EFFECT OF 1αHYROXYLATED VITAMIN D ON STEROID INDUCED CALCIUM MALABSORPTION

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Summary

As persistent bone loss is a major problem of chronic steroid therapy the effects of 3 weeks therapy with 1αhydroxycholecalciferol were studied in 10 kidney transplant recipients on chronic steroid therapy. Treatment resulted in a significant increase in intestinal calcium absorption, paralleled by a significant decrease of serum iPTH, whereas neither plasma calcium nor urinary calcium excretion rose significantly, suggesting a positive calcium balance throughout the study. It is therefore suggested that administration of active vitamin D metabolites is an effective protection against one of the pathogenic mechanisms of steroid induced osteopenia.

Introduction

It is well established that chronic administration of glucocorticoids leads to a certain form of osteopathy, termed steroid induced osteopenia. As steroids are generally used for immunosuppression in kidney transplant recipients, it is not surprising that a continuous decrease in the amount of spongy bone [1], a decrease in bone mineral content [2,3] and development of aseptic necrosis of bone [4,5] can be frequently observed in kidney allograft recipients, despite the resolution of uraemic bone lesions when good and stable transplant function has been obtained. Whereas the aetiology of steroid induced osteopenia is complex, an established cause is impaired intestinal calcium absorption [6,7]. Chestney [8] and O'Regan [9] showed that levels of 1,25 dihydroxycholecalciferol (1,25(OH)2D3), the most active vitamin D metabolite, are reduced in adolescents receiving chronic steroid therapy and suggested that this reduction may be an important pathogenic mechanism for steroid induced osteopenia. We therefore studied the effect of administration of 1αhydroxycholecalciferol (1α(OH)D3) which is converted to 1,25(OH)2D3 by the liver, on calcium absorption in chronic steroid treated kidney allograft recipients.
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<th>Ca Excretion (mg/24h)</th>
<th>Clearance Cr (ml/min)</th>
<th>TmP/GFR (mg/100ml)</th>
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n.s p<0.01 n.s n.s n.s n.s p<0.05
Patients and methods

Ten kidney allograft recipients (4 females, 6 males) with good and stable transplant function (plasma creatinine <2mg/100ml, graft survival >2 years) were studied. All patients received azathioprine and steroids for immunosuppression as usual; the steroid dosage was less than 10mg prednisolone per day in all patients. All patients were treated with 1µg 1α(OH)D₃ daily for three weeks. Before the beginning and at the end of the study the following measurements were done: plasma calcium (Ca), phosphate (Pi) and creatinine (Cr) as well as urinary Ca, Pi and Cr by routine methods (Technicon autoanalyser); TmP/GFR values were derived from Bijvoet’s nomogram [10]; serum iPTH was measured using an antibody against the C-terminal part of the PTH-molecule [11], normal range 2.0 to 6.0 mU/ml; intestinal calcium absorption was estimated after oral administration of $^{47}$Ca⁺⁺ using the method of Marshall and Nordin [12], normal range 0.25 to 1.6% D/h.

Statistical analysis was done using Student’s t-test for paired data.

Results

The observed changes in blood and urinary chemistry are given in Table I. Only plasma Pi and TmP/GFR as a measure of renal phosphate handling showed a significant increase, whereas there was neither a significant increase in plasma Ca nor in urinary Ca excretion. Furthermore there was no evidence of any deterioration period (Figure 1).

Fractional absorption rate of $^{47}$Ca⁺⁺ showed a significant increase from low normal initial values although remaining in the normal range at the end of the treatment period (Figure 1).

![Figure 1. Fractional absorption rate of calcium before and after 3 weeks therapy with 1µg 1α(OH)D₃](image_url)
Concomitantly serum iPTH values showed a significant decrease but were in the normal range at the beginning as well as at the end of the study (Figure 2).

![Graph showing serum iPTH values before and after 3 weeks therapy with 1μg 1α(OH)D₃ daily](image)

**Figure 2.** Serum iPTH values before and after 3 weeks therapy with 1μg 1α(OH)D₃ daily

**Discussion**

Our finding of a significant increase in intestinal calcium absorption by administration of 1α(OH)D₃ to chronically steroid treated kidney allograft recipients is in accordance with the study of Fox et al [13] who showed in pigs that administration of steroids in a comparable dosage to that used in our patients results in an inhibition of intestinal calcium absorption, and that this effect can be reversed by administration of 1α(OH)D₃. Similar results have been obtained by Jorgensen [14] in patients on long term steroid therapy for rheumatoid arthritis. In this study however, a twofold dosage of 1α(OH)D₃ was used and the improvement of intestinal calcium absorption was paralleled by a significant increase in plasma Ca and a marked increase in urinary Ca excretion. This is of importance, since deterioration of renal function in patients on therapy with 1,25(OH)₂D₃ has been reported [15] which can probably be attributed to associated episodes of hypercalcaemia. In our patients however, no concomitant rise in plasma Ca and no significant increase in urinary Ca excretion occurred, while intestinal calcium absorption improved, suggesting a positive calcium balance during 1α(OH)D₃ therapy.

Of further importance is the significant decrease in serum iPTH levels during administration of 1α(OH)D₃ in our patients. It has been shown that glucocorticoids cause stimulation of PTH secretion from bovine parathyroid glands in organ culture [16], that administration of cortisone causes hyperparathyroidism in the experimental animal [17] and that acute and chronic administration of glucocorticoids in man results in increased PTH secretion [18]. Although
our patients showed no signs of overt hyperparathyroidism it could be argued
that the normal serum iPTH levels found before the beginning of our study re-
presented a state of relative hyperactivity of the parathyroid glands in order to
maintain normal plasma Ca levels. Therapy with 1α(OH)D₃ would act here in a
dual fashion; a direct suppression of PTH secretion, and restoration of intestinal
Ca absorption, thereby removing an important stimulus to parathyroid gland
activity.

Although a direct effect of 1α-hydroxylated vitamin D compounds on bone
mineralisation cannot be shown by our results, our study shows that administra-
tion of 1α(OH)D₃ to chronic steroid treated kidney allograft recipients results
in an improvement of intestinal calcium absorption, thereby eliminating at least
one important mechanism of steroid induced osteopenia.

Acknowledgment

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