Original Article

Estimation of magnesium in patients with functional hypoparathyroidism

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ABSTRACT

Context: It is evident that about 30-50% of patients with Vitamin D deficiency (VDD) do not manifest develop secondary hyperparathyroidism (SHPT). A number of theories have been proposed to explain this lack of SHPT, including hypomagnesemia. **Settings and Design:** Retrospective review of laboratory database. **Materials and Methods:** We evaluated the differences in serum magnesium (Mg) levels among those with VDD with or without SHPT. A retrospective review of 6255 laboratory data of bone mineral profiles performed in the period of 2007–2013. After excluding patients with hypercalcemia, renal dysfunction/unknown kidney function and primary hypothyroidism, the remaining 1323 patient data were analyzed. SHPT was defined as serum parathyroid hormone >65 in those with VDD. **Statistical Analysis Used:** ANOVA and Wilcoxon tests as appropriate to compare means. Multivariate logistic regression to analyze relation between variables and outcome of SHPT. **Results:** We noted that 55% patients (n = 727) had VDD, and among those who had VDD, 23% (n = 170) were hypocalcemic (corrected serum calcium <8.5). Patients with VDD who did not exhibit SHPT were 56% (n = 407). The mean (±standard deviation) serum Mg levels in the entire cohort (n = 1323) was 1.94 ± 0.26 mg/dl and 1.95 ± 0.26 mg/dl in VDD cohort and 2 ± 0.31 mg/dl in the VDD-hypocalcemic cohort. There was no statistical difference in the Mg levels among those with SHPT compared to those without SHPT (P = 0.14). Serum calcium and phosphorus were lower in those with SHPT (P = 0.06 and P < 0.001, respectively). In multivariate logistic regression, serum calcium (P = 0.043), phosphorus (P < 0.001) and severe VDD (P < 0.001) independently correlated with occurrence of SHPT in VDD. **Conclusions:** Serum Mg levels did not explain the functional hypoparathyroidism seen in about half of the patients with VDD. A low normal serum calcium and phosphorus levels are more likely to be associated with VDD patients who develop SHPT.

Key words: Calcium, hyperparathyroidism, magnesium, phosphorus, Vitamin D deficiency

Introduction

Vitamin D deficiency (VDD) has been documented across all ages and gender groups from India and different parts of the world.[1-3] Vitamin D is essential to maintain calcium homoeostasis and bone mineralization.[1] A number of studies have looked into the relationship between serum Vitamin D and parathyroid hormone (PTH) levels in the normal population and those with VDD, and it is evident from these studies that not all patients with VDD manifest an elevated PTH.[4-6] This has been termed as "functional hypoparathyroidism." About 30-50% of patients do not demonstrate secondary hyperparathyroidism (SHPT), defined as serum PTH (SPTH) >65 pg/ml, despite having a frankly low serum Vitamin D levels (defined as a level <15 ng/ml).[4,5,7] After excluding the possibility of co-existing non-PTH mediated hypercalcemia, a number of theories have been proposed to explain this functional hypoparathyroidism. They include redefining the upper normal limits of PTH levels in the normal

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population,[8] intestinal calcium absorption adaptation theory (intestinal calcistat),[9-11] circadian variations in PTH,[12] magnesium (Mg) deficiency[13] and lastly the variations in Vitamin D binding protein among population[14] and its impact on the free Vitamin D levels.

Materials and Methods

We evaluated the differences in serum Mg levels among those with VDD with or without SHPT. We studied 6255 laboratory data of bone mineral profile performed in the period of 2007-2013. A single bone mineral profile consisted of serum levels of calcium, albumin, phosphorus, Mg, alkaline phosphatase, 25-hydroxy-Vitamin D (25OHD), PTH and thyroid stimulating hormone (TSH). All samples were collected only in the fasting state and processed by the Architect systems (Abbott®) (Architect is property of Abbott Laboratories in various jurisdictions. Produced by Biokit S.A., 08186 Barcelona, Spain for Abbott Diagnostics Division; Distributed by Abbott Laboratories. ABBOTT, Max-Planck-Ring 2, 65205 Wiesbaden, Germany. Abbott Park, IL 60064 USA). Serum calcium was estimated using arsenaza III, phosphorus by phosphomolybdate, Mg by enzymatic (isocitrate dehydrogenase) methodology, alkaline phosphatase by para-nitrophenyl phosphate methodology, 25OHD and PTH by chemiluminescent microparticle immunoassay. We excluded patients with hypercalcemia (corrected serum calcium >10 mg/dl), renal dysfunction (serum creatinine >2) or unknown renal function, primary hypothyroidism (TSH >10). In the remaining 1323 patient data that was analyzed, those with VDD (defined as serum 25OHD <20 ng/ml) were further divided into those with SHPT (SPTH levels >65 pg/mL) and those without SHPT. Patients with VDD were further stratified based on 25OHD levels as mild (25OHD 11-19 ng/ml); moderate (25OHD 5-10 ng/ml) and severe (25OHD <5 ng/ml) VDD.

Statistics

Continuous variables were expressed as mean ± standard deviation (SD), median and range. Means were compared between groups using ANOVA and Wilcoxon test as appropriate. Multivariate logistic regression was used to determine the correlation between bone mineral markers and occurrence of SHPT. Statistical significance was set at a $P < 0.05$.

Results

We analyzed 1323 patient data with mean (±SD) age of 50 ± 20 years (median: 52; range: 1-93) and 67% were females. We noted that 55% patients (n = 727) had VDD, and among those who had VDD, 23% (n = 170) were hypocalcemic (corrected serum calcium <8.5). Patients with VDD who did not exhibit SHPT were 56% (n = 407) and specifically 20% (n = 82) did not have SHPT despite being hypocalcemic [Figure 1]. The mean (±SD) serum Mg levels in the entire cohort (n = 1323) was 1.94 ± 0.26 mg/dl and 1.95 ± 0.26 mg/dl in VDD cohort and 2 ± 0.31 mg/dl in the VDD-hypocalcemic cohort.

Table 1 gives a distribution and differences of bone mineral profile marker values among the various strata of patients

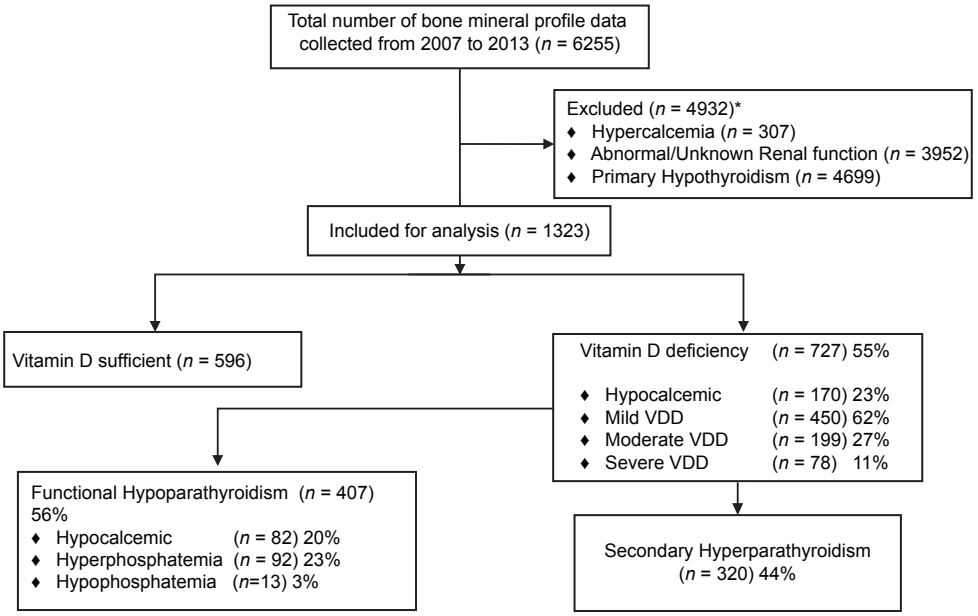

Figure 1: Consort diagram indicating the distribution of data. *Excluded groups are overlapping

Table 1: The distribution of the various bone mineral profile markers among various strata of VDD

Variables	Mild VDD (*n*=450)		Moderate VDD (*n*=199)		Severe VDD (*n*=79)		*P* (ANOVA)		
	With SHPT (*n*=165)	Without SHPT (*n*=285)	With SHPT (*n*=98)	Without SHPT (*n*=101)	With SHPT (*n*=57)	Without SHPT (*n*=21)	Comparison between the 3 strata of VDD with SHPT	Comparison between the 3 strata of VDD without SHPT	Comparison between SHPT and no SHPT
Age (years)									
Mean±SD	46.07±16.59	44.49±22.32	47.7±16.73	45.3±18.89	49.14±19.04	44.09±19.85	0.46	0.94	0.09
Median (IQR)	47 (37-58)	47 (30-61)	48 (38-60.25)	49 (34-58)	50 (38-63.5)	49 (33.5-56.5)			
Serum alkaline phosphatase									
Mean±SD	105.69±164.8	114.41±135.46	120.58±199.76	97.29±53.29	136.36±184.4	110.28±65.87	0.19*	0.79*	0.42*
Median (IQR)	83 (67-104)	87 (69-113)	85.5 (71.25-116)	88 (72-112.5)	88 (72-132.5)	88 (71.5-140)			
Serum magnesium									
Mean±SD	1.99±0.25	1.97±0.29	1.99±0.28	1.91±0.25	1.96±0.22	1.94±0.22	0.73	0.19	0.14
Median (IQR)	2 (1.8-2.17)	1.9 (1.8-2.1)	2 (1.8-2.14)	1.9 (1.7-2.1)	1.9 (1.8-2.1)	2 (1.8-2.1)			
Serum phosphorus									
Mean±SD	3.63±0.59	3.98±0.97	3.52±1.04	3.86±1.02	3.35±0.9	3.8±1.06	0.07	0.47	<0.001
Median (IQR)	3.6 (3.2-3.9)	3.9 (3.5-4.5)	3.6 (3.2-4)	3.9 (3.45-4.3)	3.5 (3-3.8)	3.8 (3.62-4.1)			
Serum PTH									
Mean±SD	97.2±42.97	41.98±13.37	125.33±88.66	45.09±12.83	178.67±186.9	44±17.67	<0.001*	0.039*	NA
Median (IQR)	82.2 (71.9-103.75)	43.2 (30.6-51.35)	97.5 (77.87-131.75)	47.7 (36.5-54.45)	123.2 (85.75-175.2)	47.5 (27.55-62.85)			
TSH									
Mean±SD	2.63±1.66	2.55±1.79	2.31±1.57	2.54±1.92	2.36±2.06	2.96±1.85	0.28	0.6	0.53
Median (IQR)	2.41 (1.55-3.39)	2.29 (1.37-3.4)	2.03 (1.31-3.18)	2.29 (0.9-3.59)	1.96 (0.88-3.22)	2.53 (1.91-3.76)			
Albumin corrected calcium									
Mean±SD	8.76±0.45	8.78±1.07	8.46±1.17	8.70±1.2	8.49±1.12	8.84±1.32	0.01	0.8	0.06
Median (IQR)	8.76 (8.49-9.09)	8.94 (8.55-9.32)	8.65 (8.41-8.98)	8.92 (8.67-9.28)	8.74 (8.38-8.95)	9.06 (8.89-9.34)			

*Wilcoxon test used. VDD: Vitamin D deficiency, SHPT: Secondary hyperparathyroidism, SD: Standard deviation, IQR: Interquartile range, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone

with VDD. Serum calcium and phosphorus were lower in patients with VDD and SHPT compared with those with VDD and no SHPT ($P = 0.06$ and $P < 0.001$ respectively). Hyperphosphatemia (>4.5 mg/dl) was noted in 23% and hypophosphatemia (<2.5 mg/dl) was noted in 3% of patients with VDD and functional hypoparathyroidism. There was no statistical difference in the Mg levels among those with SHPT and those without SHPT ($P = 0.14$) across all strata of VDD [Table 1]. Interestingly, serum alkaline phosphatase was not different in VDD patients with SHPT compared with those without SHPT. TSH levels were not significantly different amongst the groups of VDD.

A multivariate logistic regression using the markers of the bone mineral profile and outcome of SHPT, found that only serum calcium ($P < 0.043$), phosphorus ($P < 0.001$) and severe VDD ($P < 0.001$) were statistically significant related to the occurrence of SHPT.

Discussion

It has been suggested that Mg deficiency may play a role in the blunted PTH response in patients with VDD.[13] Mg deficiency, which is known to inhibit PTH synthesis/regulation related to a decrease in Mg-dependent enzyme activity.[15-17] These defects have been shown to correct within minutes following an intravenous Mg load.[17] In general, PTH-induced release of calcium from bone is substantially impaired (state of PTH resistance) when the plasma Mg concentration falls below 1 mg/dL; in comparison, diminished PTH secretion appears to require more severe hypomagnesemia. Our laboratory data analysis does not support the theory of hypomagnesemia as a possible explanation for functional hypoparathyroidism in those with VDD. Although serum Mg may not accurately reflect intracellular and tissue concentrations of Mg, none of our patients with VDD, who did not develop SHPT, have low serum Mg levels.

Dietary calcium intake and calcium absorption from the intestines are important factors that affect the rise in SPTH levels. As per our data analysis, the main difference between those who had SPTH and those who did not, were the serum values of calcium and phosphorus. It is possible that patients with VDD whose serum calcium fall below a specific threshold (in the lower limits of the normal range), exhibit the PTH rise and this PTH rise results in lowering of serum phosphorus. This supports the theory of intestinal calcistat suggested by Garg[9] to explain the relative lack of PTH rise in some patients with VDD. They hypothesize that there exist an intestinal calcistat, which controls the calcium absorption independent of PTH levels. It consists of calcium sensing receptor (CaSR) on intestinal brush border, which senses calcium in intestinal cells and Vitamin D system in intestinal cells. CaSR dampens the generation of active Vitamin D metabolite in intestinal cells and decreases active transcellular calcium transport. It also facilitates passive paracellular diffusion of calcium in the intestine. This local adaptation adjusts the fractional calcium absorption according the body requirement. They suggest that in patients with VDD who do not have SHPT, are able to maintain eucalcemia with increased calcium absorption. Patients in whom this local adaptation fails, develop SHPT.

A number of other theories have been proposed to explain this functional hypoparathyroidism. One possibility is that the upper limits of PTH provided by manufacturers could probably be too high and hence the assumption is that lowering the upper limits of normal for PTH might capture more SHPT. However, this was not proven in a study of 1824 healthy Caucasian subjects in France.[18] Other authors who have published PTH reference values in Vitamin D-replete populations found that the PTH upper limits in Vitamin D repleted population close to the current cut off.[19,20] In our data set when we lowered the cut-off of SHPT to PTH >45, about a third of patients with VDD (28%) still did not develop SHPT.

There also exists a circadian variation of PTH concentration, with a higher concentration during the late morning-early afternoon period than during early morning hours, and differences in plasma and serum values (plasma values are slightly lower than serum values) that could also affect the blood PTH levels.[12]

It has also been suggested that biological variations in Vitamin D binding protein (DBP) (particularly in African Americans),[14,21] could result in variations in levels of circulating 25OHD, but maintain normal free Vitamin D levels and hence patients with VDD who do not demonstrate PTH rise might actually have alterations in binding proteins rather than a true deficiency. However, a recent study by Ponda *et al*.[22] have shown that for Vitamin D deficient subjects undergoing repletion, total 25OHD is a true biomarker of Vitamin D activity and that DBPs levels do not appear to have an independent biologic effect.

Limitations of our study as like in any other laboratory database review includes lack of clinical information of the patient, neck surgery, their medication use, daily intake of calcium, Vitamin D and bone density data. Although we concluded that serum Mg levels did not play an important role in the functional hypoparathyroidism, the definitive test to confirm or refute our finding would be that of Mg

loading test, which is beyond the scope of this analysis. Serum creatinine <2 mg/dl was taken to indicate normal renal function, which is an over-simplification, however 10-90th centile of patients had creatinine between 0.5 and 1.1 mg/dl indicating that this assumption is unlikely to affect the results.

Conclusions

Serum Mg levels did not explain the functional hypoparathyroidism seen in about half of the patients with VDD. A low normal serum calcium and phosphorus levels are more likely to be associated with VDD patients who develop SHPT.

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