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The Relationship of IL-6 to Hormonal Mediators, Fuel Utilization, and Systemic Hypermetabolism after Surgical Trauma

外科的侵襲下におけるIL-6とホルモン分泌・栄養基質利用・エネルギー代謝亢進の関連についての臨床的研究

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索引用語：surgical trauma, insulin, glucagon, norepinephrine, IL-6, IL-1, TNF-α, resting energy expenditure, fuel utilization

Title:

The Relationship of IL-6 to Hormonal Mediators, Fuel Utilization, and Systemic Hypermetabolism after Surgical Trauma

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Shortened running title:

IL-6 and Energy Metabolism in Surgical Trauma

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Synopsis

Objective: To define the relationship between inflammatory cytokines, hormonal mediators, alteration of energy substrate and hypermetabolism during the early phase after surgical trauma.

Design: A prospective case-control study of 13 patients underwent elective surgery for carcinoma between November 1993 and January 1995.

Materials and Methods: They received parenteral supply of adequate glucose and amino acids through central venous catheter after surgery equally. Inflammatory cytokines such as TNF-α, IL-1 and IL-6, stress hormones such as norepinephrine, glucagon and insulin, and fuel utilization and hypermetabolism variables such as resting energy expenditure (REE), CRP, free fatty acid, respiratory quotient, the calculated rates of glucose and fat oxidation using indirect calorimetry were measured serially (the day before operation, the end of surgery, and postoperative day (POD)1, 2 and 5).

Measurements and Main Results: TNF-α and IL-1 were not detected during the study period. Initial elevation and steady decline of IL-6 concentrations were seen after surgical injury, and this response related significantly to post-operative norepinephrine and glucagon levels throughout the study period, and to insulin levels only at the end of surgery. %REE (REE/BEE_{HB}; basal energy expenditure according to the Harris-Benedict equation) on POD 2 and 5, and all CRP levels after surgery were significantly related to IL-6 levels more than hormone levels. Fuel utilization variables on POD 2 were related to both IL-6 and hormone levels.

Conclusions: Initial elevation of IL-6 concentration might induce stress hormones such as norepinephrine and glucagon, but not insulin after surgical trauma . Moreover not only hormonal mediators but also cytokine such as IL-6 are responsible for the development of the stress response of the alteration of energy substrate and hypermetabolism.

Ten Key Words: surgical trauma; interleukin-6; interleukin-1; TNF-α; insulin; glucagon; norepinephrine; catecholamines; resting energy expenditure; respiratory quotient

INTRODUCTION

Trauma is followed by activation of host metabolic response, characterized by the appearance of increase of energy expenditure and alterations of fuel utilization (1). Previous studies have demonstrated that the hypermetabolism is proportional to the extent of injury, increases to as much as over 24% above normal levels in patients undergoing major surgery (2, 3). It has been also described decreased oxidative metabolism of glucose despite apparent adequate blood flow and nutrient delivery to the tissue (4), hepatic and peripheral insulin resistance (5), and increased reliance on fat oxidation for energy production extent to stress in post-surgical patients (6). These metabolic changes have been documented extensively by stress-evoked neurohormonal responses, including pronounced elevations in circulating plasma levels of the counterregulatory hormones, such as glucagon, cortisole, growth hormone, and catecholamine (7, 8). However, the metabolic responses reproduced by combined infusion of these hormones, including hypermetabolism, the changes in carbohydrate metabolism and glucose intolerance are generally less compared with the measurements in traumatized patients or critically ill patients (9).

On the other hand, recent experimental studies have implicated cytokines as pivotal mediators of the host metabolic reaction in various illness. Elborn et al. demonstrate resting energy expenditure is significantly related to circulating TNF- α levels in patients with cystic fibrosis and chronic bronchial sepsis (10). A possible association between endogenous TNF- α production and insulin resistance in patients with gastrointestinal cancer has been reported (11). Administration of not only TNF- α but also IL-1 are reported to produce enhanced acute-phase protein synthesis (12), and to alter carbohydrate metabolism (13, 14). The relationship of IL-6 to resting energy expenditure (15) and alteration of glucose and protein metabolism in various tissue (12, 16, 17, 18) has been also described. Furthermore, previous studies have demonstrated that administration of some cytokines such as TNF- α and/or IL-1 in vivo increases the plasma concentration of the counter-regulatory hormones such as glucagon, adrenal glucocorticoids and catecholamines (19, 20, 14). Parallel increases in plasma insulin have been also reported in association with administration of both

cytokines (21, 14). These data suggesting that cytokines may be regarded as major mediators of stress hormones.

Thus, although the increase in energy expenditure and the alteration of fuel utilization are associated with a complex cascade of some cytokines and hormonal alterations in various illness, the network of communication signals mediated by endogenous mediators and metabolite during inflammation and tissue repair of trauma is not defined. Whereas the role of early endogenous mediators of inflammation and metabolic response following trauma has been investigated through the study of surgical patients who undergo a form of programmed trauma, the purpose of the study presented here is to examine the followed issues in patients undergoing elective abdominal surgery; 1) The relationship of inflammatory cytokines such as TNF- α , IL-1 and IL-6, to the hormonal mediators. 2) Which mediator is potential among these cytokines and hormones to the alteration of hypermetabolism and energy substrate.

PATIENTS, MATERIALS AND METHODS

Patients Selection. Five women and eight men aged 52-82 years (66.7 ± 9.5) undergoing elective surgery for carcinoma who gave their informed consent which was approved by the Institutional Review Board were enrolled in this study. The values for patients are listed in Table 1. Patients in whom extensive disease precluded surgical resection, patients with general signs of infection before surgery, and patients with clinical criteria for septicemia following surgery were excluded. Septicemia was defined as the presence of at least three of the following criteria: 1) a decrease in more than 40 mmHg of systolic blood pressure or a systolic blood pressure below 90 mmHg, 2) a decrease in urinary output below 30 ml/hr., 3) a decrease in thrombocyte counts below 100×10^9/L or a decrease in more than 50% of the preoperative value, and 4) a decrease in serum bicarbonate levels below 15mEq/L. These criteria were not applied if they could be explained by a condition other than septicemia. All patients had normal tolerance to oral glucose (22). The patients received similar premedication and anesthetic agents. Surgery was began at 09:00 hour, patients

having been fasted overnight.

Alimentation Protocol. All patients were fasting overnight on the period of preoperative measurement which was 1 or 2day before the operative day. Postoperative nutritional support is shown in Table 2. On the operative day, patients received Ringer's solution without glucose and aminoacids from the end of operation. From 00:00 on the each postoperative day (POD), they received total parenteral nutrition (TPN) at the rate of 80ml/hr of TPN solutions containing 3.1% aminoacids in 8.9% glucose on POD 1, 3.1% aminoacids in 11.7% glucose on POD 2, and 3.1% aminoacids in 15.6% glucose on POD 3,4 and 5.

Collection of Blood. Blood from patient's right femoral artery was collected at the period of the preoperative measurement, at the end of the operation, and at 9:00 AM on POD 1, 2 and 5. Serum and plasma specimens were assayed for their content of IL-6, TNF- α and IL-1 β, insulin, glucagon, norepinephrine, free fatty acid, glucose, and CRP. Blood samples were drawn into syringes, immediately transferred into sterile 10ml glass tubes for assays of cytokine and insulin, into sterile heparinized 5ml tubes for the assay of glucagon , norepinephrine and free fatty acid, and into 5ml tubes with fluoride sodium for the assay of glucose. Then they were centrifuged at 3,000 rpm for ten minutes as soon as possible at 4℃ and supernatant was immediately frozen and kept at -20℃ before assay.

Laboratory methods. Quantitative estimation of serum cytokines was measured with a highly sensitive two-site enzyme-linked immunosorbent assay (ELISA) kit; TNF- α (pg/ml): Otsuka, Tokushima, Japan, IL-1 (pg/ml): Medgenix, Fleurus, Belgium, IL-6(pg/ml): Fujirebio, Tokyo, Japan. The detection limit of the assay is 5pg/ml of TNF- α , 10pg/ml of IL-1 β, and 4pg/ml of IL-6 respectively. Samples below the detection levels were assigned zero value. Serum insulin levels were measured by radioimmunoassay with two-antibody technique (Shionogi, Osaka, Japan, μ U /ml). Plasma glucagon levels were analyzed by radioimmunoassay with two-antibody technique (Daiichi RI ,Tokyo, Japan, pg/ml). Plasma norepinephrine levels were analyzed by high performance liquid chromatography combined with electrochemical detection (23, 24) (pg/ml). Free fatty acid levels were

measured using Eiken NEFA C test kit (Eiken Chemicals, Tokyo, Japan, mEq/l), which utilizes an in vitro enzymatic method. Plasma glucose was determined using in vitro enzymatic method (Hitachi 7150 Autoanalyser, Hitachi, Tokyo, Japan) .

Indirect Calorimetry. A commercially available portable metabolic cart , the RM300 (Minato Medical Science, Osaka, Japan) for indirect calorimetry was used. This device measures the partial pressures of oxygen and carbon dioxide in expired air using a zirconium oxide oxygen analyzer and infra-red carbon dioxide analyzer (25). After calibration, oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory quotient (RQ), and energy expenditure of each patient were measured at the period of the preoperative measurement after an overnight fast, and between 8:00 and 9:00 AM on POD 1, 2 and 5. The patient was at rest and having remained supine from the time of awakening, then connected to the apparatus with a face mask. Equilibrium is reached after the patient has been breathing into the machine for about 4min (26). Observations were continued for up to 10 min whenever possible. Long periods of recording were not often possible with these postoperative patients. Measurements were only made if the patient was inspiring room air. From the rates of oxygen consumption and carbon dioxide output , the resting energy expenditure (REE) was calculated using the van de Weir equation (27). The measured values of REE were related to the standard basal energy expenditure (BEE_{HB}), which was calculated for each patient according to the formula of Harris-Benedict (28), using the patient's usual body weight, height, and age. % resting energy expenditure (%REE) was thus defined as:

$$\%REE\ (\%)=REE\times 100/BEE_{HB}$$

From the rates of oxygen consumption, carbon dioxide output and urinary nitrogen excretion, the rates of glucose and fat oxidation were calculated according to common methods (29). Urinary nitrogen levels were determined by chemiluminescence. The total volume of urine for each 24 hours was measured. The daily excretion of urinary nitrogen was calculated from these data.

Statistical Analysis. Characteristics of the population were described using means, standard deviations, and proportions. Variables including levels of cytokine, norepinephrin, insulin, glucagon,

free fatty acid, glucose, %REE, RQ, the rate of glucose and fat oxidation were represented by means and standard deviations. For examining the relationships between the hormones and cytokines, the values of norepinephrine, glucagon, insulin were chosen as the dependent variables, and postoperative serum IL-6 as independent variables , since other cytokines including IL-1 and TNF- α were not detectable over the study periods. For examining the relationships of cytokines or hormones to the metabolism including hypermetabolism or fuel utilization variables, free fatty acid, RQ, and REE were chosen as the dependent variables, and postoperative serum IL-6, plasma values of norepinephrine, glucagon, insulin as independent variables. A stepwise weighted linear regression was then performed, with the values of perioperative IL-6 or hormones forced to remain in the model using the StadView (Abacus Concepts Inc.) with the personal computer (Macintosh Co. L.T.D.) . The log of values of IL-6 were used in regressions to %REE and RQ, since the log relates to the mean and also removes the skewness of the raw values.

We assigned that there was significant difference when p value was under 0.05.

RESULT

Distribution of metabolite variables

The results are summarized in Table 3.

Cytokine levels over time. The IL-6 was not detected before operation in all patients. IL-6 levels increased markedly at the end of operation, then decreased quickly, but not reaching normal levels by POD 5. The peak values of IL-6 level were higher in the two patients undergoing transhiatal oesophagectomy, 709 and 387pg/ml in case11 and case12 respectively, than other. The TNF- α and IL-1 were not detected in all patients during the study.

Hormone Levels over time. Norepinephrine levels were elevated following operation , peaking at POD 1, then keeping the high levels by POD 5 . Glucagon was measured in 9 cases except patient number 1, 3, 5 and 13. These levels increased following operations, peaking on POD 1 or 2, then decreasing at POD 5. Insulin levels increased following operation, and were highest on POD 2

instead of less glucose administration than on POD 5 (Table 2). These data are showing the elevation of counterregulatory hormones following surgery. In addition, Glucose/insulin ratio decreased following operation, and this was lowest on POD 2 and elevated again on POD 5, whereas blood glucose levels were kept from 149.9±17.2 (g/dl) on POD 1 to 176.5±42.0 (g/dl) at the end of operation during the postoperative periods. These data are reflecting "insulin resistance" especially on POD2.

Energy Substrate and Hypermetabolism Variables over Time. Respiratory quotient was under 1.0, and calculated endogenous fat oxidations were positive in most cases not only at the period of preoperative measurement reflecting overnight fast or on the end of surgery reflecting administration of glucose free solution, but also after start of TPN despite sufficient parenteral supply of glucose presented in Table 2 which was over the calculated glucose oxidation presented in Table 3, showing utility of endogenous fat (lipogenesis). It was lowest in POD 1, increasing gradually by POD 5. Free fatty acid was high level on preoperative day, reflecting overnight fasting. It peaked at the end of surgery, reflecting glucose free infusion, then gradually decreased throughout the study period. %REE tended to increase gradually during first 2 days following operation, then decreasing and almost reaching preoperative levels on POD 5. CRP levels were, in most cases, under 1.0 (ng/ml) before operations, and CRP levels elevated following operation, peaking on POD 2, then decreased rapidly on POD 5, but not reaching preoperative levels.

Relationship of Cytokines to Hormone Levels

The results of the regressions are summarized in Table 4. The values of norepinephrine at the end of surgery and on POD 2 were significantly related to all values of IL-6 level from the end of surgery to POD 2. Although there was no significance between norepinephrine levels on POD 1 and any levels of serum IL-6, the values tended to relate to IL-6 levels on the end of surgery ($r=0.578$, $p=0.0627$). The values on POD 5 were also significantly relate to IL-6 levels at the end of surgery and POD 1, and tended to relate to IL-6 levels on POD 2 although there was no significance ($r=0.525$, $P=0.0654$). These values of norepinephrine seems to relate most significantly to IL-6

levels at the immediate phase after surgery such as the end of surgery or POD 1, which were the peak levels of IL-6 in most cases. The glucagon levels at the end of surgery tended to correlated positively with IL-6 levels at the end of surgery (r=0.741, p=0.0566), the levels on POD 1 tended to correlate positively to IL-6 levels at the end of surgery and on POD 1 (r=0.64, p=0.0634 / r=0.626, p=0.0751, respectively) although there was no significance. The levels on POD 2 correlated positively with IL-6 levels at the end of surgery, on POD 1 and 2. And the levels on POD 5 correlated positively with IL-6 levels on POD 5. Therefore, glucagon levels seem to correlate most significantly with the simultaneous values of IL-6. Insulin levels at the end of surgery correlated positively with IL-6 levels on POD 1 and 5, and the levels tended to correlate to IL-6 levels on POD 2 although there was no significance (r=0.559, p=0.0587). There were no significant correlation between insulin levels on other POD and all values of IL-6 throughout the study.

Relationship of Hormones and Cytokines to Hypermetabolism Variables and Fuel Utilization

The results of the regressions are summarized in Table 5.

Hormones and Cytokines to Fuel Utilization Variables. Respiratory quotient on POD 2 was inversely related to logarithm of IL-6 levels on the end of surgery. Moreover, it was inversely related to glucagon levels on POD 1, and positively related to insulin levels on the end of surgery. There was no correlation between RQ or free fatty acid on POD 1, 5 and all values of IL-6 and hormones. Free fatty acid on POD 2 was significantly related to serum IL-6 levels on the end of surgery, POD 1, and POD 2. Free fatty acid on all the other points did not correlate significantly with all values of IL-6 during the study. Moreover, there were also significant relationships between free fatty acid levels and some hormones. The values at the end of surgery correlated positively with norepinephrine levels on POD 1. The values at POD 5 correlated positively with glucagon levels on POD 5, the values at the end of surgery and on POD 2 tended to correlate with glucagon levels at the end of surgery (r=0.658, p=0.098 and p=0.702, r=0.0788 respectively) although there were no

significance.

Hormones and Cytokines to Hypermetabolism Variables. The values of %REE on POD 2 correlated positively with logarithm of IL-6 on POD 2. The values of % REE on POD 5 correlated positively with logarithm of IL-6 at the end of surgery and tended to correlate positively with logarithm of IL-6 on POD 1 ($r=0.57$, $p=0.0528$). Moreover, it also tended to correlate with the values of norepinephrine on the end of surgery ($r=0.596$, $p=0.0528$). There were no significant correlation between %REE on POD 1 and the all values of IL-6 or hormones during the study. CRP levels from the end of surgery to POD 2 were significantly related to all IL-6 levels from the end of surgery to POD 2. The values on POD 5 were significantly related to IL-6 levels on all points during the study. Moreover, there were also significant relationships between CRP levels and some hormones. The CRP levels at the end of surgery and on POD 1 correlated positively with glucagon levels at the end of surgery and on POD 1 respectively, the values on POD 2 correlated positively with norepinephrine levels at the end of surgery, glucagon levels on POD 1 and insulin levels at the end of surgery. The values on POD 5 correlated to norepinephrine levels at the end of surgery, on POD 2 and POD 5, and insulin levels at the end of surgery.

DISCUSSION

The study indicates that the serum IL-6 is the important of plasma stress hormones, glucagon and norepinephrine, and that this cytokine is responsible for the development of the stress response of increased metabolic rate and the alteration of fuel utilization predominantly other than stress hormones following abdominal surgery. We will discuss some issues.

Does IL-6 induce hormonal alteration in surgical trauma?

In the study, the most dramatic feature was considerable significant relationsip between serum IL-6 levels and increase in plasma norepinephrine levels. The peak levels of serum IL-6, which were at the end of surgery in most cases, preceded the peak of this hormonal alterations, suggesting that

IL-6 might, in part, induce norepinephrine excretion following surgical trauma, because IL-6 is known to be capable of eliciting norepinephrine response in vivo (30). Furthermore, it is also known that norepinephrine causes a dose-dependent inhibition of LPS-induced IL-6 production in human whole blood (31), there might be a negative feedback mechanisim of norepinephrine to inhibit ongoing IL-6 production. Our data also suggest that IL-6 might induce glucagon response as same as norepinephrine response, because there were some relationships between these two mediators, and the peak levels of IL-6 preceded the peak of glucagon. Indeed, it is demonstrated that in septic rats alterations in the rate of plasma glucagon and glucose appearance are observed and coincided with the increased mRNA expression of IL-6 and gamma-IFN (32), and that rhIL-6 infusion induces a gradual and sustained increase in plasma glucagon concentration (30). In contrast, plasma insulin levels were not related to any IL-6 levels in serum in the study period other than the end of surgery. Stouthard et al. also reported that rhIL-6 infusion to humans did not affect plasma insulin concentrations, whereas this cytokine induced increase in plasma norepinephrine, glucagon, and cortisol (30). It might be possible that IL-6 did not affect insulin release.

Does IL-6 induce alteration of fuel utilization in surgical trauma?

Our data indicate insulin resistance and utility of endogenous fat during perioperative periods, because an increase in lipolysis is responsible for the decrease in RQ and the increase in plama free fatty acid concentrations (30). In the present study, the initial increase in lipolysis might be caused by the transient increase in plasma norepinephrine concentrations because there was significant relationship between plasma free fatty acid level at the end of surgery and norepinephrine level on 1POD. However, subsequent decreased RQ and increased free fatty acid as seen on POD2 were not associated with changes in plasma norepinephrine concentrations, but related to serum IL-6 levels more significantly than other plasma hormone levels. These data suggest that alteration of fuel utilization occur in response to inflammation and the initial release of free fatty acid, i.e. lipolysis is an effect of norepinephrine, however, the role of second increase in lipolysis may include compensation

of primary pathology induced by the cytokines such as IL-6. Stouthard et al. reported that administration of rhIL-6 to humans induced transient increase in plasma norepinephrine despite of sustained increase in lipolysis, and that the second and sustained increase in lipolysis rate was not associated with changes in plasma catecholamine concentrations (30). Therefore they have posutulated that the rapid effect of IL-6 on lipolysis is mediated increase in norepinephrine, whereas the more sustained release of free fatty acid is an effect of IL-6 itself. Furthermore, it has been described that IL-6 reduces adipose LPL activity and may contribute to the loss of body fat store associated with some cases of cancer cachexia (33). Therefore, lipolysis following surgical trauma may be also induced by IL-6 directly.

Does IL-6 induce hypermetabolism in surgical trauma?

In this study, patients undergoing surgery had a rise of up to 10% above the predicted REE on POD 2, showing mild hypermetabolism, and almost fall to the baseline on POD 5. We have demonstrated the significant relationship between circulating IL-6 levels and %REE on POD 2 and 5. These data suggest that a causal link between IL-6 and hypermetabolism in the early phase following surgery. Futhermore, there was no significant relationship between either sympathetic hyperactivity or other hormones and %REE (Table 5) despite of significant relationship of IL-6 to norepinephrine following surgery during the study period (Table 4). IL-6 is predominant influence on increased metabolic rate other than these stress hormones. The relationship of IL-6 to REE has been also described by a few investigators. Falconer et al. demonstrated that rates of not only TNF- α but also IL-6 production by peripheral blood mononuclear cells were significantly greater in pancreatic cancer patients with an acute-phase responese such as elevated REE than in those without (15). This relationship of IL-6 to hypermetabolism might be involved in the action of IL-6 to stimulate acute-phase protein production of hepatocyte (16). Actually, there were significant relationships between IL-6 and CRP during the study periods (Table 5).

Don't IL-1 and TNF-α act in surgical trauma?

It is known that acute administration of the cytokines TNF-α and IL-1, alone or in combination, to humans or healthy animals sets into motion a sequence of metabolic (13, 14) and hormonal alterations (19, 20, 34) similar to that observed during severe injury, and both cytokines are detectable in the sera of burn injuly (35, 36) or septic syndrome (37). However, there is no consistent increase in plasma IL-1 or TNF-α instead IL-6 is responsive in patients of trauma (38, 39) or abdominal surgery (40, 41, 42). Indeed, we have shown no TNF-α nor IL-1 response, but only IL-6 response in this study. Although the period when detectable cytokines were present in our patients could easily have been missed because the half-life of these cytokines is of the order of minutes and these were only daily samples in this study, we postulate that there is no consistent systemical act of IL-1 or TNF-α in surgical trauma patients. However, the possibility that these cytokines may act locally is not ruled out because significant quantities of some cytokines may be detectable in the blood only when they spill over into the circulation from their site of local production at a focus of injury. If TNF-α and IL-1 act locally, it is also possible that IL-6 is a common mediator involved in surgical trauma to these polypeptides because IL-1 and TNF-α are known to stimulate or to serve as a cosignal for IL-6 production (43) and because IL-6 also mediates some of the actions of TNF-α and IL-1 in vivo (44). Furthermore, Starnes et al. have shown that metabolic, physiological, and lethal effects of TNF-α administration to mice can be blocked by pretreatment with a monoclonal antibody against IL-6 (12), suggesting that many of the metabolic effects of TNF-α may be actually mediated by IL-6.

Some problems in indirect calorimetry measurements after surgery

Indirect calorimetry variables on POD 1 did not relate to any hormones nor cytokine. It might be because most patients were not calm due to wound pain or mental anxiety. Therefore, it might be difficult to do exact measurement of indirect calorimetry in very early phase following surgical trauma such as POD 1. On the other hand, the reason for no relationship of fuel utilization variables on POD

5 to any cytokines nor hormones might be that insulin resistance was already attenuated.

In summury, our data indicate that a systemic and continuous role for IL-1 and TNF- α is not evident in the programmed trauma such as abdominal surgery, and that IL-6 may be an important mediator of the endocrinologic and metabolic response to the trauma. However, whether IL-6 induces these alteration of metabolite directly or indirectly through other mediators remains to be established.

Table 1. Characteristics of patients studied

Patient	Illness	Operative procedure	Sex	Age(yr)	Weight (kg)	Height (cm)	Operation time (minutes)	Blood loss (ml)
1	gastric cancer	total gastrectomy	woman	52	52	155	265	319
2	gastric cancer	total gastrectomy	man	68	62.6	166	245	430
3	gastric cancer	total gastrectomy	man	70	59	165	290	390
4	gastric cancer	total gastrectomy	man	71	66	169.6	410	2503
5	gastric cancer	total gastrectomy with partial pancreasectomy and splenectomy	man	45	65	161	295	382
6	gastric cancer	total gastrectomy with partial pancreasectomy and splenectomy	man	68	56	169	300	597
7	gastric cancer	total gastrectomy with partial pancreasectomy and splenectomy	woman	68	41.4	147.7	346	384
8	gastric cancer	total gastrectomy with partial pancreasectomy and splenectomy	man	73	50.3	172.5	250	305
9	Pancreatic cancer	partial pancretectomy	woman	65	46	149	230	827
10	Pancreatic cancer	pancreato-duodenectomy	woman	65	42	153	415	465
11	esophageal cancer	transhiatal oesophagectomy	man	75	74	169.1	385	630
12	esophageal cancer	transhiatal oesophagectomy	woman	65	58.7	160.5	530	777
13	cholecyst cancer	cholecystectomy with partial hepatectomy	man	82	68	161	300	575

Table 2. Caloric intake

	POD1	POD2	POD 3	POD4,	POD 5
Caloric intake:					
kcal/day	920	1140	1440	1440	1440
kcal/kg/day	16.7±3.2	20.6±3.9	26.1±5.0	26.1±5.0	26.1±5.0
Glucose intake					
mg/minute	118.1	156.25	208.3	208.3	208.3
mg/kg/minute	3.1±0.6	4.1±0.8	5.4±1.0	5.4±1.0	5.4±1.0
Nitrogen intake					
gm amino N/day	9.6	9.6	9.6	9.6	9.6
gm N/kg/day	0.18±0.03	0.18±0.03	0.18±0.03	0.18±0.03	0.18±0.03

POD, postoperative day

Values are expressed as mean±SD.

Table 3. Distribution of cytokines, hormones, fuel utilization and hypermetabolism variables

	befor operation	end of operation	POD1	POD2	POD5
IL-6 (pg/ml)	N.D.	189.8±200.7	128.1±124.2	61.2±31.4	23.2±26.0
IL-1 (pg/ml)	N.D.	N.D.	N.D.	N.D.	N.D.
TNF-α (pg/ml)	N.D.	N.D.	N.D.	N.D.	N.D.
norepinephrine (pg/ml)	218.7±115.9	742.0±508.5	1022.4±945.9	813.0±545.1	759.7±590.1
glucagon (pg/ml)	55.4±23.5	78.1±24.6	89.7±28.7	82.1±16.4	63.4±18.4
insulin (pg/ml)	7.9±4.2	12.2±6.2	16.3±16.3	24.5±9.5	17.3±9.5
glucose (mg/dl)	109.9±12.5	176.5±42.0	147.9±17.2	161.2±39.8	167.3±61.9
glucose/insulin ratio	16.4±5.8	18.1±10.4	15.7±10.2	7.3±2.7	13.5±11.0
RQ	0.94±0.09		0.87±0.11	0.94±0.11	0.97±0.10
glucose oxidation (mg/kg/min)	2.20±1.21		2.01±1.92	3.24±1.88	3.23±1.75
fat oxidation (mg/kg/day)	0.247±0.276		0.507±0.642	0.291±0.501	0.226±0.563
FFA (mEq/l)	0.57±0.31	0.70±0.44	0.41±0.31	0.18±0.14	0.20±0.15
%REE	98.1±14.5		107.2±18.2	110.4±20.2	102.0±18.2
total calory oxidation (kcal/kg/day)	20.84±2.09		22.83±3.92	23.55±3.69	21.82±4.07
CRP (pg/ml)	0.76±1.82	16.44±9.85	113.78±54.36	137.55±58.52	67.43±40.06

REE, respiratory energy expenditure; RQ, respiratory quotient; FFA, free fatty acid; POD, postoperative day; N.D., not detected
Values are expressed as mean±SD.

Table. 4 IL-6 associated with hormonal changes

	Dependent Variable	Independent Variables	Direction of Relationship	r=	p=
end of surgery	NE	IL-6 (end of surgery)	+	0.822	0.001
		IL-6 (POD1)	+	0.863	0.0003
		IL-6 (POD2)	+	0.667	0.0178
	glucagon *	(NONE)			
	insulin **	IL-6 (POD1)	+	0.665	0.0183
		IL-6 (POD5)	+	0.808	0.0015
POD1	NE ***	(NONE)			
	glucagon *	(NONE)			
	insulin	(NONE)			
POD2	NE	IL-6 (end of surgery)	+	0.674	0.0162
		IL-6 (POD1)	+	0.651	0.0159
		IL-6 (POD2)	+	0.607	0.0277
	glucagon	IL-6 (end of surgery)	+	0.675	0.0459
		IL-6 (POD1)	+	0.669	0.0486
		IL-6 (POD2)	+	0.86	0.0029
	insulin	NONE			
POD5	NE ****	IL-6 (end of surgery)	+	0.689	0.0132
		IL-6 (POD1)	+	0.613	0.0258
	glucagon	IL-6 (POD5)	+	0.755	0.0497
	insulin	(NONE)			

NE, norepinephrin
The points of postoperative serum IL-6 which relate significantly to dependent variables are presented.
"NONE" means that there are no point of IL-6 which relates to dependent variable.

*; The glucagon levels at the end of surgery tended to correlate positively with IL-6 levels at the end of surgery ($r=0.741$, $p=0.0566$), the levels on POD 1 tended to correlate positively to IL-6 levels at the end of surgery and on POD 1 ($r=0.64$, $p=0.0634$ / $r=0.626$, $p=0.0751$, respectively) although there was no significance. **; The insulin levels at the end of surgery ended to correlate to IL-6 levels on POD 2 although there was no significance ($r=0.559$, $p=0.0587$). ***; Although there was no significance between norepinephrine levels on POD 1 and any levels of serum IL-6, the values tended to relate to IL-6 levels on the end of surgery ($r=0.578$, $p=0.0627$). ****; The values of norepinephrine on POD5 tended to relate to IL-6 levels on POD2 although there was no significance. ($r=0.525$, $p=0.0654$).

Table 5. Hormones and IL-6 associated with fuel utilization and hypermetabolism variables

Points of Dependent Variables	Dependent Variable	Significant Relationship	Direction of Relationship	r=	p=
end of surgery	RQ		(not measured)		
	FFA *	NE (POD1)	+	0.644	0.0443
	%REE		(not measured)		
	CRP	IL-6 (end of surgery)	+	0.695	0.0121
		IL-6 (POD1)	+	0.737	0.0062
		IL-6 (POD2)	+	0.746	0.0053
		Glucagon (end of surgery)	+	0.772	0.0421
POD1	RQ		(NONE)		
	FFA		(NONE)		
	%REE		(NONE)		
	CRP	IL-6 (end of surgery)	+	0.788	0.0039
		IL-6 (POD1)	+	0.697	0.0188
		IL-6 (POD2)	+	0.727	0.0074
		Glucagon (POD1)	+	0.804	0.009
POD2	RQ	Log of IL-6 (end of surgery)	-	0.632	0.0274
		Glucagon (POD1)	-	0.681	0.0435
		Insulin (end of surgery)	+	0.712	0.0141
	FFA **	IL-6 (end of surgery)	+	0.578	0.049
		IL-6 (POD1)	+	0.534	0.049
		IL-6 (POD2)	+	0.581	0.0294
	%REE	Log of IL-6 (POD2)	+	0.677	0.0222
	CRP	IL-6 (end of surgery)	+	0.786	0.0014
		IL-6 (POD1)	+	0.823	0.0003
		IL-6 (POD2)	+	0.794	0.0007
		Glucagon (POD1)	+	0.768	0.0157
		NE (end of surgery)	+	0.61	0.0354
		Insulin (end of surgery)	+	0.578	0.0491
POD5	RQ		(NONE)		
	FFA	Glucagon (POD5)	+	0.795	0.0326
	%REE***	Log of IL-6 (end of surgery)	+	0.609	0.0468
	CRP	IL-6 (end of surgery)	+	0.629	0.0285
		IL-6 (POD1)	+	0.695	0.0084
		IL-6 (POD2)	+	0.801	0.001
		NE (end of surgery)	+	0.662	0.019
		NE (POD2)	+	0.66	0.0141
		NE (POD5)	+	0.618	0.0244
		Insulin (end of surgery)	+	0.772	0.0033

NE, norepinephrine; REE, resting energy expenditure; RQ, respiratory quotient; FFA, free fatty acid
Postoperative serum IL-6 or plasma hormones which relate significantly to dependent variables are presented.
"NONE" means that there are no point of IL-6 or hormones which relate to dependent variable.

*, **; Free fatty acid levels at the end of surgery and on POD 2 tend to correlate with glucagon levels at the end of surgery (r=0.658, p=0.098 and p=0.702, r=0.0788 respectively) although there were no significance. ***; The values of % REE on POD 5 tended to correlate positively with logarithm of IL-6 on POD 1 (r=0.57, p=0.0528), the values of norepinephrine on the end of surgery (r=0.596, p=0.0528), although there were no significance.

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