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Vitamin D_3 Deficiency is Associated with Late-Onset Hypocalcemia After Minimally Invasive Parathyroidectomy in a Vitamin D Borderline Area

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Abstract

Background Concurrent vitamin D_3 deficiency is common in primary hyperparathyroidism (pHPT). We aimed to examine the clinicopathologic features and short-term outcomes of vitamin D_3-deficient patients after minimally invasive parathyroidectomy (MIP).

Methods Over 2-year period, 80 consecutive MIP patients had preoperative-fasting 25-hydroxyvitamin D_3 ($25OHD_3$) checked. Forty-five patients had a $25OHD_3$ level <20 ng/ml and were defined as deficient. Intraoperative parathyroid hormone (IOPTH) assay was used for all MIP. Postoperative adjusted calcium (Ca) was checked at 6, 16 (with intact PTH), and 24 h. Oral calcium and vitamin D supplements were given if hypocalcemic symptoms developed or Ca < 2.00 mmol/l. Late-onset hypocalcemia (LOH) was defined as symptoms developed after 24 h.

Results Both deficient and nondeficient groups had similar demographic data and bone density scores. The deficient group had significantly higher PTH (190 vs. 121 pg/ml, $p = 0.015$). Although IOPTH in the deficient group were higher at induction and 0 min after excision, the percentage drop from induction to 10 min after excision was similar. Ca was similar at 6 and 16 h in the two groups but was significantly lower in the deficient group at 24 h (2.10 vs. 2.45 mmol/l, $p = 0.033$). At 1 week, the proportion of LOH was significantly higher in the deficient group (12/42 vs. 3/34, $p = 0.043$) and in those with preoperative PTH > 100 pg/ml (15/57 vs. 0/19, $p = 0.013$).

Conclusions Vitamin D_3 deficiency was associated with a higher preoperative PTH level and a greater risk of LOH after MIP. However, the likely cause of LOH remains unclear as both low preoperative vitamin D_3 and high PTH levels could be responsible.

Introduction

Vitamin D plays an essential role in serum calcium and parathyroid hormone (PTH) homeostasis. It regulates serum calcium level by increasing intestinal absorption, renal reabsorption, and bone mineralization, while at the same time it regulates serum PTH level by inhibiting PTH secretion from parathyroid glands [1]. It has been recognized that concurrent vitamin D deficiency is a common finding in patients with primary hyperparathyroidism (pHPT). It was previously shown that serum vitamin D < 20 ng/ml was found in more than 50% of pHPT patients [2]. A separate study also revealed that when compared with age- and sex-matched healthy controls, a significant proportion of pHPT patients suffered from vitamin D deficiency [3]. However, despite our recognition of this association, the exact causal relationship between vitamin D deficiency and pHPT remains poorly understood [4].

In vitamin D-deficient endemic areas such as Saudi Arabia, the United Arab Emirates, Turkey, India, and Lebanon, pHPT patients frequently presented with more severe clinical and biochemical manifestations such as osteitis cystica fibrosa, markedly raised calcium and PTH, and larger and heavier adenomas [5–7]. On the other hand, in relatively vitamin D-sufficient areas such as some parts of United States and Asia, the severity of pHPT was

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generally mild, and even in those patients with concurrent vitamin D deficiency, biochemical abnormalities were also mild and at times even normocalcemic [4, 8]. Hong Kong is situated at a subtropical latitude but has been shown to be a “vitamin D borderline” region [9, 10]. Despite the increased incidence of vitamin D deficiency over the last few decades, our incidence is still much lower than that reported in the West and our patients tend to suffer from a milder form of the disease [11]. Given these unresolved issues, the present study was aimed at examining the clinicopathologic features, biochemical parameters, and short-term outcomes of our vitamin D_3-deficient patients after minimally invasive parathyroidectomy (MIP) for solitary parathyroid adenoma.

Patients and methods

From July 2006 to December 2008, 96 consecutive patients underwent surgical treatment for pHPT. Fourteen patients who required bilateral neck exploration [6 had negative preoperative localization by Tc-99 m-sestamibi scan (MIBI) and/or ultrasound (USG), 2 had multiple foci on MIBI, and 6 had concomitant thyroidectomy] and two who had residual disease (1 persistent and 1 recurrent disease 8 months after MIP) were excluded from the study. Of the 80 patients who underwent MIP and remained normocalcemic at the last follow-up, there were 61 women and their median age was 58.1 (range = 31.2–87.3) years old. They were divided into vitamin D-deficient and vitamin D-sufficient groups according to whether their preoperative 25-hydroxyvitamin D_3 ($25OHD_3$) levels were less than 20 or 20 ng/ml or greater. This cutoff level was decided based on previous studies [3, 12, 13].

All patients had to have at least one positive preoperative localization study by MIBI and/or USG before they were eligible for MIP [14]. Depending on the patient’s preference, focused MIP was performed with a 2–2.5-cm skin incision under either general anesthesia or regional cervical block with intravenous sedation. Blood samples for intraoperative quick parathyroid hormone assay (IOPTH) and $25OHD_3$ were obtained by peripheral venous sampling after induction of anesthesia. IOPTH were repeated at 0 and 10 min after adenoma excision. A decline in IOPTH of more than 50% at 10 min compared with that at either induction or 0 min after excision of adenoma indicated surgical success.

Laboratory methods

Serum albumin-adjusted calcium, phosphate, alkaline phosphatase, and creatinine levels were measured in the hospital laboratory by standard methods using the Roche Diagnostics Modular Analytic system (Roche Diagnostics, Indianapolis, IN). Serum $25OHD_3$ was measured using a direct electrochemiluminescence immunoassay procedure (Roche Hitachi Elecsys 2010, Minato-ku, Tokyo, Japan), and the inter- and intra-assay coefficients of variation (CVs) were 6.6 and 4.0%, respectively. IOPTH was measured by Access® 2 immunoassay system (Beckman Coulter, Brea, CA), and the inter- and intra-assay CVs were 5.8 and 4.5%, respectively. Bone mineral density of the lumbar spine, the neck of the femur, and the forearm were measured by the DXA technique using the Hologic QDR® 4500 and Delphi™ W (Hologic, Bedford, MA). We obtained information on average daily ultraviolet index for that particular month and year from the Hong Kong Observatory website (http://www.hko.gov.hk/wxinfo/uvindex/english/euvtoday.htm) and then calculated an average monthly index.

Evaluation

Postoperative serum calcium and phosphate levels were obtained within 6 h, at 16 h, and at 24 h after MIP. Serum PTH was also measured 1 day, 1 month, 3 months, and 6 months after the operation. During postoperative hospitalization, those with hypocalcemic symptoms and/or a serum calcium level less than 2.00 mmol/l were given 2500-mg Oscal tablets twice daily and 0.25-mg Rocaltrol tablets twice daily before discharge from the hospital. For those not taking these medications, they were warned of the potential of delayed onset of hypocalcemic symptoms such as paresthesias and numbness of the fingertips and perioral area as these symptoms may occur on the third or fourth day after MIP. They were instructed to take 2500-mg Oscal tablets twice daily and 0.25-mg Rocaltrol tablets twice daily if symptoms arose. At 1 week follow-up they were specifically asked about the occurrence of delayed hypocalcemic symptoms and the requirement of medications. These events were recorded as late-onset hypocalcemia.

Statistical analysis

Continuous variables were expressed as medians with ranges, and their differences were analyzed with the Mann–Whitney test. Categorical variables were expressed in numbers with percentages, and their differences were analyzed using the χ^2 test and the Fisher exact test (when frequencies were <5). Correlation analyses were done by Pearson tests. The statistical analyses were performed using SPSS 11.5 for Windows (version 11.5.2.1, SPSS Inc., Chicago, IL). $p < 0.05$ was considered statistically significant.

Results

Table 1 compares the baseline demographics and biochemical characteristics between patients with preoperative-fasting $25OHD_3 < 20$ ng/ml (vitamin D-deficient) and those with preoperative-fasting $25OHD_3 \geq 20$ ng/ml (vitamin D-sufficient). Age, gender, and body mass index were similar for both groups. Vitamin D-deficient patients had a significantly higher median preoperative PTH (190 vs. 121 pg/ml, $p = 0.015$) level than that of vitamin D-sufficient patients. Preoperative serum calcium, phosphate, creatinine, alkaline phosphatase, and 24-h urinary calcium levels were similar for both groups. Preoperative bone mineral density scores were available for 40 (88.9%) vitamin D-deficient patients and 25 (71.4%) vitamin D-sufficient patients. The severity of bone disease was not different on the basis of median *t* scores and alkaline phosphatase level in the two patient groups.

The average serum $25OHD_3$ in a particular month of the year was recorded. Figure 1 depicts the monthly variation of serum $25OHD_3$ levels in relation to the average monthly ultraviolet index in our locality. A significant correlation between serum $25OHD_3$ and ultraviolet index was found in our patient cohort ($R = 0.365$, $p = 0.045$). The average monthly ultraviolet index appeared to peak in the summer season and bottom in the winter season, while there seemed to be a 1-2-month lag between the ultraviolet index and the average serum $25OHD_3$ level in our patient cohort.

Table 2 compares the intraoperative findings between the two groups of patients. Both the adenoma weight and operating times were similar. Similar to preoperative PTH levels, the IOPTH level at induction was also significantly higher in patients in the vitamin D-deficient group. Although the IOPTH at 0 min after excision was significantly higher in the vitamin D-deficient group, the IOPTH at 10 min after excision and the percentage drop from preincision to 10 min after excision were similar in the two groups ($p = 0.733$).

Table 3 compares the postoperative outcomes after MIP between the two groups of patients. The postoperative adjusted calcium levels both within 6 h and at 16 h after MIP were comparable between the two groups. Three patients (6.7%) in the $25OHD_3$ <20 ng/ml group and one patient (2.9%) in the $25OHD_3 \geq 20$ ng/ml group developed symptomatic hypocalcemia within 24 h after MIP (early-onset) and required oral Oscal and Rocaltrol tablets. The early-onset symptomatic hypocalcemia rates were similar in the two groups ($p = 0.628$). All patients were discharged within 24 h after MIP. At 1-week follow-up, in addition to the 4 patients with early-onset hypocalcaemia, 12 patients (28.6%) in the vitamin D-deficient group and 3 patients in the sufficient group reported late-onset hypocalcemic symptoms and took Oscal and Rocaltrol tablets at home. The late-onset symptomatic hypocalcemia rates were significantly different between the two groups (12/42 vs. 3/34, $p = 0.043$). However, the proportion of vitamin D deficiency and late-onset hypocalcemia were also significantly higher in those with preoperative PTH > 100 pg/ml [40/60 vs. 6/14 ($p = 0.026$) and 15/57 vs. 0/19 ($p = 0.013$), respectively]. Due to the relatively few cases of late-onset hypocalcemia after MIP, neither factors turned out to be significant in the logistic regression analysis for

Table 1 Comparison of baseline demographics and biochemical characteristics of those with preoperative-fasting 25-hydroxyvitamin $D_3 < 20$ and ≥ 20 ng/ml

	$25OHD_3 < 20$ ng/ml ($n = 45$)	$25OHD_3 \geq 20$ ng/ml ($n = 35$)	*p* Value
Age of operation (years)	59.0 (31.2–86.8)	57.5 (33.1–80.2)	0.491
Gender (male/female)	10/35	9/26	0.834
Body mass index (kg/m^2)	23.7 (15.2–33.4)	23.5 (19.8–42.8)	0.717
Preoperative highest adjusted serum calcium level (mmol/l)	2.86 (2.55–4.02)	2.81 (2.66–3.07)	0.093
Preoperative lowest phosphate level (mmol/l)	0.79 (0.41–1.05)	0.80 (0.39–1.09)	0.624
Preoperative highest PTH (pg/ml)	190 (59–1327)	121 (43–590)	**0.015**
Preoperative highest creatinine level (umol/l)	72.0 (36.0–142.0)	77.5 (41.0–235.0)	0.281
Preoperative highest serum alkaline phosphatase (U/l)	107 (26–243)	109 (42–235)	0.959
Preoperative 24-h urine calcium (mmol/day)	6.2 (1.8–17.9)	6.10 (1.6–12.2)	0.258
Preoperative $25OHD_3$ (ng/ml)	14.9 (5.5–19.42)	25.0 (20.2–84.3)	**<0.001**
Preoperative bone mineral density, *t* score			
Forearm	−1.75 (−5.10–1.20)	−2.20 (−5.30–0.20)	0.964
Lumbar	−1.50 (−5.20–0.40)	−1.60 (−3.60–0.70)	0.592
Femur	−1.45 (−3.9–0.20)	−1.70 (−3.60–0.20)	0.782

Continuous variables are expressed as median (range); categorical variables are expressed as number (percentage)

$25OHD_3$ = 25-hydroxyvitamin D_3

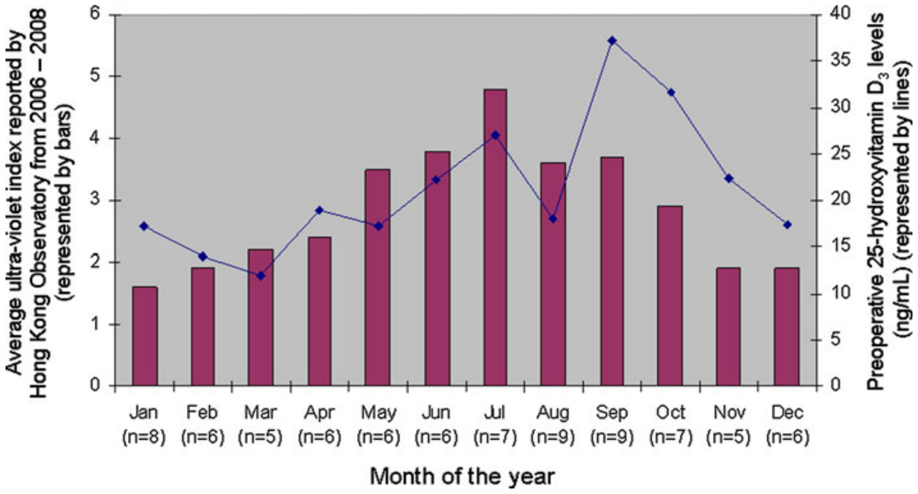

Fig. 1 Monthly variation of serum 25-hydroxyvitamin D$_3$ levels in relation to the average monthly ultraviolet index in our locality

Table 2 Comparison of intraoperative findings of those with vitamin D$_3$ < 20 and ≥ 20 ng/ml

	25OHD$_3$ < 20 ng/ml (n = 45)	25OHD$_3$ ≥ 20 ng/ml (n = 35)	p Value
Adenoma weight (mg)	530 (120–5000)	400 (130–4700)	0.219
Operating time (min)	55.0 (27.2–123.7)	69.8 (40.2–113.2)	0.159
IOPTH (pg/ml)			
Preincision	153.2 (54.3–710.3)	103.8 (29.2–366.5)	**0.043**
0 min after excision	89.9 (41.6–280.0)	58.1 (9.9–641.7)	**0.018**
10 min after excision	41.4 (11.4–127.5)	30.0 (6.7–220.5)	0.149
% drop (0-10 min)	57.8 (0.1–83.0)	35.6 (23.2–68.2)	**0.005**
% drop (induction to 10 min)	78.0 (6.71–92.9)	70.2 (13.71–88.54)	0.733

Continuous variables are expressed as median (range); categorical variables are expressed as number (percentage)

25OHD$_3$ = 25-hydroxyvitamin D$_3$; IOPTH = quick intraoperative parathyroid hormone level

late-onset hypocalcemia (data not shown). The postoperative intact PTH levels at day 1, 3 months, and 6 months were comparable between the vitamin D-deficient and vitamin D-sufficient groups.

Discussion

Marked global geographic differences in serum vitamin D are attributed not only to differences in geographic latitude and daily ultraviolet exposure, but also to a multitude of factors including clothing habits, urbanization level, and dietary intake [1]. Although Hong Kong is located at the subtropical latitude of 22.3°N, it has been recognized as a "vitamin D borderline" region due to increased urbanization, increased level of air pollution, and changing perceptions and attitudes toward sunlight exposure [9, 10]. In a recent study of 382 community-dwelling southern Chinese over 50 years old, 22.5% were found to have a serum 25(OH) vitamin D level of less than 20 ng/ml [9]. However, this condition is even more common in pHPT patients, especially in the elderly [2, 3]. This is at least partly attributed to the metabolic sequela of inherent excessive parathyroid hormone (PTH) that can convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [15, 16]. Despite our awareness of the coexistence of these relatively common conditions, the implication of a low vitamin D level in patients with pHPT remains unclear [4]. In a vitamin D-deficient endemic area, patients with pHPT tended to suffer from a severe from of the disease, including frequent bone involvement, higher preoperative calcium and PTH levels, and larger adenomas excised. In vitamin D-sufficient areas such as most parts of United States and some Western countries, pHPT patients suffer from an asymptomatic form with milder biochemical abnormalities and/or even normocalcemia [8]. One explanation for the mild biochemical disturbance might be that vitamin D actually opposes the biological effect of PTH in increasing serum and urinary Ca levels [8]. As a result, a reduced vitamin D level has led to diagnostic uncertainty and underestimation of pHPT prevalence in certain countries [8, 17]. Our present study examined the impact of vitamin D deficiency on clinicopathological and biochemical parameters as well as on short-term outcome of

Table 3 Comparison of postoperative outcomes after minimally invasive parathyroidectomy of those with preoperative-fasting vitamin $D_3 < 20$ and ≥ 20 ng/ml

	$25OHD_3 < 20$ ng/ml ($n = 45$)	$25OHD_3 \geq 20$ ng/ml ($n = 35$)	p Value
Adjusted calcium within 6 h after MIP (mmol/l)	2.53 (2.11–3.18)	2.57 (2.31–2.81)	0.462
Adjusted calcium at 16 h after MIP (mmol/l)	2.36 (2.09–2.83)	2.38 (2.14–2.71)	0.851
Adjusted calcium at 24 h after MIP (mmol/l)	2.15 (1.98–2.58)	2.45 (2.17–2.54)	**0.033**
Number of early-onset symptomatic hypocalcemia	3/45 (6.7)	1/35 (2.9)	0.628
Number of early late-onset symptomatic hypocalcemia	12/42 (28.6)[a]	3/34 (8.8)[a]	**0.043**
Postoperative day 1 PTH (pg/ml)	18.0 (<3.0–94.0)	19.0 (< 3.0–185.0)	0.873
Postoperative 3-month PTH (pg/ml)	51.0 (10.0–175.0)	57.0 (33.0–245.0)	0.788
Postoperative 6-month PTH (pg/ml)	51.0 (6.0–177.0)	41.0 (23.0–275.0)	0.509

Continuous variables are expressed as median (range); categorical variables are expressed as number (percentage)

[a] Three patients in the vitamin $D_3 < 20$ ng/ml group and 1 patient in the vitamin $D_3 \geq 20$ ng/ml group were excluded because they had early-onset symptomatic hypocalcemia before hospital discharge

pHPT patients who underwent MIP in a vitamin D borderline area.

The present study found that vitamin D deficiency ($25OHD_3 < 20$ ng/ml) was common, occurring in 56.3% (or 45/80) pHPT patients. Silverberg et al. [2] observed that 53% of their pHPT patients had serum $25OHD_3 < 20$ ng/ml, and Moosgaard et al. [3] similarly found that when compared with age- and sex-matched healthy individuals, a significantly higher incidence of vitamin D deficiency was found in pHPT patients.

In terms of association between preoperative biochemical and pathological parameters and $25OHD_3$ levels, the preoperative PTH level was observed to be significantly higher in pHPT patients with $25OHD_3 < 20$ ng/ml than those with $25OHD_3 \geq 20$ ng/ml. In contrast to other recent surgical series, associations between alkaline phosphatase, weight of adenomas, urinary Ca, and preoperative vitamin D level were not found [12, 18]. Perhaps, one possible explanation for such a difference might be that in these studies vitamin D deficiency was more severe, and, in fact, their mean vitamin D level appeared to be significantly lower than ours (mean level of 9.2 vs. 14.0 ng/ml). This would result in more extreme biochemical and pathological abnormalities in the vitamin D-deficient group. In our locality, with increased detection of pHPT as a result of a wider routine application of the multichannel autoanalyzer, severe clinical manifestations such as significant bone involvement (as indicated by raised alkaline phosphatase level and low *t* scores) have become a rare occurrence [11]. Furthermore, both the weight and the size of parathyroid adenomas had not been consistently shown to be closely associated with the preoperative vitamin D level in mild pHPT. Some have postulated that perhaps the vitamin D level might be more closely related to the amount of PTH secretion per unit of parathyroid gland volume than the absolute parathyroid size [3, 19].

With reference to the postoperative changes in calcium kinetics, there seemed to be no significant difference in the decline of calcium within the first 16 h after MIP in both $25OHD_3$-sufficient and $25OHD_3$-deficient groups and the incidence of early-onset hypocalcemia was similar between the two groups (6.7 vs. 2.9%, $p = 0.628$). However, the postoperative calcium level was significantly lower at 24 h after MIP and the incidence of late-onset symptomatic hypocalcemia was significantly higher in the $25OHD_3$-deficient group (28.6 vs. 8.8%, $p = 0.043$). In other words, patients with preoperative $25OHD_3 < 20$ ng/ml were more likely to report late-onset symptomatic hypocalcemia. Stewart et al. [20] reported a similar finding when their patients were assessed for hypocalcemia by phone conversation or clinic visits for the first 10 postoperative days. Ozbey et al. [18] reported that pHPT patients with preoperative vitamin $D < 15$ ng/ml had more frequent symptomatic hypocalcemia and this led to prolonged hospitalization. One of the shortcomings of our study was that since patients were routinely discharged within 24 h after MIP and patients were instructed to take the oral calcium for symptomatic hypocalcemia at home, we could not be certain whether these late-onset hypocalcemic episodes were indeed accompanied by biochemical hypocalcemia.

On the other hand, in contrast to other studies that did not observe any association between preoperative PTH level and postoperative hypocalcemia, our study showed that pHPT patients with a high PTH level were more likely to suffer late-onset hypocalcemia [20, 21]. Although vitamin D-deficient patients with pHPT were more likely to have late-onset symptomatic hypocalcaemia, a preoperative elevated PTH level of greater than 100 pg/ml was also associated with the same phenomenon. Because of the relatively few patients who had late-onset hypocalcemia in our study, it was not possible to separate the effects of vitamin D deficiency and high PTH on hypocalcemia.

Therefore, the exact cause of late-onset symptomatic hypocalcaemia remains unclear as it could be attributed to either vitamin D deficiency, significant pHPT with a high PTH level, or both. Perhaps future studies could focus on these two factors and examine their causal relationship with late-onset hypocalcemia.

Conclusions

Those pHPT patients with concurrent vitamin D_3 deficiency had a significantly higher preoperative PTH level and a greater chance of reporting late-onset symptomatic hypocalcemia after MIP. However, the likely cause of late-onset hypocalcemia remains unclear as both low preoperative vitamin D_3 and high PTH levels could be responsible.

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