Research Open

Endocrinology, Diabetes and Metabolism Journal

Volume 2 Issue 3

Research Article

Improvement in Bone Density with Calcitriol Substitution for Cholecalciferol in Refractory Osteoporosis induced by Prednisone

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Received: August 06, 2018; **Accepted:** August 17, 2018; **Published:** August 27, 2018;

Summary

Low BMD in subjects receiving chronic prednisone therapy is attributed to osteoporosis. This study demonstrates that osteomalacia induced by lowering of biologically active vitamin D by prednisone induced inhibition of hepatic 25 hydroxyase may also be a major contributing factor.

Abstract

Introduction/ Purpose: Decline in BMD following prednisone therapy is attributed to osteoporosis. However, osteomalacia due to low 125 OH Vitamin D and resulting hyperparathyroidism may also be contributors. Therefore, administration of 125 OH vitamin D3, Calcitriol on BMD was examined in subjects receiving chronic prednisone therapy and low BMD (T< 2.5) refractory to therapy with bisphosphanate, calcium and vitamin D3, Cholecalciferol.

Methods: 21 subjects, ages 45–56 years receiving prednisone ≥3 years with declining BMD despite therapy with Cholecalciferol, $CaCO_3$ and bisphosphanate were divided into 2 groups. Both groups continued Calcium and bisphosphanate. 10 subjects (group 1) received increased dose of Cholecalciferol, 2000 units daily while in 11 subjects (group 2), it was substituted by Calcitriol. Comprehensive metabolic panels (CMP) including serum calcium and alkaline phosphatase as well as 25 OH Vit D and 125 OH Vit D levels were determined every 6 months. BMD was determined at yearly interval.

Results: CMP including calcium and phosphorus remained normal in both groups while alkaline phosphatase declined in group 2 alone. Serum 25 OH Vit D levels were subnormal (<20 pg/ml) in both groups and normalized (53 ±6 pg/ml) only in group 2. BMD continued to decline in group1 while improving ($p<0.01$) in group 2; BMD being significantly greater than group 1 ($p<0.01$).

Conclusion: In subjects receiving chronic prednisone therapy, low BMD is induced by multiple mechanisms: osteomalacia caused by decreased 125 OH Vit D and osteoporosis caused by matrix collagen breakdown, hypogonadism and secondary hyperparathyroidism. Role of osteomalacia is confirmed by rising BMD on substituting active 125 OH vitamin D3, Calcitriol for inactive vitamin D3, Cholecalciferol.

Key Words: *Prednisone, Osteoporosis, Osteomalacia, Low 125 OH Vitamin D, Hyperparathyroidism*

Introduction

Occurrence of a significant decline in bone mineral density (BMD) following chronic therapy with immunosuppressive agents including prednisone in subjects undergoing organ transplant is well established [1–4]. Many organizations have recommended repeatedly over last several years, use of therapeutic agents in conjunction with life style modification including appropriate weight bearing exercises as tolerated by individual subject as well as adequate daily intake of vitamin D, mostly cholecalciferol 1200 units and elemental calcium, 1200 - 1500 mg in order to prevent or improve decline in bone mineral density [5–10]. Unfortunately though, the progress in implementation of these guidelines regarding preventive and therapeutic strategies has been apparently slow and less than adequate for unclear reasons [11–20].

The decline in BMD is mainly attributed to osteoporosis secondary to bone resorption [21–25]. However, several other factors may contribute to pathogenesis. Central hypogonadism caused by suppression of hypothalamic pituitary gonadal axis by prednisone may be a contributing factor [26, 27]. Alternatively, osteomalacia caused by low circulating biologically active 125 OH vitamin D induced via inhibition of hepatic hydroxylase by Prednisone may be another major pathophysiologic contributor [28–30]. Therefore, we examined impact of administration of biologically active 125 OH vitamin D3 (Calcitriol) on BMD in subjects receiving prednisone and lack of significant (3%) improvement in low BMD (T < 2.5) despite persistent therapy with biologically inert vitamin D3 Cholecalciferol, calcium and Risedronate (Proctor and Gamble Pharmaceuticals, USA) continuously over prior 3 years.

Subjects and Methods

21 adult subjects, 17 women and 4 men with ages 45–56 years while receiving prednisone ≥10 mg daily continuously for ≥3 years were referred to Endocrinology clinic at an academic Medical Center for further assessment and management for lack of improvement in low bone mineral density assessed at 2 consecutive years despite being concurrently administered daily vitamin D3 (Cholecalciferol) 1200 units, Calcium carbonate (elemental calcium, 1200- 1500 mg) and Risedronate 5 mg. All subjects had received organ transplants, e.g. Liver, kidney or heart prior to administration of prednisone along with other immunosuppressive agents, cyclosporine and methylphenidate. All women had ceased to have menstrual cycles at the time of enrollment. Subjects being treated for chronic disorders e.g. hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, hypothyroidism etc were included if stable while receiving medications in the same daily dose for duration of at least 6 months prior to entry into the study. Exclusion criteria included hospitalization for surgery, myocardial infarction, stroke and uncontrolled diabetes mellitus during 6 months prior to entry into the study. Subjects manifesting elevated liver enzymes > 2x normal, decreased effective glomerular filtration rate < 50 ml / hour and disorders of calcium metabolism and inability to sign informed consent were excluded as well.

The subjects were divided into 2 groups. In 10 subjects, 8 women and 2 men (group 1), vitamin D3 Cholecalciferol was increased to 2000 units daily while in group 2 consisting of 11 subjects, 9 women and 2 men, Cholecalciferol was substituted by 125 OH vitamin D3 Calcitriol (Rocaltrol, Validus Pharmaceuticals, Parsippany, New Jersey, USA) 0.5 mcg daily . All subjects in both groups continued Calcium and Risedronate (Actonel, Warner Chilcott (US), LLC Rockaway, NJ 07866, USA) in the same daily doses. Subjects also continued to receive immunosuppressive drugs and other previously prescribed medications for management of other disorders in the same daily dose. Hormone replacement therapy in post menopausal women and testosterone administration in men were continued with the same formulations and the same daily dose as well. Comprehensive metabolic panels (CMP) including serum calcium, phosphorus and alkaline phosphatase as well as 25 OH Vit D and 125 OH Vit D levels were determined by local laboratory in all subjects prior to grouping and at every 6 months until the end of the period of observation. BMD was determined by DEXA using the same equipment (Hologic) at yearly interval. The subjects were followed every 3 months to ensure adherence and compliance with therapeutic recommendations as well as for adverse events.

Results

In all participants, comprehensive metabolic panels including serum urea nitrogen, creatinine, liver enzymes, electrolytes, calcium and phosphorus concentrations were all normal prior to the entry into study and remained without significant changes at 2 years. However, serum alkaline phosphatase levels were normal prior to entry and remained unaltered in all subjects in group 1 whereas they were elevated in 8 out of 11 subjects in group 2 but declined significantly in all subjects individually as well as a group. Serum 25 OH Vit D (< 20 ng/ml) were subnormal at entry into the study prior to increasing the daily dose of Cholecalciferol in group 1 and prior to change over to Calcitriol in group 2 and remained unaltered in both groups at the end of observation period of 2 years. In contrast, 125 OH Vit D levels were subnormal (< 25 pg/ml) in both groups prior to entry into study and remained subnormal in group 1 (Table1). Moreover, in subjects belonging to group 2, 125 OH Vit D concentrations normalized by 6 months and remained within normal range at 2 years (Table 1). BMD (T score) continued to decline in group1 (Table 2) whereas in group 2, BMD improved significantly from baseline within a year and the improvement was progressive till the end of the study period at 2 years (Table2). Thus, BMD in group 2 was significantly greater at both year 1 and year 2 in comparison to group 1 ($p < 0.01$).

Table 1: 25 Hydroxy (OH) Vitamin D and 125 OH vitamin D in subjects increasing Cholecalciferol daily dose (Group1) and changing to Calcitriol (Group 2)

Time in years	-2	-1	0	1	2
25 OH Vit D Group 1	20 ±3	19 ±4	22 ±5	20 ±4	24 ±5
25 OH Vit D Group 2	21 ±3	22 ±5	21 ±4	22 ±5	23 ±5
125 OH Vit D Group 1	18±2	19 ±3	18 ±3	21 ±4	21 ±5
125 OH Vit D Group 2	18±3	19 ±4	19 ±5	48 ±7*†	53 ±6*†

* $p < 0.01$ vs Group 1
† $p < 0.001$ VS 0 TIME IN Group 2

Table 2: Bone Mineral density (BMD) in subjects increasing Cholecalciferol daily dose (Group1) and changing to Calcitriol (Group 2)

Time in Years	-2	-1	0	1	2
BMD Group 1	-2.8±0.2	-3.0±0.3	-2.9±0.3	-3.1±0.3	-3.3±0.1
BMD Group 2	-2.9±0.3	-3.0±0.4	-3.1±0.3	-2.6±0.2*†	-2.3±0.1*†

* $p<0.05$ vs Time 0
† $p<0.01$ vs Group 1

Discussion

The decline in BMD in subjects receiving immunosuppressive therapy including prednisone may be attributed to multiple factors [21–30]. Enhanced catabolism of matrix collagen induced by prednisone apparently plays a major pathophysiologic role in osteoporosis as evident by increased bone resorption [21–26]. Alternatively, central hypogonadism caused by suppression of hypothalamic pituitary-gonadal axis by prednisone is also a contributing factor [27–30]. Moreover, osteomalacia due to decline in circulating biologically active 125 OH Vitamin D secondary to lowered 25 OH Vitamin D due to inhibition of hepatic 25 hydroxylase induced by prednisone may facilitate the decline in BMD [31–35]. Finally, secondary hyperparathyroidism in response to decreased active vitamin D may also promote the decline in BMD [21–26,31–35].

This study demonstrates that BMD continued to decline in subjects in group 1 despite increasing the daily dose of vitamin D3, Cholecalciferol while continuing other therapeutic strategy including drugs. This data is consistent with several previous clinical trials using same therapeutic strategies including either drugs inhibiting bone resorption or anabolic agents and vitamin D3, Cholecalciferol or its

derivative, alfacalcifedol [31,32,34–39]. In contrast, supplementation with calcitriol following substitution for Cholecalciferol improved bone mineral density markedly in our study (Table 2). Lack of improvement or even stability of BMD may be attributed to impaired generation of 25 OH vitamin D from Cholecalciferol due to inhibition of hepatic 25 hydroxylase by prednisone resulting in persistent lowering of biologically active 125 OH vitamin D concentration (Table1). Alternatively, a marked rise in biologically active125 OH vitamin D levels on administration of Calcitriol instead of cholecalciferol (Table1) may have contributed to improvement in BMD via promotion of bone mineralization and inhibition of bone resorption induced by normalization of PTH. Thus, the decline or lack of stabilization or improvement in BMD in subjects receiving prednisone is a consequence of osteomalacia and secondary hyperparathyroidism in conjunction with bone resorption caused by matrix protein catabolism and hypogonadism as described previously. In the final analysis, it is apparent that decline in BMD induced by prednisone is multi factorial and is induced by osteomalacia due to lack of adequate biologically active 125 OH Vitamin D and concurrently increased bone resorption secondary to matrix collagen breakdown induced by prednisone itself as well as exacerbation by secondary hyperparathyroidism and hypogonadism. Moreover, appropriate therapy consisting of Calcitriol and adequate calcium supplementation as well as sex hormones and antiresorptive or anabolic agents based on pathophysiology alone is likely to maintain preservation or promote improvement in BMD in subjects receiving chronic prednisone administration. Therefore, we recommend that guidelines for management of glucocorticoid induced bone disease include calcitriol for vitamin D supplementation as an integral part of a total protocol including all therapeutic modalities.

Acknowledgements: The data was presented in part at Endocrine Society's 96th Annual Meeting and Expo, June, 2014

Conflict of Interest: The author Udaya M Kabadi declares that he has no conflict of interest and no disclosures.

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Citation:
Udaya M Kabadi and Salina Esmail (2018) Improvement in Bone Density with Calcitriol Substitution for Cholecalciferol in Refractory Osteoporosis induced by Prednisone. *Endocrinol* Diabetes Metab J Volume 2(3): 1–4