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NON SUPPRESSIBLE PTH WITH VITAMIN D SUPPLEMENTATION IN NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM AND LOW 25 OH VITAMIN D

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ABSTRACT

Individuals presenting with elevated PTH, normal serum calcium and subnormal Vitamin D may not all have secondary hyperparathyroidism due to Vitamin D deficiency. Enhanced conversion of 25-hydroxyvitamin D3 (25OHD) into 1,25-dihdroxyvitamin D3 (1,25OHD) in primary hyperparathyroidism has been seen in previous studies. The purpose of this study is to assess the effect of Vitamin D supplementation on serum PTH, calcium and 25OHD concentrations in subjects manifesting subnormal Vitamin D, normal serum calcium and elevated PTH levels. **Results:** Results showed that participants fell into one of two groups; 1.) PTH lowering (95 ± 12 to 48 ± 6, $p<0.01$) in response to normalization of 25OHD levels without significantly impacting serum Calcium. 2.) Lack of PTH response to normalization of 25OHD levels and an increase in serum Calcium (9.6 ± 0.4 to 11.1 ± 0.4, $p < 0.01$). **Conclusion:** Subjects manifesting low 25 OH Vitamin D, normal calcium and elevated PTH concentrations belong to two groups; 1.) Vitamin D deficiency with secondary hyperparathyroidism; 2.) Normocalcemic primary hyperparathyroidism with low 25 OH Vit D levels secondary to enhanced conversion to 125 OH Vitamin D, documented previously in hypercalcemic primary hyperparathyroidism.

FIVE KEYWORDS: Normocalcemic, Primary, Hyperparathyroidism, Vitamin D, Deficiency.

INTRODUCTION

Calcium homeostasis is maintained, in part, by contributions from Vitamin D and parathyroid hormone (PTH). PTH raises serum Calcium levels by stimulating osteoclasts to resorb bone, freeing calcium into circulation directly.[1] It also promotes the conversion of inactive 25-hydroxyvitamin D3 (25OHD) into 1,25-dihdroxyvitamin D3 (1,25OHD) in the kidneys.[2,3] 1,25OHD further increases serum Calcium levels by increasing the transcellular absorption of Calcium and Phosphorus in the intestines.[4] 1,25OHD along with elevated serum Calcium levels act as negative regulators for release of PTH in order to maintain a tightly regulated system.[3]

PTH levels are used to name disorders in this system. Elevated levels of PTH defines hyperparathyroidism. Primary hyperparathyroidism is due to autonomous secretion of PTH from the parathyroid gland without inhibition by the physiological negative feedback loop.[5] This is typically accompanied by elevated levels of serum Calcium (1) although primary hyperparathyroidism with normal levels of serum Calcium is possible.[5] Secondary hyperparathyroidism is the elevation in PTH due to another condition that causes low serum Calcium, high serum Phosphate, or low Vitamin D.[6]

Low Vitamin D seen with elevated PTH levels can be indicative of secondary hyperparathyroidism caused by Vitamin D deficiency. However, the same laboratory values may also indicate someone with primary hyperparathyroidism and concurrent Vitamin D deficiency as these can exist simultaneously.[7] It is also important to note that Vitamin D status is typically measured by 25OHD because it has a half-life of 3 weeks as compared to the shorter 4-6 hour half-life of 1,25OHD.[8] Given the physiologic action of PTH increasing conversion of 25OHD to 1,25OHD as previously outlined, elevated PTH alone can lower 25OHD levels by enhancing peripheral conversion as documented in a recent study showing elevated levels of 1,25OHD and subnormal 25OHD in patients with primary hyperparathyroidism.[9] Thus, hypercalcemia with elevated PTH and low 25OHD may indicate

presence of primary hyperparathyroidism without a concurrent Vitamin D deficiency.

Differentiating between the causes of hyperparathyroidism is important to guide treatment steps. While both PTH and Vitamin D regulate Calcium homeostasis, they are also both important for bone health due to the resorptive properties of PTH.[10] The purpose of this study is to assess the effect of Vitamin D supplementation on serum PTH, calcium and 25OHD concentration in subjects manifesting subnormal Vitamin D, normal serum Calcium and elevated PTH levels.

SUBJECTS AND METHODS

Subjects included 22 women and 18 men between ages 31 and 64 years referred to an endocrinology clinic between 01/01/2014 and 12/31/2014 for evaluation and management of Vitamin D deficiency. Serum concentrations ofCalcium, PTH and 25OHD were determined prior to treatment. Inclusion of the study required presence of normal serum Calcium between 8.5-10.5 mg/dl, subnormal 25OHD below 30 ng/ml, and elevated PTH above 65 pg/ml. Other chemistries including serum Albumin, urea nitrogen and creatinine were within normal range. All subjects were prescribed Ergocalciferol 50,000 units twice weekly. On normalization of serum 25OHD levels at 3-4 months following vitamin D supplementation, laboratory tests were reassessed. Post treatment serum concentrations of Calcium, PTH and 25OHD were compared to pre treatment levels. All determinations are reported as mean ± SEM. Statistical analysis was conducted using Student's 't' test and analysis of variance.

RESULTS

Vitamin D supplementation resulted in two variable outcomes. In one group of participants (Group 1), Vitamin D supplementation increased 25OHD levels from pretreatment subnormal levels and suppressed PTH with no effect on serum Calcium levels (Table 1). In remaining subjects (Group 2), Vitamin D supplementation normalized subnormal 25OHD levels and induced hypercalcemia with no significant alteration in elevated PTH concentrations. (Table 2).

Table 1: Serum 25 OH Vitamin D, Calcium and PTH Concentrations in 23 subjects with Vitamin D Deficiency and Secondary Hyperparathyroidism.

	Pre Rx Vitamin D	Post Rx Vitamin D	Normal Range
25 OH Vitamin D (ng/ml)	17 ± 2	44 ± 8*	31 - 75
Calcium (mg/dl)	9.4 ± 0.3	9.3 ± 0.3	8.5 - 10.5
PTH (pg/ml)	95 ± 12	48 ± 6*	15 - 65

***Significantly different from preRx, P < 0.01**

Table 2: Serum 25 OH Vitamin D, Calcium and PTH Concentrations in 17 subjects with Primary Hyperparathyroidism and Low 25 OH Vitamin D.

	Pre Rx Vitamin D	Post Rx Vitamin D	Normal Range
25 OH Vitamin D (ng/ml)	20 ± 3	44 ± 7*	31 - 75
Calcium (mg/dl)	9.6 ± 0.4	11.1 ± 0.4*	8.5 - 10.5
PTH (pg/ml)	98 ± 14	100 ± 14	15 - 65

***Significantly different from preRx, P < 0.01**

DISCUSSION

Normocalcemic Hyperparathyroidism is often secondary to multiple causes.(1-3,5-7) These frequent disorders include vitamin D deficiency, acute or chronic renal failure, Hypercalciuria of familial variety due to renal leak or drugs such as lithium and thiazides etc.(1,3,5,6) Alternatively,, these laboratory abnormalities may be attributed to normocalcemic primary Hyperparathyroidism especially in presence of aforementioned factors. Thus, it is crucial to distinguish between secondary or primary Hyperparathyroidism in order to develop timely appropriate treatment plan. 24 hour urinary excretion, other laboratory tests and withdrawal of offending drugs are the common steps in evaluation. However, vitamin D supplementation has never been reported as a possible evaluation technique in distinguishing between secondary or primary Hyperparathyroidism.

This study demonstrates that subjects manifesting low 25OHD, normal Calcium and elevated PTH concentrations belong to two groups of subjects. In 23 subjects, (Group 1), vitamin D supplementation induced a rise in Vitamin 25OHD and a decline in PTH to normalization of both concentrations while maintaining normal serum calcium, indicating Vitamin D deficiency with secondary hyperparathyroidism. These findings confirms that PTH elevation was an appropriate response to Vitamin D deficiency to maintain normal Calcium homeostasis. In the remaining 17 subjects, (Group 2), Vitamin D supplementation resulted in normalization of 25OHD and hypercalcemia, though without a significant alteration in supernormal PTH levels, indicating presence of normocalcemic primary hyperparathyroidism. Subnormal pretreatment 25OHD levels are likely to be secondary to enhanced conversion to 1,25OH documented in a recent study.[9] This finding indicates that pretreatment supernormal PTH levels in these subjects were due to autonomous PTH secretion rather than a secondary response to low Vitamin D alone. Additionally, it is apparent that normal serum calcium, despite elevated PTH levels, was secondary concurrent

vitamin deficiency. Furthermore, hypercalcemia following vitamin D supplementation intake may be attributed to increased conversion of 25OHD to 1,25OHD induced by persistent elevation of PTH levels.[9] Thus, it is apparent that Vitamin D supplementation unmasked primary Hyperparathyroidism in these subjects.

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