Metabolic Bone Disease in the Post-transplant Population

Preventative and Therapeutic Measures

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KEYWORDS

• Transplantation • Bone loss • Immunosuppressive agents • Fractures
• Investigations • Treatment

KEY POINTS

- Post-transplant bone disease contributes substantially to morbidity and mortality after fractures and leads to significant loss of quality of life.
- The mechanisms inducing bone loss are multifactorial and include preexisting bone disease before transplantation, glucocorticoids (GCs), and other immunosuppressive medications, among others.
- Monitoring via biochemistry and imaging is essential in decision making regarding treatment. A bone biopsy remains vital in excluding low-turnover bone disease where there is any doubt.
- The use of bisphosphonates, combined with vitamin D and calcium supplementation, remains the backbone of treatment.

INTRODUCTION

Transplantation is recognized as the treatment of choice in end-stage kidney disease (ESKD) and is well established in chronic liver failure. Due to refinements in surgical technique and, more importantly, advances in immunosuppressive medication, both patient and graft survival have improved. This has led to more frequent observation of the long-term complications of transplantation and the need for improvement in its management.

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Post-transplant bone disease and bone loss commonly cause significant morbidity and mortality and induce significant loss in patients' quality of life due to fractures, pain, and subsequent loss of mobility and independence. This article reviews some of the multiple pathogenic mechanisms at play and discusses the investigations, monitoring, and treatment needed for the management of both preexisting and post-transplantation bone disease related to kidney and liver organ transplantation.

EPIDEMIOLOGY: BONE MINERAL DENSITY AND FRACTURE RISK

Low bone mass and fractures commonly antedate renal transplantation. Patients with ESKD on dialysis are 4-fold more likely to have hip fractures than the general population, with a 21% increase in vertebral fracture.[1] The most significant subsequent bone loss takes place within the first 6 to 12 months after transplantation and is predominantly due to large doses of GCs. Reported rates of decrease in bone mineral density (BMD) in the first year vary between 3% and 9%.[2–4] Not only do kidney recipients have an increased fracture risk compared with the general population but also they have a 30% increase in hip fractures compared with dialysis patients awaiting transplantation.[5]

By 18 months, bone loss has been shown to be 9% from baseline, and 60% of patients have BMD less than the fracture threshold.[2,3,6] The initial rate of loss declines steeply but persists at 1% to 2% per year. This may be due to calcineurin inhibitor (CNI) effects. At 5 years after transplant, 22% of patients have been reported to have had fractures. This rises to as high as 57% at 10 years, and the cumulative incidence at 15 years is considered 3 times greater than expected.[7,8]

In liver transplant recipients, the incidence of new fractures mirrors the timing of the most rapid bone loss within the first year.[9–11] Prospective studies have shown that bone loss at the lumbar spine occurred during the first 4 to 6 months with gradual improvement thereafter, with BMD nearing or even exceeding baseline by the second post-transplant year. BMD at the femur neck also improved after 3 to 5 years but was still below baseline,[10–12] likely due to the differences between trabecular and cortical bone pathophysiology.

In kidney recipients, fractures tend to occur more commonly in cortical bone with lower limb fractures, accounting for 35% of all fractures, followed by fractures in the ribs, upper extremities, and vertebrae.[8] In contrast, liver transplant patients have a predilection for fractures of the spine, hips, and ribs. Vertebral fractures have been reported in 21% of patients in the first 2 years.[13]

The rate of post-transplant fractures may be declining due to awareness of GC side effects, introduction of GC-sparing regimens and immunosuppressive agents, and treatment of bone disease before and after transplantation.

CAUSES OF POST-TRANSPLANT BONE DISEASE

Although this review focuses on bone disease after transplantation, the impact of pretransplantation bone density and disease on subsequent bone disease is substantial. The pathogenesis of bone disease before and after transplantation is multifactorial and complex. Some but not all of the risk factors are discussed.

Pretransplantation

Risks also seen in the general population

Advanced age, smoking, excessive alcohol use, and vitamin D deficiency undoubtedly contribute to low BMD in patients with kidney failure and liver failure as well as a history of previous fractures, immobility, and being either white or female. Low muscle