ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 06, pp.21118-21128, June, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

CAUSES OF PARENTERAL NUTRITION-ASSOCIATED LIVER DYSFUNCTION IN PATIENTS RECEIVING PARENTERAL NUTRITION AT HOME — RETROSPECTIVE OBSERVATIONAL STUDY

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ARTICLE INFO

Article History:
Received 12th March, 2018
Received in revised form
17th April, 2018
Accepted 20th May, 2018
Published online 30th June, 2018

Key Words:
Parenteral nutrition.

ABSTRACT

The purpose of this study was to investigate factors related to nutrient mixture composition that contribute to the liver complications in patients chronically treated with parenteral nutrition. The retrospective study included 94 patients (53 female, 41 male), aged 24 to 81 years (mean age 54.5 years). Patients were followed up every 3 months on average, which was the basis for dividing the course of treatment of each patient into treatment periods. A single treatment period with a follow-up at the end was used as the basic unit for comparative analyses presented below. A total of 371 treatment periods were analyzed. If the follow-up laboratory tests showed increased total bilirubin levels or increased AspAT/AlAT activity, the preceding treatment period was classified into the "complications" group (group II); if the follow-up results were normal, the treatment period was classified into the "no complications" group (group I). In the treatment periods with increased aminotransferase activity and bilirubin levels at follow-up, patients received significantly more lipids and glucose per kilogram of body weight. In the entire study group, there was a correlation between glucose intake per kg/bw and occurrence of liver complications affecting aminotransferase activity and bilirubin concentration. Conclusions: high dosage of glucose and lipids is the primary factor in the pathogenesis of liver complications. The type of lipid emulsion has little significance. The maximum dosage of glucose and lipids, above which liver dysfunctions are more than 90% likely to occur, is 4.721 g of glucose kg/bw, and 1.276 g of lipids kg/bw.

Citation: Matras Przemysław, Bartoszewska Lidia, M., Prendecka Monika, Zalewski Grzegorz, Szpetnar Maria and Rudzki Sławomir, 2018. "Causes of parenteral nutrition-associated liver dysfunction in patients receiving parenteral nutrition at home — retrospective observational study", *International Journal of Development Research*, 8, (06), 21118-21128.

INTRODUCTION

In patients who lack a large portion of the small intestine (short bowel syndrome) or suffer from severe digestive dysfunction (e.g. malabsorption syndrome) (Braunschweig, 2001), parenteral nutrition is a life-saving treatment (Braga *et al*., 2009). It can be provided either in a hospital setting or at home (Staun *et al*., 2009). The increasing number of centers specializing in home parenteral nutrition (HPN) is associated not only with increased number of patients, but also with increased safety of the treatment.

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Chronic home nutritional treatment is quite an extraordinary kind of treatment. Though there are numerous potential complications associated with the therapy (Ukleja, 2007; Guglielmi *et al*., 2006), it is carried out by the patient or their family, who are typically individuals with no medical background (Schwartz *et al*., 2009). The role of HPN centers is to educate patients, and then monitor them. This is significant, as these activities have decreased the incidence of septic complications (Pittiruti *et al*., 2009) to a level several times lower than that seen in hospital settings. The primary role of an HPN center is to prescribe the composition of the nutrient mixture individually for each patient (Ciszewska-Jędrasik, 2004). Both the patient's needs and their metabolic performance are considered in the process (Rudzki, 2011;

Crook, 2000). Incorrect dosages or proportions of particular nutrients or ignoring the impact of the underlying disease are factors contributing to metabolic complications. Sadly, the incidence of these complications has only slightly decreased in recent years (Dibb *et al*., 2013; Maroulis, 2000). The main goal of nutritional treatment is to provide protein (amino acids) in the required quantity and quality (Yarandi *et al*., 2014). However, the desired clinical outcomes cannot be achieved without supplying the required amounts of non-protein energy (Boulétreau *et al*., 2005; Adolph *et al*., 2009), i.e. energy from glucose and lipids (Sobotka, 2007; Calder *et al*., 2010). Chronic parenteral nutrition often involves liver complications (Schwartz *et al*., 2009; Raman *et al*., 2007). These complications can range from very mild, involving increased transaminase activity or bilirubin concentration, to severe, involving significant liver dysfunctions, up to and including liver failure (Buchman *et al*., 2006; Grygiel-Górniak, 2010). The clinical presentation of liver complications is likely dependent on the time of diagnosis of the dysfunction. If the composition of the nutrient mixture that contributed to the dysfunction is not modified, the complications increase in severity. The etiology of these complications is not yet fully understood (Korta, 2008; Cober *et al*., 2012; Colomb *et al*., 2000).

Purpose of the study: The purpose of this study was to investigate factors related to nutrient mixture composition that contribute to liver complications in patients chronically treated with parenteral nutrition. The retrospective study model was used.

MATERIALS AND METHODS

Characteristics of the participants: Between January, 2005, and June 2016, a total of 209 patients at the Nutritional Therapy Center of the 1st Department of General and Transplantation Surgery and Nutritional Therapy of the Lublin Medical University in Lublin, Poland, were treated with home parenteral nutrition. Retrospective analyses were performed for all these patients. Patients with increased bilirubin or aminotransferase levels at the outset or during the nutritional therapy due to hepatic or biliary pathologies other than parenteral nutrition-associated liver dysfunction were excluded from the study (n=115). Patients not followed up due to death or discontinuation of treatment were also excluded.

Ultimately, the retrospective study included 94 patients (53 female, 41 male), aged 24 to 81 years (mean age 54.5 years). Parenteral nutrition was mainly administered due to malnutrition related to cancer (n=53) or short bowel syndrome (n=41). The cancers included: stomach, colon, ovarian, and pancreatic cancer. The short bowel syndrome was due to mesenteric arterial embolism, abdominal trauma or surgical complications. The mean time of treatment for the entire group was 17 months (range: 3 to 97 months), and differed depending on the diagnosis. In the cancer group, the mean time of treatment was 9 months, and in the short bowel syndrome group – 28 months. The parenteral nutrition treatment was provided to all patients using industrial double- and triple-chamber bags from various manufacturers. The names and compositions of the products are shown in Table 1. Various types of lipid emulsions were also used, including soybean oil (SO), olive oil (OO), fish oil (FO), long-chain and medium-chain triglycerides (LCT, MCT) in varying proportions (depending on the manufacturer).

Study methods: In the course of chronic nutritional therapy, each patient undergoes periodic follow-up focusing both on the nutrient mixture composition and on the treatment outcomes. The follow-up involves the basic anthropometric and laboratory parameters, i.e. body weight, BMI (body mass index), and levels of RBC, lymphocytes, albumin, bilirubin, AspAT, and AlAT. Follow-ups take place in individually chosen intervals – typically every three months in sTable patients. Sufficiently frequent follow-ups enable prompt reaction to any complications. In the analyzed group of patients, whenever metabolic complications were identified, such as liver dysfunction, the nutrient mixture composition was modified, which usually caused the symptoms to subside. If the complications persisted despite the parenteral nutrition modification, further diagnostics were used to identify causes other than the nutrient mixture. The target liver complication, was defined as an increase in total serum bilirubin above 1.2 mg/dL or AspAT/AlAT activity above 48 IU/L (i.e. the upper reference limits for the tests used in the hospital laboratory) present without other causes beside the nutritional therapy.

The routine periodic follow-ups were used for analyzing liver complication incidence in the studied group. In order to identify factors that may contribute to liver complications in the patient group, the following parameters were calculated at the end of each treatment period: total daily dosages of lipids and glucose, glucose to lipids ratio, dosage of lipids and glucose per kilogram of body weight, non-protein energy, total energy, and ratio of lipids and glucose to non-protein energy. The qualitative composition of the lipid emulsions used was also analyzed, and doses of each lipid type were calculated. A single treatment period with a follow-up at the end was used as the basic unit for comparative analyses presented below. This enhanced the value of statistical calculations by increasing the number of data analyzed to 371 treatment periods. If the follow-up laboratory tests showed total bilirubin levels or AspAT/AlAT activity above the reference values, the preceding treatment period was classified in the "complications" group (group II); if the follow-up results were normal, the treatment period was classified in the "no complications" group (group I).

If the nutrient mixture was modified in the subsequent treatment period, and follow-up tests after the period showed a decrease in AspAT, AlAT, and/or bilirubin values compared to the previous test (even if the values remained above normal), the period was not classified in the "complications" group. For statistical analysis, the treatment periods were classified into four groups. "A" groups were identified based on aminotransferase activity, while "B" groups were identified based on bilirubin levels. Both "A" and "B" groups were marked "I" if the tested values were within normal ranges, or "II" if the values were above normal at the end of the treatment period. Therefore, group IA indicates normal AspAT and AlAT activity, while group IIA indicates AspAT and/or AlAT values above 48 IU/L at the end of the treatment period. Similarly, group IB indicates normal bilirubin levels, while group IIB indicates bilirubin levels above 1.2 mg/dL at the end of the treatment period.

Statistical analysis: Statistical analysis was performed using the STATISTICA 10 software (StatSoft, Poland). Differences between groups were analyzed using the Mann-Whitney U-test, as the assumptions for parametric tests were not met. Correlations between selected factors were evaluated using

Spearman's rank-order correlation test. The analyzed variables were tested for distribution normality using the Shapiro-Wilk or Kolmogorov–Smirnov test. After eliminating outliers, linear correlation coefficients were calculated. For each coefficient, the *p* value was calculated. The error threshold used was 5%, which corresponds to a significance level of $p<0.05$ required for differences between groups to be considered statistically significant. ROC curves were used to estimate maximum glucose and lipid dosages.

RESULTS

A total of 371 treatment periods were analyzed. Abnormal bilirubin levels or aminotransferase activities were found at the end of 132 treatment periods, i.e. 36% of the total. In the groupanalyzed, increased bilirubin concentration was found in 56 treatment periods, and increased aminotransferase activity – in 114. Both abnormalities occurred jointly in 38 treatment periods. Mean bilirubin concentration in the entire sample was 0.91 (median: 0.6, SD: 1.15), median alanine aminotransferase activity was 35 (SD: 61.75), and median aspartate aminotransferase activity was 33 (SD: 37.88).

Group A: Groups IA and IIA were comparable in terms of nutritional state parameters. Mean BMI for group IA was 20.9 kg/m^2 (range: 9.96–31.43kg/m^2), for group IIA – 20.5 (8.65–33.16 kg/m^2); median RBC was 4.18 M/μL (2.46–5.80 M/μL) for group IA vs. 3.8 M/μL (1.71–5.25 M/μL) for group IIA; median lymphocyte count was 1.35 K/μL (0.15–5.69 K/μL) for group IA vs. 1.32 K/μL (0.39–8.90 K/μL) for group IIA; median albumin concentration was 4.0 g/dL(1.99–5.5 g/dL) for group IA vs. 3.8 g/dL (2.31–5.15 g/dL) for group IIA. No statistically significant differences were found between the groups. Median aminotransferase activities in group IA (n=225 observations) vs. IIA (n=114 observations) were: AlAT 27 IU/L (range 8–224 IU/L) vs. 85 IU/L (44–512 IU/L), AspAT 27 IU/L (11.00–182 IU/L) vs. 66 IU/L (37–296.00 IU/L), respectively. Mean bilirubin was 0.67 mg/dL (0.1-3.5 mg/dL) vs. 1.50 mg/dL (0.10–12.90 mg/dL). Statistically significant differences were found between the groups in terms of lipid dosage (p=0.002), glucose dosage (p=0.000004), glucose/lipid ratio (p=0.008) and non-protein energy intake (p=0.000002).Moreover, both groups were compared in terms of ratios of non-protein energy, energy from lipids, and energy from glucose to energy from amino acids. Detailed data are shown in Table 2. In the entire sample of treatment periods analyzed, correlations were found between glucose dosage and AspAT and AlAT activities, shown in Figures 1 and 2, respectively.

Group B: Mean bilirubin levels in groups IB (n=308 observations) and IIB (n=56 observations) were 0.63 mg/dL (range: 0.10–3.52 mg/dL) vs. 2.57 mg/dL (1.10–12.90 mg/dL), respectively; median aminotransferase activities were: AlAT 33 IU/L (8–512.00 IU/L) vs. 76 IU/L (8.00–247.00 IU/L), AspAT 31 IU/L (11.00–296.00 IU/L) vs. 63 IU/L (13.00–213 IU/L), respectively. No statistically significant differences were found between the groups in terms of BMI, which was 20.6 kg/m^2 (range 8.65–33.15 kg/m^2) for group IB vs. 21.19 (10.98–31.44 kg/m^2) for group II B; though some laboratory indicators of nutritional status were significantly different between the groups. Median RBC was 4.12 M/μL (2.41–5.80 M/μL) vs. 3.92 M/μL (1.71–5.37 M/μL) (p=0.02), median lymphocyte count was 1.39 K/μL (0.15–8.90 K/μL) vs. 1.15 K/μL (0.42–7.10 K/μL) (p=0.05), median albumin concentration was 4.01 g/dL (1.99–5.5 g/dL) vs. 3.7 g/dL (2.23–4.69 g/dL) (p=0.004). Differences between groups were analyzed in terms of daily lipid and glucose dosages, glucose/lipids ratio, daily non-protein energy intake; as well as the ratios of non-protein energy, energy from lipids, and energy from glucose to energy from amino acids. The results are shown in Table 3. Correlations were found between glucose dosage and total bilirubin levels in all the analyzed treatment periods, as shown in Fig. 3.

Impact of underlying disease: One cause of metabolic complications in nutritional treatment is the underlying disease. The analyzed patient group did not include those in whom the underlying disease could have directly caused the liver dysfunction. Correlations were analyzed between complication incidence and the underlying disease that necessitated the nutritional treatment. Treatment periods were classified into one of two groups based on diagnosis: cancer or short bowel syndrome. In the cancer group, increased bilirubin levels were found in 17.36% of the treatment periods, while in the short bowel syndrome group – in 14.29%. The difference was not statistically significant. However, transaminase activity was increased statistically significant more often in the cancer group than in the short bowel syndrome group: in 38.52% vs. 27.13% of treatment periods.
In both diagnosis groups, the nutrient mixture compositions were analyzed (Table 4), and their impact on the incidence of liver complications (increased bilirubin and/or aminotransferase activity) was investigated. The results are shown in Tables 5 and 6.

Impact of the product, lipid emulsion composition and dosage: Correlations were analyzed between the type of the industrial product used and the incidence of complications (**Table 7**). Preparations used in fewer than 10 treatment periods were excluded from the analysis.

Analysis of complication management methods and effectiveness: As a correlation was found between the dosage of glucose and lipids and their ratio in the nutrient mixture on the one hand, and the incidence of liver complications on the other, the methods of complication management were analyzed. In all cases, this involved a decrease of glucose and lipid dosages, but the desired therapeutic outcomes were not always achieved. Lipid and glucose dosages were compared in those treatment periods following the occurrence of complications where bilirubin and/or aminotransferase values returned to normal, and those where the values remained abnormal. Lipid dosages were found to be significantly lower (p=0.01) in the "improvement" group than in the "no improvement" group (median 0.4 mg/kg vs. 0.8 mg/kg). No statistically significant difference between the two groups was found in terms of glucose dosages (median 3.23 mg/kg vs. 4.03 mg/kg, p=0.7).

Complication threshold, ROC analysis: As the dosages of glucose and lipids were found to be most strongly correlated with the incidence of complications, the incidence was subsequently analyzed in periods where lipid and glucose dosages were above and below the median. The results are shown in Figures 4 and 5. An analysis was also performed for quartiles of glucose and lipid dosages. The results are shown in Figure 6. Using ROC curves, the minimum threshold of glucose and lipid dosages marking a statistically significant increase in complication risk was identified (Figures 7 and 8).

Table 1. Triple-chamber bags used in the parenteral nutrition treatment and their specifications – contents per 1000 mL

Product	Manufacturer	Amino acids [g]	NITROGEN [g]	Total energy [kcal]	Non-protein energy [kcal]	Glucose [g]	Q [kcal/1g of nitrogen]	Lipids [g]
Clinomel N4-550	Baxter	22	3.6	610	520	80	144	20
Clinomel N5-800	Baxter	28	4.8	910	800	100	167	40
Clinomel N6-900	Baxter	34	5.6	1015	880	120	157	40
Clinomel N7-1000	Baxter	40	6.6	1200	1040	160	158	40
Multimel N4-550E	Baxter	22	3.6	610	520	80	144	20
Multimel N5-800E	Baxter	28	4.6	912	800	100	174	40
Multimel N6-900E	Baxter	34	5.6	1015	880	120	157	40
Multimel N7-1000E	Baxter	40	6.6	1200	1040	160	158	40
OlimelPeri N4E	Baxter	25	4.0	700	600	75	150	30
Olimel N5E	Baxter	33	5.2	990	860	115	165	40
Olimel N7E	Baxter	44	7.0	1140	960	140	137	40
Olimel N9E	Baxter	57	9.0	1070	840	110	93	40
Kabiven Peripheral	Fresenius Kabi	23	3.6	700	600	65	167	34
Kabiven	Fresenius Kabi	34	5.4	900	800	100	148	40
Smof Kabiven Periferal	Fresenius Kabi	32	5.1	700	600	71	118	28
SmofKabiven	Fresenius Kabi	50	8.0	1100	900	125	113	38
Nutriflex Lipid Peri	BBraun	32	4.6	764	636	64	138	40
Nutriflex Lipid Plus	BBraun	38	5.5	1012	860	120	157	40
Nutriflex Lipid Special	BBraun	57.5	8.0	1180	956	144	120	40

Table 2. Results for groups IA and IIA

		Group	
Parameters analyzed		IA	IIA
LIPIDS	mean	0.66	0.78
[g/kg bw/day]	median	0.64	0.78
	0.25-0.75	0.45-0.82	0.56-1.02
	min-max	0.00-1.99	0.00-1.71
		p=0.002	
GLUCOSE	mean	2.62	3.43
[g/kg bw/day]	median	2.4	3.1
	0.25-0.75	1.72-3.19	2.30-4.49
	min-max	0.30-8.92	0.59-11.02
		p=0.000004	
GLUCOSE/LIPIDS	mean	4.13	5.69
[g/kg bw/day]	median	3.79	4
	0.25-0.75	2.54-4.00	3.09-5.24
	min-max	1.60-33.12	1.60-33.12
		p=0.008	
NON-PROTEIN ENERGY	mean	17.14	21.39
[kcal/kg bw/day]	median	16.77	19.5
	0.25-0.75	11.71-20.63	15.82-26.50
	min-max	3.01-43.24	5.82-54.59
		p=0.000002	
	mean	2.17	2.01
	median	2.22	2.13
	0.25-0.75	2.01-2.92	1.25-2.54
ENERGY FROM LIPIDS/ENERGY FROM AMINO ACIDS	min-max	0.53-4.00	0.53-4.00
[kcal/kg bw/day]		p=0.1	
	mean	3.2	3.41
	median	3.39	3.56
	0.25-0.75	2.51-3.64	2.91-3.78
ENERGY FROM GLUCOSE/ENERGY FROM AMINO ACIDS [kcal/kg bw/day]	min-max	0.92-6.87	1.82-5.66
		p=0.02	
	mean	5.36	5.44
	median	5.78	5.78
	0.25-0.75	4.51-6.00	4.42-6.33
NON-PROTEIN ENERGY/ENERGY FROM AMINO ACIDS	min-max	1.80-9.30	2.94-8.54
[kcal/kg bw/day]		p=0.8	

Table 3. Results for groups Ib and IIb.

Parameters analyzed		Group	
		IB	IIB
LIPIDS [g/kg bw/day]	mean	0.67	0.80
	median	0.66	0.77
	0.25-0.75	0.45-0.85	0.51-1.04
	min-max	0.00-1.99	0.18-1.73
		p=0.03	
GLUCOSE [g/kg bw/day]	mean	2.77	3.63
	median	2.50	3.30
	0.25-0.75	1.80-3.32	2.30-4.88
	min-max	0.30-11.02	0.59-6.25
		p=0.00006	
GLUCOSE/LIPIDS [g/kg bw/day]	mean	4.19	6.99
	median	3.98	4.00
	0.25-0.75	2.90-4.00	3.10-5.63
	min-max	1.60-33.12	1.60-33.12
		p=0.02	
NON-PROTEIN ENERGY [kcal/kg bw/day]	mean	17.79	22.33
	median	17.19	21.39
	0.25-0.75	12.21-20.84	15.78-27.18
	min-max	3.01-54.59	5.82-41.08
		p=0.00004	
ENERGY FROM LIPIDS/ENERGY FROM AMINO ACIDS [kcal/kg bw/day]	mean	2.14	2.00
	median	2.22	2.22
	0.25-0.75	1.98-2.90	1.18-2.54
	min-max	0.51-4.00	0.26-4.00
		p=0.4	
ENERGY FROM GLUCOSE/ENERGY FROM AMINO ACIDS [kcal/kg bw/day]	mean	3.23	3.48
	median	3.55	3.61
	0.25-0.75	2.59-3.64	3.10-3.93
	min-max	0.92-6.87	2.00-4.96
		p=0.008	
NON-PROTEIN ENERGY/ENERGY FROM AMINO ACIDS [kcal/kg bw/day]	mean	5.37	5.47
	median	5.78	5.78
	0.25-0.75	4.51-6.06	4.11-6.32
	min-max	1.8-9.30	2.94-8.15
		p=0.5	

Table 4. Composition of nutrient mixture in relation to diagnosis

	Mean, median, min, max								p
	Cancer n=121				SBS n=247				
Lipid dosage per kg bw	0.62	0.63	0.00	3.21	0.71	0.67	0.00	2.00	0.01
Glucose dosage per kg bw	2.88	2.50	0.58	6.90	2.83	2.60	0.30	11.02	0.6
Glucose to lipids ratio (g) per kg bw	5.57	4.00	0.56	33.13	4.08	3.59	1.60	16.50	0.009
Glucose to lipids ratio (kcal) per kg bw	2.35	1.60	0.39	14.72	1.70	1.53	0.67	6.76	0.008
Non-protein energy to energy from protein ratio	5.29	5.78	2.00	9.30	5.39	5.78	1.80	8.54	0.6
Non-protein energy to energy from protein ratio	1.89	2.13	0.00	5.10	2.17	2.22	0.00	4.00	0.01
Energy from glucose to energy from protein ratio	3.36	3.56	0.64	6.87	3.22	3.55	0.92	7.17	0.04
Total non-protein energy per kg bw	17.94	17.33	4.64	46.74	18.26	17.08	3.01	54.58	0.8

Table 5. Comparison of composition, parenteral nutrition mixture in patients in AI and AII and BI and BII groups in patients with cancer

	Mean or median		p	Mean or median		p
	No bilirubin increase N=99	Increased bilirubin N=21		No aminotransferase activity increase N=74	Increased aminotransferase activity N=47	
Lipid dosage per kg bw	0.63395	0.75616	0.470449	0.65267	0.61728	0.655085
Glucose dosage per kg bw	2.50000	4.46768	0.031442	2.40120	3.09478	0.050660
Glucose to lipids ratio (g) per kg bw	4.00000	4.62500	0.444582	4.00000	4.00000	0.252545
Energy from glucose to to energy from protein ratio	5.77778	4.51980	0.284820	5.77778	5.38804	0.466198
Energy from glucose to energy from protein ratio	2.13333	2.03508	0.560063	2.13333	2.13333	0.197979
Energy from glucose to energy from protein ratio	3.55556	3.27784	0.831171	3.55556	3.55556	0.848043
Total non-protein energy per kg bw	17.56870	23.65791	0.009990	17.32206	19.46970	0.056933
Glucose to lipids ratio (kcal) per kg bw	1.60000	1.85000	0.355455	1.60000	1.66397	0.120675

Table 6. Comparison of composition, parenteral nutrition mixture in patients in AI and AII and BI and BII groups in patients with the short bowel syndrome

	Mean or median		p	Mean or median		p
	No bilirubin increase N=210	Increased bilirubin N=35		No aminotransferase activity increase N=180	Increased aminotransferase activity N=67	
Lipid dosage per kg bw	0.65790	0.81081	0.021418	0.64103	0.82781	0.000067
Glucose dosage per kg bw	2.47951	3.25472	0.001031	2.42139	3.12500	0.000047
Glucose to lipids ratio (g) per kg bw	3.34211	4.00000	0.026475	3.34211	4.00000	0.036782
Energy from glucose to to energy from protein ratio	5.77778	5.85850	0.100224	5.77778	5.77778	0.297869
Energy from glucose to energy from protein ratio	2.22222	2.22222	0.533560	2.22222	2.22222	0.451658
Energy from glucose to energy from protein ratio	3.32356	3.64444	0.001921	3.31492	3.55556	0.015373
Total non-protein energy per kg bw	17.03808	20.58962	0.001124	15.80585	20.00484	0.000005
Glucose to lipids ratio (kcal) per kg bw	1.41113	1.60000	0.014173	1.39014	1.60000	0.011313

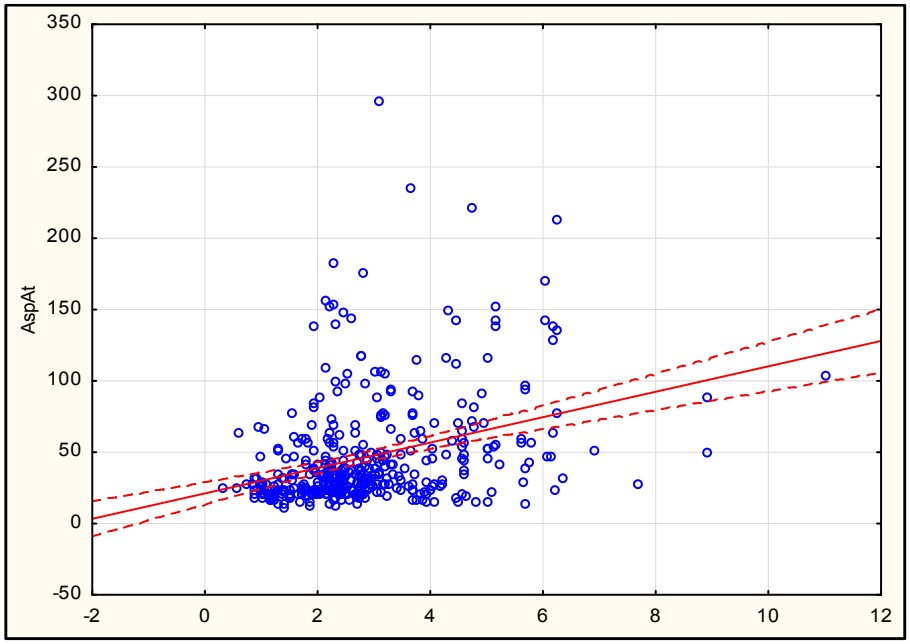

Fig.1. Correlation between glucose dosage per kg bw and AspAT activity (Spearman's Rho=0.37, p=0.000001)

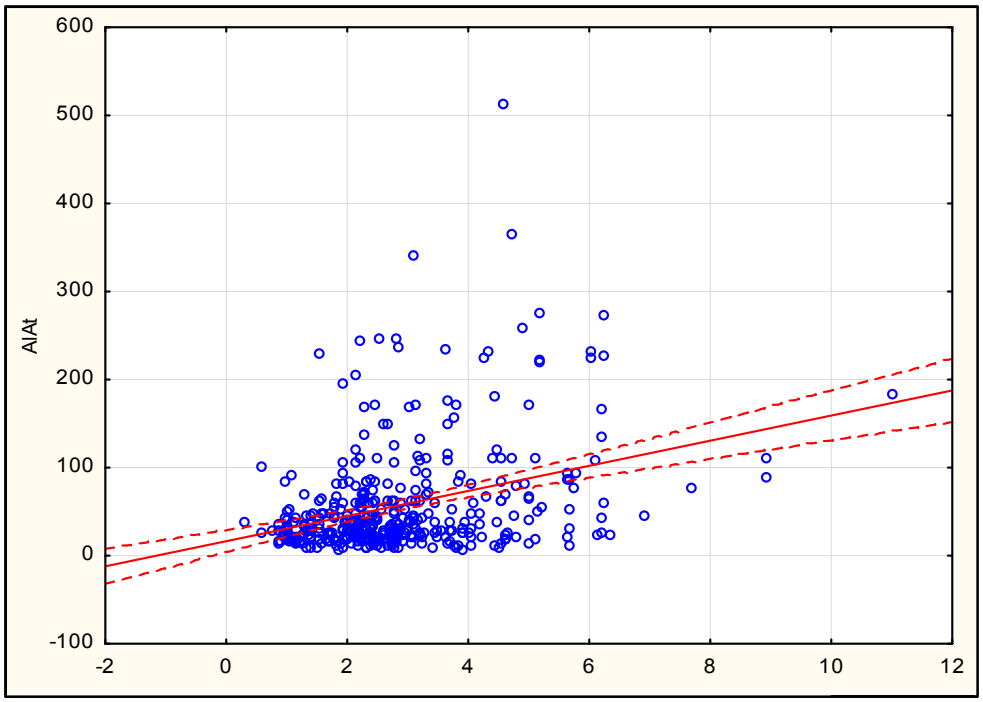

Fig.2. Correlation between glucose dosage per kg bw and AlAT activity (Spearman's Rho=0.28, p=0.00001)

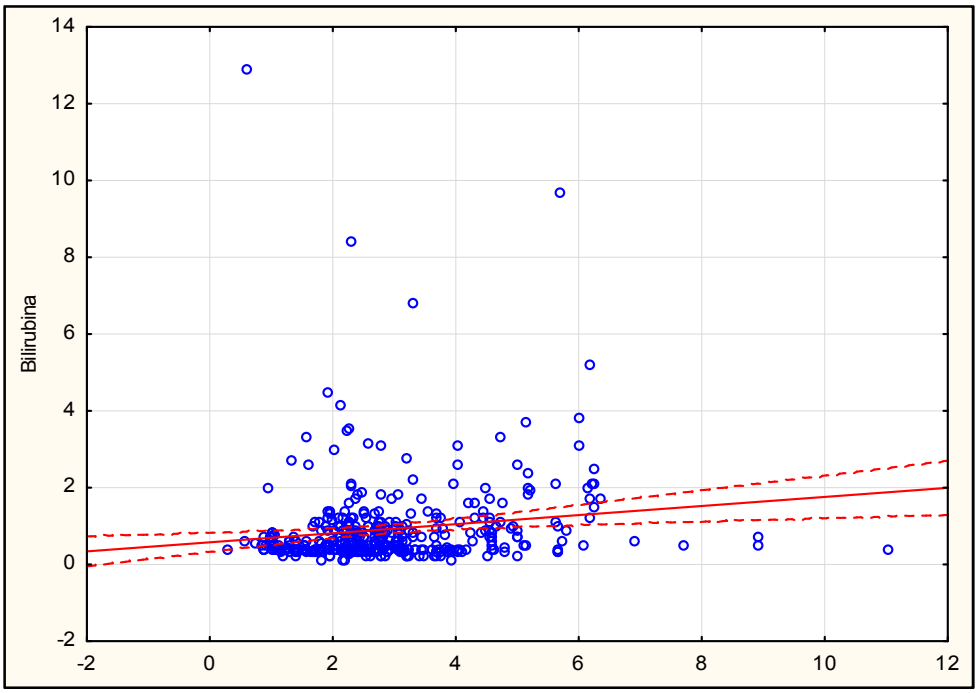

Fig.3 Correlation between glucose dosage per kg bw and bilirubin concentration (Spearman's Rho=0.24, p=0.0001)

Table 7. Incidence of complications in relation to the product used

	Bilirubin %		Aminotransferases %	
	normal	increase	normal	increase
Kabiven	79	21	52.6	47.4
Smofkabiven	93.7	6.3	78.5	21.5
Clinomel	81	19	66.7	33.3
Multimel	84.9	15.1	69.2	30.8
Olimel	100	0	100	0
Nutriflex lipid	83.6	16.4	78.2	21.8
Nutriflex lipid omega	100	0	100	0
Clinimix	100	0	88.8	11.1
p	Chi2=9.4 p=0.3		Chi2=23.9 p=0.001	

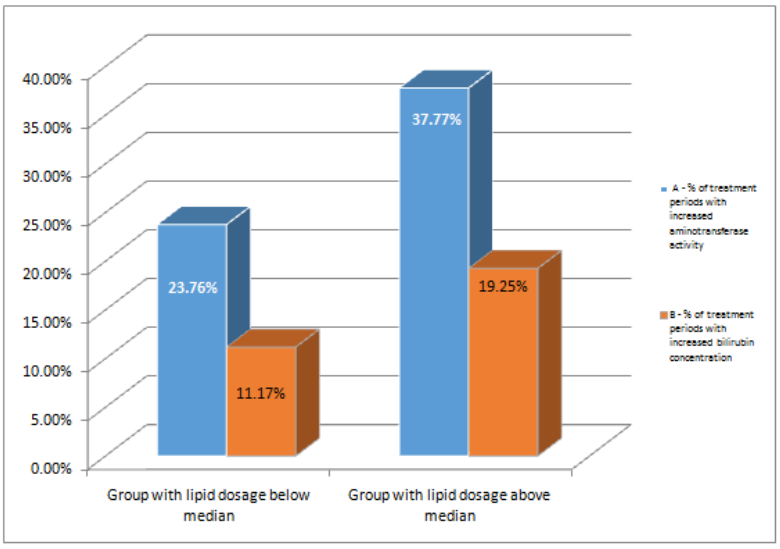

Fig. 4 Complication incidence depending on lipid dosage (above and below the median for the entire group analyzed)

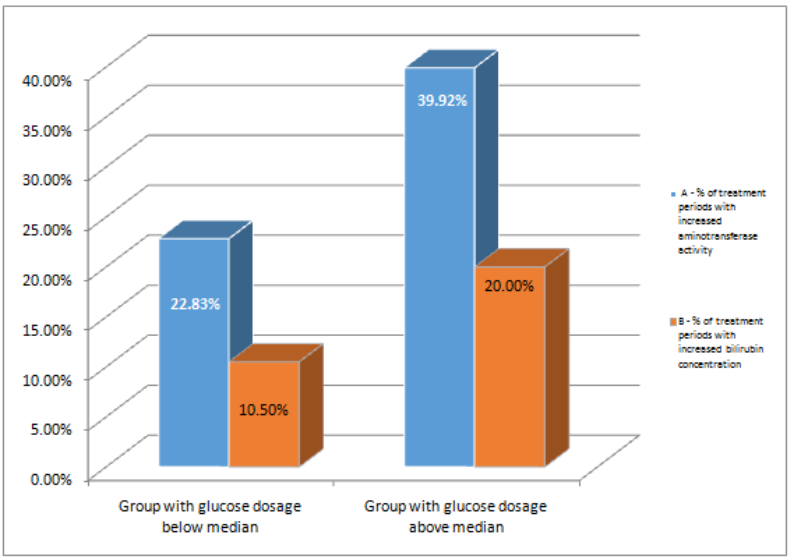

Fig. 5. Complication incidence depending on glucose dosage (above and below the median for the entire group analyzed)

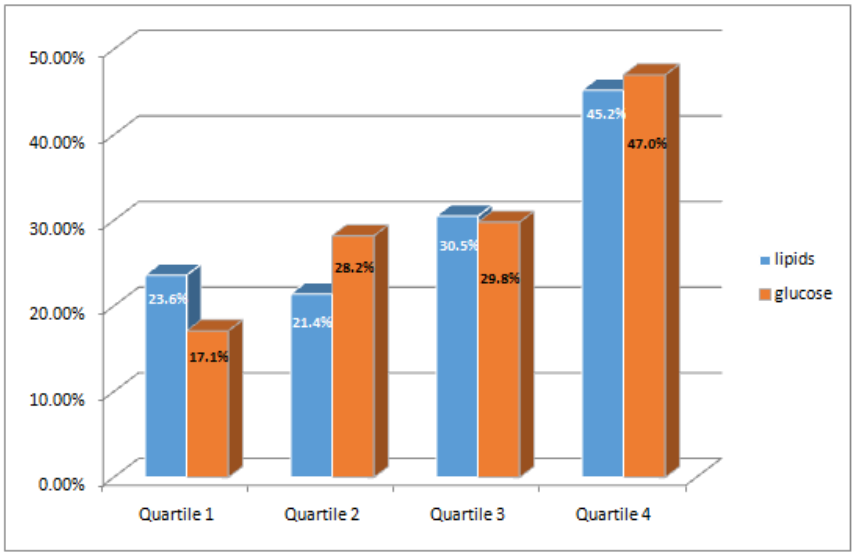

Fig. 6. Quartile analysis of complication incidence depending on glucose and lipid dosages

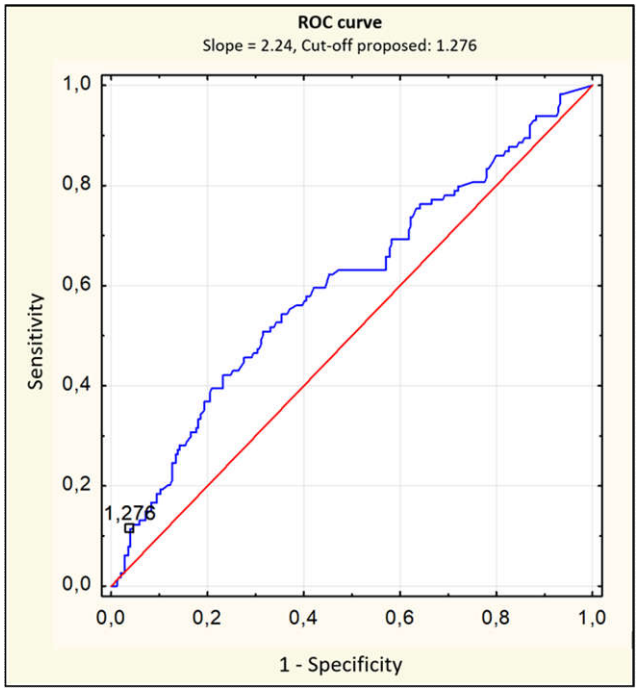

Fig. 7 ROC curve for lipids, threshold at 1.276 g/kg bw (if exceeded, there is a 95% risk of liver complications)

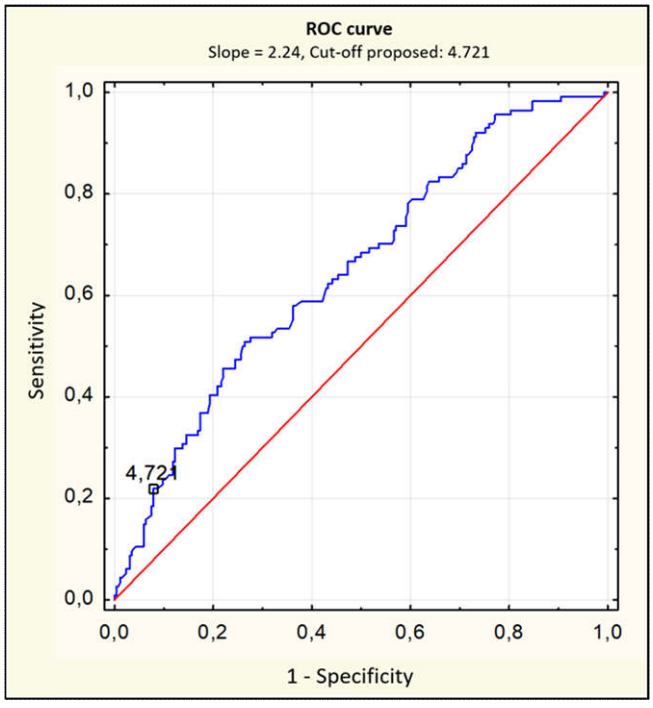

Fig. 8 ROC curve for glucose, threshold at 4.721 g/kg bw (if exceeded, there is a 93% risk of liver complications)

DISCUSSION

Liver complications associated with nutritional treatment are a group of metabolic complications occurring during chronic treatment (Raman, 2007). So far, their pathogenesis has not been described with certainty (Korta, 2008; Gabe , 2013). In the present retrospective analysis, we attempted to identify factors associated with the incidence of these complications. The analysis excluded all patients in whom the complications could have been caused by the underlying disease, as well as those found to have abnormal aminotransferase activity and/or high bilirubin at the outset of treatment.

The purpose was to identify only those dysfunctions that occurred in the course of chronic nutritional treatment. Patients were followed up every 3 months on average, which was the basis for dividing the course of treatment of each patient into treatment periods. Each treatment period, used as the basic unit for the study, was separately analyzed in terms of the impact of selected parameters on aminotransferase and bilirubin values. Liver dysfunction manifesting in increased aminotransferase activity and/or bilirubin concentration was found in 36% of the treatment periods analyzed. These were mainly slight abnormalities (median AspAT: 33 IU, AlAT: 35 IU, bilirubin: 0.6 mg/dL). No cases of liver failure were found in the entire analyzed sample. Frequent follow-ups in the course of nutritional treatment allow for prompt reaction to any complications, and the appropriate management prevents exacerbation of the dysfunctions.

Complication incidence was not shown to be dependent on a patient's nutritional status. There were no significant differences between the periods with and without liver dysfunction in terms of the selected nutritional status parameters, both anthropometric and laboratory-based. The analysis showed statistically significant differences in terms of nutrient mixture composition. In the treatment periods with increased aminotransferase activity and bilirubin levels at follow-up, patients received significantly more lipids and glucose per kg bw (tables 2and 3). Moreover, the glucose to lipids ratio in the nutrient mixture was found to be significantly higher in the group of treatment periods with complications. The findings warrant the conclusion that both lipids and glucose are associated with liver complications. The higher glucose to lipid ratio in the group of treatment periods with complications indicates a stronger contribution of glucose to the liver complications. This is demonstrated by the fact that in the entire study group, glucose dosage per kg bw was correlated with the occurrence of liver complications affecting aminotransferase activity (Figure. 1 and 2) and bilirubin concentration (Fig. 3). Meanwhile, lipid dosage per kg bw was not found to be correlated with complication incidence.

However, both factors, i.e. high glucose and lipid intakes, are required for the complications to occur. This is evidenced by the fact that in the treatment periods where the nutrient mixture used did not contain a lipid emulsion, the incidence of complications was several times lower than in those periods where the mixtures used contained lipid emulsions, despite comparable glucose dosages per kg bw. Treatment liver complications were always managed by decreasing the glucose and lipid content in the nutrient mixture. In some cases, though, this did not lead to immediate improvement. Lipid dosages were found to be significantly lower in the group where bilirubin concentration was successfully normalized than in the group with no such success. A similar correlation was not found for glucose dosages in complication management. This demonstrates that lipids are a significant contributor to complication occurrence. Notably, in the analyzed patient group, the interventions always produced the desired clinical outcome. Most likely, the frequent follow-ups allowed for early identification of dysfunctions. The analysis of complication management indicates the appropriate management strategy, i.e. decrease of lipid and glucose dosages. It also indicates that in order for parenteral nutrition to be administered safely, patients need to be followed up frequently so as to enable identification of complications at the stage where they are fully reversible.

Another important factor potentially contributing to liver dysfunction is the underlying disease (Kłęk, 2009). In our analysis, we compared the incidence of complications between patients with cancer and patients with short bowel syndrome. Both groups were also compared in terms of nutrient mixture composition and its impact on complications. The underlying disease was not found to be associated with differences in the incidence of high bilirubin levels, but aminotransferase activity was increased significantly more often in the cancer patient group. Therefore, the contribution of the underlying disease to complication incidence cannot be precluded. Moreover, the comparative analysis of nutrient mixture compositions in the cancer patient group did not show the association found both in the entire patient sample and in the short bowel patient group, which may suggest that cancer has a potential impact on the incidence of these complications. When patients are treated with parenteral nutrition using industrial bags, the key question to be answered is which product is the safest for the patient, i.e. which is associated with the least complications. Therefore, we analyzed the entire patient group for any associations between complication incidence and the product used. The only finding was that liver complications occurred more often with older, soybean oil-based, triple-chamber preparations. Otherwise, no statistically significant impact of the products used was found. This warrants the conclusion that it is the glucose and lipid dosage, rather than the type of product used, that mainly contributes to complications. This is corroborated by the statistically significant differences found in terms of complication incidence between patients administered below-median and above-median doses of glucose and/or lipids (Figures 4 and 5). Furthermore, quartile analysis showed that more than half of all complications occurred in the group where the glucose and/or lipid dosage was in the fourth quartile range (Fig. 6). In the final part of the research, ROC analysis was used in order to estimate the safe dosage of glucose and lipids. Analysis of the curve and area below curve demonstrated that the maximum safe dose of lipids is 1.276 g per kg bw. If the threshold is exceeded, there is a 95% risk of liver complications. The maximum safe dose of glucose is 4.721 g per kg bw. With higher doses, the risk of liver dysfunction is 93%.

Conclusion

- High intake of glucose and lipids is the primary factor in the pathogenesis of liver complications. The type of lipid emulsion has little significance.
- Liver dysfunction is much more likely to occur if large doses of glucose are administered in combination with lipids.
- The maximum dosage of glucose and lipids, above which liver dysfunctions are more than 90% likely to occur, is 4.721 g of glucose per kg bw, and 1.276 g of lipids per kg bw.
- The study was presented in a poster format during the 2013 ESPEN congress in Leipzig, and as an oral presentation in the highest-scoring paper session of the 2014 ESPGHAN meeting in Jerusalem.

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