Immunonutrition after major pancreatic surgery

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Abstract

The objective of the study was to investigate whether early enteral immunonutrition in comparison with standard enteral feeding affects the cellular immunity and systemic production of cytokines in malnourished patients after pancreaticoduodenectomy. The prospective randomized studies included 41 patients with pancreatic cancer who had undergone pancreatic resection. In the routine evaluation of nutritional status a weight loss, BMI, albumin concentration and lymphocyte count were taken into account. In 22 patients standard postoperative enteral nutrition and in 19 patients immunonutrition were applied. Mononuclear cell subsets (CD3+, CD4+, CD4+/CD25+, CD4+/CD38+, CD8+, CD19+, CD19+/CD95+, CD19+/CD38+, CD14+, CD14+/HLADR+) and cytokines (IL-1β, IL-1ra, IL-6, IL-8, IL-10, TNF-α, sTNFRI) were determined before and on days 1, 3, 7 and 10 after surgery using flow cytometry and ELISA test. In patients receiving immunonutrition between days 3-10 after operation, the percentage of CD19+ cells was significantly higher (standard vs. supplemented group, respectively: day 3: P=0.001, day 7: P=0.01 and day 10: P=0.001). In patients receiving standard enteral nutrition no significant changes in the subpopulation of CD4+, CD4+/CD25+, CD4+/CD38+ and CD8+ lymphocytes were noted. The percentage of remaining lymphocyte subpopulations (CD3+, CD19+/CD95+) in both groups did not significantly change. Serum concentrations of IL-1ra in the early post-operative period were significantly higher in patients treated with enteral immunonutrition than in those treated with the standard diet (day 7: P<0.001; day 10: P=0.002). Similar results were observed for IL-6 (day 10: P=0.017), IL-8 (day 1: P=0.01; days 3, 7, and 10: P<0.001) and IL-10 (days 3 and 10: P<0.001) whereas the post-operative levels of IL-1β (day 7: P<0.001) and TNF-α (day 3: P=0.006; day 7: P<0.001) were significantly higher in patients with standard enteral nutrition. Early enteral immunonutrition as compared to standard nutrition has an immunomodulative effect on the changes in the immune response after extensive surgical trauma resulting in the selective stimulation of cellular immunity and cytokines levels. Among the evaluated immune parameters only the changes in percentage of lymphocyte B (CD19+ cells) and interleukin-1 receptor antagonist (IL-1ra) in malnourished patients after pancreatic cancer resection are the earliest sensitive markers of immune response to enteral immunonutrition.

Key words: *immunotrition , immune response, pancreatic cancer surgery.*

(Centr Eur J Immunol 2008; 33 (2): 67-73)

Introduction

Malnutriton is a major global public health problem and can be defined as a state of nutrition in which a deficiency of energy, protein and other nutrients like arginine, glutamine, fatty acids, vitamins and trace elements causes measurable effects on body and tissue function and clinical outcome. It has been proved that malnutrition is associated with an impaired immunity and increased susceptibility to

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infections. The immune disorders and malnutrition are worse in the early postoperative period which considerably affects the process of wound healing, intestinal barrier function and the number of post-operative complications [1-4]. Pancreaticoduodenectomy is one of the most invasive operations in upper abdominal surgery with a high incidence of postoperative complications [5-7]. The immune disorders occurring together with the surgical injury as well as the malnutrition which worsens after surgery usually worsens outcome. The attempt to correct the postoperative nutritional disorders by introducing immunonutrition is a promising way of improving outcome, but as yet little is known about the mechanisms of correcting postoperative immune disorders by using this type of nutrition. Previous investigations suggested that applications of postoperative parenteral nutrition to patients undergoing major pancreatic resection for malignancy cannot be recommended because the complications were significantly more serious after TPN compared to the groups not receiving the adjuvant TPN [8, 9]. The enteral feeding administered through a jejunostomy catheter as compared with total parenteral nutrition (TPN) was a safe and beneficial solution for patients who have undergone duodenohemipancreatectomy for a peri-ampullary mass [10]. Braga et al. [11] proved that early enteral feeding was a suitable alternative to TPN after major abdominal surgery for gastric or pancreatic cancer and the enriched diet appears to be more beneficial in malnourished and transfused patients. In patients with neoplasms of the colorectum, stomach, or pancreas, the perioperative administration of a supplemented enteral formula (enriched with arginine, RNA, and omega-3 fatty acids) reduced post-operative infections and the length of hospital stay.

The impact of immunonutrition on the immune system of malnourished surgical patients undergoing pancreaticoduodenectomy for cancer still remains unclear. Understanding the effect of enteral immunonutrition on the compromised lymphatic immune system of pancreatic cancer patients following major surgery is crucial for therapeutic approach. The question is: to what extent can we regulate the immune response to surgical trauma using enteral immunonutrition for low local bacterial load and reduction of exaggerated hyperinflammation (SIRS: systemic inflammatory response syndrome) which leads to immune function breakdown and postoperative complications?

Any further insight into the possibility of using immunonutrition to regulate immune disorders after an extensive operative injury requires further investigation of the changes in cellular immunity and cytokine levels during immunonutrition. The aim of our study was to investigate the alterations in peripheral blood mononuclear subsets and systemic concentrations of cytokines before and after pancreaticoduodenectomy for cancer in malnourished patients receiving enteral immunonutrition and standard enteral feeding.

Materials and Methods

Patients

Sixty patients operated on for pancreatic cancer were randomized (by using numbered sealed envelopes stratified by the surgeon) to receive either the early standard diet (30 patients) or the immune-enhancing enteral diet (30 patients). After full clinical diagnostic procedures (image and laboratory tests), all patients were operated on for resection of the head of the pancreas (Whipple's pancreaticoduodenectomy). Histopathological examination confirmed the diagnosis. The indication for early post-operative enteral nutrition treatment was the pre-operative loss of body mass (greater than 6% within 2 months) and the extent of surgery (including the advancement of the tumor) questioning the possibility of receiving an oral diet covering the calorific and protein demand within 7 days after the procedure [12]. Nutritional status (loss in body mass, body mass index (BMI), albumin concentration and total lymphocyte count) was assessed before surgery and on day 7 after surgery. In order to evaluate the loss in the body mass, the body weight assessed before surgery was compared to that of the previous two months, while the body weight assessed after surgery was compared to that evaluated before surgery. The present investigation did not include patients with unrespectable pancreatic cancer, those who had had transplantation of organs, patients treated with chemo- or radiotherapy or immunosuppressors, patients with auto-immune diseases, with diabetes type 1 (insulin-dependant), chronic respiratory insufficiency (chronic obstructive pulmonary disease), cardiovascular insufficiency, and kidney and liver diseases (biopsy-proven cirrhosis or a serum total bilirubin greater than 3.0 mg/dL). According to these criteria, 19 out of the 60 patients were excluded: 8 patients in the standard nutrition and 11 patients in the supplemented group. Therefore, this prospective and randomized study included 41 patients (29 males, 12 females; mean age: 56.8±10.2 years): 22 patients received the standard diet and 19 patients received the supplemented diet. The characteristics of the two groups of patients are shown in Table 1.

Enteral Nutrition

Two enteral diets were evaluated: an early standard diet (Nutrison®, Nutricia Export BV, Zoetermeer, Holland) and an immune enhancing diet (Stresson®, Nutricia Export BV, Zoetermeer, Holland). In both groups the post-operative nutrition was carried out by using a pump and a tube installed in the distal small bowel loop during surgery. The rate of increase in the diet was gradually increased from 30 mL/h for the first 24 to 48 hours and then increased to full feeding depending on the passage of flatus and bowel action. All patients reached their nutritional goal within 72 h. The mean total feeding time for the entire group of patients was 12.3±2.0 days. The extension of enteral

Table 1. Patient characteristics and surgical parameters of the two groups of patients

Characteristics	Standard diet (No. 22)	Supplemented diet (No. 19)	P value
Age (years)	54.2±4.1	59.8±6.0	0.001[a]
Gender:			0.744[b]
– Males	15 (68.2%)	14 (73.7%)	
– Females	7 (31.8%)	5 (26.3%)	
Tumor staging (TNM):			0.507[c]
– I	8 (36.4%)	9 (47.4%)	
– II	11 (50.0%)	8 (42.1%)	
– III	3 (13.6%)	2 (10.5%)	
Duration of surgery (min)	343±45	330±60	0.434[a]
Operative blood loss (mL)	600±350	550±300	0.629[a]
Transfused patients	7 (31.8%)	6 (31.6%)	1.000[b]
Nutritional status before surgery			
Weight loss (%)	6.3±3.4	6.5±2.1	0.825[a]
BMI (kg/m^2)	22.2±3.2	23.4±4.5	0.326[a]
Albumin (g/L)	28.5±3.1	29.8±0.8	0.076[a]
Total lymphocyte count (cells/mm^3)	1,900±624	2,151±253	0.109[a]
Nutritional status after surgery			
Weight loss (%)	9.2±3.2	9.1±2.8	0.916[a]
BMI (kg/m^2)	21.8±3.0	22.4±6.3	0.693[a]
Albumin (g/L)	20.3±6.8	24.1±5.4	0.057[a]
Total lymphocyte count (cells/mm^3)	930±145	1,140±262	0.003[a]

Data are reported as mean±SD or frequencies. [a] One-way ANOVA; [b] Fisher's exact test; [c] Chi-squared: linear by linear association.

immunonutrition time in several patients resulted from delayed gastric emptying frequency which made it impossible to earlier introduce oral feeding, and occurred with similar frequency in both groups. The daily supply of the main nutritional substances in standard enteral nutrition was, on the average: 10.8±1.3 g nitrogen, 208±24 g glucose, 66.0±7.7 g fat (including 102±12 g of protein and 1.693±198 kcal) whereas, in enteral immunonutrition, it was: 14.7±2.2 g nitrogen, 177±26 g glucose, 51.4±7.5 g fat, 16.4±2.4 g glutamine, 10.9±1.6 g arginine (including 91.8±13.5 g protein and 1.529±224 kcal). The supply of calories was significantly greater (P=0.017) in the standard diet (glucose: P<0.001; fat: P<0.001; protein: P=0.014) while the nitrogen content was significantly higher in the supplemented group (P<0.001). Tolerance for both formula diets was excellent.

All patients received antibiotics for prophylaxis (1.2 g amoxicillin-potassium clavulanate combination and 2.0 g of cefoperazone) and low-particle heparin; they were given crystalline fluids intravenously as well as electrolytes, depending on actual demand.

Cellular immunity and cytokines measurement

In all patients, blood samples were collected from the peripheral vein on the day preceding surgery and on post-operative days 1, 3, 7 and 10. The phenotype of cellular sub-populations (including the percentage of the following cells: CD3+, CD4+, CD4+/CD25+, CD4+/CD38+, CD8+, CD19+, CD19+/CD95+, CD19+/CD38+, CD14+, CD14+/HLADR+) was tested by using flow cytometry (cytometer LSR Becton Dickinson, reagents supplied also by Becton Dickinson). Tests were carried out immediately after collecting blood samples.

The serum concentrations of IL-1β, TNF-α, IL-6, IL-8, IL-10, IL-1ra and sTNFRI (p55) were determined using commercially available enzyme immunoassay kits (Quantikine R&D Systems Europe Ltd, Barton Lane Abingdon, Oxon, United Kingdom). Samples were prepared and tested

Table 2. The dynamics of changes in cellular immune response (% of cells) in patients who underwent surgery for pancreatic cancer treated with standard enteral nutrition or enteral immunonutrition

Variables	Diet	Pre-operative	POD –1	POD –3	POD –7	POD –10
CD3+	standard	64.24±14.4	60.2±16.9	66.23±13.8	68.92±12.4	69.72±15.0
	supplemented	71.49±9.4	68.91±8.8	71.63±10.8	72.08±10.9	67.89±13.1
CD4+	standard	32.12±7.6	39.72±8.1	40.35±14.6	41.12±9.02	42.06±14.1
	supplemented	36.64±13.0	35.56±8.8	39.9±13.7	43.14±10.9[a]	41.58±14.4[a]
CD4+/CD25+	standard	6.87±4.1	4.47±2.3	4.92±2.9	5.3±3.3	6.34±5.1
	supplemented	3.32±2.1	3.8±2.2	3.6±1.9	4.93±3.1[a]	12.17±8.5[a]
CD4+/CD38+	standard	19.28±8.0	14.65±7.2	18.01±5.9	20.6±14.6	17.12±11.5
	supplemented	18.34±9.0	16.35±4.5	20.11±8.9	24.04±9.8[a]	24.15±10.3[a]
CD8+	standard	30.94±11.4	25.5±11.5	26.33±8.3	29.1±12.3	30.5±13.5
	supplemented	39.65±13.6	37.16±15.23	31.33±16.3[a]	29.9±13.4[a]	33.52±15.8[a]
CD19+	standard	3.63±2.4	7.28±5.41[a]	5.38±4.2[a]	5.75±4.3a	5.12±3.1
	supplemented	6.14±3.6	9.91±7.4[a]	17.53±10.2[a, b]	10.52±5.9[a, b]	17.34±4.8[a, b]
CD19+/CD95+	standard	2.83±1.4	1.8±0.6	1.57±0.9	1.86±0.7	1.95±0.8
	supplemented	1.72±1.3	1.6±0.9	1.45±0.5	1.92±1.3	1.77±0.9
CD19+/CD38+	standard	5.34±1.2	6.28±3.6	7.31±6.2	7.28±4.0	5.13±3.2
	supplemented	4.09±1.7	6.51±2.7[a]	9.46±4.9[a]	8.19±3.5[a]	5.68±2.4
CD14+	standard	10.4±8.3	26.92±16.15[a]	23.19±14.5	19.97±17.6	13.06±11.2
	supplemented	10.28±6.8	32.25±14.0[a]	26.95±13.5[a]	24.62±12.2[a]	22.87±14.8[a]
CD14+/HLA-DR+	standard	19.28±15.3	14.86±6.13	13.42±6.7	13.61±8.4	18.31±11.8
	supplemented	31.0±17.7	16.96±7.8[a]	19.82±11.6[a]	21.9±12.3[a]	28.17±13.4

[a] P<0.05, preoperative versus postoperative levels; [b] P<0.05, standard versus supplemented group; POD – postoperative day.

in duplicate according to the manufacturers' instructions. The lower limit of sensitivity of the assay for serum samples was 1 pg/mL for IL-1β, 4.4 pg/mL for TNF-α, 0.7 pg/mL for IL-6, 10 pg/mL for IL-8, 3.9 pg/mL for IL-10, 22 pg/mL for IL-1ra and 3.0 pg/mL for sTNFRI. Blood samples were stored at –80°C.

Ethics

The patients gave a written consent after the details of the protocol were fully explained. The protocol of the study was approved by the Medical University Ethics Committee and conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki.

Statistics

The data are presented as frequencies, means and standard deviations. Patient characteristics and surgical parameters of the two groups (standard vs. supplemented) were compared by using one-way ANOVA, chisquared (linear by linear association) and Fisher's exact tests according to the type of variable (continuous, ordinal, and dichotomous). A two-tailed P value less than 0.05 was selected to indicate significance. All computations were performed using the SPSS 12.0 statistical package.

Results

In comparison with the preoperative values during the postoperative period a significant rise in cellular immune response was noted in the group of patients treated with early enteral immunonutrition. Significant increase in the number of lymphocyte subpopulation CD4+ (P=0.02), CD4+/CD25+ (P=0.02), CD4+/CD38+ (P=0.006) was noted on day 7 and 10, whereas a significant decrease in CD8+ lymphocyte percentage between days 3-10 (peak on day 7, P=0.0001) was revealed. In patients receiving standard enteral nutrition no significant changes in CD4+, CD4+/CD25+, CD4+/CD38+ and CD8+ (Table 2) lymphocyte subpopulation were noted. Among the evaluated cellular immunity parameters the percentage of CD19+ cells between days 3-10 after the operation was significantly higher (standard vs. supplemented, respectively P=0.001, P=0.01 and P=0.001) only in patients treated with immunonutrition. The percentage of remaining lymphocyte subpopulation (CD3+, CD19+/CD95+) did not change significantly in both groups.

When comparing the two groups (standard vs. supplemented) during the post-operative period, significantly higher concentrations of IL-6 (day 10: P=0.017), IL-8 (day 1: P=0.01;

Table 3. Changes in kinetics of serum cytokine and cytokine antagonist levels (pg/ml) before and after surgery in patients with standard and supplemented diet

Variables	Diet	Pre-operative	POD –1	POD –3	POD –7	POD –10
IL-1β	standard	3.6±1.8	3±2.1	3.8±2.6	2.9±0.8	4.92±3.5
	supplemented	5.8±2.3[b]	3.6±1.7	2.8±1.5	1.4±0.9[b]	4.58±2.6
IL-1ra	standard	458.4±365.6	3198.7±1979.3[a]	3582.7±2044.1[a]	221.3±994.9[a]	2694.5±1223.6[a]
	supplemented	1069.5±940	2792.6±1416	4106.2±2022.9[a]	3909.2±1398.3[a, b]	4544.8±2215.2[a, b]
IL-6	standard	55.2±45.02	355.3±143.2[a]	189.1±153.6	99.9±42.7	96.1±45.0
	supplemented	13.1±8.8[b]	280.7±64.9[a, b]	233.9±159.6[a]	81.4±40.6[a]	150.5±85.8[a, b]
IL-8	standard	20±19.07	66±38.7[a]	39±29.7	26.5±18.8	47±36.1
	supplemented	85±40.1[b]	105±53.8[b]	140±58.1[b]	85±34.6[b]	110±63.9[b]
IL-10	standard	7.5±6.5	17.7±10.9[a]	8.3±7.7	20.2±14.7	7±6
	supplemented	14.3±5.3[b]	17.5±11.5	18.1±6.4[b]	24.3±15.4	45±31.7[b]
TNF-α	standard	5.6±2.5	5.9±3	4.6±3.7	9.7±8.4	7.4±5.4
	supplemented	3.1±2.1[b]	4.1±3.8	2±1.2[b]	2.5±1.1[b]	8±5.3
sTNFRI	standard	1888.3±818.2	3478.6±1177.8[a]	3821.4±2139.8[a]	3035.7±1224[a]	3561±2023.6[a]
	supplemented	1531.2±716.9	3256.4±1144.2[a]	3491.2±1385.7[a]	3297.5±1053.2[a]	3178.7±929.2[a]

[a] P<0.05, pre-operative versus post-operative levels; [b] P<0.05, standard versus supplemented group; POD – Post-operative day.

days 3, 7, and 10: P<0.001), IL-10 (days 3 and 10: P<0.001) and IL-1ra (day 7: P<0.001; day 10: P=0.002) were found in patients receiving early enteral immunonutrition (Table 3) whereas post-operative levels of IL-1β (day 7: P<0.001) and TNF-α (day 3: P=0.006; day 7: P<0.001) were significantly higher in patients with standard enteral nutrition. Nutritional status assessment after surgery also revealed significantly increased total lymphocyte count (P=0.003) in patients receiving the supplemented diet (Table 1).

Discussion

The current study investigated whether early enteral immunonutrition as compared to standard enteral feeding affected the immune response defined by dynamics of changes in systemic levels of lymphocytes and monocytes subsets and systemic production of pro- and anti-inflammatory cytokines in malnourished patients after pancreaticoduodenectomy. The results of our investigations confirm the modulative effect of immunonutrition on changes in immune response to surgical trauma in the post-operative periods which have been emphasized by other authors. Unlike previous investigations which did not cover the wide range of cellular subsets and cytokines in malnourished patients after pancreatic cancer surgery, in the current study, early enteral immunonutrition had a significant effect only on the post-operative percentage of CD19+ cells whereas concentration of majority of assessed cytokines and their inhibitors (IL-6, IL-8, IL-10 and IL-1ra) as compared to standard nutrition were elevated. It questions the advantage of early postoperative enteral immunonutrition effect as compared with standard nutrition on the level of cellular immune response.

The results obtained can be explained by the stimulating effect of immunonutrition (mainly glutamine) on the immune system of the bowel (GALT). The nutritional formula we used in our studies contained glutamine not included in standard nutrition. First of all, glutamine as a nitrogen donor for the synthesis of purines and pyrimidines is the major energy source for the immune system and cells of the small intestine, such as enterocytes. Glutamine maintains the integrity of the gut mucosa. After the enteral administration of glutamine, the number of T-lymphocytes increases in Peyer's glands [13] whereas, after parenteral administration, the concentration of serum IgA, IL-4 and IL-10 decrease in the intestinal mucous membrane [14]. Some previous studies have shown that glutamine depletion increases spontaneous apoptosis and oxidant-induced cell death in intestinal epithelial cell lines [15]. These changes can worsen in malnourished patients after an extensive surgical trauma.

Kemen et al. [16] proved that after gastrointestinal surgery for cancer, the supplementation of early postoperative enteral diet with arginine, RNA, and omega-3 fatty acids in the early postoperative period improves postoperative immune responses and helps to more rapidly overcome the immune depression after surgical trauma. The number of T lymphocytes and their subsets, helper T cells (CD4) and activated T cells (CD3, HLA-DR), were significantly higher in the supplemented diet group on postoperative days 10 and 16. B-lymphocyte indices were significantly higher in the supplemented vs. the placebo diet group on postoperative days 7 and 10. In our studies the patients receiving immunonutrition with glutamine, arginine and fatty acids (EPA,DHA) showed (only in comparison with the preoperative values) not only an increased percentage of CD4+ cells, but also the percentage of active T and B lymphocytes (CD25+, CD38+). The percentage of active monocytes (CD14+/HLA-DR+) in the group of patients treated with supplemented diet was significantly lower, which could be explained as the recovery of normal immune response to an extensive surgical trauma. Study of Schilling et al. [17] who used supplemented formulas in patients undergoing major abdominal surgery proved that after enteral immunonutrition, the expression of activated surface antigen HLA-DR was diminished on CD14+ cells. In our opinion the effect of immunonutrition on the cellular immune response in malnourished patients after pancreatic cancer resection would be more intense if the same nutrition was also received in the preoperative period. The results of most recent studies performed in patients operated on for colorectal cancer suggest that postoperative cellular immune response disorders (Th1/Th2 imbalance) should be corrected by introducing short-term (5-day-long) preoperative enteral immunonutrition [18]. However, it is known that in the group of patients suffering from colorectal cancer malnutrition is much less frequent than in patients with pancreatic cancer.

The post-operative changes in the concentration of cytokines on subsequent post-operative days can be associated with the effect of enteral immunonutrition. Intestinal requirements for glutamine appear to increase during catabolic conditions associated with decreased plasma glutamine concentrations and increased cytokine generation by gut mucosal cells [19]. In our opinion, the stimulation of intestinal immune system cells by applying immunonutrition to especially increase the production of IL-1ra in an early period after extensive surgical trauma can have a positive effect on the regulation (decrease) of the post-operative inflammatory response. At the same time, we have to ask the following question. How long should we maintain the effect (stimulation of IL-1ra production) and to what extent can it be increased by immunonutrition, for example, either by raising the dose of glutamine or arginine, or by introducing immunonutrition as early as possible in the pre-operative period. Our previous studies of malnourished patients operated on for esophageal cancer showed that the application of standard parenteral and enteral preoperative nutrition for a period of 10 days resulted in a significant increase of IL-6 and IL-1ra concentration in the peripheral blood even before surgery, but it did not affect the concentration of sTNFRI and pre-operative improvement of the nutrition status [20].

Our study has clearly indicated that the anti-inflammatory mechanisms are activated early in malnourished patients after pancreaticoduodenectomy receiving enteral immunonutrition. Early enteral immunonutrition in comparison to standard nutrition has an immunomodulative effect on the changes in the immune response after extensive surgical trauma. These consist in selective stimulation of IL-6, IL-8, IL-10 and IL-1ra production and down-regulation of IL-1 beta and TNF-α production. Among all the cytokines investigated and their inhibitors, IL-1ra is the most sensitive marker of post-operative anti-inflammatory response to enteral immunonutrition in malnourished patients with pancreatic cancer. The temporary increase in IL-1ra concentration between post-operative days 7-10 obtained as a result of enteral immunonutrition decreases the inflammatory response to extensive surgical trauma and shortens its duration; this accelerates the wound healing process/tissue regeneration and may help avoid late complications (fistulas, abscesses). It can be presumed that the lack of physiological immune response (unelevated IL-1ra concentration) after enteral immunonutrition may indicate that the intestinal immune system is impaired which may lead to bacterial translocation.

In conclusion it must be emphasized that among the evaluated immune parameters only the changes in percentage of lymphocyte B (CD19+ cells) and interleukin-1 receptor antagonist (IL-1ra) in malnourished patients after pancreatic cancer resection are the earliest sensitive markers of immune response to enteral immunonutrition.

Acknowledgements

This work was supported by the Committee for Scientific Research, Warsaw, Poland (grant number: 2PO5B/059/28).

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