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Original paper

Activity of aminotransferases as a marker of liver injury in home parenteral nutrition patients

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Abstract

Aim of the study: Parenteral nutrition associated liver disease (PNALD) is a frequently reported complication of long-term parenteral nutrition. Early diagnosis and treatment of PNALD can help prevent end-stage liver disease. The aim of the study was to evaluate the activity of aminotransferases as a marker of liver dysfunction in patients receiving home parenteral nutrition under the care of a reference center.

Material and methods: A comprehensive analysis of patients' medical records from a 9-year period (December 2012 – December 2021) was conducted and the following parameters were evaluated: parenteral nutrition mixture composition, total plasma bilirubin, activity of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), standardized time factor prothrombin (international normalized ratio [INR] factor) and serum albumin. The analysis covered 630,537 days of parenteral nutrition. The study included 251 patients (140 women and 111 men) included in the Home Parenteral Nutrition Program.

Results: PNALD was diagnosed in 11 parenteral fed patients, which gives the frequency of 8.3%/9 years of treatment. Two deaths were classified as cause of death related to liver disease but not related to PNALD. None of the patients included in the analysis developed end-stage liver failure.

Conclusions: The above analysis shows that individual selection of the composition of the mixture for intravenous nutrition significantly reduces the risk of PNALD and may prevent liver failure in this context.

Key words: liver disease, PNALD, home parenteral nutrition, aminotransferases.

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Introduction

Parenteral nutrition (PN) is a method of treating patients with gastrointestinal insufficiency in whom food supply through the gastrointestinal tract is impossible or ineffective [1-3]. A complete mixture used for parenteral nutrition contains amino acids, glucose, fat emulsion, electrolytes, vitamins and trace elements.

Long-term home parenteral nutrition (HPN) is used in patients with irreversible gastrointestinal insufficiency or in patients who require several months of preparation for reconstructive surgery. This treatment requires strict adherence to procedures, the transgression of which may be associated with the occurrence of complications, which are divided into three groups: mechanical, metabolic, and septic. Metabolic complications include blood sugar and electrolyte disturbances, as well as complications related to the functioning of organs, especially the liver and kidneys. Septic complications include catheter-related bloodstream infections and skin infections around access to the central vein. Recurrent and chronic septic conditions exacerbate liver damage. Most complications can be avoided if procedures are strictly followed (aseptic access control, mixture preparation and storage, metabolic controls, and method and timing of mixing).

Parenteral nutrition-associated liver disease (PNALD) is a commonly reported complication of long-term parenteral nutrition with an incidence of 25-100%, associated with increased mortality in patients on PN [4-7]. Abnormal blood test results indicative of liver damage (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin and serum bile acids) are observed in 30-40% of patients in PN [4, 6].

Clinical studies show that the incidence of PNALD-associated liver failure is decreasing [1]. This is related to optimization of nutritional intake and comprehensive patient care, modification of dosage and introduction of new types of fat emulsions for preparation of nutritional mixtures. Early diagnosis and treatment of PNALD can help prevent end-stage liver disease. It is difficult to clearly define the PNALD risk factors – they include both the length of the remnant bowel, the possibility of enteral feeding of the patient, disorders of hepatobiliary circulation, excessive energy intake, nutritional deficiencies and incorrect composition of the parenteral admixture (usually incorrect selection of fat emulsion) [4, 6, 8]. The risk of PNALD increases when extensive bowel resection has been performed and the patient is unable to consume food [4, 6, 8]. Data also show an increase with increasing duration of parenteral therapy [1, 8, 9].

Aim of the study

The aim of the study was to evaluate the activity of aminotransferases as a marker of liver dysfunction in patients receiving home parenteral nutrition under the care of a reference center.

Material and methods

This retrospective study comprised all adult patients (N = 251, 140 women, and 111 men) included in the HPN procedure in the reference center in Poland on December 31, 2012, according to the report of the Polish National Health Fund.

Patients were divided into three groups depending on their clinical status on December 31, 2021: group 0 – patients who died, group 1 – patients weaned off parenteral nutrition due to regaining gastrointestinal autonomy, group 2 – patients still receiving home parenteral nutrition. Group 2 was additionally divided into subgroups: 2A – patients without PNALD features, 2B – patients with PNALD features.

Demographic data of individual groups are presented in Table 1.

A comprehensive analysis of patients' medical records from the 9-year period (December 2012 – December 2021) was conducted and the following parameters were evaluated: parenteral nutrition mixture composition, total plasma bilirubin, activity of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), standardized time factor prothrombin (international normalized ratio [INR] factor) and serum albumin.

The analysis included all medical records: Home Parenteral Nutrition Procedure Qualification Cards, Hospital Discharge Cards, Hospitalization Epicrises, Death Cards, Visit Entries, and Nutrition Clinic Check-Up Cards.

Patients in group 1 were not included in further analysis of the study because they had completed nutritional treatment or had changed their HPN centers. Groups 0 and 2 were analyzed in detail for identification of liver disorders.

The research was approved by the Ethics Committee of the Centre of Postgraduate Medical Education (protocol code 94/2021, date of approval November 10, 2021).

Statistical analysis

For quantitative variables, the following measure was determined: central tendency (median), mean,

Table 1. Patients' characteristics

	Entire population	Group 0	Group 1	Group 2
Group size, *n* (%)	251 (100)	62 (25)	57 (23)	132 (52)
Sex, *n* (%)				
Female	111 (44)	30 (48)	27 (47)	54 (41)
Male	140 (56)	32 (52)	30 (53)	78 (59)
Age (years)				
Mean	62.3	62.3	60	60.2
Max	94	94	88	87
Min	24	24	25	24

min, max, standard deviation. For the categorical variables, the following measures were determined: number (*n*) and frequency (%).

In a situation where the dependent variable was on the quantitative/ordinal scale, and the independent variable on the qualitative scale, Mann-Whitney and Kruskal-Wallis non-parametric tests were used. The above tests are used when the conditions for using parametric tests are not met, including the condition of normal distribution.

Statistical analysis was performed using the SPSS program and all relationships are statistically significant when $p < 0.05$.

Results

The results were discussed based on the classification into groups.

Group 0

Sixty-three patients died during the study. In 61 patients, the cause of death was other than liver disease. The most commonly reported cause was cardiovascular failure (39%). Two deaths were classified as cause of death related to liver disease but not related to PNALD (case 1 – PBC – primary biliary hepatitis, case 2 – injury – both discussed below).

Case 1. A 63-year-old male patient was receiving parenteral nutrition due to an almost complete resection of the small intestine with an end jejunostomy (20 cm posterior to the ligament of Treitz). Blood tests showed an elevated total bilirubin concentration (mean concentration in the 4 months before death was 7 mg%, maximum concentration 12.6 mg%), elevated transaminases (ALT 96 U/l, AST 128 U/l) and an expanded INR index. An ultrasound image showed hyperechoic liver parenchyma, enlargement of its dimensions, irregular rim, and numerous small deposits in the gallbladder. Since there was no reason to diagnose any other cause, PNALD was diagnosed. Changing the quantity and quality of fat emulsion, reducing the total caloric content or modifications to the hourly intravenous infusion schedule did not improve the situation. During the diagnostic workup, a positive family history of liver disease was noted and primary biliary hepatitis (PBC) was diagnosed based on liver biopsy results. The patient was referred to a liver transplant center but was not placed on the recipient list and died of progressive organ failure.

Case 2. A 70-year-old patient who has been parenterally fed for 4 years because of short bowel syndrome with a jejunostomy who had a malignant neuroendocrine neoplasm with dissemination to the liver who was treated with somatostatin analogues. During treatment, high bilirubin levels (up to 12 mg%) with a more than twofold increase in liver enzymes were noted (ALT 62 U/l, AST 79 U/l). The percentage of involvement of the liver parenchyma by the cancer process did not indicate that this condition was the only cause of liver failure. The patient also had evidence of liver injury prior to the initiation of parenteral nutrition on a background of chronic treatment with thiamazole. It was concluded that the cause of the end-stage liver failure was an interaction of all three factors: the treatment with thiamazole, the spread of neuroendocrine neoplasms and the chronic parenteral nutrition.

Group 2

Group 2 included 131 patients who were still receiving parenteral nutrition at home on 31.12.2021.

The most common reason for qualifying for HPN in group 2 was short bowel syndrome (86.8% – group 2A, 90.9% – group 2B).

The average duration of PN at the beginning of the analysis was 11.7 years (group 2A – 11.8, group 2B – 10.9 years). The longest duration of parenteral nutrition was 33 years.

In the Department of General Surgery and Clinical Nutrition, all people made their nutritional mixtures on their own at home from preparations delivered by hospital transport. Of these, 80% circulated the nutrient mixture 7 days a week. Analysis using the Mann-Whitney *U* test showed a statistically significant difference, indicating that a slightly higher number of nutrition days applied to subjects in group 2A ($p = 0.032$) (Table 2).

Table 2. Frequency of supply of parenteral admixtures

Group	Number of feeding days					
	Mean	Median	*n*	SD	Min	Max
Group 2A	6.52	7.00	121	1.111	2	7
Group 2B	5.91	7.00	11	1.514	3	7
All	6.47	7.00	132	1.155	2	7
p Mann-Whitney *U*	0.032					

Table 3. Energy sources in home parenteral nutrition (HPN) mixtures

Group		Glucose/week (g)	Fat/week (g)	Non-protein energy per week (kcal)
Group 2A	Mean	1413.56	144.02	6950.39
	Median	1516.20	140.00	7324.80
	n	121	121	121
	SD	415.46	76.25	1939.38
	Min	0	0	0
	Max	2391.20	800	11454.80
Group 2B	Mean	1378.81	122.91	6621.42
	Median	1350.00	140.00	6480.00
	n	11	11	11
	SD	489.29	23.60	2050.17
	Min	510.00	80	3300.00
	Max	2275.00	140	10360.00
All	Mean	1410.66	142.26	6922.97
	Median	1516.20	140.00	7324.80
	N	132	132	132
	SD	420.10	73.50	1942.82
	Min	0	0	0
	Max	2391.20	800	11454.80
p Mann-Whitney *U*		0.558	0.122	0.367

The average amount of energy from non-protein sources per 7 days was 6922.97 kcal. The differences between the subgroups were not statistically significant. In group 2B, the maximum amount of non-protein energy consumed was 1094.8 kcal lower than in group 2A. Data with the distinction of carbohydrates and fats are presented in Table 3.

The type of fat emulsions the patients received was analyzed. Five preparations with different compositions per 100 ml were used: Intralipid 20%, Clinoleic 20%, Smoflipid 20%, Omegaven 10%, Lipofundin MCT 20%. Intralipid was the most commonly used treatment at baseline (74.2% of patients). Three patients in group 2A received Smoflipid and Omegaven alternately.

Eleven patients (8.3%) had elevated total bilirubin levels, including 5 patients with levels above 2 mg%. A summary of all biochemical parameters is presented in Table 4. The analysis showed that despite the higher bilirubin level in group 2A, no significant differences were found in AST, ALT, INR and albumin.

Bilirubin levels in groups 2A and 2B did not differ statistically significantly by age. In group 2A, bilirubin levels were higher in females (2.46 mg%) than in males (1.71 mg%). In group 2B, the concentrations were not significantly different between sexes. In group 2B, higher levels were found in patients who were on parenteral nutrition for more than 15 years. Group 2A showed an increasing trend in bilirubin concentration with duration of HPN treatment. Mean total bilirubin levels were also higher in those who did not take food by mouth. A correlation was observed between the amount of fat emulsion in the mixture and bilirubin levels. In addition, lower energy expenditure and less catheter-related sepsis were associated with lower bilirubin levels, but these correlations were found to be statistically insignificant.

Group 2B showed higher levels in individuals who had participated in the program for 6 to 10 years (Table 5). Group 2A showed a slightly increasing trend in relation to bilirubin concentration and the duration of HPN use (Table 6). For both analyses, $p > 0.005$.

In 5 of 11 patients in group 2A, the ultrasound image of the liver showed moderate enlargement and features of steatosis.

Discussion

Most publications indicate a high prevalence of PNALD. Cavicchi *et al.* followed a group of adult patients in France during 1986-1996 and reported the incidence of complicated liver disease associated with home parenteral nutrition in 26% at 2 years and 50% at 6 years. Liver disease was responsible for 22% of deaths

Table 4. Results of biochemical studies in patients from group 2

Group		Bilirubin	AST	ALT	INR	Albumin
Group 2A	Mean	2.0545	33.91	46.18	1.3836	35.45
	Median	1.7000	31.00	38.00	1.0700	35.00
	n	11	11	11	11	11
	SD	0.75148	17.032	27.845	0.71605	4.698
	Min	1.50	18	21	0.96	27
	Max	4.00	79	124	3.02	41
Group 2B	Mean	0.6028	32.56	48.09	1.1483	34.83
	Median	0.5000	29.00	40.00	1.0900	35.00
	n	121	121	121	121	121
	SD	0.30334	16.933	29.442	0.26938	4.539
	Min	0.10	11	13	0.90	23
	Max	1.30	83	171	2.87	45
Total	Mean	0.7238	32.67	47.93	1.1680	34.89
	Median	0.5000	29.00	39.50	1.0900	35.00
	N	132	132	132	132	132
	SD	0.53816	16.880	29.215	0.33147	4.538
	Min	0.10	11	13	0.90	23
	Max	4.00	83	171	3.02	45
p Mann-Whitney *U*		–	0.607	0.967	0.911	0.592

Table 5. Bilirubin concentration and time of home parenteral nutrition (HPN) in group 2B

Time of HPN	Mean	Median	*n*	SD	Min	Max
6-10 years	2.1833	1.9000	6	0.94745	1.50	4.00
More than 10 years	1.9000	1.7000	5	0.48477	1.50	2.70
All	2.0545	1.7000	11	0.75148	1.50	4.00
p Mann-Whitney *U*				0.782		

Table 6. Bilirubin concentration and time of home parenteral nutrition (HPN) in group 2A

Time of HPN	Mean	Median	*n*	SD	Min	Max
2-5 years	0.5000	0.4000	8	0.23905	0.30	1.00
6-10 years	0.5490	0.4050	58	0.27086	0.10	1.20
More than 10 years	0.6745	0.6000	55	0.33123	0.20	1.30
All	0.6028	0.5000	121	0.30334	0.10	1.30
p Kruskal-Wallis test				0.093		

in this group [9]. In our patient group, the incidence was much lower and was 8.3% with 0% mortality after 9 years. 2 cases of death (3.2%) were associated with liver disease but not related to PNALD. The most common cause of death was cardiovascular disease. In another study, Lakananurak and Tienchai examined 44 adults. The prevalence of PNALD was 59.1% (22.7% steatosis, 34.1% cholestasis, and 2.3% mixed type). In this study group, the presence of PNALD was found in more than half of the hospitalized patients [7]. The difference between our center and centers with a higher percentage of PNALD is the use of individually formulated nutrient mixtures for parenteral nutrition. An individually formulated mixture is used for each patient according to their metabolic capabilities and nutritional needs. In many centers, standard RTU (ready to use) prepa-

rations are used. Their composition is fixed and not always optimized for a particular patient. According to a study by Javid *et al*., the incidence of liver disease associated with parenteral nutrition is 40-60% in pediatric patients and 15-40% in adult patients. Data from the American Pediatric Intestinal Failure Consortium (PFIC) showed that about 38% of patients had bilirubin levels > 4 mg/dl at baseline, which corresponded to a 4-fold increased risk of death [10]. In 2020, Guzman and colleagues hypothesized that the lack of enteral nutrition is an important factor in liver disease associated with parenteral nutrition. They suggest that it triggers changes in signaling in the gut that contribute to liver and intestinal damage [11]. These authors suggest that the incidence of liver disease associated with home parenteral nutrition increases with the duration of parenteral nutrition and is a leading cause of death in patients on chronic parenteral nutrition. This hypothesis was not confirmed at all in our study.

Many studies show that the use of fish oil in a fatty emulsion reduces the likelihood of liver disease. However, Tran and Butcher analyzed the literature in recent years on this topic and concluded that this is irrelevant. It has not been shown that any particular fat emulsion with or without fish oil is more effective than others in improving liver function, inflammation, and other biochemical outcomes [12]. In our experience, the symptoms of PNALD syndrome can be repressed if the fat emulsion is replaced with an omega-3 component permanently or only at regular intervals. Wu *et al*. conducted studies in which one of the groups received no fat emulsion in a parenteral formulation. The lipid-free group was associated with higher incidence of liver dysfunction, higher mortality, and higher incidence of hyperbilirubinemia. Compared to the lipid-free group, the olive oil group had a lower risk of hyperbilirubinemia. In addition, the olive oil group had a significantly lower risk of mortality, while fish oil > 0.05 g/kg/day was associated with a lower incidence of liver dysfunction [13, 14].

The lack of oral nutrition results in decreased secretion of hormones that regulate gastrointestinal tract function – cholecystokinin, gastrin, and the YY peptide. With enteral nutrition, they stimulate bile flow and gallbladder contraction and maintain intestinal peristalsis. Long-term parenteral nutrition may decrease the contractility of the gallbladder and reduce secretion or stagnation of bile acids. In addition, low concentrations of these hormones can lead to intestinal dysfunction, atrophy of the intestinal mucosa, and consequently bacterial overgrowth and translocation, increasing the risk of sepsis [15, 16].

The symptoms of PNALD are mainly abnormal production of liver enzymes, cholestasis, fatty liver, occurrence of gallbladder stones, progressive fibrosis and finally cirrhosis as a result of total parenteral nutrition. Diagnosis in patients is mainly based on the exclusion of other factors of chronic liver disease [4, 17]. The clinical manifestation of fatty liver disease, which occurs in 40-55% of patients, is an increase in liver enzyme levels on blood tests. Cholestasis is the result of obstruction of the bile ducts or inappropriate secretion. It is manifested by an increase in the levels of alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGTP) and bilirubin [14, 17]. The degree and severity of liver dysfunction can be classified based on organ features observed on radiological examination – ultrasonography (USG), liver imaging with computed tomography, magnetic resonance imaging (MRI) and liver biopsy, which is the gold standard [17].

The main principle of treatment is constant monitoring of liver enzyme levels and, if possible, changing the fat emulsion administered or reducing its concentration in the nutritional mixture. Fat emulsion intake cannot be completely eliminated – lipids are not only a source of energy, but also provide fatty acids necessary for maintaining cell membrane integrity, supporting immune function, and regulating gene expression. Studies show that fish fat emulsions reduce the likelihood of PNALD [17-20].

Lipid intake depends on the patient's underlying disease, energy requirements, body weight and recent weight loss, and the body's metabolic capacity. The dose of 2.5 g lipids/kg body weight/day should not be exceeded [17, 19].

Ideally, intestinal adaptation should be accelerated, enteral nutrition introduced, and parenteral nutrition avoided. However, not all patients are able to do this, and some will be dependent on parenteral nutrition for the rest of their lives. If possible, at least trophic nutrition should be introduced [6]. It is also possible to implement hormone therapy – for example, with glucagon-like peptide-2 (GLP-2), because according to many studies, it plays an important role in stimulating intestinal adaptation [21].

In conclusion, the prevention and treatment of PNALD requires an integrated approach to the patient and the collaboration of a medical team consisting of physicians, nurses, pharmacists, dietitians, laboratory personnel and psychologists. Nutritional management involves optimizing nutrition through the gastrointestinal tract, thereby stimulating enterohepatic circulation. Liver disease associated with parenteral nutrition is a complication that can be diagnosed in chronic patients. In the studied population, only 8.3% of peo-

ple had elevated levels of total bilirubin (≥ 1.5 mg/dl) in plasma. This may suggest that a properly balanced, individualized program of nutrition parenteral treatment reduces the risk of developing PNALD.

Disclosure

The authors declare no conflict of interest.

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