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Bone Mineral Content After Renal Transplantation

Placebo-controlled Prospective Study with 1,25-Dihydroxy Vitamin D_3 *

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Summary. Forearm bone mineral content (BMC), as evaluated by photonabsorption densitometry, was measured in 28 cadaver kidney donor recipients who entered the study 8 weeks postoperatively and were followed up for 18 months. BMC decreased significantly ($p<0.05$) but marginally in placebo-treated patients ($n=14$) (initial BMC 1.09 ± 0.25 g/cm; final BMC 1.05 ± 0.24). Fourteen patients were prophylactically given $1,25(OH)_2$vitamin D_3 in a dose which avoided hypercalcemia and hypercalciuria (~0.25 µg/day); under $1,25(OH)_2$ vitamin D_3 prophylaxis a significant decrease of forearm BMC was observed no longer (initial BMC 0.94 ± 0.21 g/cm; final BMC 0.95 ± 0.21), but the difference between placebo and $1,25(OH)_2$ vitamin D_3 narrowly missed statistical significance ($p=0.066$).

It is concluded that the decrease of forearm BMC is negligible in transplant recipients with low steroid regimens. The data suggest a trend for prophylaxis with $1,25(OH)_2$ vitamin D_3 to slightly ameliorate forearm (cortical) BMC loss.

Key words: Renal transplantation – Steroid osteoporosis – 1,25-Dihydroxy vitamin D_3 – Immunosuppressive therapy

Introduction

Osteopenia is a major complication of steroid therapy [1]. This may be particularly true after renal transplantation where steroids are part of the immunosuppressive regimen [2–5]. Osteopenia represents one major risk factor in the genesis of avascular necrosis of transplanted patients [6, 7].

In animal experiments, $1,25(OH)_2$ vitamin D_3 has been shown to diminish the effect of immobilization on the skeleton [8] and prophylactic oral $1,25(OH)_2$ vitamin D_3 was shown to be effective in preventing glucocorticoid osteopenia in rats [9]. In patients chronically treated with supraphysiologic doses of glucocorticoids Hahn et al. [10] demonstrated an increase of metaphyseal and diaphyseal forearm bone mass with chronic administration of 25(OH) vitamin D_3 and calcium. The action of vitamin D metabolites is a pharmacologic one, since 25(OH) vitamin D_3 levels [10] and $1,25(OH)_2$ vitamin D_3 levels [11] are normal in steorid-treated patients. The beneficial effect of pharmacologic doses of vitamin D metabolites may be related to the reversal of steroid-induced intestinal malabsorption of calcium [11] and the associated reversal of hyperparathyroidism [12]. It is not unreasonable to expect that such reversal might be particularly beneficial in steroid-treated posturemic patients with pre-existent hyperparathyroidism.

Using forearm bone densitometry [13–15] and other techniques [16], several authors measured a variable but, on average, marked decrease of forearm mineral density in transplanted patients without vitamin D supplements, the average annual loss being 5–10% during the first year [2].

The present prospective placebo-controlled trial was designed to examine whether prophylactic administration of $1,25(OH)_2$ vitamin D_3 after renal transplantation prevents bone mineral loss as measured by forearm radiodensitometry.

Patients and Methods

Patient Selection and Protocol

From July 1980 to September 1981, 61 patients were transplanted at the University of Heidelberg. All consecutive adult graft recipients entered the study 8 weeks after transplantation unless they had serum creatinine >1.8 mg/dl, hypercalcemia, or systemic disease. The patients were randomly assigned to a treatment or a placebo group with the use of random numbers. A total of 38 patients entered the study. Ten patients (four in the treatment group, six in the placebo group) were withdrawn after randomization for the following reasons: two patients developed hypercalcemia and hyperparathyroidism; four rejected their graft and developed renal failure; four left Germany and were lost for follow-up.

Twenty-eight cadaver transplant recipients were followed up for 18 months (20 men, eight women, median age: 36 years; range: 17–53 years). Prior to transplantation, all patients had been on dialysis for a median of 42.1 months (range 1–120 months). None of the patients had symptomatic bone disease, elevated alkaline serum phosphatase, or hypercalcemia prior to transplantation. Vitamin D deficiency was excluded by normal 25(OH)vitamin D_3 levels at the time of entry into the study (182 ± 75 nmol/l).

$1,25(OH)_2$ Vitamin D_3 Therapy

The patients received either 0.25 µg 1,25-dihydroxy vitamin D_3 or placebo. The maximal dose was given that was tolerated without hypercalcemia (>2.75 mmol/l) or hypercalciuria

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Table 1. Bone mineral content (g/cm) at various times after transplantation

	2 months	5 months	8 months	11 months	14 months	17 months	20 months	Δ initial − final
Placebo ($n=14$)	1.09 (0.67–1.38)	1.07 (0.78–1.38)	1.07 (0.72–1.50)	1.02 (0.69–1.45)	1.06 (0.67–1.43)	1.06 (0.67–1.43)	1.05 (0.70–1.40)	0.04
$1,25(OH)_2D_3$ ($n=14$)	0.94 (0.59–1.34)	0.96 (0.63–1.34)	0.97 (0.63–1.33)	0.97 (0.62–1.39)	0.96 (0.68–1.38)	0.94 (0.65–1.35)	0.95 (0.63–1.38)	0.01

Data are given as median (range in parentheses)

(> 12.5 mmol/24 h). With the exception of one patient, who tolerated 0.5 µg/day, all patients received a maintenance dose of 0.25 µg/day. Therapy was monitored by measuring serum and urinary calcium at 3-weekly intervals during the first 3 months. Subsequently, serum and urine chemistry was examined every 3 months. In addition, at 3-months intervals, iPTH [18], urinary cAMP [19], and 25(OH)vitamin D_3 [20] were measured, and the bone mineral content determined.

Steroid Treatment

The patients received 1,000 mg methylprednisolone on the day of operation. In the absence of rejection crises, the steroid dose was tapered to a median of 16 mg/day 8 weeks postoperatively. Twelve months postoperatively (p.o.), the median maintenance steroid dose was 7.5 mg methylprednisolone/day (range 4–12 mg). Eight patients were on an alternate-day schedule.

Acute rejection crises were treated with 1 g methylprednisolone i.v. for 1–3 days. The median cumulative steroid dose over 18 months was 12.932 mg range (7.276–20.684 mg). The median number of rejection crises was 1.5 (range: 0–5); the median number of rejection crises in the two groups was not different.

Bone Densitometry

A bone mineral analyzer (Norland Instruments, Model 178) was used with a highly collimated beam of monoenergetic photons of a 200 mCi ^{131}I source. Uniformity of tissue absorption was achieved by applying a water-filled moulded rubber bag around the forearm. The distance olecranon-styloid process was measured. The point of transition between middle and distal third of the radius was chosen for measurement. For each determination eight measurements were made, and the results were averaged. Results were expressed as bone mineral content (BMC) in g/cm. In healthy probands, the CV for 12 replicate measurements at different days was 1.5%.

Statistics

Data are given as median and range. Initial and final BMC were compared with the sign test. In addition, relative slopes were analyzed after rank transformation using a Kruskal-Wallis test for two samples and 1 *df*.

Results

At the beginning (2 months p.o.) and end (20 months p.o.) of the study, the two groups, i.e. placebo versus $1,25(OH)_2$ vitamin D_3, were comparable with respect to serum creatinine, serum phosphorous, iPTH, and urinary cAMP. In the placebo group, median S-Crea was 1.5 mg/dl at 2 months and 20 months and S-Ca 2.4 and 2.5 mmol/l, respectively.

In the $1,25(OH)_2$ vitamin D_3-treated group, the respective values for S-Crea were 1.5 and 1.6 mg/dl and for S-Ca 2.3 and 2.3. In both groups, median activities of alkaline serum phosphatase decreased (placebo from 164 to 127 U/l; $1,25(OH)_2$ vitamin D_3 from 141 to 105). Median urinary Ca increased in both groups (placebo from 0.8 to 1.5 mmol/l; $1,25(OH)_2$ vitamin D_3 to 2.6). At 2 and 20 months, the median daily prednisolone dose was 12 mg (range: 16–20) and 6 mg (range: 4–8), respectively, in the placebo group and 12 mg (range: 8–16) vs. 6 mg (range: 4–8) in the $1,25(OH)_2$ vitamin D_3 group.

BMC at various times after transplantation in placebo- and $1,25(OH)_2$ vitamin D_3-treated patients is given in Table 1. There was a significant difference ($p < 0.05$) between initial and final BMC in the placebo group, but not in the $1,25(OH)_2$ vitamin D_3-treated group. After rank transformation, the difference of relative slopes for BMC between the two groups came close to, but did not reach, statistical significance ($p = 0.066$).

Discussion

Whereas previous authors [2, 13–16] found a variable but, on average, substantial decrease of forearm BMC in transplanted patients, such decrease was marginal, although statistically significant, in the present study. The greater change of BMC in previous studies may have been due to several factors, e.g., higher steroid dosage, severity of pre-existent hyperparathyroidism, inclusion of patients with impaired graft function, age, etc. Steroid dosage is presumably the most important factor to explain the above differences. A dose-dependent effect of steroids on calcium metabolism is suggested by the failure to observe changes of intestinal calcium absorption at less than 15 mg prednisolone/day [20], while such decrease was readily demonstrable at high steroid doses [21]. Following the suggestions of McGeown [22] steroid doses have been reduced considerably in recent years and have even been further reduced since completion of the present study.

We found only a marginal, but statistically significant, decrease of BMC in placebo-treated patients. The limited magnitude of decrease is not due to the insensitivity of the photonabsorption technique. In particular, the error of replicate measurements was quite small (CV 1.5%).

Cortical bone makes an overriding contribution to BMC at the site of our forearm measurements. However, it is spongy bone as the metabolically most active osseous tissue with the highest turnover rate which decreases most after steroid administration [24, 25]. Furthermore, spongy bone is of special importance in the genesis of avascular bone necrosis [26]. Loss of

spongy bone may not be optimally reflected by measurements assessing preferentially cortical bone in patients with renal disease [16] or other disease states [27]. In transplanted patients, prophylactic administration of $1,25(OH)_2$ vitamin D_3 tended to reduce bone loss when compared with placebo, although the difference between placebo and $1,25(OH)_2$ vitamin D_3 did not quite reach statistical significance. This finding is in general agreement with previous experimental [9] and clinical [10] studies in non-renal animals or subjects. However, given the small magnitude of forearm BMC change in placebo-treated controls, this finding is of questionable biologic significance. Consequently, on the basis of these results it would not appear justified to recommend prophylactic administration of $1,25(OH)_2$ vitamin D_3 in transplant recipients who have normal renal function and are on low maintenance doses of steroids. However, a significant reduction in the incidence of osteonecrosis in recipients of renal homografts was noted recently, when a vitamin D_2 supplement was administered prophylactically [28]. This clinical observation validates the rationale underlying our study.

The tendency to use lower steroid doses is presumably responsible for the diminishing incidence of avascular femoral head necrosis. Formerly, it tended to be above 10% [6] but has diminished ever since. In 339 patients consecutively transplanted in our center, the incidence of aseptic necrosis was 4.12% [7], and an incidence below 1% was reported when still lower doses of steroids were chosen [20]. In the future, steroid-free immunosuppressive regimens may hopefully largely eliminate the problem in transplanted patients. However, the need to reduce secondary hyperparathyroidism and the attended risk of osteopenia will persist for steroid-treated non-renal patients [28].

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References

1. Hahn TJ, Boisseau VC, Avioli LV (1974) Effect of chronic corticosteroid administration on diaphyseal and metaphyseal bone mass. J Clin Endocrinol Metab 39:274–282
2. Aird EGA, Pierides AM (1978) Photonabsorptometry in hemodialysis and transplant patients in Newcastle upon Tyne, England. Fourth International Conference on Bone Measurement, University of Toronto, pp 217–230
3. Bailey RR, Stokes A (1978) Bone mineral content of patients on hemodialysis and following renal transplantation. Fourth International Conference on Bone Measurement, University of Toronto, pp 211–215
4. Alvestrand A, Dalen N (1977) X-ray spectrophotometry in evaluation of renal osteodystrophy. In: David DS (ed) Calcium metabolism in renal failure and nephrolithiasis. Wiley, New York, p 235
5. Huffer WE, Kuzela D, Popovtzer MM, Starzl TE (1975) Metabolic bone disease in chronic renal failure. Am J Pathol 78:385–398
6. Ibels LS, Alfrey AL, Hutter WE, Weil R (1978) Aseptic necrosis of bone following renal transplantation: Experience in 194 transplant recipients and review of the literature. Medicine 57:25–45
7. Ritz E, Dreikorn K, Weisschedel E, Mehls O (1982) Aseptische Knochennekrosen nach Nierentransplantation. Nieren- und Hochdruckkrankh 11:240–247
8. Yoshihiro I, Makita T, Hino S (1981) Immobilisation, osteoporosis and active vitamin D: effect of active vitamin D analogues on the development of immobilisation osteoporosis in rats. Calcif Tissue Int 33:623–630
9. Lindgren JU, De Luca HF (1983) Oral $1,25(OH)_2D_3$: An effective prophylactic treatment for glucocorticoid osteopenia in rats. Calcif Tissue Int 35:107–110
10. Hahn TJ, Halstead LR (1979) Altered mineral metabolism in glucocorticoid-induced osteopenia. J Clin Invest 64:655–665
11. Hahn TJ, Halstead LR, Baran DT (1981) Effect of short-term glucocorticoid administration on intenstinal calcium absorption and circulating vitamin D metabolite concentrations in man. J Clin Endocrinol Metab 52:111–115
12. Ritz E, Kreusser W, Rambausek M (1983) Effects of glucocorticoids on calciuria. Proceedings of the First International Colloquium on Glucocorticoid Effects, Siena, September 22–24, 1982. Plenum Press (in press)
13. Aird EGA, Pierides AM (1977) Photon-absorptiometry of bone after successful renal transplantation. Br J Radiol 50:350–356
14. Lindsay R, Mac Pherson SG, Anderson JB, Smith DA (1976) The value of bone density measurements in predicting the risk of developping avascular necrosis of bone following renal transplantation. 11th European Symposium on Calcified Tissue, Copenhagen. Tissue Res 21:242–247
15. Banzer D, Schneider U (1974) A computerized method of determination of bone mineral content by a transmission scanner. Proceedings of the International Conference on Bone Mineral Measurement. University of Toronto, pp 206–213
16. Nielsen HE (1978) Bone mineral content in renal transplant patients. Clin Nephrol 10:186–200
17. Alvestrand A, Dalen N (1977) X-ray spectrophotometry in evaluation of renal osteodystrophy. In: David DS (ed) Calcium metabolism in renal failure and nephrolithiasis. Wiley, New York, pp 235–248
18. Bouillon R, Koninckx P, De Moor P (1974) Radioimmunoassay and related procedures in medicine. International Atomic Energy Agency, Vienna
19. Tovey KD, Oldham KG, Whelan JEM (1974) A simple direct assay for cyclic AMP in plasma and other biological samples using an improved protein binding technique. Clin Chim Acta 56:221–234
20. Belsey RE, DeLuca HS, Patts JT (1974) A rapid assay for 25-OH-vitamin D_3 without preparative chromatography. J Clin Endocrinol Metab 38:1046–1051
21. Lekkerkerker J, van Woudenberg F, Doorenbos H (1972) Influence of low dose steroid therapy on calcium absorption. Acta Endocrinol 69:488–496
22. Klein RG, Arnaud SB, Gallagher JC, DeLuca HF, Riggs BL (1977) Intestinal calcium absorption in exogenous hypercortisonism role of 25 hydroxy vitamin D and corticosteroid dose. J Clin Invest 60:253–259
23. McGeown MG, Douglas JF, Brown WJ (1979) Low dose steroid from the day following transplantation. Proc EDTA 16:395–399
24. Hahn TJ (1980) Drug-induced disorders of vitamin D and mineral metabolism. Clin Endocrinol Metab 9:107–129
25. Jee WSS, Clark I (1981) Glucocorticoid-induced osteoporo-

sis. In: DeLuca HF, Frost HM, Jee WSS, Johnston AM, Parfitt M (eds) Osteoporosis, recent advances in pathegenesis and treatment. University Park Press, Baltimore, pp 331–342
26. Davidson JK (1976) Aseptic necrosis of bone. Excerpta Medica, Amsterdam
27. Genant HK, Cann CE, Ettinger B, Gordan GS (1982) Quantitative computed tomography of vertebral spongiosa: A sensitive method for detecting early bone loss after oophorectomy. Ann Int Med 97:699–705
28. Scholz D, Mebel M, Töpelmann I, Grossmann I, Scholze J (1983) Prevention of osteonecrosis following renal transplantation by using vitamin D_2 (ergocalciferol). Abstr 20th Congr Eur Dial Transplant Assoc, London, June 19–22 [A 85]
29. Suzuki F, Ichikawa Y, Saito E, Homma M (1983) Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. Metabolism 32:151–156

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