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Vitamin D Insufficiency in Patients With THA

Prevalence and Effects on Outcome

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Abstract

Background The consequences of vitamin D insufficiency in the elderly remain controversial. The prevalence and potential effects of its chronic insufficiency on quality of life and physical function in patients undergoing THA have received little attention.

Question/purposes We determined (1) prevalence of preoperative vitamin D insufficiency in patients undergoing THA and (2) relationships of insufficiency to patient-perceived outcomes (PPOs) and hip scores.

Methods We retrospectively reviewed 62 consecutive patients who underwent 66 primary THAs. We excluded two patients with missing data and the second hip of bilateral THAs, leaving 60 patients (60 hips) for final inclusion. Based on preoperative plasma 25-hydroxyvitamin-D3 levels, patients were retrospectively assigned into a normal or insufficient group. We used two different thresholds (20 and 30 ng/mL) to define insufficiency; groups were set twice. We compared demographics, BMI, American Society of Anesthesiologists score, Charlson Comorbidity Index; albumin, transferrin, calcium levels; and total lymphocyte count between groups. The insufficient group had a higher mean BMI with the 20-ng/mL cutoff but not with the 30-ng/mL cutoff. We compared the 20-ng/mL cutoff groups (adjusting for BMI) and the 30-ng/mL cutoff groups in terms of preoperative and postoperative Quality of Well-being Scale, SF-36, WOMAC, Harris hip, and Merle d'Aubigné-Postel scores. Mean followup was 11 months (range, 3–24 months).

Results The prevalence of vitamin D insufficiency was 30% (using 20 ng/mL) and 65% (using 30 ng/mL). Preoperative and postoperative Harris hip and Merle d'Aubigné-Postel scores were lower in patients with

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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insufficiency using 30 ng/mL. No differences in PPOs or hip scores were found using 20 ng/mL.

Conclusions Hypovitaminosis D was common in patients with THA and associated with lower hip scores. Standardization of the definition of hypovitaminosis D is urgently needed so that further studies can properly evaluate its real prevalence, potential negative effects on function, and therapeutic effects of reversing insufficiency before THA.

Level of Evidence Level III, therapeutic study. See the Instructions for Authors for a complete description of levels of evidence.

Introduction

Vitamin D is obtained from solar ultraviolet B radiation, diet, and dietary supplements. Fortified milk and breakfast cereals represent the major dietary sources of vitamin D in US and Canadian diets [18]. In the skin, solar radiation converts 7-dehydrocholesterol to previtamin-D3, which is transformed to vitamin-D3 (cholecalciferol). Vitamin-D3 from the diet and skin is then transported to the liver where it is metabolized to 25-hydroxyvitamin-D3 (calcifediol); then it is metabolized in the kidneys to its active form, 1,25-dihydroxyvitamin-D3 (calcitriol). Afterwards, activated vitamin D binds to a single nuclear receptor (vitamin D receptor) that subsequently attaches to specific zones of DNA [17, 18]. Production of 1,25-dihydroxyvitamin-D3 in the kidney is regulated by plasma parathyroid hormone levels, serum calcium, and phosphorus levels [11, 18, 23].

Vitamin D plays a key role in calcium homeostasis and bone turnover. It has also been implicated in the risk of overall mortality [26], cancer [19, 21, 26], diabetes [21, 26], musculoskeletal disorders [16, 26], hypertension [21, 26], heart disease [21, 26], multiple sclerosis [19], stroke [21], and even falls [4, 8, 20]. Recent epidemiologic data suggest a widespread deficiency of vitamin D [13, 18]. It has been estimated that 1 billion people worldwide have subnormal levels of this nutrient [11]. However, a recent report of the Institute of Medicine states that most persons in the United States and Canada are getting enough vitamin D and calcium to maintain bone health [22]. There is no consensus on the actual prevalence of its subnormal levels (insufficiency or deficiency) primarily because there is no consensus on what levels should be considered the low end of the normal range [22]. Calcifediol is the serum marker commonly used to determine a patient's vitamin D status [11, 16, 23] and is the one we studied in the current investigation. The Institute of Medicine, which is the institution that proposes dietary reference intakes for calcium and vitamin D, considers 25-hydroxyvitamin-D3 serum levels of 20 ng/mL or more as normal [21, 22]. In contrast, the International Osteoporosis Foundation, Osteoporosis Canada, and many authors consider 30 ng/mL to be the lowest normal value based on responses of parathyroid hormone and optimal calcium reabsorption to vitamin D levels [18]. Disagreement exists today not only about the controversial associations of vitamin D deficiency with many pathologic conditions but also about its true prevalence in the general population. Even though hypovitaminosis D is the accepted term for insufficient or deficient levels [18], in view of the current lack of consensus on what level defines the low end of the normal range (and much more on the derived terms), we will refer to all patients with subnormal levels as patients with insufficiency for the sake of simplicity. What appears clear is that this vitamin is associated with a number of diseases [16, 18, 26] and, in some reports, with poorer results after surgery [14, 15, 18]; however, findings on the latter point have varied among studies [24, 25].

Accordingly, we determined (1) the prevalence of preoperative vitamin D insufficiency in patients undergoing primary THA and (2) the relationships of vitamin D insufficiency to preoperative and postoperative patient-perceived outcomes (PPOs) and clinical hip scores. We hypothesize that patients with normal levels have better PPOs and hip scores than patients with insufficiency.

Patients and Methods

We retrospectively reviewed 66 consecutive primary THAs performed in 62 patients from June 2010 to November 2011. The inclusion criterion was exclusively patients having primary THA. We excluded two patients who had no data available and the second hip of four bilateral THAs, resulting in the final inclusion for statistical analysis of 60 patients who underwent 60 primary hips. All surgeries were performed by the senior author (CJL) at a single institution using cementless total hip prostheses. Surgeries were performed through a modified Hardinge direct lateral approach. Most patients were discharged to home within 3 to 4 days in the absence of complications. Patients were seen by the senior author during the second and sixth postoperative week for clinical evaluation. All patients were managed by an internist. Some of the internists chose to not treat the patients with low vitamin D, based on their own preference. Patients were not actually experiencing symptoms of vitamin D deprivation. All included patients provided informed consent for this institutional review board-approved study.

During the study period, serum plasma levels of 25-hydroxyvitamin-D3 were routinely collected in all patients scheduled for a primary THA. The inpatient charts of patients included in the study were reviewed to collect data. Demographic and clinical data collected included age, sex (female/male), race (black/white), ethnicity (Hispanic/non-Hispanic), BMI, American Society of Anesthesiologists (ASA) score [1, 2], and Charlson Comorbidity Index [6]. Albumin, transferrin, calcium, and total lymphocyte count were also noted. The hospital laboratory employed high-performance liquid chromatography to determine 25-hydroxyvitamin-D3 levels; standard automated laboratory methods were used for the other tests. Only preoperative laboratory data were collected and analyzed. Serum levels of 25-hydroxyvitamin-D3 were then used to determine patients with insufficiency and patients without it; the other markers were used to establish the nutritional baseline status of the patients. At our institution, PPOs and clinical hip scores are routinely collected in a prospective fashion (in a joint registry database) both preoperatively and postoperatively at 3 months, 6 months, 1 year, and annually thereafter. Preoperative and postoperative PPOs and hip scores were consequently recorded prospectively in our joint registry database but retrospectively studied. PPOs included the Quality of Well-being Scale (QWB-7) total score [12]; the physical function, role physical, bodily pain, general health scales, and physical health summary score, as well as the vitality, social functioning, role emotional, mental health scales, and mental health summary score of the SF-36 [1, 2]; and the physical function, pain, stiffness, and total scores of the WOMAC [3]. Hip scores included the Harris hip score (HHS) [10] and the Merle d'Aubigné-Postel hip score [7].

After a review of the literature on the subject, we used the two values most commonly used in publications performed in major orthopaedic and medical journals to define the low end of the normal range for 25-hydroxyvitamin-D3 serum levels: (1) 20 ng/mL or more [11, 18, 21, 22] and (2) 30 ng/mL or more [18]. The Institute of Medicine considers levels of 20 ng/mL or more as normal [21, 22] while the International Osteoporosis Foundation and Osteoporosis Canada consider 30 ng/mL to be the lowest normal value [18]. For each definition of normal levels, patients were stratified into two groups: those with normal levels and those with insufficiency. Using 20 ng/mL as the low end of the normal range, 42 patients had normal levels and 18 patients were insufficient. Using 30 ng/mL instead, 21 patients had normal levels and 39 patients were insufficient. To determine differences in baseline patient characteristics, the demographics, comorbidity scores, and nutritional laboratory serum markers were compared between groups (groups set twice, one instance for each cutoff value used). We also investigated the associations of preoperative vitamin D insufficiency with preoperative and postoperative PPOs and hip scores. Minimum followup was 3 months (average, 11 months; range, 3–24 months).

Statistical analyses were performed using SPSS® software (Version 16.0; IBM Corp, Armonk, NY, USA). Percentages were used to describe the prevalence of vitamin D insufficiency. Crosstabulation, Pearson chi-square, and Fisher exact tests were used to assess for differences between the insufficient and normal groups in terms of sex, race, ethnicity, ASA score; serum albumin, transferrin, calcium levels; and total lymphocyte count. Independent t-tests assessed for differences between groups in terms of age, BMI, and Charlson Comorbidity Index. In the initial analysis, mean BMI was found to be significantly different between the normal and insufficient groups set using the 20-ng/mL cutoff (34 [range, 21–53] versus 27 [range, 18–40]; $p < 0.001$). However, mean BMI was not significantly different between groups set using the 30-ng/mL cutoff (30 [range, 18–53] versus 27 [range, 22–40]; $p = 0.096$]. All other baseline patient characteristics (demographics, comorbidities, nutritional serum markers) were not significantly different between groups regardless of the cutoff value used (Table 1). Therefore, we assessed differences in PPOs and hip scores using multivariate analysis of covariance (MANCOVA) adjusting for BMI between groups set using the 20-ng/mL threshold and using independent t-tests between groups set using the 30-ng/mL threshold. This analysis was completed for preoperative and postoperative evaluations. A p value of less than 0.05 was considered statistically significant. For each variable, analysis was made on available data.

Results

The prevalence of vitamin D insufficiency in our patients was 30% (18 of 60; using the 20-ng/mL threshold) and 65% (39 of 60; using the 30-ng/mL threshold).

Hypovitaminosis D was associated with lower clinical hip scores only when the groups were set using the 30-ng/mL threshold. Using 20 ng/mL to set the groups, we found no significant differences in preoperative PPOs or hip scores between groups. However, when the groups were set by 30 ng/mL, we found that patients with insufficiency had a lower mean HHS (43 versus 52; $p = 0.035$) and a lower mean Merle d'Aubigné-Postel score (10 versus 12; $p = 0.007$) preoperatively than patients with normal levels (Table 2). Using 20 ng/mL as the low end of the normal range, we found no significant differences in postoperative PPOs or hip scores between groups. However, when we used the 30-ng/mL threshold instead, patients with insufficiency had a lower mean HHS (83 versus 92; $p = 0.002$) and a lower mean Merle d'Aubigné-Postel score (14 versus 17; $p < 0.001$) postoperatively than patients with normal levels (Table 3).

Table 1. Demographic, comorbidities, and baseline nutritional serum markers comparisons between patients with and without vitamin D insufficiency (groups set by each threshold)

Dependent measure	Insufficiency threshold set at 20 ng/mL			Insufficiency threshold set at 30 ng/mL		
	Insufficient group (n = 18)	Normal group (n = 42)	p value*	Insufficient group (n = 39)	Normal group (n = 21)	p value*
Mean age (years)	69	71	0.584	70	70	0.901
Sex (female/male) (number of patients)	16/2	32/10	0.317	32/7	16/5	0.737
Race (white/black) (number of patients)	16/2	41/1	0.212	37/2	20/1	1.000
Ethnicity (Hispanic/non-Hispanic) (number of patients)	13/5	29/13	1.000	29/10	13/8	0.381
BMI (kg/m^2)	34	27	< 0.001	30	27	0.096
Mean Charlson Comorbidity Index	1.61	1.38	0.576	1.44	1.48	0.919
ASA grade (number of patients)						
1	0	1	0.733	1	0	0.746
2	8	19	0.733	17	10	0.746
3	9	17	0.733	17	9	0.746
Hypoalbuminemia (%)	0	0	†	0	0	†
Subnormal transferrin (%)	40	15	0.068	28	11	0.183
Subnormal total lymphocyte count (%)	19	31	0.510	22	37	0.341
Hypocalcemia (%)	0	0	†	0	0	†

* Independent t-tests were used for numerical data and Pearson chi-square or Fisher's exact test for categorical data; †no statistics could be computed; ASA = American Society of Anesthesiologists; hypoalbuminemia = serum level of < 3.5 g/dL; subnormal transferrin = serum level of < 226 mg/dL; subnormal total lymphocyte count = a count of < 1500/mm; hypocalcemia = serum calcium level of < 8.22 mg/dL.

Table 2. Comparison of preoperative patient-perceived outcomes and clinical hip scores between patients with and without vitamin D insufficiency (groups set by each threshold)

Dependent measure	Insufficiency threshold set at 20 ng/mL			Insufficiency threshold set at 30 ng/mL		
	Insufficient group (n = 18)	Normal group (n = 42)	p value*	Insufficient group (n = 39)	Normal group (n = 21)	p value†
QWB-7 total score (points)	0.525 ± 0.05	0.531 ± 0.04	0.837	0.523 ± 0.04	0.538 ± 0.04	0.185
SF-36 physical component summary score (points)	21 ± 5	22 ± 4	0.841	22 ± 5	22 ± 6	0.757
SF-36 mental component summary score (points)	58 ± 9	60 ± 7	0.280	59 ± 8	60 ± 8	0.558
WOMAC total score (points)	57 ± 14	58 ± 15	0.480	59 ± 15	54 ± 19	0.306
Harris hip score (points)	40 ± 17	49 ± 15	0.316	43 ± 15	52 ± 15	0.035
Merle d'Aubigné-Postel hip score (points)	9 ± 3	11 ± 3	0.414	10 ± 3	12 ± 3	0.007

Values are expressed as mean ± SD; * multivariate analysis of covariance was used to adjust for BMI and compare the groups set using the 20-ng/mL cutoff; †independent t-tests were used to compare the groups set using the 30-ng/mL cutoff; QWB-7 = Quality of Well-Being Index.

Discussion

Although the primary function of vitamin D is to maintain serum calcium homeostasis, it has also been associated with disease and poor results after surgery [8, 18–21, 26]. Controversy exists on the actual prevalence of vitamin D insufficiency worldwide in large measure because of the lack of consensus on how to define adequate serum levels of 25-hydroxyvitamin-D3 [22]. Further, the results on diseases or medical conditions (ie, fractures, falls, etc) of vitamin D supplementation alone or combined with calcium have not been consistent [8, 9]. Using two definitions

Table 3. Comparison of postoperative patient-perceived outcomes and clinical hip scores between patients with and without vitamin D insufficiency (groups set by each threshold)

Dependent measure	Insufficiency threshold set at 20 ng/mL			Insufficiency threshold set at 30 ng/mL		
	Insufficient group (n = 18)	Normal group (n = 42)	p value*	Insufficient group (n = 39)	Normal group (n = 21)	p value†
QWB-7 total score (points)	0.549 ± 0.04	0.577 ± 0.08	0.378	0.602 ± 0.12	0.587 ± 0.1	0.772
SF-36 physical component summary score (points)	42 ± 6	42 ± 5	0.385	45 ± 4	40 ± 7	0.103
SF-36 mental component summary score (points)	55 ± 1	55 ± 3	0.395	55 ± 2	56 ± 3	0.307
WOMAC total score (points)	2 ± 0	4 ± 4	0.717	4 ± 4	3 ± 3	0.478
Harris hip score (points)	85 ± 6	89 ± 10	0.334	83 ± 9	92 ± 6	0.002
Merle d'Aubigné-Postel hip score (points)	14 ± 4	16 ± 2	0.257	14 ± 3	17 ± 2	< 0.001

Values are expressed as mean ± SD; * multivariate analysis of covariance was used to adjust for BMI and compare the groups set using the 20-ng/mL cutoff; †independent t-tests were used to compare the groups set using the 30-ng/mL cutoff; QWB-7 = Quality of Well-Being Index.

of normal vitamin D levels, one employed by the Institute of Medicine [21, 22] (≥ 20 ng/mL) and the other recommended by The International Osteoporosis Foundation and Osteoporosis Canada (≥ 30 ng/mL) [18], we determined (1) the prevalence of preoperative vitamin D insufficiency in patients undergoing primary THA and (2) the relationships of vitamin D insufficiency to preoperative and postoperative PPOs and clinical hip scores.

Our results should be interpreted in light of several limitations. First, this is a retrospective study. The clinical scores were collected prospectively, but the research questions were posed retrospectively, raising the concern in particular for selection bias. However, the initial sample reviewed was consecutive and for the analyses we only dropped two patients without data and the second hip of four bilateral THAs to keep the key assumption of independent observations. Second, we found preoperatively that BMI was significantly different between the insufficient and normal groups set using the 20-ng/mL threshold, suggesting BMI may be a confounding variable. This was not the case using the 30-ng/mL threshold. To mitigate the possible effect of this confounder, we performed comparisons in terms of PPOs and hip scores between groups based on the 20-ng/mL threshold using MANCOVA adjusting for BMI. Finally, the current lack of consensus on the definition of what the normal serum 25-hydroxyvitamin-D3 levels are makes all research on the subject somewhat confusing and hard to compare. We opted to use the low end of the normal range employed by the Institute of Medicine (≥ 20 ng/mL) [21, 22] and the one recommended by The International Osteoporosis Foundation and Osteoporosis Canada (≥ 30 ng/mL) [18] due to the influential effect of these institutions on the subject.

Regarding the prevalence of vitamin D insufficiency, 30% of our patients had insufficiency using the 20-ng/mL cutoff; this number increased to 65% when we used the 30-ng/mL cutoff. Our findings are in agreement with the literature [5, 15, 18, 24, 25]. Bogunovic et al. [5] (using a 32-ng/mL cutoff) found that 43% of patients undergoing orthopaedic surgery had subnormal levels. Unnanuntana et al. [25] also found that 46.6% of patients undergoing THA had hypovitaminosis. Evidently, the insufficiency of vitamin D in patients who undergo THA is fairly prevalent, regardless of the threshold value used. We were surprised by the high prevalence found in our study given that the current investigation took place in south Florida, which has many sunny days. We could only speculate that most probably dietary issues could have played a role and be responsible for such high numbers. Regarding insufficiency and baseline patient characteristics, our patients with insufficiency had higher BMI (using the 20-ng/mL threshold). This particular finding agrees with previous reports [5, 13, 24, 25]. However, in contrast to previous reports, we did not find associations between insufficiency and any other baseline patient characteristic (age, sex, race, comorbidities) (regardless of the threshold used) [5, 24, 25]. Bogunovic et al. [5] found that patients between the ages of 18 and 50 years were at more risk of having inadequate vitamin D levels ($p = 0.018$), as well as male sex and patients with darker skin tone (black and Hispanics) ($p < 0.001$ for both). Unnanuntana et al. [25] found that there were more women with normal levels and more men with subnormal levels ($p = 0.008$). Unnanuntana et al. [24], in a separate study of three groups (deficiency, insufficiency, and normal), found that the proportion of patients who had an ASA score of 3 or 4 was significantly higher in patients with deficiency (52.9%, 22.6%, and 23.9%, respectively, $p = 0.032$). We only found associations with BMI. We speculate that insufficiency and BMI were associated in our study because both may be the end result of an unbalanced diet in our predominantly Hispanic population. In other studies, however, the lack of sunny days and not dietary issues might have been responsible. We had no patients with ASA 4 and this might explain the lack of significant associations in this regard in the current investigation.

In our study, we found a fairly consistent association between hypovitaminosis D and lower hip scores only in the groups set using the 30-ng/mL threshold. Our insufficient and normal groups were not significantly different in terms of PPOs regardless of the threshold used. The main conclusion from this is that different definitions of normal levels led to different results and a clear definition of the low end of the normal range is urgently needed. Keeping this in mind, however, our results are in agreement with those of Unnanuntana et al. [25] who in patients undergoing THA found no significant differences in the SF-36 physical function domains between subnormal and normal patients (using 30 ng/mL as the threshold). Regarding the HHS, our results also agree with those of Nawabi et al. [15] who studied 62 consecutive patients with THA and found that patients with subnormal levels (40 nmol/L threshold) had a lower mean HHS preoperatively ($p = 0.018$) and patients with normal levels had significantly more excellent HHSs postoperatively.

In conclusion, hypovitaminosis D was common in patients undergoing THA and was associated with higher BMI and lower preoperative and postoperative hip scores. However, the lack of a standard definition seems to lead to mixed results, which represents a real obstacle for future investigations. The standardization of the definition of hypovitaminosis D is urgently needed so that further studies can properly evaluate its real prevalence, potential deleterious effects on function, and therapeutic effects of reversing insufficiency before THA.

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