *J Clin Endocrinol Metab* 1999; 84: 2438.
7. Moses AG, Dowidar N, Holloway B, Waddell I, Fearon KC, Ross JA. Leptin and its relation to weight loss, ob gene expression and the acute-phase response in surgical patients. *Br J Surg* 2001; 88: 588.
8. Stratton RJ, Dewit O, Crowe E, Jennings G, Villar RN, Elia M. Plasma leptin, energy intake and hunger following total hip replacement surgery. *Clin Sci* 1997; 93: 113.
9. Wallace AM, Sattar N, Mcmillan DC. The co-ordinated cytokine/hormone response to acute injury incorporates leptin. *Cytokine* 2000; 12: 1042.
10. Bornstein SR, Licinio J, Tauchnitz R, *et al.* Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm, in cortisol and leptin secretion. *J Clin Endocrinol Metab* 1998; 83: 280.
11. Janik JE, Curti BD, Considine RV, *et al.* Interleukin 1 $\alpha$  increases serum leptin concentrations in humans. *J Clin Endocrinol Metab* 1997; 82: 3084.
12. Zumbach MS, Boehme MW, Wahl P, Stremmel W, Ziegler R, Nawroth PP. Tumor necrosis factor increases serum leptin levels in humans. *J Clin Endocrinol Metab* 1997; 82: 4080.
13. Glaser F, Sannwald GA, Buhr HJ, Kuntz C, Mayer H, Klee F, *et al.* General stress response to conventional and laparoscopic cholecystectomy. *Ann Surg* 1995; 221: 372.
14. Karayiannakis AJ, Makri GG, Mantzioka A, Karousos D, Karatzas G. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg* 1997; 84: 467.
15. Mealy K, Gallagher H, Barry M, Lennon F, Traynor O, Hyland J. Physiological and metabolic responses to open and laparoscopic cholecystectomy. *Br J Surg* 1992; 79: 1061.
16. Altman DG. Serial measurements. In: Altman DG, ed. *Practical statistics for medical research*. London: Chapman & Hall, 1991: 426.
17. Schoeller DA, Cella LK, Sinha MK, Caro JF. Entrainment of the diurnal rhythm of plasma leptin to meal timing. *J Clin Invest* 1997; 100: 1882.
18. Weigle DS, Duell PB, Connor WE, Steiner RA, Soules MR, Kujper JL. Effect of fasting, refeeding, and dietary fat restriction on plasma leptin levels. *J Clin Endocrinol Metab* 1997; 82: 561.
19. Boden G, Chen X, Mozzoli M, Ryan I. Effect of fasting on serum leptin in normal human subjects. *J Clin Endocrinol Metab* 1996; 81: 3419.
20. Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci* 1990; 79: 161.
21. Henrich CA, Cannon JG, Wolff JM. Interleukin 6 and the acute phase protein response. *Biochem J* 1990; 265: 621.
22. Mantzoros CS, Moschos S, Avramopoulos I, *et al.* Leptin concentrations in relation to body mass index and the tumor necrosis factor- $\alpha$  system in humans. *J Clin Endocrinol Metab* 1997; 82: 3408.
23. Granowitz EV. Transforming growth factor- $\beta$  enhances and proinflammatory cytokines inhibit ob gene expression in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 1997; 240: 382.

24. Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Tumor necrosis factor- $\alpha$  contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. *J Clin Invest* 1997; 100: 2777.
25. Newcomer JW, Selke G, Melson AK, Gross J, Vogler GP, Dagogo-Jack S. Dose-dependent cortisol-induced increases in plasma leptin concentration in healthy humans. *Arch Gen Psychiatry* 1998; 55: 995.
26. Pappaspyrou-Rao S, Schneider SH, Petersen RN, Fried SK. Dexamethasone increases leptin expression in humans in vivo. *J Clin Endocrinol Metab* 1997; 82: 1635.
27. Sliker LJ, Sloop KW, Surface PL, *et al.* Regulation of expression of ob mRNA and protein by glucocorticoids and cAMP. *J Biol Chem* 1996; 271: 5301.

## CORRECTION

In *European Cytokine Network's* last issue (Vol. 15 n° 4, December 2004) please read in the article *Interleukin-7 (IL-7): immune function, involvement in the pathogenesis of HIV infection and therapeutical potential*, by S. Beq, J.F. Delfraissy and J. Theze p. 286 :

**“Acknowledgements.** This review was completed during S.B.'s PhD theses. Jean-Hervé Colle, Nicole Israel and F. Barré-Sinoussi are warmly acknowledged for numerous and critical discussions during this period. The constant support of M. Morre and Cytheris SA has been essential for the realization of that work.”