Journal of Nutritional Disorders & Therapy

Matras et al., J Nutr Disorders Ther 2018, 8:1
DOI: 10.4172/2161-0509.1000227

Original Article Open Access

"When is Glutamine Supplementation Beneficial?"

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Received date: February 24, 2018; **Accepted date**: March 26, 2018; **Published date**: March 31, 2018

Abstract

The role of glutamine in metabolic processes has been quite extensively researched and described, though no consensus exists as to its role in treatment. It is considered significant mainly for ICU patients; though no clear criteria for including glutamine in treatment have been defined. It is known that glutamine should be administered as a complement to nutritional treatment, and not independently. The purpose of the paper was to identify practical criteria for determining the clinical benefits of glutamine supplementation. The study was performed in the years 2007-2015 at the 1st Department of General and Transplantation Surgery and Nutritional Therapy of the Lublin Medical University in Lublin, Poland. It included patients scheduled for surgery due to a gastrointestinal cancer. The final study group included 105 patients, 48 female and 57 male.

We found that low blood concentration of glutamine was correlated with a higher incidence of postoperative complications. ROC analysis allowed for identification of glutamine concentration below which there is a very high risk of complications. The threshold glutamine value identified was 205.15 nmol/ml. Low total lymphocyte count and serum albumin concentration can help identify patients in whom glutamine supplementation can decrease postoperative complication incidence, especially in the case of malnourished patients. Glutamine supplementation before a scheduled surgical procedure may benefit patients with a preoperative glutamine concentration below 205.15 nmol/ml. Glutamine supplementation can benefit malnourished patients.

Keywords: Immunonutrition; Clinical nutrition; Malnutrition; Complication postoperative

Research to date indicates the importance of glutamine supplementation in patients in serious clinical condition [1,2], and a lack of indications for the treatment in patients in good overall condition [3-5]. Guidelines are quite vague and based on clinical criteria ("ICU patients", "in critical condition", "after serious trauma", "with extensive burns") [6-9].

There is no clear indication of the precise moment when supplementation is required. Throat or upper gastrointestinal surgery patients who are malnourished are known to benefit from an immunomodulatory diet [10-14]. This is also reflected in the ESPEN guidelines [15-17]. However, the guidelines only refer to the need for administering a mixture of immunoactive substances, not to specific substances such as glutamine [18,19].

All study models verifying whether glutamine supplementation reduces postoperative complications have been based on comparisons between groups treated and not treated with preparations containing this amino acid [20-30]. There is a shortage of studies on the impact of glutamine deficiency on complications, or on the degree of deficiency necessitating supplementation.

The increased incidence of postoperative complications in malnourished patients is obvious [31-33]. Therefore, the question arises as to whether glutamine is involved in the process. Its role in the body suggests it indeed is involved [34-37].

Also, there is the question about other ways to increase its concentration in the blood, and whether these methods effect a decrease in complication incidence. Answers to these questions could indicate how to manage patients both pre- and postoperatively [38], and are thus the basis for the present paper.

The premise of the study was to test serum glutamine concentrations in patients who were not administered glutamine or glutamine-containing nutritional preparations and to investigate ways of identifying patients in need for glutamine supplementation using routine clinical and laboratory-based parameters.

The purpose was to identify situations where glutamine supplementation is required in surgical patients. The secondary objective is to identify patients requiring this treatment in the simplest and cheapest way possible.

Materials and Methods

The study was performed in the 1st Department of General and Transplantation Surgery and Nutritional Therapy of the Lublin Medical University, Poland. Patients were recruited in the years 2007-2015.

Patients were included in the study if they were scheduled for an abdominal surgery procedure due to gastrointestinal cancer. The diagnoses and procedures are listed in Table 1.

All patients had a similar stage of disease development. In order to be included, on the day of recruitment each patient had to be:

- in overall good condition (ASA<2),
- free from cardiovascular insufficiency (NYHA<2),
- free from diabetes,
- free from kidney and/or liver failure, and
- not treated with immunosuppressants within at least six months preceding recruitment.

Diagnosis	Diagnosis code	Number	Procedure	Procedure code	Group 1	Group 2	Group 3	Total
Stomach cancer	1	24	Subtotal gastrectomy	I	7	9	0	16
			Total gastrectomy	II	4	4	0	8
Pancreatic cancer	2	19	Whipple procedure	III	2	7	2	11
			Distal pancreatectomy	IV	2	5	1	8
Liver cancer	3	5	Partial hepatectomy	V	0	2	3	5
Small intestine cancer	4	5	Partial enterectomy	VI	3	1	1	5
Colon cancer	5	26	Left colectomy	VII	6	2	9	17
			Right colectomy	VIII	3	1	5	9
Rectal cancer	6	26	Proctectomy	IX	4	2	6	12
			Abdominoperineal resection	X	4	3	7	14
		105			35	36	34	105

Table 1: Diagnoses and procedures performed.

Additionally, the patients could not be treated with any preparations containing glutamine or other immunomodulatory substances (omega 3 fatty acids, arginine, nucleotides) within the previous six months or more.

Exclusion criteria were:

- indications for urgent surgery;
- deteriorated physical status (ASA >3),
- cardiovascular insufficiency (NYHA >3),
- preoperative kidney failure (creatinine >2 mg% or urea >100 mg %), and
- preoperative liver failure (bilirubin >2 mg%, AspAT >100 IU, AlAT >100 IU).

All patients were informed of the study procedure and purpose. All patients expressed their consent in line with the protocol approved by the Bioethics Committee of the Lublin Medical University (decision no. KE0254/31/2006).

117 patients, 59 female and 58 male, were recruited for the study. Based on general medical consultation and laboratory tests, patients were excluded from the study if after recruitment:

- their physical status deteriorated (two patients), or
- they experienced a cardiovascular insufficiency exacerbation (one patient).

At the preoperative stage, nine patients were referred for an urgent procedure. These patients were also excluded from the study.

The final study group included 105 patients, 48 female and 57 male.

The endpoint was the occurrence of complications within the follow-up period, i.e. within 30 days of the surgical procedure. The complications were listed and defined before patient recruitment. Table 2 lists the complications and their definitions.

Complications (type)	Definition
Infectious	
Superficial surgical wound infection	Surgical wound dehiscence. Partial or total rupture of any layer of the sutured wound. Identified by the surgeon in physical examination, or confirmed in an ultrasound examination in cases of fascial dehiscence exceeding 3 cm.
Deep surgical wound infection	Infection symptoms appear within 30 days of the procedure or within a year of the procedure if synthetic materials are used. The infection affects the deeper layers of the incision site (fascia and muscle). Physical examination shows purulent discharge from the deeper layers of the wound; the wound opens spontaneously or is opened by the surgeon; purulent discharge from under the fascia is found during wound revision, or bacteriology is positive.

Organ (space) infection – abdominal abscess	Symptoms appear within 30 days of the procedure, or within a year of the procedure if synthetic materials are used. The infection involves an organ or cavity at a site other than the incision site. Purulent discharge from the drained cavity and/or pus in the body cavity or organ found in additional tests (ultrasound, CT, MRI); positive pus culture.
Urinary tract infection	Dysuria and increased wbc/hpf in urinalysis and/or positive urine culture (significant bacteriuria >105)
Bacteremia	Positive blood culture with no systemic inflammation symptoms.
Septicemia	Positive blood culture with systemic inflammation symptoms (fever exceeding 40oC, tachycardia, hypotonia, oliguria).
Central venous line infection – catheter-related infection	Bacteremia or septicemia associated with central venous catheterization. Systemic inflammation symptoms and/or positive blood culture.
Pneumonia	Clinical inflammation symptoms, confirmed in a bacteriological examination of respiratory secretions or bronchoalveolar lavage (BAL), and/or chest radiograph.
SIRS	Long, systemic inflammatory response with symptoms of inflammation, increased CRP levels, increased body temperature, increased WBC with no apparent reason.
Surgical	
Eventration	Total dehiscence of all layers of the surgical wound in the abdominal wall, resulting in a protrusion of peritoneal cavity contents through the wound. Found during physical examination; does not require additional confirmation.
Surgical wound dehiscence	Opening of the surgical wound. Partial or total rupture of any layer of the sutured wound. Identified by the surgeon in physical examination, or confirmed in an ultrasound examination in cases of fascial dehiscence exceeding 3 cm.
Fluid collection in the surgical wound	Collection of serous fluid (exudate or lymph) requiring the opening and/or drainage of the surgical wound. Identified by the surgeon in physical examination, or confirmed in an ultrasound examination in cases of reservoirs exceeding 3 cm.
Hematoma in the surgical wound	Collection of blood in the surgical wound requiring opening and external drainage. Identified by the surgeon in physical examination.
Delayed stomach emptying	Need for stomach pumping or nasogastric intubation for more than 8 days post-surgery, with nausea and/or vomiting and/or sensation of abdominal fullness and/or burning sensation at the sternum and/or inflammation in the respiratory tract. Identified in physical examination; inflammatory processes found in physical examination and confirmed in chest radiograph.
Post-surgical bowel obstruction	Lack of peristalsis persisting for more than 5 days post-surgery, abdominal distension, lack of flatulence and bowel movement despite conservative treatment administered to stimulate peristalsis. Identified by the surgeon in physical examination.
Intestinal fistula	Any appearance of gastrointestinal contents outside of gastrointestinal tract lumen. Requires confirmation by examination using an oral contrast medium and/or contrast-enhanced examination of the fistula.
Pancreatic fistula	Presence of secretions with measured pancreatic amylase activity in the drainage. The measured amylase activity exceeds serum amylase activity 3-fold or more. Physical and laboratory examination.
Systemic	
Arrhythmia	Heart rhythm disorders.
Cardiovascular insufficiency	Hypotension necessitating the administration of fluid therapy and pressor amines.
Heart failure	Decrease of cardiac output below 20%.
Respiratory failure	Tachypnea (respiratory rate >35), partial pressure of CO2 above 70 mmHg.
Neurological complications	Ischemic stroke, hemorrhagic stroke, consciousness/cognitive disorders.
Death	

Table 2: Complications and definitions.

Secondary endpoints included duration of postoperative hospitalization and the type of complications that occurred in a patient at the postoperative stage.

In order to investigate the impact of various factors on glutamine levels and to control for their impact on the primary and secondary endpoints, patients were divided into groups, based on their perioperative management.

Each of the three groups was managed differently in terms of nutritional treatment, depending on the patients' nutritional status before the procedure and the type of procedure administered.

Group 1, including patients who were malnourished before the procedure, was created in order to investigate the impact of nutritional status on perioperative glutamine levels and on study endpoints, if present.

Group 2 was created in order to verify the potential impact of postoperative nutritional treatment on glutamine levels.

Group 3 was a control group for the remaining two, where neither preoperative glutamine levels nor their perioperative variations were associated with malnutrition or nutritional treatment.

The classification of patients into groups and their final composition are shown in Figure 1.

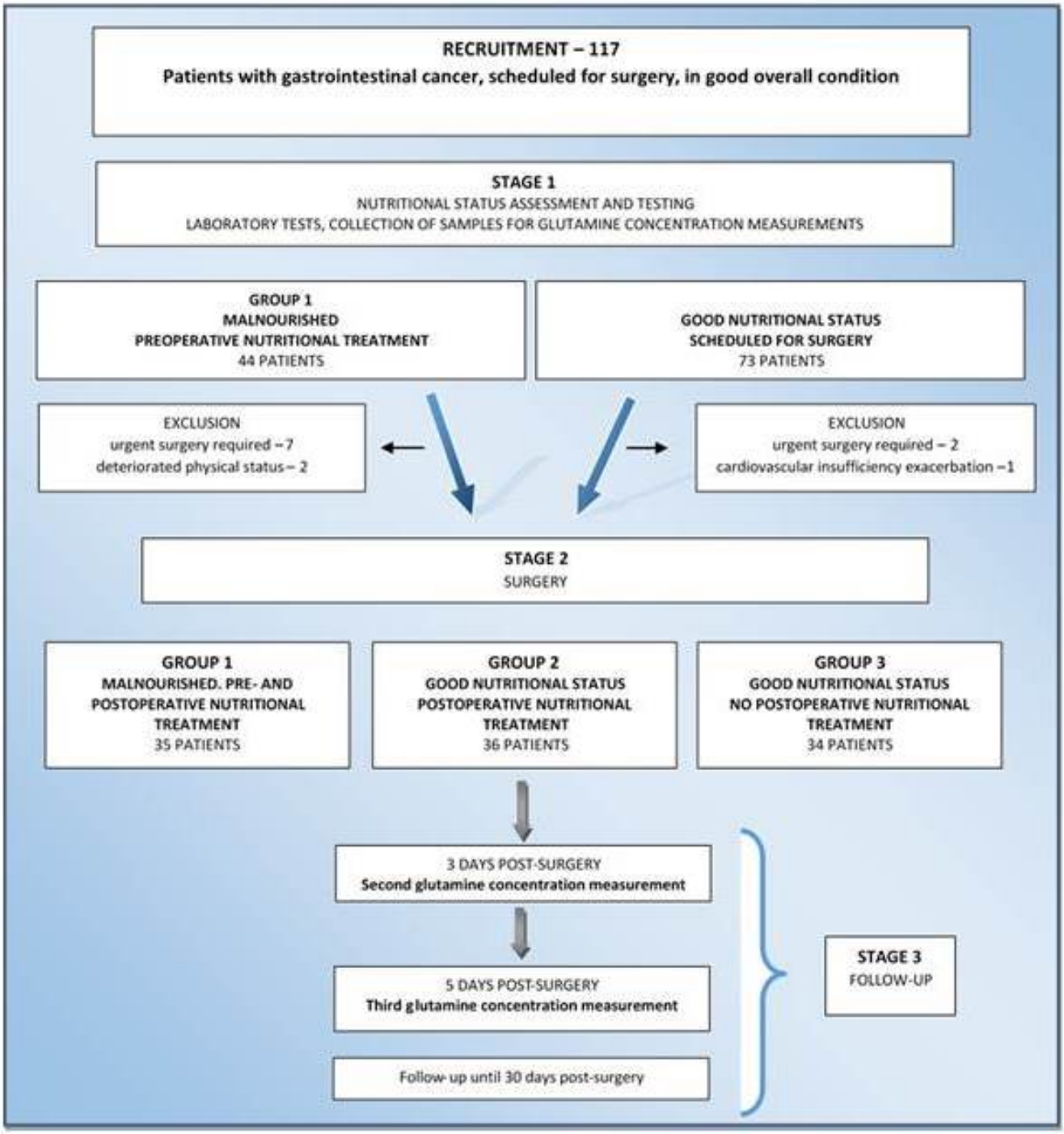

Figure 1: Graphic representation of the study protocol.

The parenteral nutrition treatment was administered using triple-chamber bags from various manufacturers, containing a mixture of amino acids, glucose and lipid emulsion (RTU bags).

The RTU bags were supplemented with vitamins, trace elements, electrolytes and minerals as needed by a given patient. Ready-made preparations were used to supplement the nutrient mixture.

Each patient included in the study underwent nutritional status assessment.

Malnutrition was diagnosed if three or more of the following factors were found:

- body weight loss exceeding 10% in the six months preceding the study,
- body mass index (BMI) below 18.9,
- a nutritional status score of three or less in the NRS 2002 scale,
- total lymphocyte count below 1.5·1012/L,
- albumin concentration below 3.5 g/L,
- total protein concentration below 6.0 g/dL, or
- total cholesterol concentration below 170 mg/dL.

Laboratory assessments included the basic nutritional status tests: peripheral blood count, and serum concentrations of protein, albumin, and total cholesterol. For this purpose, the specialized hospital laboratory performed tests routinely used in preoperative patient assessments.

Blood samples for laboratory tests were collected at recruitment, and on the 3rd and 5th day post-surgery. At the same time, a blood sample was collected for serum glutamine concentration test. Blood collected into citrate anticoagulant was centrifuged immediately. The obtained serum was frozen at -70°C until the test.

Glutamine concentrations were determined using the Moore-Stein-Spackman method in the AAA 4000 automated amino acid analyzer from INGOS, Prague [39]. The serum containing a mixture of free amino acids was separated by ion-exchange chromatography using an OSTION LG FA resin [40].

Statistical analyses were performed using the Statistica 6.0 software. Quantitative characteristics were compared between groups using the Kruskal-Wallis test and the post-hoc Mann-Whitney test; for qualitative characteristics, the Chi-squared test was used. Within groups, variables were compared using the Wilcoxon test. Findings at $p<0.05$ were considered statistically significant.

Correlation analyses for quantitative variables were performed using Spearman's correlation test, and for qualitative variables, using the Mann-Whitney test. Correlations at $p<0.05$ were considered statistically significant.

Results

The analyses included 105 patients, 47 female and 58 male, as per the study protocol (Figure1). Patient characteristics are shown in Table 3.

Characteristic		All patients (n=105)	Group 1 (n=35)	Group 2 (n=36)	Group 3 (n=34)
Age		65 (59–73)	67 (59-71)	64.5 (59-75.5)	63.5 (57-74)
Sex	1	47 (44.8%)	15 (42.9%)	15 (41.7%)	17 (50%)
	2	58 (55.2%)	20 (57.1%)	21 (58.3%)	17 (50%)
BMI		25.5 (21.0-29.0)	24.0 (21.0-28.0)	25.0 (21.4-28.5)	27.0 (21.0-29.5)
Diagnosis	1	24 (22.9%)	11 (31.4%)	13 (36.1%)	0
	2	18 (17.1%)	4 (11.4%)	11 (30.6%)	3 (8.8%)
	3	6 (5.7%)	0	3 (8.3%)	3 (8.8%)
	4	5 (4.8%)	3 (8.6%)	1 (2.8%)	1 (2.9%)
	5	26 (24.8%)	9 (25.7%)	3 (8.3%)	14 (41.2%)
	6	26 (24.8%)	8 (22.9%)	5 (13.9%)	13 (38.2%)
Procedure	I	16 (15.2%)	7 (20.0%)	9 (25.0%)	0
	II	8 (7.6%)	4 (11.4%)	4 (11.1%)	0
	III	11 (10.5%)	2 (5.7%)	7 (19.4%)	2 (5.9%)
	IV	8 (7.6%)	2 (5.7%)	5 (13.9%)	1 (2.9%)
	V	5 (4.8%)	0	2 (5.6%)	3 (8.8%)
	VI	5 (4.8%)	3 (8.6%)	1 (2.8%)	1 (2.9%)

	VII	17 (16.2%)	6 (17.1%)	2 (5.6%)	9 (26.5%)
	VIII	9 (8.6%)	3 (8.6%)	1 (2.8%)	5 (14.7%)
	IX	12 (11.4%)	4 (11.4%)	2 (5.6%)	6 (17.6%)
	X	14 (13.3%)	4 (11.4%)	3 (8.3%)	7 (20.6%)
	none	82 (78.1%)	24 (68.6%)	29 (80.6%)	29 (85.3%)
Complications	present	23 (21.9%)	11 (31.4%)	7 (19.4%)	5 (14.7%)
Days hospitalized		9 (9-12)	11 (9-14)	9 (8-12)	9 (9-12)
Initial body weight		79.9 (68.5-91.0)	83.0 (69.3-92.2)	75.6 (64.0-87.1)	80.2 (67.5-95.9)
	no	69 (65.7%)	8 (22.9%)	32 (88.9%)	29 (85.3%)
Weight loss exceeding 10%	yes	36 (34.3%)	27 (77.1%)	4 (11.1%)	5 (14.7%)
% weight loss		7.1 (1.1-12.7)	13.6 (9.5-16.0)	6.6 (0-8.9)	3.0 (0-7.6)
	0-2	44 (41.9%)	0	19 (52.8%)	25 (73.5%)
NRS 2002	3-6	61 (58.1%)	35 (100%)	17 (47.2%)	9 (26.5%)
*quantitative variables shown as median (interquartile range), qualitative variables as number (percentage in the group)					

Table 3: Clinical characteristics of the patients studied.

Analysis of the results obtained demonstrated that in the group of patients who experienced surgical complications, preoperative glutamine concentrations were significantly lower than in the group of patients with no complications.

Parameter	No complications (n=82)	Complications (n=23)	p
Gln 0 nmol/ml	228.1 (209.6-241.2)	205.2 (195.1-229.6)	0.0172
Gln 3 nmol/ml	201.8 (184.0-224.1)	164.6 (148.2-208.9)	0.0016
Gln 5 nmol/ml	233.1 (211.3-249.4)	201.4 (180.4-229.3)	0.001
D Gln 0-3 nmol/ml	-20.1 (-31.4 – -12.0)	-33.2 (-49.2 – -21.2)	0.0087
D Gln 0-5 nmol/ml	5.4 (-4.5-20.3)	-2.9 (-11.4-13.2)	0.089
Albumin 0 g/L	3.7 (3.5-3.9)	3.5 (3.4-3.8)	0.0057
Albumin 3 g/L	3.2 (2.9-3.5)	2.9 (2.7-3.1)	0.0017
Albumin 5 g/L	3.7 (3.6-3.8)	3.6 (3.5-3.7)	0.0139
D Albumin 0-3 g/L	-0.5 (-0.7--0.2)	-0.6 (-0.7 - -0.4)	0.4841
D Albumin 0-5 g/L	-0.1 (-0.3-0.2)	0.1 (-0.3-0.4)	0.1712
* p<0.05			

Table 4: Comparison of glutamine and albumin levels between patients with and without complications (medians and interquartile ranges), Mann-Whitney test.

Additionally, complications were associated with a larger postoperative decrease of glutamine levels. Similar correlations were found for albumin levels.

The postoperative decrease was larger in the group of patients with complications, though not in a statistically significant manner (Table 4).

Perioperative glutamine level variations were found to be a significant risk factor for complications, with a similar OR (Table 5).

Parameter	OR	95% CI	p
Glutamine 0	1.05	1.02-1.08	0.001
Glutamine 3	1.05	1.03-1.08	0
Change 0–3	1.04	1.01-1.08	0.015
Glutamine 5	1.05	1.02-1.08	0

Table 5: Odds ratio for complication incidence with decrease of glutamine level by one unit.

Parameter	r	p
Glutamine 0	-0.251	0.019
Glutamine 3	-0.379	0
Change 3-0	-0.283	0.008
Glutamine 5	-0.321	0.002
Change 5-0	-0.174	0.105

Table 6: Pearson's linear correlation coefficients (r) for glutamine levels and duration of hospitalization.

Lower preoperative glutamine levels, lower glutamine levels on the 3rd and 5th day post-surgery, and a larger postoperative decrease in

the parameters were also related to significantly longer hospitalization (Table 6).

At the next stage of the analysis, factors affecting glutamine concentrations were investigated. Glutamine levels were compared between patients who were malnourished and those with normal nutritional status before the procedure (group 1 vs. groups 2+3). Statistically significant differences were found between the compared groups, both before and after the procedure.

No significant differences between the groups distinguished by preoperative nutritional status were found in terms of postoperative glutamine level decrease (Table 7). Differences in perioperative glutamine levels depending on pre- and postoperative management were also investigated (Table 8).

Parameter	Group 1 (n=35)	Groups 2+3 (n=70)
Gln 0 nmol/ml	209.6 (194.7-229.5)	228.6 (213.2-243.5)1
Gln 3 nmol/ml	179.8 (148.2-204.8)	206.2 (184.6-224.3)1
Gln 5 nmol/ml	214.5 (183.2-245.9)	233.6 (207.8-254.3)1
D Gln 0-3 nmol/ml	-25.6 (-43.1 – -15.7)	-21.7 (-31.4 – -13.0)
D Gln 0-5 nmol/ml	4.6 (-9.2-18.5)	4.0 (-4.1-19.8)
1 – p<0.05 compared to group 1		

Table 7: Comparison of glutamine concentrations depending on preoperative nutritional status – median (interquartile range).

Parameter	All patients n=105	Group 1 n=35	Group 2 n=36	Group 3 n=34
Hematocrit 0 - %	40.0 (38.0-44.0)	39.0 (36.0-41.8)	40.0 (38.0-43.0)	43.0 (39.0-46.0)1,2
Hematocrit 3 - %	39.0 (35.0-40.0)	35.0 (33.0-40.0)	38.0 (35.0-40.0)	39.5 (38.0-41.0)1
WBC 0 - 1012/L	8.2 (6.5-9.6)	7.8 (5.6-9.3)	8.0 (6.9-9.2)	8.9 (9.8)
TLC 0 - 1012/L	1.5 (1.4-1.7)	1.4 (1.3-1.7)	1.5 (1.4-1.6)	1.6 (1.5-1.7)1
TLC 3 - 1012/L	1.5 (1.4-1.6)	1.4 (1.2-1.8)	1.5 (1.4-1.6)1	1.6 (1.4-1.7)*1
TLC 5 - 1012/L	1.6 (1.5-1.6)	1.5 (1.4-1.6)*#	1.6 (1.5-1.6)*#	1.6 (1.5-1.8)*#1
Total protein- g/L	6.1 (5.9-6.7)	5.7 (5.2-6.0)	6.4 (6.1-7.1)1	6.4 (6.1-6.9)1
Total protein 3 - g/L	6.1 (5.5-6.4)	5.4 (5.1-5.7)	6.3 (6.0-6.4)1	6.3 (6.1-6.5)1
Albumin 0 - g/L	3.7 (3.5-3.9)	3.4 (2.9-3.5)	3.8 (3.6-3.9)1	3.8 (3.7-3.9)1
Albumin 3 - g/L	3.1 (2.9-3.5)*	3.0 (2.7-3.5)*	3.1 (2.9-3.5)*	3.2 (3.1-3.5)*1
Albumin 5 - g/L	3.6 (3.5-3.8)#	3.6 (3.6-3.7)#*	3.6 (3.5-3.8)#*	3.7 (3.6-3.8)#*
Cholesterol - mg/dL	223.0 (198.0-246.2)	203.0 (175.0-244.0)	224.0 (204.5-247.0)	224.0 (212.0-246.0)
Urea 0 mg/dL	41.0 (39.0-47.2)	49.0 (41.2-56.0)	39.0 (38.0-41.5)1	41.0 (39.0-43.0)1
Urea 3 mg/dL	39.0 (36.0-41.0)	39.0 (36.5-42.0)	38.5 (35.5-40.0)	38.5 (36.0-41.0)
Gln 0 nmol/ml	224.4 (203.8-239.5)	209.6 (194.7-229.5)	222.3 (204.3-236.2)1	232.5 (217.3-245.1)1
Gln 3 nmol/ml	201.1 (174.8-221.1)*	179.8 (148.2-204.8)*	197.9 (178.8-218.8)*1	215.3 (198.1-234.1)*1.2
Gln 5 nmol/ml	227.8 (204.0-249.3)#	214.5 (183.2-245.9)#	226.4 (202.5-251.8)#1	238.6 (215.4-268.1)#1.2
D Gln 0-3 nmol/ml	-21.9 (-34.1 - -13.2)	-25.6 (-43.1 - -15.7)	-26.3 (-40.0 - 12.4)	-19.2 (-26.2 - -13.6)
D Gln 0-5 nmol/ml	4.6 (-5.3-19.6)	4.6 (-9.2-18.5)	1.5 (-8.0-21.4)	6.0 (-2.0-17.4)
*p<0.05 compared to preoperative values (0)				
#p<0.05 compared to postoperative values (3)				
Quantitative variables compared using the Kruskal-Wallis test and Mann-Whitney post-hoc test: 1 – p<0.05 compared to group 1; 2 – p<0.05 compared to group 2.				

Table 8: Quantitative variables – median (interquartile range); Wilcoxon test used for comparison.

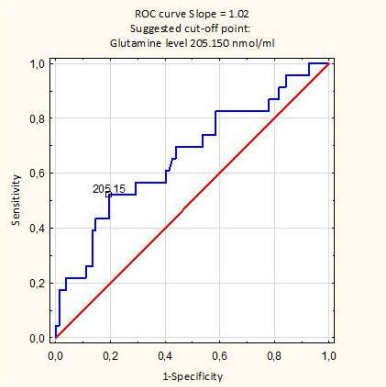

Figure 2: ROC analysis.

Subsequently, as per the study protocol, ROC analysis was performed to determine the preoperative glutamine level below which there is a statistically significant increase in complication risk (Figure 2).

Parameter	All patients (%)	Malnourished patients (%)
Body weight loss >10%	30.5	33.3
Albumin	58.33	58.3
TLC	52.63	63.15
Cholesterol	26.6	40
NRS 2002	37.5	40

Table 9: Percentage of cases where abnormal nutritional parameters co-occur with glutamine levels below 205.15 nmol/ml.

Due to the complexity of glutamine level testing and lack of routine tests for this purpose, we attempted to identify those routine preoperative laboratory tests that are the most strongly correlated with glutamine levels. Similar correlations were found for albumin levels and total lymphocyte count. Table 9 shows the co-occurrence of abnormalities in routinely used nutritional status parameters with glutamine levels below 205.15 nmol/ml.

Discussion

Glutamine metabolism [41], including the impact of glutamine (or rather of its deficiency) on patients' clinical condition and treatment outcomes [42-45], has been understood for many years. However, the criteria for glutamine supplementation are vague. Glutamine administration is known to have a positive impact on intensive care patients [46], but no clear indications are available as to when a patient should be considered critically ill [47].

Some studies demonstrate that glutamine supplementation in patients undergoing elective surgery has no benefits and potentially increases complication risk because of the parenteral administration route. Gianotti et al. [48] reported that glutamine supplementation, though it does increase the patients' serum glutamine levels, is not correlated with decreased perioperative complication incidence. Similar findings were reported by Kłęk et al. [49]. The authors showed that not only does glutamine supplementation have none of the expected benefits, but there are also no statistically significant differences in perioperative complication incidence and hospitalization duration between patients receiving parenteral vs. enteral supplementation. In other work Kłęk et al. [50] concluded that the clinical supplementation of glutamine in patients with severe gastric cancer is of no significance.

In the present study, a correlation was found between preoperative glutamine concentration and treatment outcomes. Lower preoperative glutamine levels were associated with a higher incidence of postoperative complications. The correlation was found in the entire study group, which reflects the importance of this amino acid. Patients with complications had significantly larger decreases of glutamine levels immediately after the surgery. This may suggest a link between glutamine metabolism and the pathophysiology of surgical complications. Using odds ratios, the risk of complications with a decrease of glutamine levels by one unit was calculated (Table 6). A correlation was also found between glutamine concentration and hospitalization duration in the entire group, in all glutamine level measurements, both pre- and postoperative. These observations prove the importance of glutamine. They also demonstrate the potential benefits of glutamine supplementation in terms of treatment outcomes.

The next stage of the analysis concerned the impact of various parameters on glutamine levels. Patients who were malnourished before the procedure were found to have the lowest glutamine concentrations out of all patients studied. This suggests that nutritional status is a significant factor determining the blood concentration of glutamine. Other factors that affect glutamine levels include surgery-related stress and perioperative hydration. In all patients analyzed, a significant decrease in glutamine levels occurred peri-operatively, regardless of their initial nutritional status. Similar findings concern other protein parameters (total protein and albumin levels). No differences were found in the intensity of glutamine level decrease between normally nourished and malnourished patients. This demonstrates that nutritional status affects the serum concentration of glutamine, but not its metabolism. However, glutamine decrease was larger in patients who experienced postoperative complications, which shows its association with complication incidence. This is a well-known association that became the motivation behind attempts to limit perioperative complications by preoperative glutamine supplementation. However, the studies cited above showed no benefits of glutamine supplementation in terms of treatment outcomes. Likely, the authors did not consider both malnutrition and initial glutamine concentration in their analyses. In the present study, patients with complications had significantly lower glutamine concentrations preoperatively, 3 days post-surgery, and 5 days post-surgery than patients without complications. This observation suggests that glutamine supplementation could potentially have decreased complication incidence. This requires corroboration in studies on the impact of glutamine supplementation on treatment outcomes in patients with low serum glutamine levels.

ROC analysis allowed for identification of glutamine concentration below which there is a very high risk of complications. The threshold glutamine value identified was 205.15 nmol/ml. Patients scheduled for surgery who have an initial glutamine concentration below this threshold would likely benefit from glutamine supplementation. However, glutamine concentration tests are expensive and complex. Therefore, we attempted to determine which routine preoperative

laboratory tests could help identify patients most likely to have glutamine levels below the critical threshold. We found that in the entire group, albumin levels below the reference values and low total lymphocyte count co-occurred with glutamine concentrations below 205.15 nmol/ml in more than half of the cases. Cholesterol concentration below the reference values and a positive result of NRS 2002 malnutrition screening are also quite likely to be associated with indications for glutamine supplementation. The predictive value of these tests is higher in patients found to be malnourished before the surgery.

Conclusion

- Low blood concentration of glutamine is correlated with a higher incidence of postoperative complications.
- Glutamine supplementation before a scheduled surgical procedure may benefit patients with a preoperative glutamine concentration below 205.15 nmol/ml.
- Low total lymphocyte count and serum albumin concentration can help identify patients in whom glutamine administration can decrease postoperative complication incidence, especially in the case of malnourished patients.
- Glutamine supplementation can benefit malnourished patients.

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