Osteoporosis following solid organ transplantation

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'Despite the introduction of new immunosuppressive regimens designed for renal allograft recipients … post-transplantation bone disease remains a major complication in this population.'

Since the introduction of new immunomodulatory 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 immunomodulatory 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 phosphatonins, 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

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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 phosphatonins, 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 phosphatonins, 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 biphosphonates, 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 biphosphonates.

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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

1. Smets YF, van der Pijl JW, de Fijter JW, Ringers J, Lemkes HH, Hamdy NA: Low bone mass and high incidence of fractures after successful simultaneous pancreas–kidney transplantation. *Nephrol. Dial. Transplant.* 13(5), 1250–1255 (1998).
2. Leidig-Bruckner G, Hosch S, Dodidou P *et al.*: Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. *Lancet* 357(9253), 342–347 (2001).
3. Vautour LM, Melton LJ III, Clarke BL, Achenbach SJ, Oberg AL, McCarthy JT: Long-term fracture risk following renal transplantation: a population-based study. *Osteoporos. Int.* 15(2), 160–167 (2004).
4. Ramsey-Goldman R, Dunn JE, Dunlop DD *et al.*: Increased risk of fracture in patients receiving solid organ transplants. *J. Bone Miner. Res.* 14(3), 456–463 (1999).
5. Cohen A, Sambrook P, Shane E: Management of bone loss after organ transplantation. *J. Bone Miner. Res.* 19(12), 1919–1932 (2004).
6. Maalouf NM, Shane E: Osteoporosis after solid organ transplantation. *J. Clin. Endocrinol. Metab.* 90(4), 2456–2465 (2005).
7. Suzuki Y, Ichikawa Y, Saito E, Homma M: Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. *Metabolism* 32(2), 151–156 (1983).
8. Sakakura M, Takebe K, Nakagawa S: Inhibition of luteinizing hormone secretion induced by synthetic LRH by long-term treatment with glucocorticoids in human subjects. *J. Clin. Endocrinol. Metab.* 40(5), 774–779 (1975).
9. Krueger BA, Trakshel GM, Sluss PM, Maines MD: Cyclosporin-mediated depression of luteinizing hormone receptors and heme biosynthesis in rat testes: a possible mechanism for decrease in serum testosterone. *Endocrinology* 129(5), 2647–2654 (1991).
10. Canalis E, Delany AM: Mechanisms of glucocorticoid action in bone. *Ann. NY Acad. Sci.* 966, 73–81 (2002).
11. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC: Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J. Clin. Invest.* 102(2), 274–282 (1998).
12. Epstein S: Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. *J. Bone Miner. Res.* 11(1), 1–7 (1996).
13. Cvetkovic M, Mann GN, Romero DF *et al.*: The deleterious effects of long-term cyclosporine A, cyclosporine G, and FK506 on bone mineral metabolism *in vivo*. *Transplantation* 57(8), 1231–1237 (1994).

14. Compston JE: Osteoporosis after liver transplantation. *Liver Transpl.* 9(4), 321–330 (2003).
15. Monegal A, Navasa M, Guanabens N *et al.*: Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. *Calcif. Tissue Int.* 60(2), 148–154 (1997).
16. Diez A, Puig J, Serrano S *et al.*: Alcohol-induced bone disease in the absence of severe chronic liver damage. *J. Bone Miner. Res.* 9(6), 825–831 (1994).
17. Gallego-Rojo FJ, Gonzalez-Calvin JL, Munoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D: Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. *Hepatology* 28(3), 695–699 (1998).
18. Janes CH, Dickson ER, Okazaki R, Bonde S, McDonagh AF, Riggs BL: Role of hyperbilirubinemia in the impairment of osteoblast proliferation associated with cholestatic jaundice. *J. Clin. Invest.* 95(6), 2581–2586 (1995).
19. Floreani A, Mega A, Tizian L *et al.*: Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. *Osteoporos. Int.* 12(9), 749–754 (2001).
20. Compston JE, Thompson RP: Intestinal absorption of 25-hydroxyvitamin D and osteomalacia in primary biliary cirrhosis. *Lancet* 1(8014), 721–724 (1977).
21. Shane E, Silverberg SJ, Donovan D *et al.*: Osteoporosis in lung transplantation candidates with end-stage pulmonary disease. *Am. J. Med.* 101(3), 262–269 (1996).
22. Aris RM, Neuringer IP, Weiner MA, Egan TM, Ontjes D: Severe osteoporosis before and after lung transplantation. *Chest* 109(5), 1176–1183 (1996).
23. Aris RM, Renner JB, Winders AD *et al.*: Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. *Ann. Intern. Med.* 128(3), 186–193 (1998).
24. Ionescu AA, Nixon LS, Evans WD *et al.*: Bone density, body composition, and inflammatory status in cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 162(3 Pt 1), 789–794 (2000).
25. Lark RK, Lester GE, Ontjes DA *et al.*: Diminished and erratic absorption of ergocalciferol in adult cystic fibrosis patients. *Am. J. Clin. Nutr.* 73(3), 602–606 (2001).
26. Haworth CS, Selby PL, Webb AK *et al.*: Low bone mineral density in adults with cystic fibrosis. *Thorax* 54(11), 961–967 (1999).
27. Haworth CS, Webb AK, Egan JJ *et al.*: Bone histomorphometry in adult patients with cystic fibrosis. *Chest* 118(2), 434–439 (2000).
28. Elkin SL, Vedi S, Bord S, Garrahan NJ, Hodson ME, Compston JE: Histomorphometric analysis of bone biopsies from the iliac crest of adults with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 166(11), 1470–1474 (2002).
29. Shane E, Mancini D, Aaronson K *et al.*: Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *Am. J. Med.* 103(3), 197–207 (1997).
30. Pisani B, Mullen GM: Prevention of osteoporosis in cardiac transplant recipients. *Curr. Opin. Cardiol.* 17(2), 160–164 (2002).
31. Hruska KA, Teitelbaum SL: Renal osteodystrophy. *N. Engl. J. Med.* 333(3), 166–174 (1995).
32. Alem AM, Sherrard DJ, Gillen DL *et al.*: Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 58(1), 396–399 (2000).
33. Stehman-Breen CO, Sherrard DJ, Alem AM *et al.*: Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int.* 58(5), 2200–2205 (2000).
34. Pabico RC, McKenna BA: Metabolic problems in renal transplant patients. Persistent hyperparathyroidism and hypophosphatemia: effects of intravenous calcium infusion. *Transplant Proc.* 20(1 Suppl. 1), 438–442 (1998).
35. Green J, Debby H, Lederer E, Levi M, Zajicek HK, Bick T: Evidence for a PTH-independent humoral mechanism in post-transplant hypophosphatemia and phosphaturia. *Kidney Int.* 60(3), 1182–1196 (2001).
36. Rosenbaum RW, Hruska KA, Korkor A, Anderson C, Slatopolsky E: Decreased phosphate reabsorption after renal transplantation: evidence for a mechanism independent of calcium and parathyroid hormone. *Kidney Int.* 19(4), 568–578 (1981).
37. Jonsson KB: The role of fibroblast growth factor 23 in renal disease. *Nephrol. Dial. Transplant.* 20(3), 479–482 (2005).
38. Bhan I, Shah A, Holmes J *et al.*: Post-transplant hypophosphatemia: tertiary 'hyper-phosphatoninism'? *Kidney Int.* 70(8), 1486–1494 (2006).
39. Ghanekar H, Moe OW, Sakhaee K: Post renal transplantation hypophosphatemia: natural history and pathogenesis. *Am. J. Transplant.* 7(5) 1193–1200 (2007).
40. Elder G: Pathophysiology and recent advances in the management of renal osteodystrophy. *J. Bone Miner. Res.* 17(12), 2094–2105 (2002).
41. Canalis E: Clinical review 83: mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. *J. Clin. Endocrinol. Metab.* 81(10), 3441–3447 (1996).
42. Martin KJ, Olgaard K, Coburn JW *et al.*: Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. *Am. J. Kidney Dis.* 43(3), 558–565 (2004).
43. Cueto-Manzano AM, Konel S, Crowley V *et al.*: Bone histopathology and densitometry comparison between cyclosporine a monotherapy and prednisolone plus azathioprine dual immunosuppression in renal transplant patients. *Transplantation* 75(12), 2053–2058 (2003).
44. Ponticelli C, Aroldi A: Osteoporosis after organ transplantation. *Lancet* 357(9268), 1623 (2001).
45. Grotz W, Mundinger A, Gugel B, Exner V, Reichelt A, Schollmeyer P: Missing impact of cyclosporine on osteoporosis in renal transplant recipients. *Transplant. Proc.* 26(5), 2652–2653 (1994).
46. McIntyre HD, Menzies B, Rigby R, Perry-Keene DA, Hawley CM, Hardie IR: Long-term bone loss after renal transplantation: comparison of immunosuppressive regimens. *Clin. Transpl.* 9(1), 20–24 (1995).
47. Goffin E, Devogelaer JP, Lalaoui A *et al.*: Tacrolimus and low-dose steroid immunosuppression preserves bone mass after renal transplantation. *Transpl. Int.* 15(2–3), 73–80 (2002).
48. Diamond TH, Stiel D, Lunzer M, McDowall D, Eckstein RP, Posen S: Hepatic osteodystrophy. Static and dynamic bone histomorphometry and serum bone Gla-protein in 80 patients with chronic liver disease. *Gastroenterology* 96(1), 213–221 (1989).
49. Guichelaar MM, Malinchoc M, Sibonga J, Clarke BL, Hay JE: Bone metabolism in advanced cholestatic liver disease: analysis by bone histomorphometry. *Hepatology* 36(4 Pt 1), 895–903 (2002).
50. Cuthbert JA, Pak CY, Zerwekh JE, Glass KD, Combes B: Bone disease in primary biliary cirrhosis: increased bone resorption and turnover in the absence of osteoporosis or osteomalacia. *Hepatology* 4(1), 1–8 (1984).

51. Shane E, Rivas M, McMahon DJ *et al.*: Bone loss and turnover after cardiac transplantation. *J. Clin. Endocrinol. Metab.* 82(5), 1497–1506 (1997).
52. Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD: Rapid loss of vertebral mineral density after renal transplantation. *N. Engl. J. Med.* 325(8), 544–550 (1991).
53. Floreani A: Osteoporosis is not a specific complication of primary biliary cirrhosis (PBC). *Gut* 50(6), 898; author reply 898–899 (2002).
54. Guo CY, Johnson A, Locke TJ, Eastell R: Mechanisms of bone loss after cardiac transplantation. *Bone* 22(3), 267–271 (1998).
55. Pichette V, Bonnardeaux A, Prudhomme L, Gagne M, Cardinal J, Ouimet D: Long-term bone loss in kidney transplant recipients: a cross-sectional and longitudinal study. *Am. J. Kidney Dis.* 28(1), 105–114 (1996).
56. Sambrook PN, Kelly PJ, Keogh AM *et al.*: Bone loss after heart transplantation: a prospective study. *J. Heart Lung Transplant.* 13(1 Pt 1), 116–120 (1994).
57. Berguer DG, Krieg MA, Thiebaud D *et al.*: Osteoporosis in heart transplant recipients: a longitudinal study. *Transplant. Proc.* 26(5), 2649–2651 (1994).
58. Van Cleemput J, Daenen W, Nijs J, Geusens P, Dequeker J, Vanhaecke J: Timing and quantification of bone loss in cardiac transplant recipients. *Transplant. Int.* 8(3), 196–200 (1995).
59. Thiebaud D, Krieg MA, Gillard-Berguer D, Jacquet AF, Goy JJ, Burckhardt P: Cyclosporine induces high bone turnover and may contribute to bone loss after heart transplantation. *Eur. J. Clin. Invest.* 26(7), 549–555 (1996).
60. Shane E, Addesso V, Namerow PB *et al.*: Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N. Engl. J. Med.* 350(8), 767–776 (2004).
61. Shane E, Rivas M, Staron RB *et al.*: Fracture after cardiac transplantation: a prospective longitudinal study. *J. Clin. Endocrinol. Metab.* 81(5), 1740–1746 (1996).
62. Leidig-Bruckner G, Hosch S, Dodidou P *et al.*: Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. *Lancet* 357(9253), 342–347 (2001).
63. Shane E, Papadopoulos A, Staron RB *et al.*: Bone loss and fracture after lung transplantation. *Transplantation* 68(2), 220–227 (1999).
64. Grotz WH, Mundinger FA, Gugel B, Exner V, Kirste G, Schollmeyer PJ: Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation* 58(8), 912–915 (1994).
65. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am. J. Kidney Dis.* 42(4 Suppl. 3), S1–S201 (2003).
66. American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders. *Gastroenterology* 125(3), 937–940 (2003).

Website

101. Scientific registry of transplant recipients (2007) www.ustransplant.org.

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