D-Hormones for Prevention of Bone Loss After Organ Transplant

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ABSTRACT. In addition to bisphosphonates, D-hormones appear to be effective agents in the prevention of post-transplant osteoporosis. In this article studies on D-hormone agents for prevention of post-transplant bone loss are reviewed. Potential reduction in immunosuppressive requirements with D-hormone is an additional consideration. Based upon available evidence, prophylaxis should involve a bisphosphonate, with D-hormone considered as adjunctive or alternative therapy. (J Rheumatol 2005;32 Suppl 76:41-43)

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INTRODUCTION

Large reductions in bone mineral density (BMD), with subsequent increased fracture risk, have been reported after most different types of organ transplant.

Although varying reductions in bone density can occur before transplant depending upon the underlying disease, the most rapid bone loss following transplant usually occurs in the initial 12-18 months, suggesting interventions to prevent bone loss immediately after transplant are likely to be most effective in reducing skeletal morbidity. Contributing factors to post-transplant bone loss include (1) immunosuppressive agents including prednisone and cyclosporine; (2) the underlying disease itself, which may be associated with metabolic bone disease prior to transplant (so that the degree of loss may vary by organ type transplanted); and (3) treatment of the underlying disease prior to transplant[1].

RATIONALE FOR USE OF D-HORMONES IN TRANSPLANT OSTEOPOROSIS

Glucocorticoids (GC) are an important part of most immunosuppressive regimens after organ transplant, but are also known to affect bone metabolism through multiple pathways[2]. Vitamin D metabolites may reduce post-transplant bone loss by reversing GC-induced decreases in intestinal calcium absorption and mitigating secondary hyperparathyroidism, which seems a prominent mechanism of bone loss[3]. These features may be also be due to renal impairment (reduced creatinine clearance) partly induced by cyclosporin A and/or the underlying diseases, with increased levels of cytokines, resulting in a reduction of 1α–hydroxylation of 25-hydroxy-vitamin D to D-hormone[3]. D-hormones (active vitamin D metabolites such as calcitriol and 1α-hydroxyvitamin D, or alfacalcidol) have been shown to be effective in preventing bone loss in patients starting corticosteroids[4,5], suggesting a role for these agents also in post-transplant osteoporosis.

Another mechanism whereby D-hormones might prevent post-transplant osteoporosis may relate to their immunomodulatory properties[6]. Currently it is unclear whether their bone-preserving effects relate purely to actions on calcium metabolism or may also reflect an ability to use reduced dosages of immunosuppressive drugs such as cyclosporine and/or corticosteroids.

CLINICAL EXPERIENCE WITH D-HORMONES IN TRANSPLANT OSTEOPOROSIS

The combination of calcium and simple vitamin D has been used as adjunctive therapy in most clinical trials of transplant-associated bone loss. These studies indicate plain vitamin D, in doses of 400-1000 IU/day, cannot prevent significant post-transplant bone loss[7-9], which could be explained by reduced activation of vitamin D in the kidney[3]. Studies of D-hormones in the transplant setting have therefore shown better results, although interpretation of these trials needs to take account of differing doses employed (with 0.5 µg of calcitriol about equivalent to 1 µg alfacalcidol), the use of concomitant therapy, variable timing after transplant, and varying immunosuppressive regimens.

Neuhaus, *et al*[10] explored a range of doses of calcitriol, enrolling 509 patients (213 women, 296 men, mean age 47 yrs) in a parallel-group, nonrandomized study. Patients were assigned to 5 treatment groups started 6 months after liver transplant and followed up for 18 months. Treated patients received either calcitriol 0.25 µg daily (Group 1, 35 patients), calcitriol 0.25 µg plus calcium 1000 mg daily (Group 2, 37 patients), calcitriol 0.5 µg daily (Group 3, 76 patients), or calcitriol 0.5 µg daily plus calcium 1000 mg daily (Group 4, 86 patients). A fifth group received calcitriol 0.5 µg daily plus 1000 mg of cal-

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cium plus sodium fluoride 25 mg daily (49 patients). Overall, calcitriol led to an improvement in BMD at both the spine and hip in all treatment groups or prevented further bone loss. Patients treated with 0.5 μg of calcitriol (Groups 3 and 4) showed a superior response in spine and hip BMD to patients treated with 0.25 μg daily. In Groups 3 and 4, the mean increment in BMD was 10% for the spine and 5.6% for the femoral neck. Patients in Group 1 also showed a large increment of 5.6% for the spine and 4% for the femoral neck. Better results were obtained in Group 2, with an increment of 7.3% for the spine and 3.9% for the femoral neck.

Since after liver transplant virtually all spinal bone loss occurs in the first 6 months, with recovery usually evident between 6 and 12 months, this study should be considered as secondary rather than primary prevention. The incidence of atraumatic fractures was significantly lower in the treated patients (2 of 238) in contrast to the control group (7 of 246). In summary, these data suggest D-hormones reduced bone loss after liver transplant in a dose-dependent fashion.

Sambrook, *et al*[11] examined D-hormones for primary prevention in a 2 year randomized double-blind study of 65 patients undergoing cardiac or single lung transplant. Patients were randomly allocated to receive either placebo or calcitriol (0.5-0.75 μg/day) for either 12 months or 24 months after transplant (i.e., 3 groups). All groups received 600 mg calcium per day as well. Bone loss at the proximal femur was significantly reduced or prevented at all 3 sites by treatment with D-hormone for 2 years compared with treatment with calcium alone. Bone loss at 24 months averaged 8.3% for those treated with calcium alone compared to 5.0% for those treated with D-hormone for 2 years. However, treatment with D-hormone for 12 months followed by calcium for 12 months resulted in similar proximal femoral bone loss to that seen in those patients treated with calcium alone for 24 months (7.4%), suggesting prophylaxis needed to be continued beyond 12 months. Although at the lumbar spine there were no significant differences in BMD between groups, over 2 years 22 new vertebral fractures/deformities occurred in 4 patients treated with calcium alone compared with one new vertebral fracture in one patient treated with D-hormone. Mild hypercalcemia was common with this dose of calcitriol, as was mild hypercalciuria (59% of patients vs 10% controls), but there were no significant differences between groups in serum creatinine after 2 years. These data suggest D-hormones may have a role in reducing bone loss after cardiac or lung transplant, but treatment needs to be continued beyond one year.

The effect of treatment with D-hormone on bone loss has also been examined in the first 6 months after renal transplant[12]. A total of 111 renal transplant recipients (65 men, 46 women, mean age 47 yrs) were randomized to treatment with either alfacalcidol (0.25 μg/day) plus calcium (1000 mg/day) or no treatment. In both groups, a significant decrease in lumbar BMD was observed during the first 3 months (alfacalcidol, –3.3%, $p < 0.0001$; controls –4.1%, $p < 0.0001$). Between 3 and 6 months, lumbar BMD slightly recovered in the D-hormone group, but it decreased further in the control group (total loss 0 to 6 mo: alfacalcidol, –2.6%, $p < 0.001$; controls, –5.0%, $p < 0.0001$), and the amount of bone loss at 6 months was significantly different between the groups ($p = 0.02$). Loss of BMD at the various hip sites was also significantly reduced in the D-hormone group. Apart from a trend toward more frequent hypercalcemia in the alfacalcidol group, no clinical or biochemical differences existed between the groups. It was concluded that treatment with D-hormone partially prevented bone loss at the lumbar spine and proximal femur during the first 6 months after renal transplant.

Ugur, *et al*[13] performed a randomized prospective trial in 45 patients after renal transplant assigned to either no treatment, calcium alone, calcium plus calcitriol 0.5 μg/day, or calcium plus calcitriol plus nasal calcitonin 200 IU second daily (i.e., 4 groups). However, all patients were more than 12 months post-transplant. Patients receiving D-hormone were protected from further bone loss, unlike the calcium and no treatment groups, who lost bone at the spine and hip over the subsequent 12 months.

COMPARISON OF D-HORMONES WITH BISPHOSPHONATES

One of the earliest comparative studies of D-hormones with bisphosphonates was by Van Cleemput, *et al*[14], who randomized 48 patients to receive either cyclical etidronate (400 mg daily for 14 days every 3 mo) or alfacalcidol (starting at 0.25 μg and going to 1 μg/day) plus calcium carbonate after cardiac transplant. Treatment with alfacalcidol reduced bone loss in the spine and femoral neck more than cyclical etidronate, with spinal loss at 6 months averaging 4.6% with alfacalcidol and 7.7% with etidronate. Two vertebral deformities occurred in the alfacalcidol group over 2 years, compared with 8 in the etidronate group.

To determine whether the rapid phase of bone loss after transplant was a transient phenomenon, Henderson, *et al*[15] compared the efficacy of 6 months of treatment by 2 cycles of etidronate or calcitriol 0.5 μg/day immediately post-cardiac or lung transplant in 41 patients. Patients were followed for a further 18 months, and there were no significant differences between groups with respect to age or cumulative dose of prednisone or cyclosporine over the 2 years. Bone loss did not differ between groups after 6 months but, despite this 6 month treatment phase, bone loss was significant in both groups after 18 months. Compared with an untreated historical control group, both therapies offered significant protection at 6 months.

Recently, the potent oral bisphosphonate alendronate has been studied in a post-transplant setting. Shane, *et al*[16] conducted a 2 year double-blind randomized trial to compare alendronate 10 mg daily with calcitriol 0.5 μg daily for 12 months in 149 patients after cardiac transplant. Rates of loss were compared to 27 control subjects concurrently transplanted, but not randomized to therapy. Subjects randomized to alendronate and calcitriol did not experience significant bone loss, in contrast to the control group. The 12 month change in spinal BMD was +0.3% with alendronate, –0.6% with calcitriol, and –3.2% in controls. The 12 month change in hip BMD was –1.3% with alendronate, –0.4% with calcitriol, and –6.2% in controls. Levels of urinary N-terminal telopeptides of collagen type 1 fell by 34% with alendronate, 26% with calcitriol, but were unchanged with controls. New vertebral fractures occurred in 6.8% of subjects treated with alendronate, 3.6% of subjects treated with calcitriol, and 13.6% of the control subjects. In the second year after discontinuation of both agents, BMD remained stable despite increases in bone turnover in the calcitriol group.

IMMUNOSUPPRESSIVE THERAPY POST-TRANSPLANT AND D-HORMONES

From 2 of the studies referred to above[11,15], 99 heart transplant recipients followed for 2 years offered an opportunity to examine whether D-hormones were associated with reduction of routine immunosuppression. Fifty-one patients had been randomly assigned to treatment with calcitriol to reduce bone loss (17 with 0.5 μg for 6 months, 18 with 0.5-1 μg for 12 months, and 18 with 0.5-1.0 μg for 2 years). Outcomes examined were cumulative doses of corticosteroid and cyclosporin A, as well as episodes of rejection, infection, and survival[17]. Patients treated with calcitriol had lower corticosteroid doses at 3, 6, 12, 18, and 24 months after transplant ($p < 0.05$ at 3 and 24 mo). Cyclosporine dosage, which was adjusted according to blood levels, was also consistently lower in the patients treated with calcitriol ($p < 0.05$ at all timepoints). These differences could not be explained by concomitant therapy with diltiazem, mycophenolate, tacrolimus, or total lymphoid irradiation, all of which were used in comparable numbers of patients between groups. These data suggest that D-hormones may have a synergistic immunomodulatory effect in combination with routine triple therapy for immunosuppression, reducing the doses of cyclosporine and corticosteroids required to prevent organ rejection without any detectable change in episodes of rejection, infection, or deaths.

SUMMARY

There is increasing evidence that a number of agents are effective in prevention of post-transplant bone loss of various organs. Further clinical trials are necessary to establish the comparative efficacy of different agents, but primary prophylaxis for osteoporosis should be considered in patients undergoing organ transplant. Although data from clinical trials suggest bisphosphonates are effective agents for prevention and treatment of post-transplant osteoporosis, the studies reviewed above suggest D-hormones are also effective agents in preventing post-transplant bone loss. A potential reduction in immunosuppressive requirements with D-hormones is an additional consideration. Based upon available evidence, prophylaxis should involve a bisphosphonate, with D-hormones considered as adjunctive or alternative therapy.

REFERENCES

1. Shane E, Cohen A. Osteoporosis after solid organ and bone marrow transplantation. Osteoporosis Int 2003;14:617-30.
2. Sambrook P, Lane NE. Corticosteroid osteoporosis. Ballieres Best Pract Res Clin Rheumatol 2001;15:401-13.
3. Cooper AM, Locke TJ, Eastell R. Secondary hyperparathyroidism associated with heart transplantation is reversed by 1 alpha hydroxyvitamin D[abstract]. J Bone Miner Res 1996;11:S544.
4. Sambrook P, Birmingham J, Kelly PJ, Kempler S, Pocock NA, Eisman JA. Prevention of corticosteroid osteoporosis; a comparison of calcium calcitriol and calcitonin. New Engl J Med 1993;328:1747-52.
5. Reginster JY, Kuntz D, Verdickt W, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporosis Int 1999;9:75-81.
6. Sambrook PN. Alfacalcidol and calcitriol in the prevention of bone loss after organ transplantation. Calcif Tissue Int 1999;65:341-3.
7. Ferrari SL, Nicod LP, Hamacher J, et al. Osteoporosis in patients undergoing lung transplantation. Eur Respir J 1996;9:2378-82.
8. Shane E, Rivas M, McMahon DJ, et al. Bone loss and turnover after cardiac transplantation. J Clin Endocrinol Metab 1997;82:1497-506.
9. Massenkeil G, Fiene C, Rosen O, Michael R, Reisinger W, Arnold R. Loss of bone mass and vitamin D deficiency after hematopoietic stem cell transplantation: standard prophylactic measures fail to prevent osteoporosis. Leukemia 2001;15:1701-5.
10. Neuhaus R, Kubo A, Lohmann R, Rayes N, Hierholzer J, Neuhaus P. Calcitriol in prevention and therapy of osteoporosis after liver transplantation. Transplant Proc 1999;31:472-3.
11. Sambrook P, Henderson NK, Keogh A, et al. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res 2000;15:1818-24.
12. De Sevaux RG, Hoitsma AJ, Corstens FH, Wetzels JF. Treatment with vitamin D and calcium reduces bone loss after renal transplantation. A randomized study. J Am Soc Nephrol 2002;13:1608-14.
13. Ugur A, Guvener N, Isiklar I, et al. Efficiency of preventive treatment for osteoporosis after renal transplantation. Transplant Proc 2000;32:556-7.
14. Van Cleemput J, Daenen W, Geusens P, Dequeker J, Van der Werf F, Vanhaecke J. Prevention of bone loss in cardiac transplant recipients: a comparison of bisphosphonates and vitamin D. Transplantation 1996;61:1495-9.
15. Henderson NK, Eisman JA, Keogh A, et al. Protective effect of short term calcitriol or cyclical etidronate on bone loss after cardiac or lung transplantation. J Bone Miner Res 2001;16:565-71.
16. Shane E, Addesso V, Namerow PB, et al. Alendronate or calcitriol and prevention of bone loss after cardiac transplantation. New Engl J Med 2004;350:767-76.
17. Briffa NK, Keogh AM, Sambrook PN, Eisman JA. Reduction of immunosuppressant therapy requirements in heart transplantation by calcitriol. Transplantation 2003;75:2133-4.