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REGULATION OF INSULIN AND INSULIN-LIKE ACTIVITY IN MALNOURISHED PATIENTS WITH CARCINOMA VENTRICULI SUBJECTED TO TOTAL GASTRECTOMY AND PERSONALIZED NUTRITIONAL SUPPORT

KONTROLA INSULINSKE I AKTIVNOSTI SLIČNE INSULINU KOD NEUHRANJENIH PACIJENATA SA TUMOROM ŽELUCA PODVRGNUTIH TOTALNOJ GASTREKTOMIJI I LIČNO ADAPTIRANOJ ISHRANI

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Summary

Background: Insulin and insulin-like growth factor (IGF) activities are disturbed during critical illness. Time-course changes in the concentrations of insulin, IGF-I and IGF-binding proteins (IGFBPs) were monitored in this study and their correlation with interleukin (IL)-6 was assessed in patients subjected to total gastrectomy and specific nutritional regime.
Methods: Patients were fed post-operatively according to the following scheme: parenteral nutrition on day 1, enteral nutrition combined with parenteral form from day 2 to 7, peroral nutrition from day 8 and full oral nutrition from day 14. Blood samples were taken periodically and the levels of IL-6, insulin, IGF-I and IGFBP-1 to -4 were determined.
Results: On day 1 post-operatively, the concentration of IL-6 reached its maximum and decreased afterwards. The concentration of insulin increased until day 3 and then started to fall. The concentration of IGF-I, already low pre-operatively, continued to decrease. The concentration of IGFBP-1 peaked on day 1 post-operatively, whereas the concentration of IGFBP-3 decreased on that day. The concentration of IL-6 correlated positively with the concentration of IGFBP-1 and negatively with IGFBP-3. On day 14, the concentrations of IL-6, insulin and IGFBP-1 returned to or were close to their basal levels, whereas the concentrations of IGF-I and IGFBP-3 remained reduced.

Kratak sadržaj

Uvod: Aktivnost insulina i faktora rasta sličnih insulinu (IGF) izmenjena je u kritičnom stanju. U ovoj studiji je praćena promena koncentracije insulina, IGF-I, IGF vezujućih proteina (IGFBP) i utvrđivana njihova korelacija sa interleukinom (IL)-6 kod pacijenata sa tumorom želuca, koji su podvrgnuti totalnoj gastrektomiji i specifičnom režimu ishrane.
Metode: Pacijenti su postoperativno hranjeni prema sledećem režimu: parenteralna ishrana prvog dana, enteralna ishrana u kombinaciji sa parenteralnom od drugog do sedmog dana, peroralna ishrana osmog dana i redovna ishrana četrnaestog dana. Periodično su uzimani uzorci krvi i određivane koncentracije IL-6, insulina, IGF-I i IGFBP-1 do -4.
Rezultati: Koncentracija IL-6 je dostigla maksimum prvog dana nakon operacije i dalje je opadala. Koncentracija insulina je rasla do trećeg dana, a zatim je počela da pada. Koncentracija IGF-I, koja je bila niska pre operacije, nastavila je da opada. Prvog dana posle operacije, koncentracija IGFBP-1 je porasla, dok se koncentracija IGFBP-3 smanjila. Promene IGFBP-1 i IGFBP-3 su bile izraženije sa većim skokom IL-6. Četrnaestog dana su se koncentracije IL-6, insulina i IGFBP-1 vratile ka referentnim vrednostima, dok su koncentracije IGF-I i IGFBP-3 ostale smanjene.
Zaključak: Četrnaestodnevni postoperativni oporavak, koji je obuhvatao specifičan režim ishrane, pokazao se odgova-

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Conclusions: A 14-day post-operative recovery, which included specific nutritional support, was suitable to restore insulin concentration and re-establish IGFBP-1 regulation primarily by nutrition. Very low IGF-I level on day 14 after surgery and IGFBP-3 concentration still lower than before surgery indicated that the catabolic condition was not compensated.

Keywords: enteral nutrition, insulin, insulin-like growth factor I, insulin-like growth factor binding proteins, interleukin 6, total gastrectomy

rajućim za uspostavljanje kontrole koncentracije insulina i IGFBP-1. Sa druge strane, vrlo niska koncentracija IGF-I, kao i koncentracija IGFBP-3 ispod preoperativne vrednosti, ukazuju na to da katabolički stres kod ovih pacijenata i dalje nije kompenzovan.

Ključne reči: enteralna ishrana, insulin, faktor rasta sličan insulinu I, vezujući proteini za faktore rasta slične insulinu, interleukin 6, totalna gastrektomija

Introduction

Impaired metabolic processes accompany critical illness. The effects of surgical treatment and malnutrition superpose to the initial clinical state, resulting in even more serious catabolism. One of the hallmarks in the treatment of patients, both pre-operatively and post-operatively, is the nutrition. Nutritional support, both immunological and pharmacological, was shown to be an important tool in the management of critical illness (1, 2). Numerous clinical studies have documented lower mortality rates in critically ill patients subjected to nutritional support adjusted to their clinical and biochemical status (1). Oral and enteral nutrition have advantages over the parenteral, as they are natural nutritional pathways, and they stimulate the function of the gastrointestinal tract and reduce the possibility of bacterial translocation (3–5). Chen et al. (6) have shown that enteral nutrition, and specifically enteral immunonutrition, was effective in restoring defense capacity in patients with gastric cancer who underwent major surgery, measured by several parameters including pro-inflammatory cytokine interleukin (IL)-6. The study of IL-6-associated pathways in gastric carcinoma, in general, is important as increased IL-6 levels seem to be associated with cancer invasion and lymph node metastasis (7–9). Additionally, the elevation of IL-6 is used to monitor post-operative complications in patients after gastrectomy. The concentration of IL-6 on day 1 post-operatively correlates with morbidity in gastric cancer patients (10).

Insulin-like growth factor I (IGF-I) has been under consideration as a nutritional biomarker, since its synthesis is tightly controlled by nutrition (11). Many other factors, however, influence the concentration of IGF-I, so the reliability of its utilization as a marker of nutritional status is still under evaluation. Hormones and cytokines affect IGF-I production, several IGF-binding proteins (IGFBPs) affect its distribution and bioavailability, and proteases modulate its activity and binding to receptors (12). In critically ill patients, insulin and the IGF system are tightly connected to the survival rates (13) and IGF-I, being an essential growth factor and promoter of DNA synthesis (14), is crucial for tissue healing.

Molecules of the IGF system are also responsible for tumor growth. IGFs act mostly via type 1 IGF receptor (IGF-1R) which has been under investigation as a potential anti-tumor therapeutic target for some time (15). In general, a high concentration of IGFs is associated with increased risk of cancer, but it also exerts negative feed-back control on the IGF-1R expression (16). Reported results on the IGF system and its activity in gastric cancer, however, show some inconsistency. For example, Wang et al. (17) have found increased IGF-I expression in gastric mucosa due to cancer, whereas Gryko and his group (18) have detected increased expression of IGF-1R in gastric carcinoma. Different IGFBPs were reported to be present in different human gastric cancer cells (19) and, so far, no studies on anti-IGF-1R targeted therapy in gastric cancer have been reported (20).

Malnourished patients with gastric cancer (carcinoma ventriculi), subjected to total gastrectomy and personalized post-operative nutritional support, were investigated in this study. It seemed relevant to monitor time-course changes in the concentrations of insulin, IGF-I, IGFBP-1, -2, -3 and -4, and to assess which of them and to what extent is correlated to the alterations in interleukins, namely the IL-6. Patients were fed according to the following nutritional scheme: parenteral nutrition on day 1, enteral nutrition combined with parenteral form from day 2 to 7, peroral nutrition from day 8 to 13 and full oral nutrition from day 14. Blood samples were taken periodically (pre-operatively and on days 1, 3, 7 and 14 post-operatively). The aim of the follow-up was to determine the rate at which biochemical parameters change, in order to assess the recovery rate in the regulation of insulin and insulin-like activity.

Materials and Methods

Patients and samples

Patients diagnosed with carcinoma ventriculi were subjected to total gastrectomy. Characteristics of the patients and their post-operative nutritional regime are given in *Table I*. They had Adenocarcinoma ventriculi diffusum invasivum. Three patients died within days 3–7 post-operatively due to septic complications, thus the entire follow-up was done for 26 individuals who recovered and left the hospital after day 14 (they also appeared at regular controls scheduled after surgery).

Table I Characteristics of patients and their post-operative nutritional regime.

	Data
Number of patients (male + female)	29 (18+11)
Age of patients (years)	63±11
BMI of patients (kg/m^2)	17±2
TNM grading score	T2N2M0 (17) and T3N2M0 (12)
Histology grading	G2 (3) and G3 (26)
Survivals (left hospital after day 14 and appeared at regular controls after surgery)	26/29
Post-operative complications	5/29 (1 transitory ischemic attack, 1 post-operative bleeding, 1 infection of the wound, 1 pancreatic fistula and 1 pleural effusion)
Pre-operative parenteral nutrition	3/29
Post-operative nutritional regime	Day 1: Parenteral nutrition Day 2: Enteral nutrition (400 kcal on day 2 up to 1100 kcal on day 7) Day 8: Peroral nutrition Day 14: No restrictions

Patients were categorized as malnourished according to one or more nutritional risk factors: weight loss of 10–15% within 6 months before surgery, Subjective Global Assessment Grade C and the concentration of serum albumin ≤ 30 g/L (5). All patients consumed food enterally to the limit of their personal tolerance, until 12 h pre-operatively. Parenteral nutritional support was given to three patients who had bleeding in the upper digestive tract. They all survived and left the hospital, but the number of cases was too small to form a specific group to evaluate the effect of pre-operative nutritional support on the final recovery.

Total gastrectomy was performed, followed by reconstruction by the Roux-en-Y method. All patients were subjected to individually formulated diets post-operatively, starting with parenteral nutrition and followed by enteral feeding 24 h after the end of the operation. The nutritional goal was 25 kcal/kg per day and the enteral diet used was Fresubin Standard R (Fresenius Kabi AG, Bad Homburg, Germany), composed of 70% of calories originating from carbohydrates and 30% from triglycerides (4). Until the day 7 post-operatively, parenteral nutrition (Fresenius Cabiven 1550 R) was combined with enteral feeding (4). Oral feeding started on day 8 and gradually changed from liquid to semiliquid food. Patients were followed-up clinically and biochemically in a standard manner. Five patients had certain post-operative complications (*Table I*), but they all recovered and were released from the hospital on day 14 after surgery.

Blood samples were collected in the morning, after 12 h fasting, on the day before surgery and on days 1, 3, 7 and 14 after the operation. Sera were separated within 45 min, aliquoted and stored frozen at –20 °C. The concentrations of IL-6, insulin and IGF-I were measured by immunoassay, whereas the relative quantities of IGFBP-1, -2, -3 and -4 were determined by immunoblotting. The work described here was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and each patient agreed to his/her serum samples being used for the purpose of this study.

Determination of IL-6, insulin, IGF-I, total protein and albumin concentrations

The concentration of IL-6 was measured by electrochemiluminescence immunoassay (ECLIA-IL-6, Hoffmann-La Roche, Basel, Switzerland), the concentrations of insulin and IGF-I were measured by radioimmunoassay (RIA-Insulin and RIA-IGF-I, INEP, Belgrade, Serbia) and the concentrations of total protein and albumin were determined by Biuret and bromocresol green reagents (Human GmbH, Wiesbaden, Germany). The referent values, appropriate for the age group involved in the study, were: ≤ 6 ng/L for IL-6, 5–25 mIU/L for insulin, 9–30 nmol/L for IGF-I, and 35–55 g/L for albumin.

Determination of IGFBP-1, -2, -3 and -4 by immunoblotting

Proteins in serum samples (diluted to 2 g/L) were separated by denaturing, reducing electrophoresis in 10% gels, transferred to a nitrocellulose membrane and immunoblotted using goat anti-human IGFBP-1, -2, -3 and -4 primary antibodies (Santa Cruz Biotechnology, Santa Cruz, USA), HRP-coupled swine anti-goat IgG secondary antibody (Biosource, Camarillo, USA) and HRP substrate luminol (Pierce Biotechnology, Rockford, USA). Immunoreactive proteins were visualized by autoradiography, evaluated by densitometry and their relative quantity was expressed in densitometric units (DU).

Statistical analysis

The results were expressed as the mean ± standard deviation (SD). The differences between time intervals were analyzed by a nonparametric repeated measurement ANOVA test and the correlation

between different parameters was assessed by Spearman's correlation coefficient. The SPSS software was used for statistical analysis.

Results

Alterations in IL-6, insulin, IGF-I and albumin levels

Patients who had undergone total gastrectomy demonstrated the most dramatic changes in biochemical parameters on day 1 post-operatively, as expected (*Figure 1*). The concentration of IL-6 increased the most compared to the pre-operative value, on average 40 times. The concentration of insulin doubled, whereas the concentration of IGF-I, already low in the pre-operative samples, continued to decrease on day 1. The concentration of albumin decreased as well compared to the pre-operative value. The concentration of IL-6 in the serum samples collected in the morning on day 3 was significantly decreased compared to day 1, approximately 3 times, but the level was still very high. The concentration of insulin continued to increase and reached its maximum, whereas the IGF-I and albumin levels continued to fall. On day 7, the concentration of IL-6 was significantly lower than on day 3, the concentration of insulin began to decrease, but the concentration of IGF-I also continued to decrease. Concentration of albumin exhibited a moderate increase.

On day 14, the concentration of IL-6 was lower than on day 7, but it was still much higher than before surgery and well above the reference limit. The concentration of insulin returned to its basal level and was even lower than before surgery. The concentrations of IGF-I and albumin, however, remained lower than before surgery and also lower than the reference. This general profile of IL-6, insulin, IGF-I and albumin alterations was common to all patients included in this study, but there were two types of responses at the level of IGFBPs. The changes in the concentration of IGFBPs were correlated to the changes in the concentration of IL-6 and not to those of insulin, IGF-I or albumin.

Alterations in IGFBPs levels

Immunoblotting of serum samples obtained from patients pre-operatively and on days 1, 3, 7 and

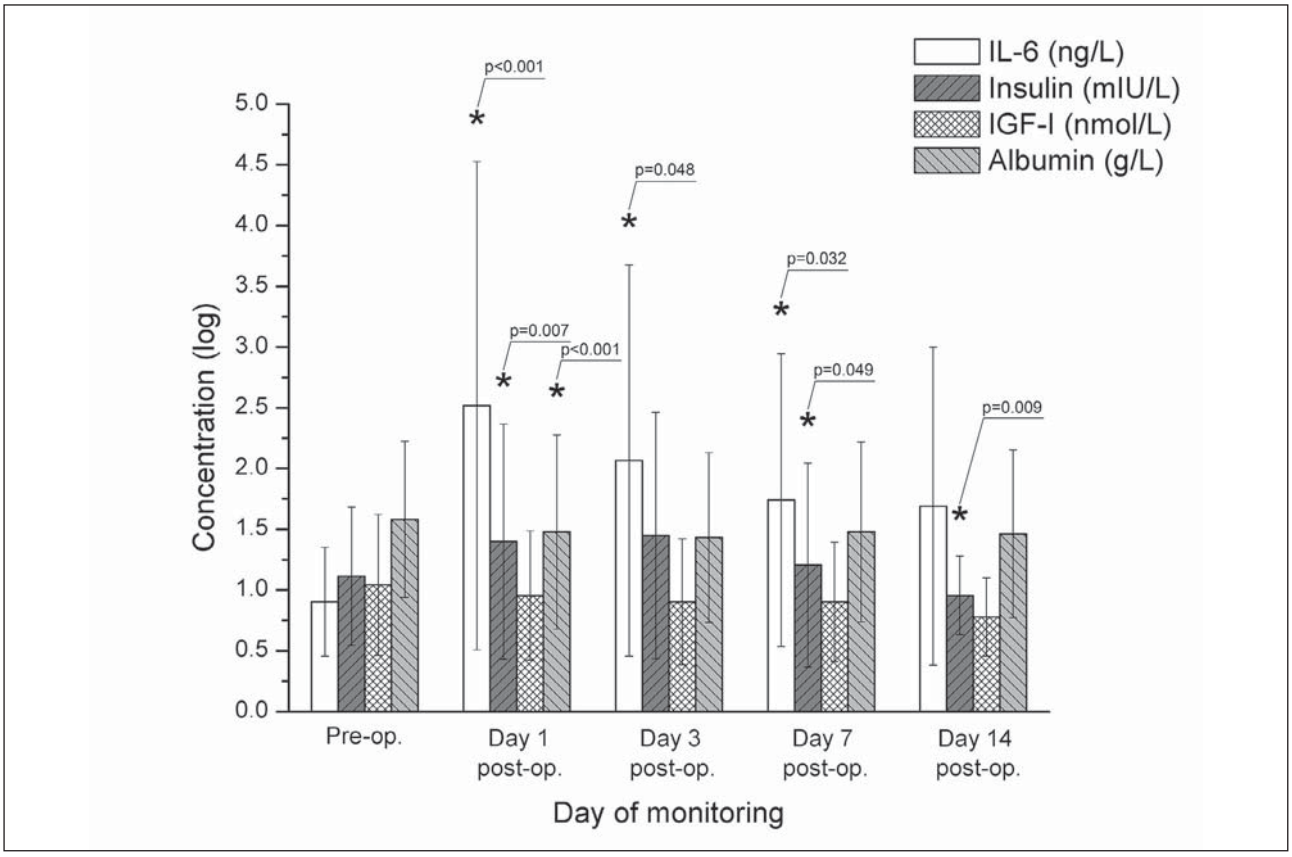

Figure 1 Serum IL-6, insulin, IGF-I and albumin concentrations in patients with carcinoma ventriculi subjected to total gastrectomy and specific nutritional regime (*: statistically significant difference between two successive time intervals expressed as p value).

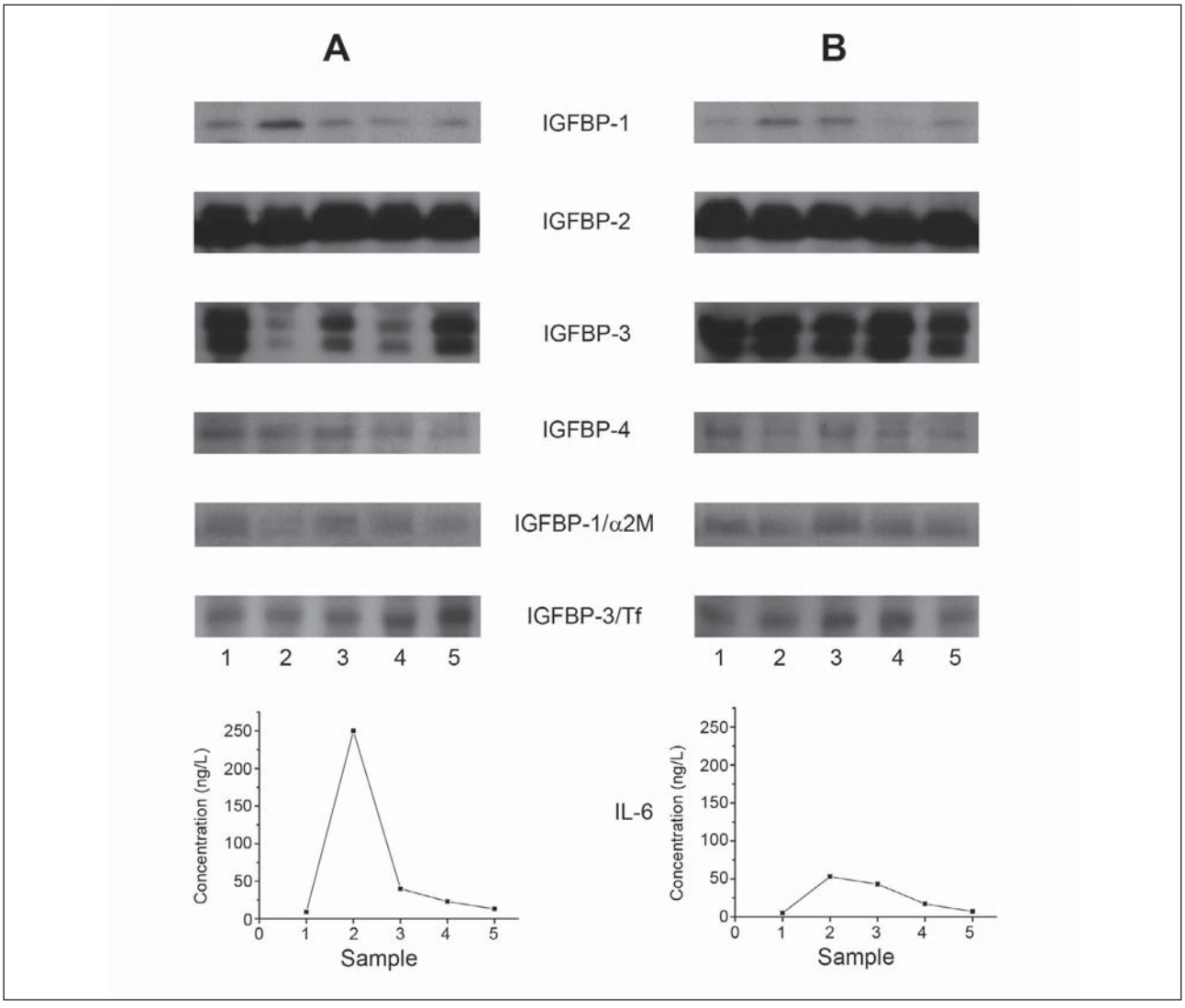

Figure 2 The profiles of IGFBP-1, -2, -3, -4 and IL-6 alterations during 14-day post-operative recovery of patients with carcinoma ventriculi subjected to total gastrectomy and specific nutritional regime. Representative profiles are given for two groups of patients, group 1 (A) and group 2 (B), who had very high (A) or moderately high (B) concentrations of IL-6 on day 1 post-operatively. Blood samples 1–5 were collected pre-operatively and on days 1, 3, 7 and 14 post-operatively.

14 post-operatively demonstrated that only IGFBP-1 and IGFBP-3 were prone to considerable alterations (*Figure 2*, representative results for two patients). The levels of IGFBP-2 and IGFBP-4 did not exhibit significant changes along the post-operative recovery period (*Figure 2*). IGFBP profiles, dependent on the concentration of IL-6, are shown in *Figure 3* (groups 1 and 2). Patients were divided into two groups according to the cutoff criterion for IL-6 peak: group 1 ≥ 100 ng/L and group 2 < 100 ng/L. The cutoff criterion was established after examination of all IGFBP profiles, as a point which most adequately differentiated the effect of IL-6 (although changes of IGFBPs with IL-6 maximal concentration were gradual). In patients with a very high concentration of IL-6 on day 1, the concentration of IGFBP-1 was higher and the concentration of IGFBP-3 lower (*Figure 2A* and *Figure 3A*) compared to patients whose concentration of IL-6 was not so dramatically raised on day 1 (*Figure 2B* and *Figure 3B*). In both groups of patients the concentration of IGFBP-1 was reduced on day 3 and continued to drop along with a decrease in IL-6 concentration. On day 14, IGFBP-1 concentration was similar to the pre-operative value. The concentration of IGFBP-3, however, was significantly reduced, compared to the pre-operative value, only in patients with a very high concentration of IL-6. It began to rise post-operatively with a decrease in IL-6 concentration, but still remained lower on day 14 than pre-operatively. The calculated correlation coefficients (*Figure 3*) pointed to a positive correlation between IL-6 and IGFBP-1 and a negative one between IL-6

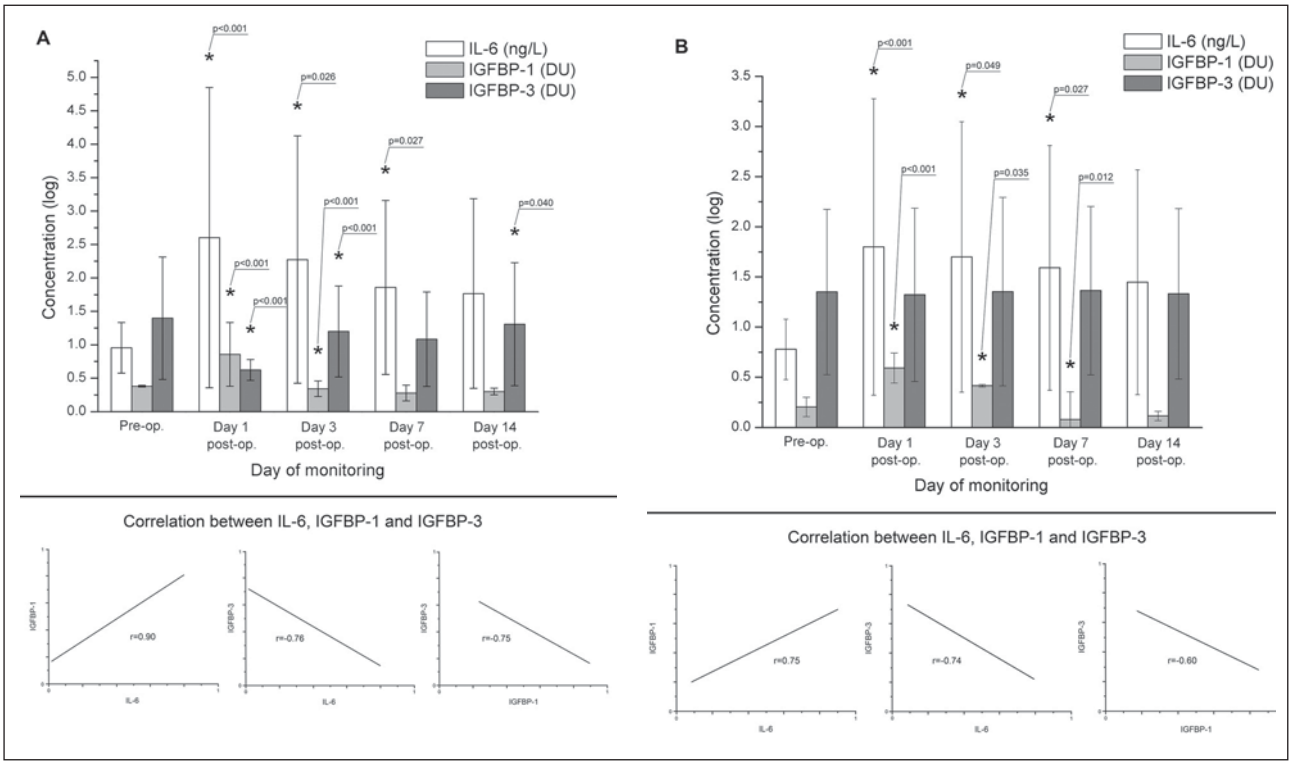

Figure 3 Serum IL-6 concentration and relative abundance of IGFBP-1 and IGFBP-3 in patients with carcinoma ventriculi subjected to total gastrectomy and specific nutritional regime, classified into group 1 (A) and group 2 (B), who had very high (A) or moderately high (B) concentrations of IL-6 on day 1 post-operatively (*: statistically significant difference between two successive time intervals expressed as p value; r: correlation coefficient between IL-6, IGFBP-1 and IGFBP-3 alterations).

and IGFBP-3. Consequently, the correlation between IGFBP-1 and IGFBP-3 was negative.

IGFBP-1 is known to interact with α2-macroglobuline, α2M (21) and IGFBP-3 with transferrin, Tf (22), so the presence of these complexes (at molecular masses previously determined at approximately 200 and 100 kDa) was also investigated. Protein bands corresponding to these complexes (*Figure 2*) seemed not to be affected significantly by acute changes in IGFBP-1 or IGFBP-3 concentrations.

Discussion

Malnutrition and major surgery in patients with gastric cancer are associated with catabolism and stress response, affecting metabolic, endocrine and immune systems, possibly causing organ dysfunction, complications in wound healing or even death. Acute phase reaction is a systemic response to a critical state and it is mediated by pro-inflammatory molecules. Cytokines induce a series of changes including activation of the hypothalamic-pituitary axis, reduction of GH secretion, catabolism and change in hepatic function (23). In malnutrition, a general reduction of protein synthesis in the liver occurs. Cytokines which have the most profound metabolic effects are IL-1, IL-6 and tumor necrosis factor α, TNF-α (23). IL-6 is the major stimulator of hepatocytes to synthesize acute phase proteins, whose concentrations increase within several hours after inflammatory onset (24, 25). Hepatocytes are also responsible for the synthesis of IGF-I, IGF-II and some of the IGFBPs, such as IGFBP-1, IGFBP-2 and IGFBP-4 (26).

Results of this study demonstrated that gastrectomy induced a significant increase in the IL-6 concentration, as expected (10), causing an increase in insulin and IGFBP-1 levels. Post-operative treatment lasting two weeks, which included reduction of stress and pro-inflammatory processes, and well-balanced nutritional support, was able to reduce the concentrations of insulin and IGFBP-1, suggesting improved response of IGFBP-1 to nutrition and re-establishment of the negative feed-back relation between insulin and IGFBP-1. IGFBP-1 levels were previously shown to increase under stimulation of IL-6, IL-1β and TNF-α (27, 28) and to correlate with mortality outcome in critically ill patients (29). IGFBP-1 expression is naturally suppressed by insulin and the concentrations of these two proteins change in counter directions in healthy persons. In critical illness, as liver becomes insensitive to insulin, the signaling pathways dependent on it, including IGFBP-1 gene regulation, become impaired (29). It is not clear whether the effect of insulin resistance or IL-6 stimulation is dominant and whether these two effects are associated. In the experiment with HepG2 cells, insulin

was unable to prevent IL-6-stimulated increase in IGFBP-1, when both peptides were present in the medium (28). In a clinical study in which patients were treated with insulin supplementation, the therapy lowered the concentration of glucose, but had no effect on serum IGFBP-1 or the patient outcome (29). This result implied that insulin was not lowering blood glucose by affecting gluconeogenesis in the liver, but it induced intracellular transport of glucose and its utilization. Early nutritional support administrated to critically ill patients involved in this study demonstrated a suppressive effect of food intake on IGFBP-1 levels in blood even in the absence of negative feed-back relation between insulin and IGFBP-1.

Contrary to IGFBP-1, IL-6 secretion after surgery caused reduction in the IGFBP-3 level. A 14-day post-operative period was unable to fully return the concentration of IGFBP-3 to its pre-operative value in the case of dramatic increase in IL-6 level. The concentration of IGF-I in patients with gastric cancer was low pre-operatively and this result was in accordance with the literature data (30). The level of IGF-I further slightly decreased after gastrectomy, but remained unaffected by the reduction in the concentration of IL-6. The pre-operative level of IGF-I was not re-established after 14 days and the data correlated well with the behavior of the negative acute phase proteins such as albumin (31). Since the production of both IGF-I and IGFBP-3 is under the control of growth hormone (32), a disbalance in the concentration of IGF-I and IGFBP-3 post-operatively suggests strong influence of other factors which regulate their synthesis and/or clearance rates. Decreased levels of IGFBP-3 may be attributed to increased IGFBP-3 proteolysis, activated by IL-6 after surgery (33). Proteolysis of IGFBP-3 was found to correlate with the concentration of IL-6 in cancer cachexia (34). The IL-6 up-regulates gene expression of cathepsins and matrix metalloprotease-13, which are able to degrade IGFBP-3 (35). At the moment, it is not known whether IL-6 can directly affect the synthesis of IGFBP-3 in Kupffer cells, which are the major sites of IGFBP-3 production in the liver (26). Additionally, IGFBP-3 is a tumor suppressor whose anti-proliferative effect is IGF-independent (36). Its lower concentration in the circulation of patients with cancer may be regarded as an unfavorable event not only from the aspect of nutrition, but also from the point of depressed tumor-growth inhibitory potential.

To conclude, a 14-day post-operative recovery, which included specific nutritional support administrated to the patients, taking into account their personal clinical and metabolic status, was suitable to restore insulin concentration to the pre-operative level and to re-establish IGFBP-1 regulation primarily by nutrition. Therefore, it may be postulated that by lowering IGFBP-1 and increasing IGFBP-3 concentration, the mortality risk was reduced and personalized nutritional support is probably responsible for the shorter length of stay of patients in the intensive care unit and the hospital. On the other hand, very low albumin and IGF-I levels on day 14 after surgery and IGFBP-3 concentration still lower than the pre-operative one, indicated that restoration of their concentrations had not occurred yet and that catabolic stress was not compensated. The concentrations of IGFBP-1 and IGFBP-3 were directly correlated with the concentration of IL-6, the first one positively and the second one negatively. The alteration of insulin concentration was phase-shifted compared to the IL-6. Finally, the concentrations of IGF-I, IGFBP-2 and IGFBP-4 did not seem to be directly IL-6-dependent.

Thus, when we compare the levels of specific parameters of the insulin/IGF/IGFBP axis before surgery and after, it can be seen that some of them were not affected by gastrectomy and enteral feeding, others changed but returned to their pre-operative levels (or almost), whereas some remained altered after 14 days of recovery. According to these results, it is evident that each member of the system which expresses or regulates insulin-like activity is under a specific combination of control factors.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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