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Analysis of Nutritional Status and Nutritional Intervention in Infants undergoing Liver Transplantation

Hong L[1*], Pan L[1], Gao XJ[2], Bao YW[1], Liu YM[1]

[1]Department of Clinical Nutrition, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

[2]Department of gastroenterology, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fujian, China

[*]Corresponding author:

Li Hong,
Professor of Pediatrics, Director of the Department of Clinical Nutrition, Shanghai Children's Medical Center/National Children's Medical Center, Shanghai Jiao Tong University School of Medicine.
1678 Dongfang Road, Shanghai 200127, China,
Tel: +86 21 38626161,
E-mail: hongliscmc@163.com

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1. Abstract

1.1. Objectives: The primary aim of the study was to assess the nutritional status of pediatric liver transplant outpatients in nutrition clinic, particularly the nutritional status of their bones.

1.2. Methods: One hundred thirty-eight pediatric liver transplant outpatients, who had visited the nutrition clinic in Shanghai Children's Medical Center between January 2017 and December 2019, were recruited. The bone mineral density [BMD] z-scores were determined by dual energy X-ray absorptiometry [DXA]. Nutritional assessment was performed, and their corresponding height-for-age z-scores [HAZs]/weight-for-age z-scores [WAZs]/BMI-for-age z-scores [BMIZs] were obtained.

1.3. Results: A total of 138 patients came to our nutrition outpatient clinic, including 68 boys [49.3%] and 70 girls [50.7%]. The average age was [1.48±1.56] years. Among these patients, 44 [31.9%] had acute malnutrition with WAZ/BMIZ value [-1.22±1.64], 55 [38.4%] had chronic malnutrition with HAZ value [-1.43±1.59], and 96 [69.6%] had a BMD lower than normal. The BMD z-score was significantly correlated with the WAZ/BMIZ value [Spearman's correlation coefficient=0.334, $p<0.001$]. A total of 37 infants re-visited the nutrition clinic for a follow-up after [147±127] days. The WAZ/BMIZ value of the re-visiting patients [-0.91±1.49] and the BMD z-score of the re-visiting patients [-0.00±0.78] were significantly improved compared to those of the first-visit patients [t=-3.16, p=0.003; t=-3.10, p=0.004 respectively].

1.4. Conclusion: Malnutrition, particularly malnutrition in bones, is common in pediatric liver transplant patients. Nutritional assessment by nutrition professionals is necessary. Individualized nutritional guidance and recommendations of vitD supplementation are significant to improve patients' overall nutritional status and particularly that of their bones.

2. Introduction

Liver transplantation is a relatively developed organ transplantation technology, and is the preferred treatment for patients with end-stage liver disease. With the continuous development of immunosuppressive technology after liver transplantation, the survival rate of patients after liver transplantation has been greatly improved, and the complications of liver transplantation have been getting more and more attention. Patients' nutritional status is one of the independent risk factors contributing to mortality rates after liver transplantation. Bone disease or osteoporosis is also one of the issues of concern. This study aimed to assess the nutritional status of pediatric liver transplant outpatients in nutrition clinic, and to assess the nutritional status of liver transplant

patients' bones based on BMD measured by DXA. We also aimed to observe patients' nutritional status after nutritional intervention, including any improvement of nutritional status of patients' bones. Our ultimate purpose was to define the significance of nutritional intervention in improving the nutritional status of liver transplant infants, particularly the nutritional status of their bones.

3. Materials and Methods

3.1. Research subject and data collection

One hundred thirty-eight pediatric liver transplant outpatients, who went to the nutrition clinic in Shanghai Children's Medical Center between January 2017 and December 2019, were selected as study subjects. Patients' basic information including gender, height, weight, primary disease, date of liver transplantation and feeding status were collected. The BMD of the infants was measured and the BMD z-score was determined by DXA [DXA-3000, Shanghai Osteosys Co., Ltd.]. A z-score equal to or greater than zero indicated a normal BMD. Serum calcium, serum 1,25-$[OH]_2$-VitD3, serum alanine aminotransferase, and serum AKP levels were also measured.

This study was approved by the ethics committee of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine.

3.2. Nutritional assessment and intervention

The height and weight of outpatients who visited our nutrition clinic were measured. The nutritional status of patients aged 0-2 was assessed according to HAZs/WAZs, and that of patients aged greater than 2 was assessed according to BMIZ values. An application [version 3.2.2] provided by WHO for height/weight/BMI measurements was downloaded from http://www.who.int/childgrowth/software/en/. It was used to assess patients' nutritional status according to their height/weight/BMI-for-age/HAZ/WAZ/BMIZ values. A WAZ/BMI z-score lower than -2 was defined as acute malnutrition, and a HAZ lower than -2 was defined as chronic malnutrition. We also carefully asked about patients' nutritional intake, particularly the intake of vitD. Individualized diets were made according to children's food intake and nutritional status, where the energy intake was recommended to be 110%-150% RNI. Nutrients in the diets were distributed as follows: 12%-16% total kcal was from protein, 30%-40% was from fat, and 40%-45% was from carbohydrate. We recommended patients to take high-quality protein and high MCT formulas. Patients after liver transplantation should also pay careful attention to the supplementation of water-soluble vitamins and minerals, including selenium, zinc, calcium, and magnesium. We recommended a supplementation of 800-1000 IU/d of vitD for patients with negative BMD z-scores, and a supplementation of 400-800 IU/d of vitD for patients with zero or positive BMD z-scores.

3.3. Follow-up visit

Patients were recommended for a follow-up visit to our nutrition outpatient clinic in 1-2 months. We re-measured children's height, weight, BMD, and AKP levels during their follow-up visit.

3.4. Statistical analysis

SPSS 16.0 software was used for statistical analysis. Measurement data were presented as mean ± standard deviation. Wilcoxon test was used for the comparison of data of the same category. Mann Whitney rank sum test was applied for the comparison of BMD z-scores between those of malnourished and non-malnourished infants. Spearman correlation analysis and cross table analysis were used for determining the relationship between BMD z-scores and nutritional status z-scores, and that between BMD z-scores and AKP levels. A p value <0.05 was considered statistically significant.

4. Results

4.1. General and baseline characteristics of patients

A total of one hundred thirty-eight children with liver transplantation in perioperative period visited our nutrition outpatient clinic, and their BMD were measured. Among 138 pediatric patients, 68 were boys [49.3%] and 70 were girls [50.7%]. The average age of the patients was [1.48±1.56] years old, of which 113 [81.9%] were under 2 years old and 25 [18.1%] were over 2 years old. The study population included 13 patients [9.4%] before liver transplantation, 80 patients [58.0%] within 100 days after transplantation, and 45 patients [32.6%] more than100 days after transplantation. 115 patients' primary disease was biliary atresia. All the above information was shown in Table 1.

Table 1: General and Baseline Characteristics of Pediatric Patients with Liver Transplantation

Clinical Status	
Gender(n,%)	
Boys	68(49.3%)
Girls	70 (50.7%)
Age(years old)	1.48±1.56
Primary disease(n, %)	
Ornithine aminotransferase deficiency	1(0.7%)
Progressive familial intrahepatic cholestasis	1(0.7%)
Wilson's disease	1(0.7%)
Alagille Syndrome	4(2.9%)
Propionic acidemia	1(0.7%)

Biliary atresia	115(83.4%)
Cholestasis	3(2.3%)
Hepatoblastoma	2(1.5%)
Liver cirrhosis	1(0.7%)
Methylmalonic acidemia	4(2.9%)
Antitrypsin deficiency	1(0.7%)
Langerhans cell histiocytosis	1(0.7%)
Tyrosinemia	1(0.7%)
Cavernous transformation of portal vein	1(0.7%)
Niemann-Pick disease	1(0.7%)
At the clinic visit, had liver transplantation or not (n, %)	
Before liver transplantation	13(9.4%)
Within 100 days after transplantation	80(58.0%)
More than 100 days after transplantation (including 100 days)	45(32.6%)

4.2. Nutritional status assessment and BMD measurements

Patients' nutritional status was assessed based on their WAZ, HAZ, and BMIZ values. Forty-four patients [31.9%] had acute malnutrition with WAZ/BMIZ value [-1.22±1.64], and fifty-three patients [38.4%] had chronic malnutrition with HAZ value [-1.43±1.59]. Among patients under 2 years old, 41 of them [36.3%] with WAZ value of [-1.50±1.51] had acute malnutrition, and 43children [38.0%] with HAZ value of [-1.40±1.62] had chronic malnutrition [Table 2]. Patients were grouped according to whether they already had liver transplantation or not when they visited the nutrition outpatient clinic. Among 13 patients who visited our nutrition outpatient clinic before liver transplantation, 7 [53.8%] had acute malnutrition, and 4 [30.8%] had chronic malnutrition. Among patients who visited our nutrition outpatient clinic within 100 days after liver transplantation, 26 [32.5%] had acute malnutrition, and 30 [37.5%] had chronic malnutrition. Among patients who visited our nutrition outpatient clinic more than 100 days after liver transplantation, 11 [24.4%] had acute malnutrition, and 19 [42.2%] had chronic malnutrition [Figure 1 and 2]. The more days' patients were after liver transplantation, the lower proportion of acute malnutrition was, and the higher proportion of chronic malnutrition was. However, there was no statistically significant differences between different groups [p=0.062 and 0.435 respectively by chi square test]. 96 patients [69.6%] had a BMD lower than normal, and 42 patients [30.4%] had a normal BMD [z≥0]. The average BMD z-score of patients was [-0.33±0.84]. For patients who visited our nutrition outpatient clinic before liver transplantation, the average BMD z-score was [-0.57±0.49]. The average BMD z-score of patients who visited nutrition clinic within 100 days after liver transplantation was [-0.34±0.85], and that of patients who visited nutrition clinic more than 100 days after liver transplantation was [-0.24±0.91]. Spearman correlation analysis was used to analyze the relationship between patients' BMD results and WAZ/HAZ/BMIZ values. As a result, there was a significant correlation between BMD z-scores and WAZ/BMIZ values [Spearman correlation coefficient=0.334, p<0.001], but there was no significant correlation between BMD z-scores and HAZ values [Spearman correlation coefficient=0.131, p=0.128].

Table 2: Changes of Anthropometric Parameters, BMD Levels, and Serum Indexes in Patients' First and Follow-up Visits

	At first visit	**At follow-up visit**	**T-value**	**p-value**
WAZ/BMIZ-values	-1.22±1.64	-0.91±1.49	-3.16	0.003
HAZ values	-1.43±1.59	-1.52±1.68	0.20	0.841
BMD z-values	-0.33±0.84	-0.00±0.78	-3.10	0.004
1,25-$(OH)_2$-D3(ng/ml)	25.18±11.25	/		
Serum calcium levels(mmol/L)	1.68±0.93	/		
Serum ALT levels(IU/L)	52.63±74.24	83.21±145.81	-1.14	0.261
Serum AKP levels (IU/L)	295.65±221.17	335.74±164.08	-2.65	0.012

Abbreviations: WAZ/BMIZ: weight-for-age z-scores/BMI-for-age z-scores; HAZ: height-for-age z-scores; BMD:bone mineral density

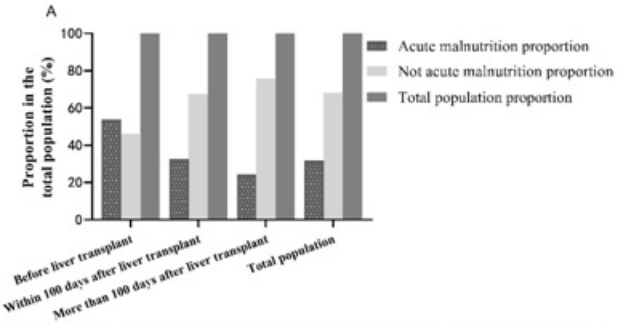

Figure 1A. A comparison of the proportion of acute malnourished patients in different groups when visited our nutrition outpatient clinic

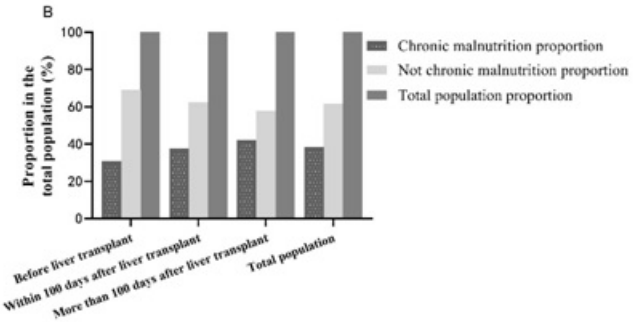

Figure 1B. A comparison of the proportion of chronic malnourished patients in different groups when visited our nutrition outpatient clinic

Figure 1: Comparison of the proportions of acute and chronic malnourished patients in different groups when visited our nutrition outpatient clinic.

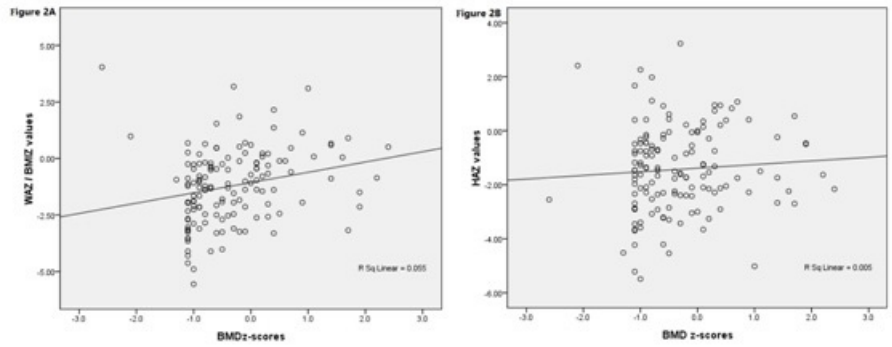

Figure 2: The correlation analysis between BMD z-values and anthropometric z-values.

Figure 2A: There was a significant positive relationship between BMD z-values and WAZ/BMIZ values (Spearman correlation coefficient=0.334, p<0.001).

Figure 2B: There was no significant relationship between BMD z-values and HAZ values (Spearman correlation coefficient=0.131, p=0.128).

4.3. Patients' follow-up visits to nutrition outpatient clinic

A total of 37 children re-visited our nutrition outpatient clinic after [147±127] days of their last visit. The WAZ/BMIZ value of these patients [-0.91±1.49]at the follow-up visit was significantly improved compared to that at their first visit [t=0.20, p=0.841]. The HAZ value of these patients [-1.52±1.68]at the follow-up visit was not statistically different from that at their first visit [t=0.20, p=0.841]. The BMD z-score [-0.00±0.78] of the re-visited patients was significantly improved from that of patients at their first visit [t=-3.10, p=0.004].

4.4. Serological examination

At patients' first clinic visit, their serum 1,25-$[OH]_2$-VitD3 level was [25.18±11.25]ng/mL [normal range: >30ng/mL], serum calcium concentration was [1.68±0.93] mmol/L [normal range: 2.23-2.8mmol/L], serum ALT level was [52.63±74.24] IU/L [normal range: 0-75IU/L], and serum AKP level was [295.65±221.17] IU/L [normal range: 40-150 IU/L]. At patients' follow-up visit, their serum ALT level was [83.21±145.81] IU/L, and their AKP level was [335.74±164.08] IU/L.

5. Discussion

The liver is the largest and the most important metabolic organ of human body. It plays a key role in the metabolism of various macronutrients and micronutrients [1]. With the continuous development of surgical technology in the field of liver transplantation,

liver transplantation has become the optimal treatment for pediatric patients with end-stage liver disease, liver failure, liver-based genetic metabolic diseases and liver tumors that cannot be treated with conventional treatments [2,3].

As the surgical technology continues to improve, the 1-year survival rate of pediatric liver transplant patients could reach 90%, and the 15-20-year survival rate of them could reach 75% [4]. Therefore, long-term maintenance of life quality after liver transplantation has become more and more significant. The nutritional status of patients is a relevant factor to determine the progression of liver disease. Metabolic disorders, inadequate nutrients intake, absorption disorders, and a hyper metabolic status may lead to malnutrition in patients during the perioperative period of liver transplantation, increase the surgical risk, increase the incidence of postoperative complications, prolong the length of hospital stay, increase the cost of hospitalization, and affect the prognosis of patients after liver transplantation [5,6,7].

As the results of this study, 31.9% of the patients who have visited our nutrition outpatient clinic had acute malnutrition, and 38.4% of them had chronic mal nutrition. After we provided nutritional guidance and individualized diets for liver transplant patients, the nutritional status of the patients in their follow-up visit was significantly improved from that in their first visit, where the difference had a statistical significance.

In 2017, the Nutrients Magazine published a review article on suggestions and literature review of the nutritional status assessment and nutrition care plan management for perioperative liver transplantation patients. It was suggested that the management of liver transplant patients should include a comprehensive nutritional assessment. Adequate nutritional support should be given at all stages of liver transplantation. Oral nutrition was the primary choice, and nutritional formulas, tube feeding and other modes of nutrition support could be selected as needed to achieve the goal of calorie intake. Due to the higher requirements for nutritional intake of pediatric patients during growth and development stage scientific feeding guidance and management was critical to reduce the incidence of malnourishment, thus affecting patients' long-term prognosis [8].

In this study, we assessed the nutritional status of all the patients who visited our nutrition outpatient clinic. The results showed that in the patients before liver transplantation, the proportion of acute malnourished infants was higher than that of chronic malnourished infants. In the patients more than 100 days after liver transplantation, the proportion of chronic malnourished infants was higher than that of acute malnourished infants.

Individualized diets were made for patients based on their target nutrition intake, dietary habits and current diets. Formulas high in calorie and MCT were delivered to increase patients' intake of calories and various nutrients, so as to improve patients' nutritional status.

Bone mass loss is common in liver transplant patients [9,10]. Studies have found that only 15% liver transplant patients had a normal BMD. Most patients already had bone mass loss before liver transplant, which would lead to bone pain, growth retardation, and even bone fracture. Bone mass loss is particularly common in patients within one year after liver transplantation [11-14]. In the early stage after liver transplantation, because of the use of high-dose glucocorticoids and other immunosuppressive drugs, the loss of patients' bone mass was rapid, particularly the loss of bone mass in the spine and proximal femur. BMD measurement is one of the key methods for the diagnosis of nutritional status of bones. It is of great significance for fracture risk prediction, care plan determination, and follow-up management. A study has reported that malnutrition exerts a negative impact on BMD in non-cirrhotic individuals [15]. Currently being recognized as the "gold standard" for the diagnosis of osteoporosis, the DXA can eliminate the effects of surrounding soft tissues and bone fats on the measurement results. It is known to be convenient, safe, noninvasive, accurate, and precise. Another key advantage of DXA is the low radiation exposure. The BMD, BMD z-score, and other result values were calculated based on the bone mineral content [BMC] of the measured body position. In this study, we used DXA to measure the BMD in liver transplant patients. It was easy to operate, and also took a short measurement time. Almost all pediatric patients were cooperative to complete the measurement. Approximately 70% of the patients had a low BMD.

In a retrospective study conducted by Xuguang Zhang et al., 55,925 children's serum samples were collected to study the serum vitD levels. They found that the overall rate of hypo vitaminosis D of 65.60% [16] was similar to our study results. We further analyzed the correlation between BMD and nutritional status. As a result, the decrease of BMD was significantly correlated with the index of acute malnutrition [WAZ/BMIZ], suggesting that the daily intake of nutrients has a significant impact on nutritional status of bones in pediatric patients. Our nutrition outpatient clinic provided nutritional guidance and recommended a 400-800 IU/d vitD supplementation. The BMD was significantly improved when the patients re-visited our nutrition clinic.

Vitamin D is a type of fat-soluble ring opening steroid. It has extra skeletal effects on body's muscles, cardiovascular system, metabolism, immunity, tumorigenesis, pregnancy and fetal development. The main physiological functions of vitD are to promote the absorption of calcium and phosphorus in the intestine, to inhibit the release of parathyroid hormone, to maintain the normal serum calcium and phosphorus levels, so as to maintain bone health and normal neuromuscular function. By mitigating the glucocorticoid induced reduction of intestinal calcium absorption, active vitamin D3 can alleviate the secondary hyperparathyroidism of parathy-

roid glands, promote the differentiation and maturation of osteoblast precursors, enhance the immunosuppressive effect of cyclosporine A, and reduce bone loss after liver transplantation [17,18].

Even in healthy children, vitamin D deficiency is very common. China and other countries have all issued domestic and international guidelines for the prevention and treatment of vitD deficiency [19,20]. Healthy infants, kids and adolescents are recommended to take 400 IU of vitamin D per day, and high-risk groups should take 800-1000 IU of vitamin D per day. It has been reported that parents' misunderstandings often affect their children's intake of vitD. The more scientific facts parents were educated on, the more appropriate their children's vitD supplementation was. In this study, about 70% of the liver transplant children had a low BMD when visited our nutrition outpatient clinic for the first time, and their parents didn't have enough knowledge on vitD supplementation. Through the nutritional guidance given at our nutrition clinic, the BMD of the follow-up children was significantly improved than that of the first-visit ones [p=0.004]. It is suggested that liver transplant patients should be followed up not only in the transplantation outpatient clinic, but also in the nutrition outpatient clinic. In nutrition clinic, patients' nutrition related problems could be observed in time, and scientific guidance of nutrients supplementation could be given to them, so as to improve their nutritional status including that of their bones. Ultimately, an improvement of the quality of life and the prognosis of patients are expected.

6. Conclusion

Malnutrition, including malnutrition in bones, is common in pediatric patients undergoing liver transplantation. Professional nutritionists and dietitians are needed to conduct nutritional assessment, and to provide individualized nutritional guidance plus vitD supplementation suggestions for liver transplant pediatric patients. The ultimate goal of improving patients' nutritional status including that of their bones will be achieved then.

7. Statement of Conflicts of Interest

The authors declare that they have no conflict of interests.

8. Funding

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9. Financial Disclosure

The authors have indicated they have no financial relationships relevant to this article to disclose.

10. Conflict of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

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