# Changes in interleukin-6 and cytokines antagonists serum concentrations in patients after pancreatic cancer surgery receiving nutritional support

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***Abstract***

*The objective of the study was to investigate the alterations in systemic production of IL-6, sTNFRI and IL-1ra before and following pancreaticoduodenectomy in patients receiving enteral nutrition with and without postoperative complications. The prospective studies included 29 patients with pancreatic cancer who had undergone pancreaticoduodenectomy. In the routine evaluation of nutritional status a weight loss, BMI, albumin concentration and lymphocyte count were taken into account. Serum concentrations of IL-6 and IL-1ra, sTNFRI (p55) were measured by ELISA. In enteral nutrition Nutridrink, Nutrison and Stresson (Nutricia) were applied. Thirteen of the 29 patients developed postoperative complications (included 2 subjects receiving enteral nutrition). Sixteen uninfected patients (including 10 patients with enteral nutrition) recovered from surgery without postoperative complications. This study provided the following information: a/ higher preoperative serum IL-6 and IL-1ra concentrations in patients without postoperative complications receiving enteral nutrition, b/ lack of significant increase in IL-6 and IL-1ra levels after major surgery in patients with uneventful postoperative course receiving pre- and postoperative enteral nutrition, and c/ high early postoperative increase of serum IL-6 levels over the preoperative values in patients without preoperative and early postoperative enteral nutrition who developed serious complications after surgery. We suggest that pre- and postoperative enteral nutrition protects against the development of postoperative complications and SIRS- type reaction after Whipple procedure. Measurement of serum IL-6, IL-1ra and sTNFRI concentrations on the 1st day after pancreaticoduodenectomy may predict the development of postoperative infectious complications often requiring re-operations.*

*Key words: pancreas surgery, complications, nutrition, cytokines*

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## Introduction

Undernourishment occurs in 50% of patients suffering from alimentary tract tumors admitted to surgical wards and is a serious social and medical problem. It considerably grows in the postoperative period, which affects the frequency of grave postoperative complications. First of all, it refers to oncological patients who require major surgery, including patients suffering from pancreatic cancer. It has been proved that malnourishment is one of the main reasons for cellular and humoral immunity disorders. Still little is known about the influence of nutritional treatment on the changes in cytokine production in malnourished surgical patients who underwent major surgery. In the majority of patients with high risk of postoperative complications, the nutritional treatment is applied without monitoring the changes in immunity

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response both pro- and anti-inflammatory in spite of more and more frequent usage of nutritional mixtures containing immunoactive substances (immunonutrition). Comparative investigations intended for proving an advantageous influence of nutritional treatment on immune system are difficult because of a variety of nutritional mixtures used and different administration routes as well as ununiformed material of patients treated mainly in intensive care units. Among many important factors having a significant influence on the investigated immune parameters there are such as: increased catabolism in postoperative period, intensifying malnourishment, the extent of surgical trauma and accompanying complications. In spite of the above mentioned problems some clinical investigations revealed that nutritional treatment enriched with glutamine, arginine, non-saturated fatty acids (omega-3) or nucleotides has a significant influence on improving outcomes in seriously ill patients with infections or after major surgery as well as on reducing the costs of treatment. No significant influence of nutritional treatment on the reduction of mortality rate has been noted [1].

In randomized studies it has been found that enteral immunonutrition improves the clinical course, decreases the frequency of severe infections, shortens hospital stays and reduces medical costs [1-4]. In patients with severe trauma receiving immunonutrition significant decreases in the duration of SIRS and in the frequency of MOF [4] have been found. Total parenteral nutrition (TPN) enriched with glutamine significantly decreases mortality in severely ill patients with MOF and reduces treatment costs by 50% [5]. The studies have been performed in various populations of patients, which makes it difficult to compare their results. The most frequently included patients were the ones with transportation traumas (ISS>20) treated in intensive care units [3, 4]. In the majority of those studies, the changes in immunity status in the course of standard nutrition or immunonutrition have not been monitored. A better knowledge of the impact of nutrition on immune inflammatory reaction mediators requires studying the kinetics of changes of selected cytokines and their inhibitors in patients with surgical trauma receiving nutrition.

The objective of the presented studies is to evaluate pre- and postoperative changes of selected immune parameters in patients with pancreatic cancer receiving enteral nutrition. In this study we measured serum levels of sTNFRI (p55), IL1ra and IL6 before and after operations. Cytokine antagonists and IL-6 were selected from an array of pro- and anti-inflammatory cytokines profile, as in our previous studies they were found to be the most sensitive markers of the postoperative inflammatory response to minor surgical trauma and major surgery with complications [6, 7].

## Materials and methods

### Patients

Twenty-nine consecutive patients with pancreatic carcinoma (tumor location in the head of pancreas) and without jaundice (patients underwent preoperative biliary drainage) undergoing standard Whipple's procedure were studied (18 men, 11 women; age range 37 to 75, median 61 years). In all patients, the diagnosis was confirmed by histopatological examinations. The clinical data of patients following pancreatoduodenectomy have been presented in Table 1. According to TNM classification, majority of the patients was with II° stage. Patients had no other severe underlying diseases. Because of preoperative malnutrition 12 moderately malnourished patients (according to body weight loss, body mass index, triceps skin fold and biochemical evaluation) were supplied for 10 days with additional preoperative and early postoperative enteral nutrition (using Nutricia products: Nutridrink, Nutrison, Stresson; 15-25 kcal/kg). Total parenteral nutrition (TPN) was administered continuously in each patient after reoperation with

**Table 1.** Clinical data for patients after pancreatic cancer resection and reoperations

| Clinical data | | Patients without complications | Patients with complications | Patients requiring re-operations |
|---|---|---|---|---|
| number of patients | | 16 | 13 | 9 |
| age [median years] | | 59 (37-75) | 60 (38-75) | 61 (42-75) |
| gender [M:F] | | 11:5 | 7:6 | 5:4 |
| tumor staging | I | 6 | 2 | 1 |
| | II | 9 | 3 | 3 |
| | III | 1 | 7 | 5 |
| | IV | 0 | 1 | 0 |
| duration of operation [min] | | 305 (210-450) | 325 (270-420) | 335 (270-420) |
| patients with postoperative blood transfusions | | 4 | 5 | 5 |

aminoacids, glucose, lipid emulsions, electrolytes, vitamins and oligoelements (25 kcal/kg).

### Blood Samples

In all patients blood samples were collected from the peripheral vein on the day preceding operation and on days 1, 3, 7 and 10 thereafter. Serum samples were prepared and stored at -80°C until further use.

### Cytokine and cytokine antagonists measurement

The serum concentrations of IL6, IL1ra, and sTNFRI were measured by enzyme immunometric assay (Quantikine R&D Systems Europe Ltd, Barton Lane Abingdon, Oxon). Each sample was examined in duplicate. The lower limit of sensitivity of the assay for serum samples was 0.7 pg/ml for IL6, 22 pg/ml for IL1ra, and 3,0 pg/ml for sTNFRI. As controls, serum concentrations of IL-6, IL-1ra and sTNFRI were measured in 16 healthy adult volunteers. In this group the IL6 concentration was 1.75±4.2 pg/ml, IL-1ra 327.6±435.2 pg/ml and sTNF-RI 869±143.3 pg/ml.

Protocol of the study was approved by the Medical University Ethics Committee. All patients signed an informed consent before entering the study.

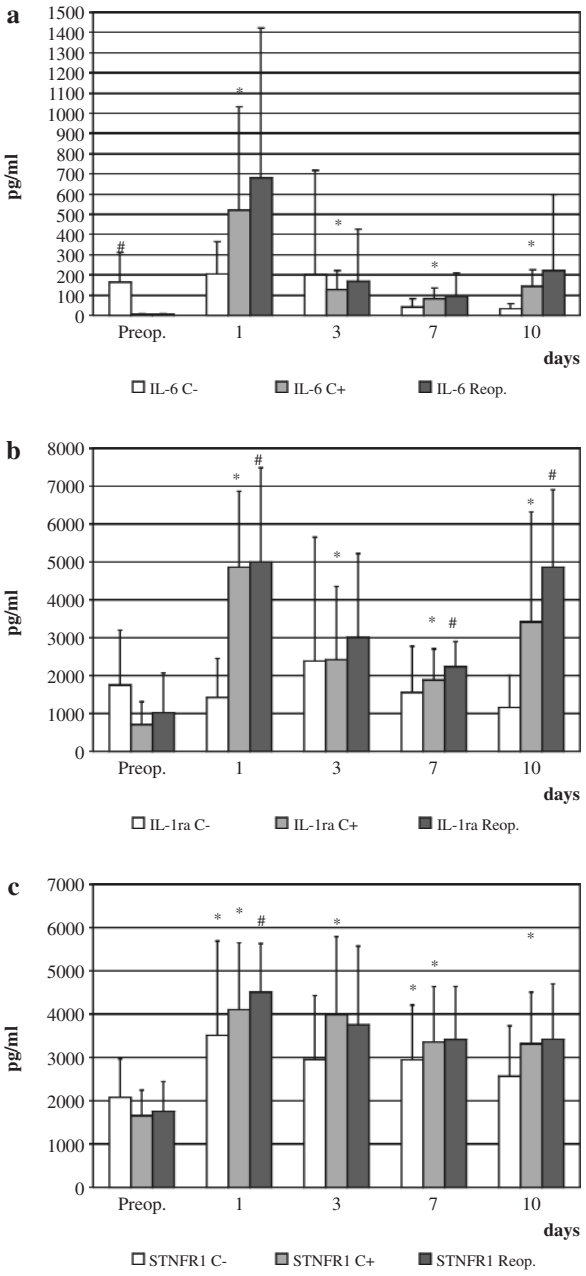
### Statistical analysis

Results were expressed as mean values ±SD [shown in figures]. Statistical analysis was started with determining the distribution of the analyzed data using the Kolmogorov-Smirnow test. Depending on the distribution of data, to assess the dynamics of postoperative changes in a specified group of patients, the analysis of variance or Friedman's test and corresponding with them Tukey's HSD test were employed, whereas the results obtained in the particular groups of patients were compared with each other using, depending on the distribution of data, t-Student test for independent variables or Mann-Whitney test. All calculations were performed by means of a statistical software package by Statistica assuming the level of statistical significance at $p<0.05$.

## Results

### Outcome

Sixteen uninfected patients (including 10 patients with enteral nutrition) recovered from surgery without postoperative complications. Nine patients had delayed gastric emptying after Whipple resection. No significant improvement in preoperative nutritional status was observed, whereas their postoperative nutritional status worsened. Thirteen of the 29 patients developed postoperative complications (included 2 subjects receiving enteral nutrition), as massive abdominal wound infections, intraabdominal abscess, anastomosis dehiscence, intestinal obstruction, intraabdominal bleeding and MOF (Table 1). Surgical reintervention was carried out in 9 patients developed severe septic complications.




* **Fig. 1a, b, c.** Serum concentrations of interleukin 6 (IL-6) (**a**), interleukin 1 receptor antagonist (IL-1ra) (**b**) and soluble tumor necrosis factor receptor (sTNFRI) (**c**), in patients without complications (□), with complications (■) and with complications requiring re-operations (■); *p<0.05 (pre- *versus* postoperative levels); # p<0.05 (uninfected *versus* re-operations)

### Patients with uneventful postoperative course

The preoperative serum IL-6 level was significantly higher in patients with uneventful postoperative course when compared with infected group (163.32±149 pg/ml in

uninfected group *versus* 4.69±3.6 pg/ml in infected group, p=0.001). There was also a tendency toward the highest preoperative level of IL-1ra in this group of patients (1750.96±1447 *versus* 706.62±604, p=0.06). In patients with uneventful postoperative course pancreatic resection did not resulted in a significant increase of serum IL-6 concentrations. The IL-6 serum concentration increased from 163.32±149 pg/ml before surgery to 204.37±162 pg/ml, 200.6±517 pg/ml on day 1 and 3, to decrease to 41.19±39 pg/ml and 34.71±24 pg/ml on day 7 and 10 (Fig. 1a).

The highest level of IL-1ra of 2384.82±3268 pg/ml was observed on day 3 to decrease on day 7 to 1551.34±1220 pg/ml and to 1157.3±852 pg/ml on day 10. The differences between pre and postoperative levels of IL-1ra were not significant (Fig. 1b).There was, a significant increase in sTNFRI level from 2078.64±887 pg/ml to 3512.08±2178 pg/ml (p=0.03), 2955.2±1473 pg/ml (p=0.02) and 2944.12±1265 pg/ml (p=0.04), on day 1 to 7 respectively in uninfected patients (Fig.1c).

### Patients with postoperative complications

In the group of patients with postoperative complications pancreatoduodenectomy resulted in a striking significant increase of serum IL-6 concentrations on day 1 followed by decline between day 3 to 10 (Fig. 1a). The IL-6 serum level rose from 4.69±3.6 pg/ml before operation to 520.72±511 pg/ml on day 1 and to 128.6±94 pg/ml, 83.38±50 pg/ml and 144±82 pg/ml on days 3, 7 and 10 respectively (before vs. after surgery, all p=0.007). There were no significant differences when comparing IL-6 concentrations in patients requiring reoperations with the uninfected ones. In the group of patients requiring reoperations, the IL-6 serum level rose from 3.85±2.4 pg/ml to 679.4±742 pg/ml on day 1 and 169.1±257 pg/ml, 93.25±115 pg/ml and 220.5±377 pg/ml on days 3, 7 and 10 respectively (before vs. after surgery, all p=0.007).

After pancreatic resection the serum IL-1ra concentration was significantly increased in infected group and reached concentration of 4860±2005 pg/ml, 2419.5±1933 pg/ml, 1883.37±818 pg/ml and 3416.25±2906 pg/ml on day 1, 3, 7 and 10 respectively (before vs. after surgery, all p=0.01). In patients who required reoperations IL-1ra concentrations were significantly higher as compared with uninfected group on day 1 (4998±2447 pg/ml *versus* 1422.48±1028 pg/ml, p=0.04), 7 (2233.4±665 pg/ml *versus* 1551.34±1220 pg/ml, p=0.04) and 10 (4681.5±2043 pg/ml *versus* 1157.30±852 pg/ml, p=0.01) (Fig. 1b).

The serum sTNFRI rose significantly from 1653.57±590 pg/ml before first surgery to 4105.35±1544 pg/ml (p=0.01), 3982.14±1807 pg/ml (p=0.02), 3357.14±1280 pg/ml (p=0.01) and 3316.07±1191 pg/ml (p=0.003) on days 1, 3, 7 and 10 after and was significantly higher in patients requiring reoperations as compared with uninfected group on day 1 following pancreatic resection (4507.5±1123 pg/ml *versus* 3512.08±2178 pg/ml in uninfected group, p=0.03) (Fig. 1c).

## Discussion

The primary postoperative immune response depends on the mass of traumatized tissues and their location. It is mediated by the proinflammatory cytokines, among others, interleukin- 1 (IL-1), IL-6 and tumour necrosis factor (TNF), and modulated by the naturally occurring antagonists of these cytokines as soluble TNF receptor (sTNFR) and IL-1 receptor antagonist (IL-1ra) [8, 9]. The postoperative complications as pancreatic leakage, intra-abdominal abscesses and surgical reintervention may further stimulate cytokines and cytokine antagonists production leading to the development of systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS) [8, 10, 11]. This may be expected especially after major surgical procedures on the pancreas with postoperative complications [12]. We have previously found that infective complications at the site of colon anastomosis bring about a sharp increase in plasma sTNFRI already on day 1 and of IL6 and CRP on day 3 after the operation [7]. Thus, serum cytokine antagonist levels may be a good early indicator of the development of postoperative complications .

The first important finding of our study was that the patients without complications showed no early postoperative rise of serum IL-1ra and IL-6 concentrations over preoperative values. Analysis of this group revealed that the majority of patients as a result of preoperative malnutrition received pre- and postoperative enteral nutrition. Interestingly, the preoperative serum IL-6 level (163 pg/ml) was significantly higher in this group of patients. There was also a tendency to a higher preoperative concentration of IL-1ra in patients with uneventful postoperative course. These results suggest that not only surgical trauma, but also preoperative IL-6 and IL-1ra levels, as well as malnutrition and nutritional support were the main factors which may influence the postoperative IL-6 and IL-1ra levels. An additional factor was the neoplastic process advancement (Table 1).

Low postoperative pro-(IL-6) and anti-inflammatory (IL-1ra) response to pancreatic surgery in patients without infections may reflect the pancreatic cancer immunosupression and patients malnutrition. In pancreatic cancer, soluble factors produced by and for the protection of the tumor environment have been detected and are often distributed to the victim's circulatory system where they may effect a more generalized immunosupression. Our study has shown that in patients without postoperative complications after Whipple resection only sTNFRIp55 level was significantly increased between day 1 and 7 (Fig. 1c). These results suggest that the plasma sTNFRI concentration changes occurring after pancreaticoduodenectomy constitute a very sensitive independent of malnutrition marker of anti-inflammatory response to pancreatic surgery. As a result of malnutrition patients undergoing pancreaticoduodenectomy often require postoperative artificial nutrition. The early postoperative enteral nutrition has recently been suggested to surgeons as a way of

improving the postoperative outcome of patients with major surgery of the gastrointestinal tract [13]. Our study confirmed these observations. Despite the normal preoperative nutritional status, the majority of patients without early postoperative enteral nutrition after pancreaticoduodenectomy developed serious complications. There is a hypothesis that the early enteral nutrition prevents gut mucosal atrophy, which subsequently results in maintaining the mucosal barrier and thereby protects against bacterial translocation. Several clinical studies have demonstrated that early postoperative enteral nutrition can reduce septic complications and improve whole body protein kinetics and wound healing [1, 14].

The results of our study indicate that the high early postoperative rise of serum sTNFRI, IL-1ra and IL-6 levels over the preoperative values, may predict the outcome in oncologic patients after pancreatoduodenectomy (Fig. 1a, b, c). This SIRS- like reaction on day 1 after Whipple procedure in patients developed (between day 8 to 21) serious postoperative septic complications requiring reoperations, has an important clinical implication. Early detection by clinical examination of these complications within the first postoperative days is difficult. If systemic spillover and persistent release of anti-inflammatory mediators is diagnosed early, a faster diagnostic (early searching of infections sources) and therapeutic approach (e.g. faster surgical or nutritional intervention) can prevent the development of late septicemia and formation of an abscess or fistula. Increase of the suppressive mediators might be closely related to the development of severe sepsis and MOF in trauma patients [15], but the estimation of critical levels for sTNFRI and IL-1ra in each patient after pancreatoduodenectomy is difficult. In our study in the group of patients requiring reoperations sTNFR p55 reaches the peak level of 4507 pg/ml (Fig. 1c) which is at the same time a 1000pg/ml higher than in uninfected patients. This significant difference between physiological reaction to major surgical trauma and massive anti-inflammatory response on day 1 after Whipple procedure reflects early excessive immunosupression that precedes the development of serious complications. Anti-inflammatory mediators seem to be prerequisite for controlling and down-regulating the inflammatory response leading to a depression of the immune system of patients. Cytokine inhibitors such as soluble tumor necrosis factor receptor (sTNFR) I and II, IL-1ra, or soluble IL-1 receptors (sIL-1r) are significantly increased in the circulation of patients with sepsis. Higher levels of IL-6, IL-1ra, and sTNFR were detected in patients with severe sepsis and early hemodynamic deterioration [16]. The elevated levels of the anti-inflammatory cytokines, TNFR I, and TNFR II, appeared to reflect an attempt to suppress the shock syndrome [17]. It was found that the administration of exogenous sTNFR and IL-1ra might provide a therapeutic benefit in patients at high risk of sepsis [18-20]. High plasma concentrations of IL-1ra, an anti-inflammatory mediator, which inhibits IL-1 binding to receptor without agonist activity, have also been demonstrated in critically ill septic patients, in patients with MOF after major torso trauma, following some operative trauma and in response to endotoxin. The release of anti-inflammatory mediators after major torso trauma correlates with the development of postinjury multiple organ failure [21]. Schwenk et al. [22] reported that plasma concentrations of IL-1ra increased after colorectal resections and remained above the preoperative levels during the first postoperative week. A study of Pruitt et al. [23] revealed the peak plasma concentrations of IL-1ra (at 2-4 h) in patients undergoing thoraco-abdominal aneurysm repair, bowel resection and in patients with sepsis. Similarly, O'Nuallain [24, 25] has shown that IL-1ra can be induced as an early-response cytokine following major trauma in the absence of an infection. The highest IL-1ra level was detected in patients 4 hr after the commencement of an abdominoperineal colon resection and within 24 hr it reached the preoperative values. After partial hepatectomy, Kimura et al. [11] demonstrated that plasma IL-1ra concentration did not differ significantly between the infected and uninfected groups.

Our study has indicated that anti-inflammatory mechanisms are activated early after pancreaticoduadenectomy. Since increased levels of sTNFRI, IL-1ra and IL-6 correlate with serious complications requiring reoperations, they may contribute to our understanding of the pathogenesis as well as prediction of outcome. High levels of serum antagonists to TNF and IL-1 after pancreas resection suggest tissue level involvement of these cytokines in postinjury hyperinflammation. Previous studies revealed that in patients undergoing pancreaticoduodenectomy, a large increase in portal, and a significantly lower increase in peripheral, IL-6 levels were observed, but no significant increase in TNF levels was noted [26].

Summarizing, the results of our study confirmed the usefulness of cytokine antagonists and IL-6 measurement in patients after pancreaticoduodenectomy for early recognition of local infective complications and they also partly explain the mechanism of lack of early postoperative rise of serum IL-1ra and IL-6 concentrations over preoperative values in patients without complications when majority of patients received pre- and postoperative enteral nutrition. We suggest that pre- and postoperative enteral nutrition protects against the development of postoperative complications and early SIRS-type reaction by inhibiting cytokine and cytokine inhibitors production after surgical trauma. The possibility of influence of neoplastic process stage and nutritional status in patients on the changes in the immune parameters being studied requires further investigations. Measurement of serum IL-6, IL-1ra and sTNFRI concentrations on the 1st day after pancreaticoduodenectomy may predict the development of postoperative infectious complications often requiring reoperations.

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