Osteoporosis following solid organ transplantation

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Since the introduction of new immunosuppressive agents, the number of organ transplants has increased significantly worldwide. Approximately 28,000 subjects received solid organ transplants in the USA from 2005 to 2006 [101] – approximately double the number of solid organ transplants performed in 1988. Despite the introduction of new immunosuppressive regimens designed for renal allograft recipients, including cyclosporine and tacrolimus, post-transplantation bone disease remains a major complication in this population. It was once thought that the introduction of these new immunosuppressive agents and the limited use of glucocorticoids would ameliorate this complication. However, the sustained loss of bone mineral density and spontaneous bone fractures remain a major cause of morbidity in these subjects [1–5].

The pathophysiologic mechanisms responsible for osteoporosis following organ transplantation are diverse and multifactorial [6]. The most common responsible factors include the underlying conditions leading to transplantation, lifestyle and nutritional changes, hormonal dysregulations, including abnormalities in calcitropic and gonadal hormones, and the skeletal effects of immunomodulatory agents [7–9]. Most commonly, medical immunosuppression has been implicated as the leading catalyst in the development of post-transplantation bone disease [10–13]. However, various renal, hepatic, cardiac and pulmonary diseases also have specific pathophysiologies that may contribute to the outcome of bone disease in this population [14–33]. Careful consideration should be given to the unique clinical picture of each individual patient before and after transplantation. Such a characterization will facilitate optimal management of this diverse group of patients to decrease the incidence of bone fractures and ultimately improve their quality of life.

Bone disease is commonly encountered in chronic renal failure patients who experience a continual decline in renal function. Secondary hyperparathyroidism may persist following successful renal transplantation and potentially accentuate the adverse effects of immunosuppressive drugs on the development of bone disease [34]. In addition, the synergistic effect of parathyroid hormone and elevated serum concentrations of phosphatonin, including FGF-23, which has been demonstrated to be elevated after renal transplantation, result in renal phosphorus wasting by reducing renal tubular reabsorption [35–38]. Persistent phosphorus depletion will potentially contribute to defective bone mineralization and progression to osteomalacia and low bone turnover. However, these complications have been largely unnoticed. Therefore, the magnitude of skeletal abnormalities following renal transplantation are much broader than in other solid organ transplantations [39]. These factors may be partly responsible for the continued loss of bone mineral density and increased cumulative risk of new fractures following renal transplantation [3].

Moreover, glucocorticoid treatment, by uncoupling of bone resorption and bone formation, may attenuate the recovery of an impaired bone turnover caused by adynamic bone disease – the most predominant skeletal lesion encountered in patients during dialysis treatment [11,31,40–42].

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Although cyclosporine has been reported to increase bone turnover by enhancing bone resorption and bone formation in rats [12], its effects on the human skeleton have not been fully examined. Several investigations in post renal transplant subjects comparing cyclosporine monotherapy with combined immunosuppressive treatment, such as prednisolone and azathioprine, have shown inconsistent results [43–46]. The effect of tacrolimus treatment alone in post-renal...
transplant patients is very limited. One study noted that the combination of tacrolimus and low-dose steroids caused lower bone mineral density loss compared with cyclosporine and normal-dose steroids in a small group of post-kidney transplant subjects. This result may be largely due to a steroid-sparing effect in the tacrolimus group [47].

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Osteoporosis and bone fractures are commonly encountered in patients with chronic liver disease [14]. Several histomorphometric bone analyses have shown an increased osteoclastic bone resorption and diminished osteoblastic bone formation in this population [48–50]. The pathophysiologic mechanisms underlying bone resorption include hypogonadism [15,19] and vitamin D deficiency [14]. Impaired bone formation may be due to decreased production of IGF-1 [17] and the direct effect of alcohol [16] and bilirubin [18] on osteoblasts. Bone mineral density declines rapidly during the first 3 to 6 months following liver transplantation [19,51,52]. However, during the second year, bone mineral density stabilizes and ultimately may even increase for several years [53,54]. This particular pattern of change is similar to cardiac and pulmonary organ recipients but different from post-renal transplantation, in which an early decrease in bone mineral density is followed by several years of continued loss [55]. The early significant reduction in bone mineral density is similar in all solid organ transplantations and is perhaps related to high-dose glucocorticoids used during this immediate stage following transplantation [14,52,54]. However, the exact mechanism of the later bone recovery observed after solid organ transplantations, other than renal transplants, has not been fully elucidated.

No specific metabolic abnormalities are responsible for the development of osteoporosis and bone fractures following cardiac transplantation. Abnormalities in calcitropic and gonadal hormones in patients with end-stage cardiac disease have been noticed to be transient and progressively improve following cardiac transplantation [51]. Bone loss involving both the spine and femoral neck occurs most rapidly during the first year after cardiac transplantation [51,56–60]. This loss in bone mineral density is associated with a significant rate of fracture involving the vertebral spine, mostly during the first year post-transplantation [60–62].

The pathogenetic mechanisms of bone loss in end stage lung disease are multiple and may be related to smoking, low body weight, hypogonadism, vitamin D deficiency and inflammatory cytokines— in addition to the chronic use of steroids [23–25]. The prevalence of osteoporosis in lung transplant patients is significantly elevated, and fracture rates during the first year range from 18 to 37% [63]. Although bone mineral density measurements may not be a reliable predictor of fracture incidence following solid organ transplantations, the American Gastroenterological Association and the Kidney Disease Outcomes Quality Initiative Group recommend bone mineral density measurement to be considered for the selection of solid organ transplantation recipients [2,61,64–66].

Most available studies have used bone mineral density as the primary diagnosis of osteoporosis after solid organ transplantation, mainly owing to the well-known effect of glucocorticoids on bone [38,39]. However, it may be argued that bone mineral density changes in this population do not exclude the possibility of osteomalacia. Such an assumption may lead to improper selection of treatment.

The persistent deterioration of bone mineral density and the increased cumulative incidence of bone fracture and impaired bone mineralization are specific features following renal transplantation. Therefore, one may conclude that factors other than immunosuppressive treatments may play a key role in the development of bone disease in this population. Potential candidates can be phosphatonin, which, in conjunction with parathyroid hormone, may result in chronic phosphorus depletion in the renal transplant recipient. Further studies are needed to explore the possibility of the link between phosphatonin, persistent renal phosphorus wasting and specific skeletal lesions in this population.

Pathophysiologic mechanisms of bone disease following solid organ transplantation are diverse and may be related to the effect of immunosuppressive treatment in addition to dysregulations of calcitropic and gonadal hormones, lifestyle factors and to the specific metabolic abnormalities related to the underlying disease.
Despite the heterogeneity in pathophysiologic mechanisms, clinical studies have demonstrated that a significant and early loss of bone mineral density occurs concomitantly with the marked increase in the prevalence of bone fractures. The prevalence of fractures diminishes gradually after the first year in certain organ transplantations, including liver, lung and heart recipients. However, bone fractures progress following renal transplantation due to the as yet unexplained factors that must be fully explored. Prevention and management options are now limited to general measures including lifestyle modifications, correction of vitamin D and gonadal hormonal deficiencies and treatment with antiresorptive agents. Despite, consistent results demonstrating the efficacy of these therapies in increasing bone mineral density following all solid organ transplantations, to date, antifracture efficacy of these agents has not been tested in large-scale, randomized, controlled clinical trials. Further studies are needed to delineate the effects of short-term antiresorptive treatment, specifically bisphosphonates, during the rapid phase of bone loss in cardiac, lung and liver organ transplantations. The stability of bone mineral density and perhaps recovery of bone mineral loss, which may arise naturally and independently of the drug effect, may preclude the long-term use of these agents. Such drug withdrawal will allow normal bone remodeling to proceed and could prevent the high skeletal burden that is anticipated to occur with bisphosphonates.

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Executive summary

- Pathophysiologic mechanisms of post-solid organ transplantation bone disease are diverse and include the underlying conditions leading to transplantation, lifestyle and nutritional changes, hormonal dysregulations and the effects of the immunomodulatory agents.

- Bone mineral density measurements may not reliably predict the occurrence of bone fracture following solid organ transplantation.

- Loss of bone mineral density and cumulative risk of bone fractures may persist several years after renal transplantation. However, the loss of bone mineral density and bone fractures occur mainly during the first year after cardiac, liver and lung transplantations.

- Long-term, controlled, randomized studies are required to delineate antifracture efficacy of antiresorptive agents after solid organ transplantation.

Bibliography


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