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Original Research

The frequency and risk factors of low bone mineral density one year after liver transplantation in children: a study in Shiraz Organ Transplant Center

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ABSTRACT

Objective: Osteoporosis is a severe epiphenomenon that follows liver transplantation (LT). There is an inconsistency regarding risk factors of developing osteoporosis in LT children. In this article, we address the frequency of low bone mineral density (BMD) in LT children. **Methods:** This is a prospective study performed on children aged <18 years old, referred to the Shiraz Organ Transplant Center. The study was conducted from March 2009 until March 2014. Those with at least one year passed from the transplantation were included. Lumbar and hip bone densities were checked by Dual-Energy Radiograph Absorptiometry. **Results:** From the total of 84 included children, 32 (38.1%) and 52 (61.9%) were males and females respectively. The underlying diseases included cryptogenic (32, 28.1%), biliary atresia (18, 21.4%), Wilson disease (9, 10.7%), autoimmune hepatitis (9, 10.7%), tyrosinemia (6, 7.1%), acute liver failure (5, 6%), and hypercholesterolemia (5, 6%). Overall, 53 children (63.1%) had normal BMD, while 31 (36.9%) revealed lower than normal BMD. The means of lumbar and hip z scores were -1.04±1.47 (median of -0.75) and -0.98±1.92 (median of -0.60), respectively. There was no significant association between bone density and the age of transplantation, sex, weight, height, or underlying diseases (P>0.05). None of the immunosuppressive drugs were associated with low BMD. The patients who received pulse therapy showed a significantly higher rate of low BMD respective to the patients who did not receive pulse therapy (P=0.03). **Conclusion:** The frequency of low BMD is relatively high in LT children. Pulse therapy may increase the risk of low BMD and osteoporosis in LT children.

Key words: Liver transplantation, Bone mineral density, osteoporosis

INTRODUCTION

The liver is an organ, detoxifying various metabolites, and synthesizing hormones, and other proteins that are necessary for cellular biological functions. Other roles of the liver include regulating drugs metabolism, participating in hematopoiesis and synthesizing blood coagulation factors, energy production, protection against infections, and iron storage. The liver also produces proteins, such as albumin, prothrombin, fibrinogen, lipoproteins and heparin, and stores compounds such as triglycerides, glycogen, and vitamins [1,2].

Currently, there are no long-term ways to compensate for liver failure. Thus, liver transplantation (LT) is the sole definite therapy for treating grave liver failure [2]. Patients with liver dysfunction, end-stage liver disease (ESLD), hepatic tumors, and a variety of disorders, associated with liver insufficiency are candidates for LT. Although LT is a life-saving intervention, the patients risk developing certain post-surgery complications, including overweight, insulin resistance, diabetes, hyperlipidemia, hypertension, and other metabolic disorders [3]. However, whether these complications result from the transplantation itself, or immunosuppressive drugs is unclear [3–6].

Around a half of organ transplanted patients are reported to develop the post-surgery osteoporosis [7]. Bone damage may be characterized by four discrete phases, including deformities in patients with the end-stage disease before surgery, the progression of the damage by immunosuppressive drugs after surgery, a temporary stabilization and recovery of bone microenvironment due to a reduction of immunosuppression, and finally osteoporosis secondary to graft rejection [8]. These phases are particularly noticeable in case of a kidney transplantation [8].

Osteoporosis is accompanied by a reduction in bone density, and bone structural defects is a potential and severe complication of LT. This phenomenon has been especially associated with fractures of the wrist, femoral joints, and lumbar [9]. Lumbar fractures have

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been one of the most commonly reported events in LT[10]. Lumbar fractures have been reported in 3-44% of liver cirrhotic patients[11]. Low bone generation in patients with chronic liver diseases may be attributed to multiple factors, such as vitamin D deficiency, low physical activity, the lower muscular mass, and glucocorticoids. Reduction in lumbar bone mineral density (BMD) has been described in 3.5-24% of LT patients during the first 3 to 6 months following the surgery, with the highest rate of fractures observed within the first year[11]. Although some risk factors (such as the underlying diseases, immunosuppressive drugs, lifestyle, parathyroid disorders, calcium and vitamin D deficiencies, gonadal-pituitary disorders, and advanced age) have been established[12], there is a shortage of reliable predictors of osteoporosis and fractures in LT patients, especially in the pediatric age group.

Considering the elevated risk of osteoporosis and bone fractures in LT patients, it seems necessary to screen them for BMD, especially during the first months and years following the surgery. On the other hand, the number of children undergoing LT is increasing, and because LT usually precedes reaching maximum BMD in children, osteoporosis can be a particularly problematic phenomenon in these children. There are few studies associating osteoporosis with the frequency of low BMD in LT children. We here aim to address this.

METHODS

This study was performed on children, aged under 18, referred to the Shiraz Organ Transplant Center (affiliated with Shiraz University of Medical Sciences) from March 2009 until March 2014.

The patients included had undergone the LT procedure at least one year before the onset of the study. Informed written consent was obtained from the participants' parents. The study was conducted according to the Ethical guidelines of the Ethic Committee of Shiraz University of Medical Sciences.

Demographic data (such as age, sex, weight, BMI, time lapsed from the transplantation, underlying disease, immunosuppressive regimens, and laboratory tests) were recorded. Lumbar and hip Bone densities were determined by the X-ray procedure (DXA; Hologic discovery wi, Waltham, MA) and analyzed by the APEX software version 3.3. DXA results and Z scores were normalized for age and sex.

Statistical analyses were performed by SPSS 21 software. Normal distribution was assessed by Kolmogorov–Smirnov test. One-way ANOVA, independent samples student t-test and chi-square were used for inferential analyses. P values of <0.05 were considered as statistically significant.

RESULTS

From the total of 84 included children, 32 (38.1%) were males and 52 (61.9%) females. Furthermore, 53 (63.1%) had normal BMD, while in 31 (36.9%) subjects, BMD was lower than normal. There was no association between gender and BMD (**Table 1**). The mean of lumbar and hip z scores was -1.04±1.47 (median of -0.75) and -0.98±1.92 (median of -0.60), respectively. Based on Pearson correlation, there were significant correlations between BMD and lumbar (r=-0.517, P=0.001) and hip (r=-0.692, P=0.001) z scores.

The underlying diseases included cryptogenic (32, 28.1%), biliary atresia (18, 21.4%), Wilson disease (9, 10.7%), AIH (9, 10.7%), tyrosinemia (6, 7.1%), acute liver failure (5, 6%), and hypercholesterolemia (5, 6%). There was no significant association between BMD and underlying diseases (P=0.685). The distribution of normal and low BMD among different underlying diseases is presented in **Table 2**.

There was no significant difference in the mean age of transplantation between patients with normal (7.46±4.16) or low (9.22±4.87) BMD (P=0.083). Furthermore, the Spearman correlation coefficient between the age of transplantation and BMD was obtained as r=0.176, which was not statistically significant (P=0.110). Likewise, there were no significant differences between the means of weight and height among those patients with normal (36.28±18.22 kg and 136.65±22.07 cm respectively) or low (37.19±16.32 kg and 139.40±22.88 cm respectively) BMD (P=0.822 and 0.596 respectively). Furthermore, there was no significant association between any of immunosuppressive drugs and low BMD; however, 8 out of 18 patients that received pulse therapy revealed low BMD (P=0.03, **Table 3**).

DISCUSSION

LT has been established as a reliable therapeutic approach for liver failure in recent decades. Currently, LT is the sole practical way to treat ESLD; nevertheless, this approach boosts the risk of osteoporosis and osteoporotic fractures, which in turn decreases survival chances and deteriorates the quality of life[4–6].

The data analysis on BMD of children who had received liver allografts in our center in Shiraz more than a year before the study revealed, that from the total of 84 patients, 31 (36.9%) had low BMD. There were significant negative correlations between hip (r=-0.692) and lumbar (r=-0.517) z scores with BMD

Table 1: Bone mineral density in male and female patients undergone liver transplantation

Bone density		Gender		p
		Male	Female	
Bone density	Normal	33 (39.3)	20 (23.8)	0.9
	Low	19 (22.6)	12 (14.3)	

Table 2: Bone mineral density distribution in children with different etiologies of liver failure requiring liver transplantation

Underlying diseases	Bone density	
	Normal	Low
Wilson disease (N=9)	6 (7.1)	3 (3.6)
Autoimmune hepatitis (N=9)	4 (4.8)	5 (6)
Tyrosinemia (N=6)	3 (3.6)	3 (3.6)
Cryptogenic (N=32)	22 (26.2)	10 (11.9)
Biliary atresia (N=18)	10 (11.9)	8 (9.5)
Acute liver failure (N=5)	4 (4.8)	1 (1.2)
Hypercholesterolemia (N=5)	4 (4.8)	1 (1.2)
Total	53 (63.1)	31 (36.9)

Table 3: The distribution of low and normal bone mineral density in liver transplanted children received different immunosuppressive drugs

Immunosuppressive drugs		Bone density		P
		Normal	Low	
Prednisolone	No	20 (25.3)	16 (20.3)	0.192
	Yes	30 (38)	13 (16.5)	
Cyclosporine	No	48 (61.5)	27 (34.6)	0.925
	Yes	2 (2.6)	1 (1.3)	
Tacrolimus	No	5 (6.3)	6 (7.6)	0.186
	Yes	45 (57)	23 (29.1)	
Mycophenolate	No	32 (40.5)	13 (16.5)	0.097
	Yes	18 (22.8)	16 (20.3)	
Prednisolone	No	45 (60.0)	20 (26.7)	0.097
	Yes	5 (6.7)	5 (6.7)	
Acute graft rejection	No	5 (20.8)	2 (8.3)	0.751
	Yes	11 (45.8)	6 (25.0)	
Pulse therapy	No	7 (28.0)	0 (0.0)	0.032
	Yes	10 (40.0)	8 (32.0)	

(P<0.001). The rate of lumbar fractures was reported in 3-44% of cirrhotic patients[11]. The frequency of osteopenia and osteoporosis have also been noted as 47.7% and 23.1% among Iranian patients with chronic liver diseases who also represented lower BMD in femur and lumbar respective to healthy individuals[13]. Another study, conducted in Iran on patients with chronic liver diseases (including cirrhosis, AIH, primary biliary cirrhosis, and primary sclerosing cholangitis), showed that BMD and the incidence of osteoporosis were lower and higher in patients than controlled subjects[14]. The report by Guthery *et al.* shows, that 7.3% of 109 children, who had undergone LT had decreased BMD[15]. In patients who received LT due to cirrhosis, low BMD in femur and lumbar were reported as 20% and 44% showing significantly higher rates than healthy population[16]. Analyzing 15 years of follow-up examinations after the LT surgery, Hamburg et al. noted that the lumbar BMD was most significantly decreased within the second year after LT, while no notable changes were seen afterward[17]. Furthermore, Reimens *et al.* reported a decrease of 4.5% in lumbar-spinal BMD during the first three months after LT with no significant changes afterward. Yet, hip BMD gradually decreased within the first year following LT[18].

We noticed no significant association between gender and BMD. Likewise, gender has not been associated with BMD in the study of Lesanpezeshki *et al.*[19]. There was no significant relationship between gender and BMD in LT children who survived at least five years post-transplant[20]. In a four-year follow-up, Ninkovic *et al.* reported no association between the gender and osteoporosis among 234 LT patients[21].

We detected neither significant association, nor the correlation between either weight or height and BMD. According to the report of Asomaning *et al.* (2006), women with lower BMI were at higher risk of osteoporosis[22]. In another report, the patient's weight played a higher role in developing BMD, compared to height, BMI, and age[23].

Our results revealed that the mean age at transplantation was lower in patients with normal (7.46) than those with reduced (9.22) BMD; however, this difference was not significant. Likewise, no significant correlation was found between BMD, the age of transplantation, and the period elapsed since surgery. However, a study performed on 33 patients with chronic liver disease reported that femur BMD decreased following four months after LT[24]. Another report showed that ratios of patients experiencing at least one lumbar fractures were 14% and 21% in one- and two-years post LT respectively[25]. Furthermore, a recent study documented that one-third of the observed patients experienced one or more lumbar fractures during the third and fourth year after LT[25].

In our population, seven underlying diseases were identified with no significant association between these conditions and BMD. There was no meaningful relationship found between underlying diseases and BMD among 130 patients undergone LT[25–27].

Our patients administered prednisolone, cyclosporine, tacrolimus, mycophenolate, and sirolimus as the immunosuppressive drugs. No significant difference was identified among patients who received different kinds of immunosuppressive drugs. However, a significant correlation was found between administration of pulse therapy and BMD (r=0.43, P=0.03).

Previous studies noted that cyclosporine and tacrolimus could induce osteopenia[28,29]. In contrast, other reports asserted that there was no significant association between cyclosporine usage and fractures[29,30]. In the study of Leidig-Bruckner, the researchers found, that LT patients, who received cyclosporine and tacrolimus suffered from at least one lumbar fracture in 20% and 5% of patients, respectively[25]. Switching the therapeutic protocol from low-dose cyclosporine to low-dose tacrolimus in LT men resulted in an increase in lumbar BMD during 12 months post-transplant in 9 out of 10 patients[31]. On the other hand, Monegal *et al.* showed that lumbar BMD decreased during six months post-transplant in patients, received tacrolimus[32]. Most studies found no significant relationship between immunosuppressive therapies and BMD in LT patients. Overall, the association between immunosuppressive regimens and BMD has been less characterized, and there is a need for more conclusive evidence.

Regarding pulse therapy, a study on 33 patients showed no significant difference in BMD in patients, who received methylprednisolone versus oral prednisolone[33]. On the other hand, Frediani *et al.* reported that lumbar and femoral BMD decreased more after 6- and 12-months post-transplant in patients, administered oral prednisolone, relatively to those, who received methylprednisolone pulse therapy[34]. Nevertheless, intravascular methylprednisolone has been associated with a severe decrease in BMD in another report[35].

We observed no significant association between acute graft rejection and decreased BMD. In line with this, Hardinger *et al.* stated that graft rejection could not predict BMD and risk of fracture[36]. In contrast, Guthery *et al.* suggested that BMD screening can be beneficial in transplanted patients with a history of graft rejection[15].

CONCLUSION

The frequency of low BMD among LT children was 36.9%. There were significant negative correlations between BMD and both hip and lumbar z scores. However, no significant associations were found between BMD and gender, age of transplantation, weight, height, underlying diseases, immunosuppressive drugs, and acute graft rejection. A significant correlation was found between pulse therapy and BMD. It is recommended to routinely assess more variables and skeletal locations in more extended period to divulge reliable predictors of low BMD and risk of fracture in LT patients.

ABBREVIATIONS

LT: liver transplanted
BMD: bone mineral density
ESLD: end-stage liver disease
AIH: autoimmune hepatitis

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Seyed Mohsen Dehghani: Concept and designs, Anis Amirhakim, Mahboobeh Hashemi, and Homa Ilkhanpour: Collecting clinical data, Iraj Shahramian: Concept, Critically revising the manuscript, Ali Bazi: Drafting the manuscript and data analysis.

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