

# Osteoporosis in Pediatric Liver Transplantation

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## Abstract

Liver transplantation provides an important, often life-saving treatment for end-stage liver disease. Osteoporosis post-liver transplantation has been described in adults; however, this has not been described in the pediatric population to date. We present a case of a 13-year-old female patient who underwent an orthotopic liver transplant for cryptogenic liver cirrhosis. Her immunosuppressants were tacrolimus and prednisone. Four months posttransplant, she started complaining of bilateral lower limb pain and limping while walking, progressing to a point where she was almost immobile. Magnetic resonance imaging of the pelvis showed bilateral avascular necrosis involving the weight-bearing surfaces of both femoral heads, in addition to the extensive edema involving both hip joints. Bone mineral densitometry was below normal for her age at the hip and forearm. She was started on high-dose calcium and vitamin D supplement, as well as zoledronic acid with a remarkable symptomatic and functional improvement.

## Keywords

liver transplantation, osteoporosis, pediatric

## Introduction

Liver transplantation has been established to be a highly effective therapy for end-stage liver disease. It provides an important, often life-saving treatment for patients having this disease. Its efficacy has risen especially since the advancement of immunosuppression, which has caused the rate of survival to increase greatly over the years, along with the perioperative advances that occurred.

## Case Presentation

A 13-year-old female patient presented to our institution with liver failure in June 2011. She had no medical history or surgical history. She was diagnosed to have psoriasis in October 2010 with generalized eruption all over her body. She was treated with ultraviolet sessions, and psoriasis was resolved. She had progressive jaundice for which liver biopsy, gastroscopy, bone marrow biopsy, and metabolic studies were done, and all were nonrevealing. The patient also developed fever and chills, as well as dyspnea at rest with cough. The patient reported an episode of abdominal pain, and increase in abdominal girth was noted. She had a full investigation panel that revealed idiopathic or cryptogenic liver cirrhosis causing her liver failure: Her virology (hepatitis A, B, and C) was negative; autoimmune workup including antinuclear antibodies, anti-smooth muscle antibodies, anti-DNA, anti-liver kidney

microsomal antibodies, anti-tissue transglutaminase, and anti-endomysial immunoglobulin A were negative. Liver function tests were also performed, and the following results were reported: alkaline phosphatase was 119 IU/L, serum glutamic oxaloacetic transaminase (aspartate aminotransferase) was 105 IU/L, serum glutamic pyruvic transaminase (alanine aminotransferase) was 16 IU/L, and g-GT was <3 IU/L. Other investigatory tests were performed to rule out Wilson disease: normal urine organic acid profile; no succinylacetone, ceruloplasmin, and copper in blood; normal levels of urine copper; normal  $\beta$ -glucosidase level; and amino acid profile showed slightly elevated citrulline, methionine, and tyrosine. An ophthalmology test was also performed, and it was normal. Her  $\alpha$ -antitrypsin was normal. An ultrasound was done as well showing findings consistent with advanced cirrhosis with portal hypertension, including splenomegaly and mild ascites.

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**Table 1.** Bone Mineral Densitometry (BMD) Was Below Normal for Her Age at the Hip and Forearm.<sup>a</sup>

Skeletal Region	Bone Density (g/cm <sup>2</sup> )	SD Above or Below the Mean for Age-Matched Controls
AP spine (L1-L4)	0.741	-1.8
Femur total neck	0.639	-2.7
	0.642	-1.9
Forearm (radius 33%)	0.537	-2.2
Total body	0.875	-1.7

Abbreviation: AP, anterior-posterior; SD, standard deviation.

<sup>a</sup>Bone density 0.63 g/cm<sup>2</sup>, -2.7 below the standard deviation.

Liver biopsy was performed and showed confluent hepatic necrosis, bile duct proliferation, and acute and chronic inflammation. In January 2013, she underwent orthotopic liver transplantation for cryptogenic liver cirrhosis. Her liver was sent to pathology, and the comments were as follows:

The architecture of the liver is distorted by thick fibrous bands forming complete nodules. The fibrous bands contain numerous small bile ducts and a mild chronic inflammatory cell infiltrate. Inside the nodules, the hepatocytes show focal macrosteatosis, cholestasis, and bile plugs. Central veins are not identified.

The final diagnosis was macronodular cirrhosis. During the transplantation, the patient was given a 500 mg induction dose of methyl prednisone intravenously in the anhepatic phase. This was followed by 3 days of a 16 mg dose, also intravenously. The immunosuppressant regimen was tacrolimus and prednisone. Prednisone doses started with 20 mg for 4 weeks and then tapered 15 mg for 3 weeks, followed by 10 mg for another 3 weeks to be maintained at 5 mg/d for 4 weeks, and then it was stopped. In May 2013, 4 months posttransplantation, she started complaining of bilateral lower limb pain and she started limping while walking. This progressed to a point where she was almost immobile and in need of crutches. Bone mineral densitometry showed considerable bone loss at the hip and forearm (Table 1). Magnetic resonance imaging revealed bilateral avascular necrosis involving the weight-bearing surfaces of both femoral heads with more than 50% involvement of the surface area, in addition to the extensive edema involving both hip joints (Figure 1).

It is worth noting that the patient had no preexisting condition and did not have joint pain before the transplantation. Moreover, her psoriasis was only cutaneous, and it did not involve the joints, and thus it did not cause any bone abnormalities. An endocrinologist was consulted, and she was started on a high dose of calcium and vitamin D supplement, as well as zoledronic acid, which led to a remarkable symptomatic and functional improvement (Table 2).

## Discussion

Among the liver transplant recipients, the pediatric population makes up a significant percentage. However, the long-term complications that occur for adult transplant recipients might

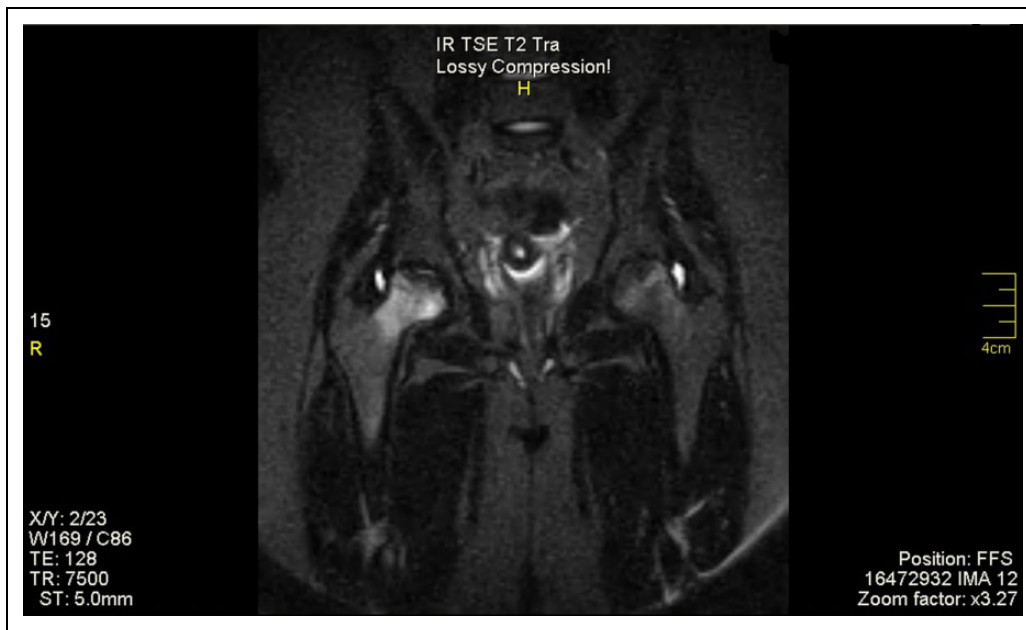
differ from those affecting pediatric recipients. In general, liver transplant recipients have a higher risk of developing osteoporosis, chronic renal disease, and atherosclerotic heart disease.<sup>1</sup> From these, osteoporosis is one of the serious complications that is mainly a result of the usage of steroids for immunosuppression.

According to numerous studies, steroids have been found to have a direct effect on the bone mass index. Osteoporosis occurring post-liver transplantation has been extensively described in adults in the literature; in children, though, the effect of liver transplantation on bone density is not well defined.<sup>1</sup> Numerous articles in the literature have mentioned that the long-term use of steroids will decrease bone density in pediatric patients. Bucuvalas et al has noted that the bone density of pediatric transplant recipients goes back to normal after a year.<sup>2</sup> On the other hand, Nightingale et al reported that corticosteroid exposure after liver transplant did not influence bone mass density. However, children undergoing liver transplant who are 10 years or older and those with low body mass index posttransplantation may have the greatest risk of poor bone health in the future.<sup>3</sup>

Since patients who undergo liver transplantation must remain for life on different regimens of immunosuppressants including glucocorticoids, they mainly develop symptomatic osteoporosis and fractures that could negatively impact their quality of life. Lan et al has delineated the effects of immunosuppressive agents on the skeleton and found that glucocorticoids have several systemic effects, among them are reducing net intestinal calcium absorption, increasing urinary calcium excretion, increasing parathyroid hormone, and decreasing production of skeletal growth factors.<sup>4</sup> Glucocorticoids have direct effects on the bones, among them are decreasing bone formation by osteoblasts and increasing bone resorption. Tacrolimus, an immunosuppressive agent, has been shown to cause marked osteoporosis by inhibiting osteoclast formation.<sup>5</sup>

Patients with liver disease have low bone mass and abnormal mineral metabolism,<sup>6,7</sup> leading to an increased risk of osteoporosis. Several studies showed that liver transplant patients have rapid bone loss and a high incidence of fragility fractures.<sup>8</sup> Rapid bone loss has been demonstrated in the adult population but not well described in the pediatric population. Osteoporosis is described as reduced bone mass and disorder of bone architecture, leading to bone fragility, particularly at the wrist, hip, and spine.<sup>9</sup> At the cellular and tissue levels, there are 2 basic mechanisms of bone loss, namely increased bone turnover and remodeling imbalance.<sup>9</sup> Many studies have demonstrated rapid bone loss within the first 3 to 6 months posttransplantation.<sup>10-12</sup> Osteoporosis post-liver transplantation has been described thoroughly in adults; however, this has not been described in the pediatric population to date since it is a very rare incidence.

It is recommended that osteoporosis be excluded in pediatric patients presenting with lower extremity pain after liver transplantation when steroids are part of the immunosuppressive regimen. Patients should also be assessed for osteoporosis risk



**Figure 1.** Magnetic resonance imaging (MRI) of the pelvis showing bilateral avascular necrosis and extensive edema involving hip joints.

**Table 2.** Follow-Up Laboratory Results Over Period of 6 Months.

	July	August	September	October	November	December
Calcium	10.5	9.6	9.5	9.1	9.4	8.6
Phosphate	5.5			3.5	4.3	4.1
Vitamin D 25(OH)	6	29.3	33.3		21.9	
PTH	27.7					
TSH		4.84	5.04	4.57		
T4-free				1.27		
T3-free				3.98		

Abbreviations: OH, hydrogen; PTH, parathyroid hormone; TSH, thyrotropin.

before the transplantation, in order for protective and preventive measures to be taken.

### Declaration of Conflicting Interests

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