

Review article

The importance of nutrition for pediatric liver transplant patients

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Abstract

Pediatric liver transplantation has changed the poor prognosis for children with liver failure, some metabolic diseases and liver tumors. With the increase of survival, long-term maintenance has become a priority. Therefore, obtaining appropriate nutrition, physical growth, bone metabolism, endocrine function and psychosocial development has become one of the most important long-term objectives. This article presents an up-to-date review and recommendation of nutrition assessment, both before and after liver transplantation.

Key words: transplant recipients, nutrition, children.

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Introduction

The well-known pediatric hepatologist Professor Deirdre Kelly from Birmingham Children's Hospital in the book *Pediatric Solid Organ Transplantation* emphasized that "The most important aspect in achieving normal quality of life after liver transplantation is to return to normal nutrition" [1].

Liver transplantation (LT) is the treatment of choice for many infants and children with chronic and acute liver failure, as well as oncologic and metabolic diseases. As a result of better post-operative care, advances in surgical techniques and new immunosuppressive drugs, the current post-transplant pediatric patient 1-year survival rate is 90% and 75% at 15 to 20 years [2]. Therefore, obtaining appropriate nutrition, physical growth, bone metabolism, endocrine function and psychosocial development has become one of the most important long-term objectives.

The main indications for liver transplantation in pediatric patients are cholestatic diseases, mainly biliary atresia. According to the European Liver Transplant Registry, 74% of recipients under 2 years of age and more than 40% of older children had cholestasis.

Malnutrition in liver transplant recipients

The clinical complications of malnutrition in children with chronic cholestasis are very wide and include growth failure, rickets, bleeding and life-threatening infections. Many authors have clearly shown that a declining nutritional status and malnutrition are the major factors that adversely affect survival, both on the waiting list for orthotopic liver transplantation and following surgery. Malnutrition is also one of the main factors negatively affecting growth after the transplant [3-5].

Patients who are especially at risk of malnutrition are those under 2 years of age, those suffering from severe cholestasis (bilirubin > 70 mmol/l, > 50% conjugated) with progressive liver disease (biliary atresia, neonatal cholestasis) and awaiting liver transplantation.

In chronic liver diseases, there are a number of potential causes of malnutrition, such as reduced nutrient intake, increased energy expenditure, decreased fat and fat-soluble vitamin absorption, and impaired protein and carbohydrate metabolism [6, 7].

Poor oral intake may be caused by recurrent infections, gastroesophageal reflux with oesophagitis, anorexia, nausea and vomiting. It may be aggravated by

hepatosplenomegaly and ascites, which makes the mechanics of food intake more difficult. In addition, some children do not tolerate the restriction of food intake, especially a salt-free diet [8]. Approximately 60% of children undergoing assessment for liver transplantation are malnourished, with a weight and/or height less than two standard deviations below the mean.

Pre-operative nutritional support

Children with cholestatic liver disease require up to 80% more calories than healthy children to achieve adequate physical development and growth. Aggressive nutritional support before liver transplantation improves patient and graft survival. Moukarzel *et al.* analyzed a group of 119 pediatric recipients. In the group of more malnourished patients, the incidence of infections was twice as high (61% vs. 37%). Also surgical complications, such as vascular complications, bile leak and intestinal perforation, were statistically more frequent (46% vs. 23%) [9]. When oral nutrition is inadequate, enteral feeding with a nocturnal gastric tube should be introduced. In the case of gastrointestinal intolerance, severe malnutrition and gastrointestinal bleeding, parenteral nutrition should be considered [9, 10].

Early post-transplant nutrition

Surgical stress during the transplant procedure increases energy demand and catabolism in liver recipients. That is why administration of sufficient calories is essential, in order to avoid infection and promote wound healing. During this period a calorie level of 120% of the basal energy expenditure is necessary. In addition, poor utilization of glucose may lead to the consumption of muscle protein, which may result in muscle atrophy. Both the combined effects of immunosuppression and a continuing protein and caloric deficit can aggravate severe malnutrition and predispose patients to postoperative complications such as sepsis and delayed wound healing and may prolong post-transplant rehabilitation [11]. In the early post-surgery period, nutritional support with total parenteral nutrition (TPN) is required. However, as soon as possible, enteral nutrition (EN) should be administered. In severely malnourished patients both methods (parenteral and enteral) should be combined. A delay in oral intake mainly concerns patients who were critically ill before the transplant, those with prolonged intratracheal intubation and mechanical ventilation, and those with delayed recovery of consciousness or delayed bowel recovery. Such patients may need prolonged intravenous hyper-alimentation

in order to obtain sufficient caloric administration. However, because of immunosuppression, a catheter infection may occur [12]. Wicks *et al.* compared two groups of adult patients. Fourteen received enteral feeding and ten received total parenteral nutrition. A double-lumen enteral tube was used to deliver the feed directly into the jejunum, with the second lumen of the tube being used for gastric aspiration. Enteral feeding was started post-operatively, within 18 h. It was well tolerated, and of comparable efficacy to total parenteral nutrition. The median number of days for patients to start eating and to achieve 70% of their estimated requirements orally did not differ significantly between the two groups [13]. The question is, what is better – total parenteral nutrition or enteral nutrition? It is well documented that total parenteral nutrition reduces post-operative complications, providing a sufficient caloric supply for patients who cannot perform oral intake. However, unfortunately, it also leads to gut mucosal atrophy and to functional and structural disruption of the gut. And, as was mentioned before, immunocompromised patients are at a greater risk of catheter infection. Enteral nutrition is more physiological. It can prevent bacterial translocation and mucosal damage, and, what is very important after liver transplantation, it can prevent bile stasis. It also promotes protein metabolism and maintains gut immunity.

Return to normal nutrition and the catch-up of linear growth

After liver transplantation, in patients with adequate graft function, weight gain appears to recover fully, despite previous malnutrition. Linear growth improves, but catch-up growth is mainly dependent on the etiology of the pre-transplant disease and steroid use [14, 15]. Mohammad *et al.* analyzed a multi-center cohort of 892 pubertal children who survived their first liver transplant by > 1 year [16]. They found that linear growth impairment remains prevalent post-transplant and survivors are likely to be shorter adults than their parents. Among patients whose parental height data were available, the height z-score was lower than the calculated mid-parental height z-score ($p < 0.005$). Height impairment at the time of transplant, long-term steroid use, re-transplant, and metabolic disease were independent risk factors for lower height outcomes. Delay in pubertal development is common, with boys more likely to be affected than girls. A return to normal nutrition begins in the first 6-12 months after the transplant. A very important aspect of normal nutrition is the development of normal eating behavior. Some children may develop feeding problems and

temporarily require nutritional support with nocturnal enteral feeding. Some children, especially those on corticosteroids, may have excessive weight gain due to an increase in appetite and salt/water retention. Fortunately, the majority of patients return to their normal weight within 12 month.

The metabolic syndrome and obesity

The United Network of Organ Sharing (UNOS) data analyzed for the period 1987-2010 showed that less than 15% of children receiving LT were obese, while the proportion of adult recipients approaches 30% [17]. These comorbidities place adult and pediatric LT patients at a higher risk for serious cardiovascular diseases. They are more likely to have post-transplant diabetes, hyperlipidemia, and hypertension and an increased possibility of post-transplant late mortality. Everhart *et al.* analyzed more than 770 adult recipients from three US transplant centers – 14.5% were obese (BMI > 30) before and 21.6% 2 years after liver transplantation. After an evaluation of the numerous potential risk factors, the following ones played an important role: the patient's BMI before transplantation, a higher cumulative dose of prednisone, treatment with cyclosporine A (vs. tacrolimus) and episodes of acute rejection. What was surprising, they also found that among the risk factors was origin of livers from overweight donors [18]. Wawrzynowicz-Syczewska *et al.* observed that in their group of 75 adult liver recipients, poor dietary habits and a lack of physical activity may play a major role in weight gain after transplantation [19]. UNOS data showed that in a group of recipients below 2 years of age 14% were overweight. In an older group 16% were overweight and 13% obese. The prevalence of post-transplant obesity remains high in long-term follow-ups and ranges from 20 to 50%. Weight at transplant is the strongest predictor of a patient becoming overweight after the transplant [17].

Supplementation with probiotics

Treatment with probiotics influences the gut commensal micro-flora, resulting in improved intestinal barrier and immune system function. It is especially recommended for children on antibiotic therapy. Many studies have shown that probiotics may prevent diarrhea, commonly caused by enteric pathogens, especially rotavirus, and may play a role in the prevention of various upper respiratory tract infections. In 2007, we published a study on the treatment of liver transplant children with probiotics [20]. Twenty-five children after liver transplantation, aged between 3 and

17 years, were enrolled in the study. Two months after bacteria application, the levels of activity of β -glucuronidase, β -glucosidase, and urease enzymes decreased, reaching statistical significance for β -glucuronidase and β -glucosidase. Generally these enzymes contribute to mucosal tissue damage and to the production of mutagens. Unfortunately, the beneficial effect of probiotic treatment was limited to the period of bacteria intake. A complete rebound in enzyme activity was observed a few months after the end of probiotic supplementation.

Supplementation with vitamin D

Metabolic bone disease is a well-known complication in patients with end-stage liver disease. The most important causes of osteoporosis are cholestasis, malnutrition, and the deficiency of vitamin D, minerals, such as calcium, magnesium and phosphorus and hormones. The potential risk factors contributing to bone disease in the post-transplant period are prolonged immobilization, high doses of corticosteroids and pre-existing osteoporosis. Legarda *et al.* in a multicenter study evaluated 199 pediatric recipients with a median age of 10 [21]. The median level of vitamin D was 19.5 ng/ml (range: 4.4-71.4). A total of 53% of children had low vitamin D levels (< 20 ng/ml) and 14% showed vitamin D deficiency (< 12 ng/ml) and 39% vitamin D insufficiency (12-20 ng/ml). The only factors found to be associated with vitamin D deficiency were the season of sampling (lower in winter and spring) and ethnicity (lower in non-white children). Vitamin D deficiency was more prevalent during the first year after transplantation. In our study we evaluated 20 children prior to and 3 months, 6 months, and 9 months after transplantation. Three months after liver transplantation significant increases of osteocalcin, collagen type 1 C-telopeptide, parathormone and $1.25(\text{OH})\text{D}_3$ levels were found, but there was no further increase during the next 9 months [22].

Conclusions

1. Chronic malnutrition in children with cholestasis can contribute to gradual hepatic deterioration and death from liver failure.
2. The increased success of programs for pediatric liver transplantation, especially living related liver transplantation, has demonstrated the importance of adequate nutritional management.
3. Aggressive nutritional support is essential when liver transplantation is being considered.

4. The pre-transplant nutritional status of the patient has a great impact on their postoperative morbidity and survival.
5. The importance of intensive nutritional support, prior to marked linear growth impairment, while waiting for the allocation of organs and the early weaning off of steroids after the transplant are all strategies which can help to avoid linear growth impairments.
6. To optimize long-term outcomes in pediatric liver transplant recipients, monitoring for obesity and its comorbidities is very important.
7. Treatment with probiotics, especially during high infection seasons, should be considered.
8. All liver transplant patients should be monitored and treated for vitamin D deficiency in order to maintain vitamin D levels > 25-30 ng/ml.
9. Nutritional support in liver transplant recipients should be individualized both before and after transplantation.

Disclosure

Author reports no conflict of interest.

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