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Is Additional Enrichment of Diet in Branched-Chain Amino Acids or Glutamine Beneficial for Patients Receiving Total Parenteral Nutrition after Gastrointestinal Cancer Surgery?

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Objectives. Total Parenteral Nutrition (TPN) is necessary in patients unable to receive oral or enteral feeding for a period of at least 7 days. Branched-chain amino acids (BCAA): valine (Val), leucine (Leu), and isoleucine (Ile) are essential amino acids, which are important regulators in protein metabolism. They are also the main nitrogen source for glutamine synthesis in muscles. In this process they undergo irreversible degradation and cannot be reutilised for protein synthesis. In catabolic states, like cancers, glutamine demand increases and therefore also its utilisation, which can decrease the level of BCAA required for Gln synthesis. The purpose of this study was to evaluate the necessity of BCAA or glutamine-enriched TPN in patients after gastrointestinal cancers surgery.
Material and Methods. Our aim was to investigate changes of plasma BCAA and glutamine concentrations in patients operated for colorectal, small intestine or pancreatic cancer and who are either receiving TPN or not in the postoperative period. Free amino acids plasma concentrations were determined by the ion-exchange chromatography.
Results. Surgery in the control group caused a decrease in Val, Ile and Leu concentrations in the postoperative period. In TPN patients this depression was inhibited beginning from the third day after surgery, except for Val and Leu in colorectal cancer group. In control and TPN patient groups, Gln concentration decreased after the surgery and subsequently increased beginning from the third day after the operation.
Conclusions. Gastrointestinal cancer patients' surgery results in decrease in BCAA concentrations. Standard TPN exerts a beneficial effect on the BCAA level in patients with pancreatic and small intestine cancer. In colorectal cancer such TPN should be enriched with Leu and Val (**Adv Clin Exp Med 2014, 23, 3, 423–431**).

Key words: branched-chain amino acids, glutamine, postoperative TPN, gastrointestinal cancer; surgical stress.

A decrease in body mass and malnutrition are the most frequently appearing symptoms observed in gastrointestinal (GI) cancer patients with prolonged catabolic stress, and in over 60% of patients malnutrition increases with the progress of the disease. In the majority of untreated cancer patients, cachexia is observed, but the frequency of cachexia occurrence is dependent on the tumour type. As distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism, cancerous cachexia is associated with increased morbidity [1, 2]. Recent studies have shown positive effects of nutritional support in the postoperative period such as: improved protein balance, improved immune response, reduced morbidity and reduced length of hospitalization after operation [3, 4].

Total Parenteral Nutrition (TPN) is necessary in patients, in which postoperative complications caused an impairment in the gastrointestinal function and therefore are unable to receive and absorb oral or enteral feeding for a period longer

than 7 days [5]. The routine use of postoperative TPN has proved to be useful neither in well-nourished patients nor in these with adequate oral intake within a week after surgery [6]. Amino acid requirements in TPN are higher in patients after gastrointestinal cancer surgery than in non-operated cancer subjects.

Branched-chain amino acids (BCAA) such as valine (Val), leucine (Leu), and isoleucine (Ile) are essential amino acids. They exert a regulatory effect on synthesis and degradation of protein. Furthermore, they are the major nitrogen source for synthesis of glutamine (Gln) and alanine (Ala) in muscles. Glutamine (Gln) is the most abundant free amino acid in the human body. It plays an important role in gluconeogenesis and acts as an important energy source for enterocytes and for the cells of the immune system, which are rapidly dividing cells. Glutamine is produced by the transamination of carbon skeletons with amino groups from the BCAA, which are irreversibly degraded and cannot be reutilized for protein synthesis.

The TPN mixture has all the essential amino acids, which cannot be produced by the human body, so they do not contain glutamine. However, glutamine is considered as an amino acid of conditional essentiality in malnutrition and cancerous cachexia, where the demand for Gln outstrips its synthesis from endogenous precursors [7, 8]. There are studies confirming that enteral BCAA can reduce protein loss and improve the nutritional status of patients with liver diseases [9]. It still remains unclear if standard TPN-mixture is sufficient and beneficial for patients after GI cancer surgery. BCAA-enriched TPN, unbalanced Val, Leu or Ile-enriched diet or glutamine containing TPN may be more effective for certain type of cancer.

Regarding the presented facts, our study aims to evaluate changes of plasma glutamine and BCAA concentrations in patients operated due to small intestine cancer, pancreatic cancer or colorectal cancer and then receiving TPN in vs. a group of patients, who were operated due to gastrointestinal cancers and then received typical nutrition.

Material and Methods

Patients

All patients, after a detailed diagnosis, were clinically categorised according to the classification of the International Union Against Cancer (UICC) as stages II and III. None of the patients were subjected to prior radiation, surgery or chemotherapy. Patients with congestive heart failure, hepatic failure, renal failure, shock as well as patients with metabolic disorders associated with impaired nitrogen utilisation and those classified as stage IV were excluded from this study.

Table 1 presents demographic data of the studied patients and their preoperative characteristics.

Supplementation with amino acids was similar among all the groups before the surgery. The postoperative dietary intake was controlled by the clinical nutrition team. The composition of the TPN mixtures is presented in Tables 2 and 3.

The overall number of 86 patients, who participated in the study, was divided into 4 groups:

- C – control group, i.e. patients, who were operated due to gastrointestinal cancer. They received intravenously typical amounts of liquids and essential electrolytes for 5 days from the operation.
- I – patients who were operated due to colorectal cancer. They received TPN after the operation.
- II – patients who were operated due to small intestine cancer. They received TPN after the operation.
- III – patients who were operated due to pancreatic cancer. They received TPN after the operation.

Table 1. Characteristics of the studied patients

	C (n = 22)	**I (n = 22)**	**II (n = 16)**	**III (n = 20)**
Sex (male/female)	12/10	10/12	9/7	11/9
Age (years ± SD)	65.3 ± 13.2	69.1 ± 10.4	58.0 ± 12.0	60.2 ± 7.1
Body weight (kg ± SD)	58.6 ± 12.4	53.8 ± 10.6	54.3 ± 11.3	56.2 ± 9.6
Associated medical diseases:				
diabetes	5	3	4	5
hypertension	3	4	2	2
coronary artery disease	2	2	1	3

C – control; I – colorectal cancer; II – small intestine cancer; III – pancreatic cancer.

Table 2. Composition of TPN mixture (per 1 litre) (acc. previous study Szpetnar et al. [36])

Parameter	Group I		Group II		Group III	
	mean	SD	mean	SD	mean	SD
Nitrogen (g)	5.61	0.12	6.02	0.96	5.98	0.56
Amino acids (g)	38.25	3.11	39.80	7.63	39.95	5.15
Carbohydrates (g)	98.30	24.04	105.45	26.21	114.00	32.28
Lipids (g)	47.60	3.76	51.05	8.85	48.00	3.55
Energy from lipids (kcal)	431.50	68.17	472.50	102.71	446.25	69.72
Energy from carbohydrates (kcal)	368.00	75.23	396.00	101.28	444.00	123.73
Non-peptide energy (kcal)	799.50	7.05	834.75	144.11	853.75	172.09
Energy from amino acids (kcal)	151.00	14.10	159.75	29.98	166.00	35.45
Total energy	950.50	7.05	993.00	166.10	1 019.75	202.20
Osmolarity (mOsm/kg)	896.00	37.61	884.50	70.45	937.00	148.29
Na (mmol)	46.05	5.92	42.40	17.13	46.00	7.53
K (mmol)	31.35	4.82	29.25	12.38	32.25	7.45
Mg (mmol)	3.05	0.22	3.57	0.74	3.33	0.46
Ca (mmol)	2.87	0.17	2.94	0.77	3.07	0.47
Cl (mmol)	45.08	4.29	45.66	14.96	45.61	6.95
Zn (mmol)	0.02	0.02	0.01	0.02	0.02	0.02
Acetates (mmol)	45.98	11.49	43.58	20.60	47.20	15.09
Phosphates (mmol)	11.09	5.22	11.63	6.18	12.62	5.99

I – colorectal cancer; II – small intestine cancer; III – pancreatic cancer.

Table 3. Average levels of amino acids (g/L) given in TPN

Amino acid	Group I		Group II		Group III	
	mean	SD	mean	SD	mean	SD
Thr	1.69	0.20	1.86	0.39	1.86	0.30
Ser	2.60	0.63	2.70	0.89	2.83	0.66
Gly	2.18	0.83	2.56	1.27	2.47	1.29
Ala	5.44	0.93	6.14	2.05	6.09	1.97
Pro	3.05	0.55	3.23	0.88	3.34	0.62
Val	2.39	0.32	2.61	0.58	2.63	0.44
Ile	2.23	0.17	2.42	0.55	2.46	0.40
Leu	2.92	0.33	3.16	0.71	3.20	0.52
Met	1.77	0.30	1.93	0.45	1.93	0.35
Phe	3.01	0.78	3.20	0.98	3.28	0.80
Trp	0.58	0.01	0.65	0.15	0.64	0.13
Lys	2.16	0.16	2.40	0.48	2.38	0.39
His	1.35	0.16	1.52	0.44	1.51	0.41
Arg	3.03	0.52	3.42	1.13	3.39	1.09

I – colorectal cancer; II – small intestine cancer; III – pancreatic cancer.

In the control group the blood samples were collected as follows: 1st measurement – one day before the operation, 2nd measurement – three days after the operation, 3rd measurement – five days after the operation. In the other groups the samples were collected also at three time points: 1st measurement – one day before the operation, 2nd measurement – three days after applying TPN, 3rd measurement – five days after applying TPN.

The Bioethical Commission of the Medical University in Lublin approved the study (No KE-0254/31/2006).

The patients were hospitalised in the I Chair and Department of General and Transplant Surgery and Nutritional Treatment of the Medical University in Lublin. They accepted the study protocol and agreed to participate in it.

Glutamine and Branched--Chain Amino Acids Examinations

The plasma from each blood sample was collected immediately after centrifugation at 2000 × g for 15 min and then stored at –20°C until analysis. For free amino acids concentration measurements, plasma was deproteinised with 6% sulphosalicylic acid in lithium – citrates buffer (pH = 2.8) and centrifuged at 12000 × g for 12 min. Amino acids were determined by the automated ion-exchange chromatography with five lithium-citrate buffers by Moore et al. [10] using Amino Acids Analyser (AAA 400) by Ingos, Czech Republic.

Statistical Analysis

To perform statistical analysis of the obtained results, SPSS 12.0 PL (Statistical Package for Social Sciences) software was used.

The outcomes were tested by variance analysis or its non-parametric equivalents. Compatibility of studied variables distribution with normal distribution was tested by Shapiro-Wilk test.

Distributions of dependent variable did not differ significantly from normal distribution in most cases; therefore, mixed pattern of variance analysis (ANOVA model) was used for further analysis. When the above assumption was not true, non-parametric equivalents of variance analysis were applied. The influence of the measurement date on investigated dependent variable level was then analysed by the Friedman test. Differences between variables pairs were examined using Wilcoxon signed-rank test. The influence of appurtenance to patient group on the level of dependent variable was analysed by Kruskall-Wallis test. The Mann Whitney *U* test was applied to examine the differences among dependent variable values for single measurements.

Results

Mean values of BCAA (valine, isoleucine, leucine) and glutamine concentrations as well as standard deviations (SD) are shown in Table 4. Table 5 presents statistics of differences significance tests for studied amino acids' measurements (1st, 2nd 3rd measurement). Table 6 presents statistics of differences significance tests for studied amino acids' measurements in groups of patients (group C, I, II, III). Evaluation of the influence of the measurement date showed statistically significant differences for Val concentration between 1st–2nd and 2nd–3rd measurements (Chi-squared = 17.987; $p < 0.05$). Statistically significant differences between C-II and II-III groups were found (Chi-squared = 12.870, $p < 0.05$).

In the case of Ile, statistically significant differences were shown between the 2st and 3rd measurements ($F = 4.564$; $p < 0.05$) as well as between C-I and C-III groups ($F = 4.641$; $p < 0.05$).

Statistically significant differences in Leu concentration were found between 1st–2rd and 2st–3rd measurements ($F = 12.373$; $p < 0.05$). Evaluating groups of patients, significant changes were found between C-II and I-II groups ($F = 4.395$; $p < 0.05$).

In the case of all BCAA concentrations, statistically significant differences were stated between 1st–2rd and 2st–3rd measurements ($F = 11.279$; $p < 0.05$) and between I-II and II-III groups ($F = 4.599$; $p < 0.05$).

The evaluation of the influence of the measurement date showed statistically significant differences for Gln concentration between 1st–2rd, 1st–3rd and 2nd–3rd measurements (Chi-squared = 57.799; $p < 0.05$). The evaluation of the influence of appurtenance to patient groups showed statistically significant differences between C-II and I-II groups (Chi-squared = 10.848; $p < 0.05$).

Figures 1 and 2 show concentrations of BCAA and glutamine and their standard deviation in all operated patients (groups I–III) receiving postoperative parenteral nutrition. Mean BCAA concentration in patients receiving TPN in the 5th day of the therapy was significantly higher than before the operation and significantly higher than in the control group ($p < 0.05$). Mean Gln concentration in the 5th day of TPN application was significantly

Table 4. Gln and BCAA concentration (μmol/L) in blood plasma of patients

Group	Measurement	Gln		Val		Ile		Leu		BCAA	
		mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
C	1	199.80	48.61	190.40	32.44	56.20	15.60	121.45	24.41	122.68	17.93
	2	154.70	44.87	154.40	51.95	52.45	29.88	98.55	44.69	101.80	38.76
	3	208.00	29.40	165.30	53.60	44.65	17.38	101.80	47.36	103.92	34.37
I	1	187.85	45.47	189.55	58.29	72.45	22.81	119.80	37.57	124.92	34.32
	2	150.30	29.90	160.25	49.71	62.50	19.73	91.80	26.55	101.27	24.23
	3	215.65	59.89	167.90	55.83	67.60	22.12	96.85	32.84	114.95	29.85
II	1	224.05	53.92	137.30	25.94	54.85	14.03	85.55	25.64	93.67	23.69
	2	199.00	54.14	140.60	37.34	51.70	16.24	73.35	18.37	87.45	15.98
	3	246.00	54.82	162.17	47.34	64.55	14.84	86.65	19.06	104.15	25.10
III	1	182.40	52.03	188.25	58.29	60.75	17.65	103.10	25.16	116.90	24.70
	2	182.80	70.06	186.89	44.44	57.00	12.59	93.00	25.71	111.55	30.01
	3	227.90	77.28	215.02	63.63	74.95	17.43	108.40	29.24	131.17	28.14

C – control; I – colorectal cancer; II – small intestine cancer; III – pancreatic cancer
1 – first measurement (1 day before operation); 2 – second measurement (3 days after operation or TPN application); 3 – third measurement (5 days after operation or TPN application).

Table 5. Statistically significant differences tests for studied amino acids measurements

AA	Test's statistics	Level of significance	Post-hoc
Val[2]	17.987	0.000(*)	1–2; 2–3
Ile[1]	4.564	0.012(*)	2–3
Leu[1]	12.373	0.000(*)	1–2; 2–3
BCAA [1]	11.279	0.000(*)	1–2; 2–3
Gln[2]	57.799	0.000(*)	1–2; 1–3; 2–3

1 – first measurement (1 day before operation); 2 – second measurement (3 days after operation or TPN application); 3 – measurement (5 days after operation or TPN application).
[1] Parametric test – ANOVA with mixed pattern: test F statistic.
[2] Nonparametric test – Friedman's test for comparison between measurements. Wilcoxon signed rank test for comparison of pairs.
* significant distinction on the level $p < 0.05$.

Table 6. Statistically significant differences for studied amino acids measurements in patient groups

AA	Test's statistics	Level of significance	Post-hoc
Val[2]	12.870	0.005(*)	C-II; II-III
Ile[1]	4.641	0.005(*)	C-I; C-III
Leu[1]	4.395	0.007(*)	C-II; I-II
BCAA[1]	4.599	0.005(*)	I-II; II-III
Gln[2]	10.848	0.013(*)	C-II; I-II

C – control; I – colorectal cancer; II – small intestine cancer; III – pancreatic cancer
[1] Parametric test – ANOVA with mixed pattern – test F statistic.
[2] Nonparametric test – Kruskall-Wallis test for comparison of groups; Mann-Whitney *U* test for comparison of pairs.
* significant distinction on the level $p < 0.05$.

higher than before the operation and in the 3rd day of the therapy, but also significantly higher in comparison to the control group.

Discussion

Changes of amino acids concentrations in different types of cancer depend on many factors such as: kind of cancer, cancer stage, the age of patients, the way of treatment and nutrition [11]. Moreover, depletion of particular amino acids could be a significant marker of specific cancer and therefore nutritional therapy providing deficient amino

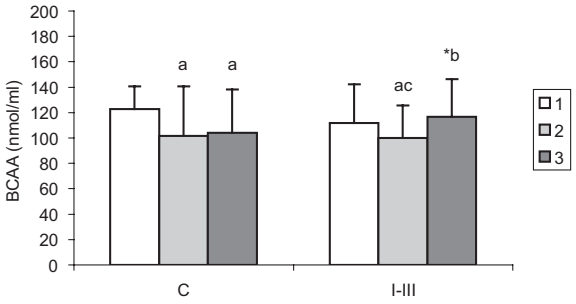

Fig. 1. BCAA concentration in blood serum of patients with gastrointestinal cancer
C – patients operated because of gastrointestinal cancer who were received no TPN; I-III patients operated because of cancer and given TPN after the operation. 1 – first measurement (1 day before operation); 2 – second measurement (3 days after operation or TPN application); 3 – third measurement (5 days after operation or TPN application).
* statistically significant vs. control group ($p < 0.05$).
[a] statistically significant vs. 1st measurement ($p < 0.05$).
[b] statistically significant vs. 2nd measurement ($p < 0.05$).
[c] statistically significant vs. 3nd measurement ($p < 0.05$).

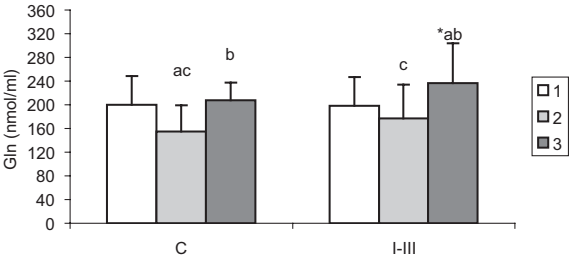

Fig. 2. Glutamine concentration in blood serum of patients with gastrointestinal cancer
C – patients operated because of gastrointestinal cancer who were received no TPN; I-III patients operated because of cancer and given TPN after the operation. 1 – first measurement (1 day before operation); 2 – second measurement (3 days after operation or TPN application); 3 – third measurement (5 days after operation or TPN application).
* statistically significant vs. control group ($p < 0.05$).
[a] statistically significant vs. 1st measurement ($p < 0.05$).
[b] statistically significant vs. 2nd measurement ($p < 0.05$).
[c] statistically significant vs. 3nd measurement ($p < 0.05$).

acids might be required [12–14]. Our results confirm the observation regarding plasma amino acids abnormalities in cancer patients [11, 13].

Beginning from the third day after the operations, BCAA concentrations in control group decreased. In groups of patients receiving TPN, BCAA concentrations on the third day after applying TPN were lower in comparison with the values noted before the operation, and from that day they began to increase. In control group, Gln concentration decreased after the surgery and subsequently increased beginning from the third day after the operation. A similar tendency was observed in TPN patients, which was probably caused by the use of BCAA for Gln synthesis. BCAA loss was observed in the group of patients with normal feeding after the operation, whereas in TPN ones it was partially compensated. It was found that BCAA use for the synthesis of Gln resulted in their reduction in skeletal muscles and in plasma. Low concentrations of BCAA are characteristic for protein-energy malnutrition and for plasma protein loss [15]. Additionally, cancer modifies metabolic response of muscles to surgical stress that stimulates partial or complete proteolysis and subsequently accelerates a release of Gln to the circulatory system [16]. In cancer and malnutrition, hyperammonemia is observed. It is caused by the incapability of the liver to detoxify ammonia. The use of BCAA for Gln synthesis causes partial detoxication of ammonia [17].

The metabolic properties of BCAA and observations regarding their enhanced oxidation in sepsis, burn and cancer allow applying the treatment with these amino acids in patients with catabolic illnesses. BCAA therapy can actually improve serum albumin concentration in patients with liver cirrhosis [18]. However, the incidence of hepatocellular carcinoma seems to be similar in patients with and without BCAA treatment. Lee et al. [13] noticed that concentrations of BCAA in liver disease were different from those observed in liver cancer and in colorectal cancer. They claimed that in the plasma of liver cancer patients, concentrations of most exogenous amino acids were depleted. The progress of the disease caused a decrease in concentrations of both exogenous and endogenous amino acids, which intensified BCAA depletion. Comparing liver cancer patients with cirrhosis ones, Charlton [19] found that BCAA concentrations were decreased in both groups, but Gln concentration was significantly depressed only in liver cancer subjects. That suggested accelerated using of Gln in cancer.

Several studies have demonstrated that BCAA-enriched amino acid mixture can reduce protein loss and improve the nutritional status of patients with liver diseases [9, 20]. Animal studies performed by Holecek et al. [21] displayed that the BCAA infusion did not affect protein synthesis improvement in septic rats, although it increased BCAA concentrations in plasma, muscles, liver and the small intestine. The administration of Gln caused an increase in Gln concentration in plasma, muscles as well as simulated protein synthesis in

liver. In a few studies, tumor growth inhibition or enhanced tumor response to anticancer drugs was seen in animals fed with Gln [22, 23]. Conversely, Gln supplementation corrects host Gln depletion and reverses impairment of intestinal functional and structural integrity associated with the tumor-bearing state [22, 24].

The question if BAAA-enriched parenteral nutrition use in patients with gastrointestinal cancer is the most beneficial solution still remains unclear. According to Cano et al. [25] BAAA-enriched TPN applied in patients operated due to gastrointestinal cancers may improve nitrogen balance, biochemical and nutritional parameters as well as may influence the reduction of oxidative stress in these patients. Similarly, Sun et al. [26] showed that the administration of BCAA-enriched TPN in malnourished patients after GI cancer (esophageal, gastric and colorectal) surgery can markedly improve nitrogen balance and serum albumin and prealbumin levels in comparison with patients receiving standard TPN.

The results of our studies indicate that surgery caused a decrease in concentrations of Val, Ile and Leu, which was maintained during the whole postoperative period. However, in TPN patients this tendency was overcome from the third day after surgery, except for Val and Leu in colorectal cancer group. The conclusion is that standard TPN is insufficient and it should be modified in patients with colorectal cancers. In the case of those patients, BCAA-enriched TPN or deficit amino acids-enriched diet could be more beneficial.

Considerably, some studies suggest that leucine-enriched nutrition mixture can stimulate muscle protein synthesis in a greater degree than a balanced mixture, because Leu influences the process of protein synthesis and plays a specific role in the regulation of optimal essential amino acids profile in blood serum [27, 28]. Its catabolism increases 7–8 h after BCAA administration, which proves intensified BCAA transamination, glutamate production and increased glutamine synthesis *de novo* [29]. Nitrogen derived from Leu as well as Ile and Val may be directly used for Gln synthesis in skeletal muscles [30]. In studies of Biolo et al. [31] patients with colorectal cancer after the operation were parenterally administered a standard mixture of amino acids and BCAA-enriched mixture. Both mixtures were isonitrogenous and the ratios of leucine to total amino acid (grams) in the two mixtures were 0.09 and 0.22, respectively. A standard diet did not influence protein kinetics and Gln synthesis. BCAA-enriched TPN accelerated the turnover of muscles proteins through the stimulation of protein synthesis and Gln synthesis. Furthermore, it was reported that standard TPN did not cause an increase in protein synthesis, in spite of exogenous amino acids concentrations being enhanced in plasma. On the contrary, enriched-BCAA TPN stimulated protein synthesis, increased Leu concentration and optimal concentrations of other exogenous amino acids several hours after applying TPN.

The outcomes of both these and other studies revealed that Leu displayed a specific capability of initiating protein synthesis in muscles through a modulation of mRNA translation [26, 32]. The underlying mechanism may involve activation of the mammalian target of the rapamycin (mTOR) signalling to enhance translation initiation and inhibit autophagy in liver and muscle. Other two BCAA – isoleucine and valine, have no effect on mTOR phosphorylation and muscle protein turnover [33]. However, Murata and Moriyama [34] showed that isoleucine prevented liver metastases in a mouse colon cancer metastatic model, whereas the leucine-treatment mice had multiple metastases in liver. They found that isoleucine prevented tumour growth via a novel mechanism by the inhibition of vascular endothelial growth factor production (VEGF), partially through the mTOR pathway, independent of hypoxia-inducible factor 1-α (H1F1-α). In these researches, the serum albumin concentration in the leucine-treated mice was lower than in the isoleucine-treated ones. Besides, Lynch et al. [35] showed that prolonged chronic dietary supplementation with Leu alone caused disturbances in both body weight and muscle mass gain in rats.

If is probable that unbalanced, BCAA-leucine-enriched mixture can not only disturb BCAA metabolism, but also induce tumour development and metastasis to the liver, a balanced TPN-enriched diet seems to be more beneficial for patients.

In patients with pancreas and small intestine cancers receiving TPN, the increase in BCAA concentration is followed with the increase in glutamine synthesis. Therefore, glutamine supplementation seems not to be necessary in such a situation. In the case of colorectal cancer, BCAA-enriched may also cause an increase in glutamine synthesis. Such a conclusion can be drawn from the studies of Biolo et al. [31], where the rate of muscle glutamine *de novo* synthesis did not significantly change after the infusion of the balanced amino acid mixture but increased during the infusion of the BCAA-enriched mixture.

Furthermore, glutamine administration in gastrointestinal cancer might alleviate glucose intolerance and protect muscle tissue against tumour-induced atrophy. However, the role of glutamine in GI cancers requires further clinical research.

Our studies included those patients who could not tolerate any form of nutrition other than

TPN. In our studies patients received standard TPN, nutrition recommended by some scientists, i.e. parenteral immunological nutrition, which caused the fast decrease of proinflammatory cytokines and other different necrosis markers was not applied.

Concluding, our studies showed that in gastrointestinal cancer patients, surgery results in a decrease in BCAA concentrations. Application of TPN in the postoperative period was beneficial and caused an increase in Val, Ile and Leu concentrations in patients with pancreatic cancer and small intestine cancer. However, in colorectal cancer, such treatment is not sufficient and parenterally administered mixture should contain BCAA-enriched formula.

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