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**Title:** Pitfalls in the diagnosis and management of skeletal complications of liver transplantation  
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Summary and Conclusions
In this Thesis, we establish that skeletal complications are common after liver transplantation. Although this is predominantly in the form of osteopenia and mild grade vertebral fractures, it has nonetheless been clearly shown that both osteopenia and grade 1 fractures are also associated with increased fracture risk. The morbidity and the mortality associated with fractures dictates that all liver transplant recipients should be evaluated for these complications in addition to evaluating and correcting any vitamin D deficiency.

In Chapter 1, we review the important role of the liver in the tightly regulated, well-balanced process of bone remodelling. Through its metabolic and excretory function, the liver plays an important role in the absorption of the lipid-soluble vitamins A, E, D and K, the last two important in bone metabolism, and for the metabolism of vitamin D, IGF-1 and gonadal hormones also important for bone remodelling. In liver diseases, factors other than decreased liver function may influence bone turnover such as the underlying primary liver disease if due to inflammation (as seen in viral hepatitis and sclerosing cholangitis associated with inflammatory bowel diseases) or direct toxicity to bone cells (alcohol abuse in alcoholic liver disease or iron overload in hereditary haemochromatosis or bile salts in cholestatic liver disease). In patients awaiting liver transplantation, end-stage liver disease is often associated with a decrease in bone mass and an increase in fracture risk likely to be due to a decrease in bone quality, as not always associated with actual bone loss. After liver transplantation, significant bone loss still occurs despite recovery of liver function due to several factors predominantly including the high dose of corticosteroids used for immunosuppression and in the treatment of rejection episodes and the use of calcineurin inhibitors for immunosuppression with associated risk of renal impairment. Within the first year after OLT, fracture incidence is very high, with fractures occurring in 25-35% of transplanted patients within the first year after OLT.

In Chapter 2, we evaluated the prevalence of low bone mass and of vertebral fractures. We found a high prevalence of skeletal pathology in the form of mostly osteopenia and vertebral fractures, predominantly grade 1 fractures. We did take these fractures in consideration because these mild vertebral fractures have recently been shown to be clinically relevant as also predictive of increased future fracture risk. No association could be found between bone mineral density (BMD) and prevalent fractures, with a large number of patients having prevalent fractures despite normal or mildly decreased BMD. The independence of fracture risk from bone mineral density measurements suggest that decreased bone quality rather than bone quantity may play an important role in the increased fracture risk observed in these patients.

In Chapter 3, we studied the changes in bone mass after liver transplantation. We demonstrated that after the rapid bone loss observed within the first six months after transplantation, bone mass stabilizes at the femoral neck and improves at the
lumbar spine with spontaneous recovery to pre-transplant values at two years after transplantation. Nevertheless, new vertebral fractures occur in a third of transplanted patients within the first year after transplantation. There was no association between BMD and prevalent fractures at time of screening and fracture risk after liver transplantation. Of all potential risk factors, only male gender and higher age were associated with increased risk of fractures after transplantation but other factors including vitamin D deficiency and severity of liver disease were not.

It has been proven difficult to identify factors associated with increased fracture risk in liver transplant recipients. The association between clinical parameters such as primary liver pathology or severity of liver disease, and of bone mineral density (BMD) and fracture risk has thus been shown to be inconsistent and generally poor. Biochemical markers of bone turnover are widely available for use in the clinic, although their role in the prediction of bone loss and of fracture risk remains inconclusive and their value in the management of post-transplantation bone disease remains highly debatable. In the case of chronic liver disease, before and after liver transplantation, this is largely due to the many pitfalls in the interpretation of the measurements in the presence of abnormal liver connective tissue metabolism resulting in increased extraskelatal collagen type I synthesis and degradation as well as because of post-solid organ transplantation confounding factors such as use of corticosteroids and calcineurin inhibitors. In Chapter 4 we report that although procollagen type 1 N-terminal propeptide (P1NP) levels were increased and osteocalcin levels were decreased at screening before OLT, these markers as well as baseline bone alkaline phosphatase were neither predictive for prevalent BMD or prevalent vertebral fractures before transplantation, nor were they predictive for bone loss or increased fracture risk after transplantation. High C-terminal telopeptide (CTX) levels before liver transplantation and an increase in bone-alkaline phosphatase (BALP) after liver transplantation probably reflect best the risk of bone loss and fracture in patients with end-stage liver disease in the first year after OLT. However, because of the many pitfalls in the interpretation of the most commonly used collagen-derived bone turnover markers in patients with liver disease, caution is strongly advocated with their use in the clinic in therapeutic decision making in the management of skeletal complications before and after liver transplantation.

In the previous Chapters we have shown that skeletal pathology is highly prevalent in liver transplant recipients. However, it is unclear how these patients should be treated in order to prevent further bone loss and decrease or prevent further fractures after transplantation. In Chapter 5, we conducted a comprehensive review of the literature on the efficacy of bisphosphonate treatment in liver transplant recipients, which showed that treatment initiated shortly after OLT generally decreases bone loss and improves bone mass. However, data on the long-term effect of bisphosphonate
treatment on BMD are conflicting, and whereas some studies show a beneficial effect of bisphosphonates on fracture risk, others did not. In this Chapter, we also report on a case series of 39 patients treated with bisphosphonates within the first year after transplantation a median of 185 days after OLT, using as controls patients transplanted in the same time period but not receiving bisphosphonates. We observed that BMD increased in both treated and untreated patients with no significant difference between groups. These results suggest that bisphosphonate treatment not immediately initiated after transplantation may be too late to prevent or decrease bone loss characteristic of the early post-transplantation period and its associated increased fracture risk.

CONCLUDING REMARKS AND CLINICAL IMPLICATIONS

Low bone mass and vertebral fractures are highly prevalent in patients with end-stage liver failure awaiting liver transplantation, there is a rapid bone loss early after liver transplantation and the incidence of new fractures significantly increases within the first year after transplantation despite significant recovery of bone mass. Fractures represent a significant cause of morbidity and mortality so that it is of high clinical relevance to identify factors associated with this skeletal complication of liver transplantation. In this Thesis we show that neither clinical parameters such as primary liver pathology or severity of liver disease nor BMD measurements or bone turnover markers can reliably predict fracture risk before or after liver transplantation. It is clear that factors other than bone quantity play a significant role in the increased fracture risk and altered bone quality is a prime contender for this role. There are to date no reliable means of assessing bone quality, and it is not clear whether currently available bone-modifying treatments may positively influence bone quality to decrease or prevent future fractures. Taken together, findings from this Thesis are clinically very relevant, as they suggest that awareness should be raised amongst physicians caring for patients with liver disease about the inevitable skeletal complications associated with failure of the metabolic and excretory function of the liver, and all attempts made at early correction of all reversible aspects of this failure to try and avoid the increased bone fragility associated with altered bone quality.