The Association of Vitamin D Status and Pre-operative Physical Activity in Patients with Hip or Knee Osteoarthritis

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ABSTRACT

Background: Vitamin D is important for musculoskeletal health and may have significant implications for maintaining physical activity in elderly patients. Our goal was to investigate whether serum 25-hydroxyvitamin D (25OHD) levels are associated with pre-operative physical activity in patients who are offered elective knee or hip joint replacement surgery.

Methods: We performed a single-center, retrospective analysis of patients who had elective knee or hip replacement surgery from 2002 to 2012. To investigate the association of serum 25OHD levels with pre-operative physical activity, as assessed by the University of California, Los Angeles (UCLA) activity scale, we performed a multivariable logistic regression analysis while controlling for age, sex, race, body mass index, American Society of Anesthesiologists physical status score, and season.

Results: We identified 182 patients who met inclusion criteria. Mean (± standard deviation) 25OHD level and UCLA activity scale score were 29±13 ng/mL and 4±2, respectively. Patients with 25OHD levels <20 ng/mL were almost three times more likely to have UCLA activity scale scores ≤3 [adjusted odds ratio 2.78; 95% confidence interval 1.72–9.17]. Further adjusting for "type of 25OHD assay" or "type of joint surgery" did not materially change this result.

Conclusion: In our cohort of knee or hip joint replacement surgery patients, 25OHD levels were associated with pre-operative physical activity scores. Prospective, randomized, clinical trials are needed to verify whether optimizing pre-operative vitamin D status may improve physical activity and influence clinical decision-making in knee or hip joint replacement surgery candidates.

Keywords: Vitamin D; 25OHD; Joint replacement; Arthroplasty; Physical activity

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INTRODUCTION

Osteoarthritis (OA) afflicts over 12 million elderly Americans and is one of the leading causes of disability amongst non-institutionalized adults.[1,2] It often leads to decreased mobility, lower functional status, and reduced quality-of-life (QoL).[3] Conservative management of OA includes avoidance of high-impact activities, weight loss, non-steroidal anti-inflammatory drugs (NSAIDs), glucosamine/chondroitin supplements, and physical therapy.[4] When such management is no longer effective, joint replacement surgery may be offered to patients to alleviate pain, optimize function, and improve QoL.

Total knee replacement (TKR) and total hip replacement (THR) are two of the most commonly performed surgical procedures in the United States.[5] In 2010 alone, 719,000 TKRs and 332,000 THRs were performed[5] at a cost to the healthcare system likely in excess of $18 billion.[6] It is estimated that nearly 4.5 million joint replacements will be performed by 2030 at a cost of greater than $50 billion annually.[7] With an increasingly obese and aging population, and a healthcare system seeking to reduce expenditures, it is critical to identify factors that may improve OA pain, joint functionality, and QoL while utilizing conservative management strategies.

Physical activity is a known prognostic factor in the etiology and prognosis of OA.[4] High impact activities and sports are thought to mechanically induce degeneration of cartilage and bone (Figure 1).[8–10] Conversely, low impact physical activity, such as swimming, walking, or bicycling may protect against the functional decline of joints.[11–13] Indeed, patients with OA are often prescribed such low impact physical activities to functionally stretch ligaments and to restore joint range of motion.[4] However, compliance with such exercise routines may be challenging in the setting of pain or muscular atrophy, and tends to dwindle over time.[14]

While vitamin D is generally known to be essential for optimal bone health (Figure 2),[15] its potential therapeutic benefits for overall musculoskeletal health have recently gained wider attention.[16] Serum 25-hydroxyvitamin D (25OHD) levels are generally regarded as the best marker of total body vitamin D status,[17] and recent evidence from heterogeneous patient cohorts[18–20] and from the general

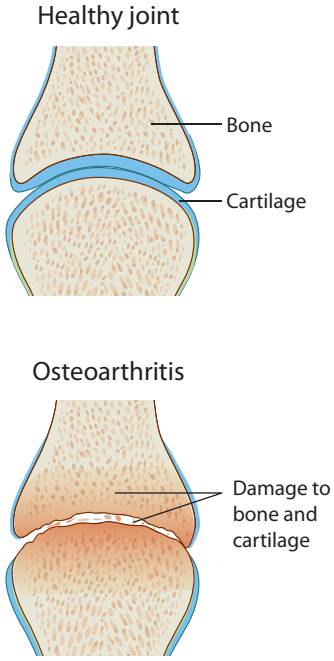

Figure 1: Pathophysiology of osteoarthritis.

population[21] suggests that 25OHD is inversely associated with skeletal muscle pain, physical activity, and QoL. However, the role of vitamin D status assessments in OA patients with symptomatic hip or knee pain remains unclear. Given that the prevalence of low 25OHD levels may exceed 40% in patients who are offered joint replacement surgery,[22] our goal was to investigate whether vitamin D status before surgery is associated with pre-operative physical activity level in TKR and THR patients.

METHODS

After obtaining approval from the local Institutional Review Board, we performed a single-center, retrospective analysis of patients from the Massachusetts General Hospital (MGH), a major teaching hospital in Eastern Massachusetts.

The Department of Orthopaedic Surgery at MGH manages an extensive clinical research database of joint replacement surgery patients. Demographic information, clinical data, and key outcomes are all logged and maintained after multiple verification

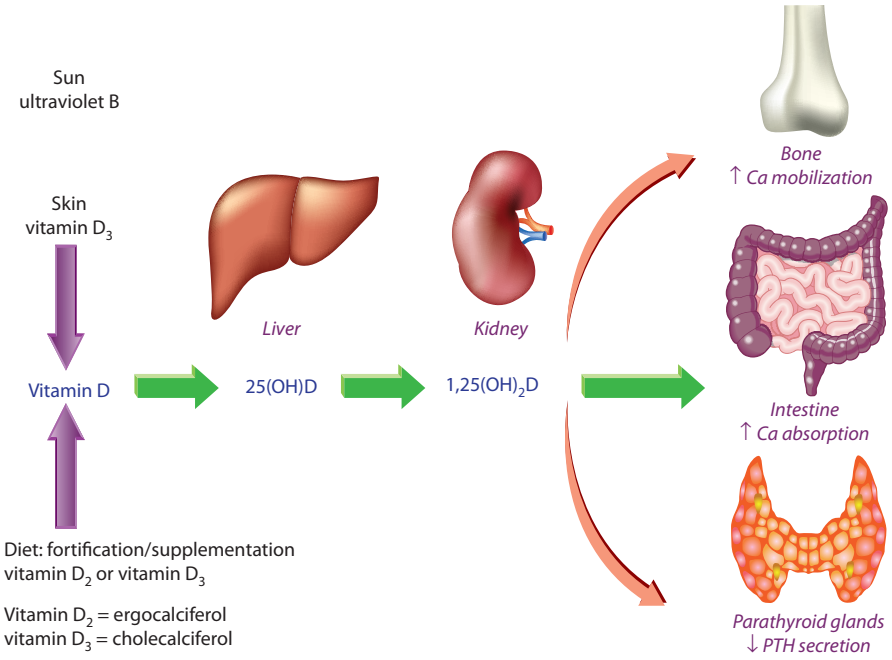

Figure 2: Effect of absorption and metabolization of vitamin D on bone health.

steps to ensure data accuracy. We queried this database to identify patients who had elective knee or hip joint replacement surgery at the MGH between 2002 and 2012. This was cross-referenced with the MGH Research Patient Data Registry (RPDR) to obtain results from laboratory testing. The RPDR is a comprehensive database of all patients who obtain medical care through the MGH and its affiliates,[23] which has been used extensively to report the association between different biomarkers and various diseases.

We focused our search on patients who met the following inclusion criteria: 1) age of ≥18 years; 2) diagnosis of OA and/or age-related joint degeneration; 3) received an elective, primary TKR or THR (not related to trauma); 4) had 25OHD measured during a routine medical visit within 90 days before the date of surgery; and 5) completed a University of California, Los Angeles (UCLA) activity scale assessment within 90 days before surgery. We excluded patients who had a joint revision or bilateral surgery, were diagnosed with an underlying inflammatory or systemic disease that would explain joint involvement (rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus), those who had 25OHD assessments performed as part of the medical work-up for an existing/suspected underlying medical diagnosis (e.g., primary hyperparathyroidism), or those who had been hospitalized between the time of their 25OHD assessment and their date of surgery. For patients who had more than one 25OHD assessment performed before surgery, we considered only the value closest to the date of when the UCLA activity scale was completed.

Based on existing national guidelines regarding vitamin D status,[24] descriptive statistics were calculated for patients with 25OHD levels <20 ng/mL vs. those with levels ≥20 ng/mL. Continuous data were reported as means with standard deviations (SD) and compared using *t*-tests. Categorical values were expressed as proportions and compared using chi-square tests.

To investigate the association of vitamin D status with activity level in TKR and THR patients, we performed a multivariable logistic regression analysis. The exposure of interest was pre-operative 25OHD level within 90 days of surgery, and in accordance with existing national guidelines, we dichotomized 25OHD levels as <20 ng/mL vs. ≥20 ng/mL for our analysis.[24] The primary outcome of interest was pre-operative activity level as assessed by the UCLA activity scale completed

within 90 days of surgery. The UCLA activity scale is a simple 10-item questionnaire that is widely accepted as the most appropriate scale for assessing physical activity in patients scheduled to receive a total joint replacement surgery.[25] To focus our analysis on patients with significant functional disability vs. those with mild disruptions in their activities of daily living, we dichotomized the UCLA activity scale scores as >3 (where a score of 4=regularly participates in mild activities) vs. ≤3 (where a score of 3=sometimes participates in mild activities, such as walking, limited housework and limited shopping). Covariates in our analysis included age, sex (female vs. male), race (non-white vs. white), body mass index (BMI), American Society of Anesthesiologists (ASA) physical status score, and season. To simplify our analysis, we dichotomized season as low ambient ultraviolet radiation (December to May) vs. high ambient ultraviolet radiation (June to November).

We performed an *a priori* sample size calculation using available data regarding prevalence of 25OHD levels <20 ng/mL among TKR and THR patients,[22] as well as the association between 25OHD and physical activity in the general population of the United States.[21] Assuming that 25% of patients with 25OHD ≥20 ng/mL and 55% of patients with 25OHD <20 ng/mL would have a UCLA activity scale score of ≤3, and with alpha set at 0.05, we would be able to detect this difference with a power of 0.8 with a minimum of 41 patients in each group. All analyses were performed in STATA 12.0 (StataCorp LP, College Station, TX). A two-tailed $P<0.05$, or an odds ratio (OR) with a 95% confidence interval (CI) that did not span 1, was considered statistically significant.

RESULTS

We identified 14,684 patients who had elective hip or knee surgery at the MGH between 2002 and 2012. Based on our inclusion and exclusion criteria, 182 patients comprised the final analytic cohort. Baseline characteristics of these patients are shown in Table 1. The mean (± standard deviation) age was 73±14 years. Most patients were women (62%) and white (89%). Overall mean BMI was 28±6 kg/m^2 and mean ASA score was 2±1. Mean

Table 1: Characteristics of the analytic cohort (*n*=182).

	25OHD ≥20 ng/mL (*n*=123)	25OHD <20 ng/mL (*n*=59)	*P*-value
Age (years)	75±11	68±20	**0.01**
Sex (%)			0.38
Female	60	66	
Male	40	34	
Race (%)			0.05
Non-white	10	20	
White	90	80	
BMI (kg/m^2)	28±5	29±8	0.38
ASA physical status score	2.2±0.5	2.5±0.5	**<0.001**
Season (%)*			0.32
Low ambient UV radiation	57	53	
High ambient UV radiation	43	47	
Type of surgery (%)			0.48
Hip replacement	48	43	
Knee replacement	52	57	
25OHD level (ng/mL)	33±12	14±4	**<0.001**
UCLA activity scale score	4.5±1.9	3.6±1.1	**<0.001**

Data are presented as mean±standard deviation or proportions. *t*-test and chi-square tests, were used, respectively, to compare patients with 25-hydroxyvitamin D levels ≥20 ng/mL to those with levels <20 ng/mL. Statistically significant *P*-values (<0.05) are shown in bold.
BMI, body mass index; ASA, American Society of Anesthesiologists; UV, ultraviolet; 25OHD, 25-hydroxyvitamin D; UCLA, University of California, Los Angeles.
*Low ambient UV radiation=December to May; high ambient UV radiation = June to November.

25OHD level for the study cohort was 29±13 ng/mL and mean UCLA activity scale sore was 4±2. A little over half of all the patients received a TKR (54%).

Patients with 25OHD levels <20 ng/mL were almost 3 times more likely to report UCLA activity scale scores of ≤3 (OR 2.79; 95% CI: 1.72–9.17) when compared with patients with levels ≥20 ng/mL, despite adjusting for clinically relevant covariates. The type of assay used to measure 25OHD varied over the study period; either chemiluminescence assay, radioimmunoassay, or liquid chromatography–mass spectroscopy was used at different time points. Adjusting for the type of 25OHD assay used did not materially change these results (adjusted OR 2.81; 95% CI: 1.77–8.91). Moreover, further adjusting for the type of surgery (i.e., TKR vs. THR) did not materially change the results either (adjusted OR 2.81; 95% CI: 1.79–8.99). The only additional covariate found to be significantly associated with activity level in our regression model was the ASA physical status score (OR 0.18; 95% CI 0.06–0.53).

DISCUSSION

In this retrospective, cohort study, we investigated whether vitamin D status is associated with pre-operative physical activity in patients who subsequently received a lower extremity joint replacement surgery. We demonstrated that serum 25OHD levels <20 ng/mL were associated with significantly lower pre-operative physical activity in this cohort of patients. However, because of the observational nature of this study, a causal relationship between vitamin D status and pre-operative physical activity cannot be inferred – yet, the biological evidence to support such a relationship is undeniable.

In vitro studies have shown that human articular chondrocytes (HAC) from the cartilage of OA patients highly express the vitamin D receptor (VDR) compared with subjects without evidence of OA.[26] Stimulation of VDR by 1,25-dihydroxy-vitamin D (the most biologically active vitamin D metabolite) in HAC regulates production of matrix metalloproteinases (MMPs) and prostaglandin E_2 (PGE_2). Both MMPs and PGE_2 have been implicated in the pathophysiology of OA.[27,28] As such, these data support the notion that vitamin D may play an important role in maintaining articular joint health. Indeed, recent evidence suggests that in asymptomatic, healthy subjects, 25OHD levels are inversely associated with distal femoral cartilage thickness.[29] And while earlier prospective, observational studies[30] failed to demonstrate a relationship between 25OHD levels and joint health, more recent studies have demonstrated a strong association of vitamin D status with cartilage thickness and joint pain.[31,32] Randomized, controlled studies of vitamin D supplementation in patients with OA are limited and unfortunately, have reported conflicting results.[33,34] In a study involving 146 patients with symptomatic knee OA, supplementation with vitamin D over 2 years to a target 25OHD level >36 ng/mL did not demonstrate any clinical benefit.[33] However, mean baseline 25OHD level in participants was around 22 ng/mL, thereby making it unlikely to detect a significant treatment effect with the selected sample size and vitamin D dosing schemes. Moreover, it is important to note that in this study, only 61% of patients in the intervention arm reached goal 25OHD level after 2 years of supplementation. Conversely, in another study involving 107 patients with knee OA, vitamin D supplementation for 1 year resulted in improved pain and physical function compared with placebo.[34] Given the lack of conclusive data regarding the relationship between vitamin D status and physical activity in patients with OA, our study findings raise intriguing questions that merit further investigation. As vitamin D supplementation is associated with relatively benign negative effects, and that improving 25OHD levels may benefit patients with suboptimal musculoskeletal health, clinicians may wish to consider existing guidelines[35] to assist with dosing strategies while awaiting more definitive results of future studies.

Although cohort studies provide observational evidence, they have several potential limitations, such as confounding, reverse causation, or the lack of a randomly distributed exposure. These issues may certainly decrease the generalizability of our results. Despite adjustment for multiple potential covariates, there may still be residual confounding that contributed to the observed differences in outcomes. Specifically, low 25OHD levels may be

a marker for the general condition of patients, for which we are unable to fully adjust. Moreover, our analytic cohort was selected from a single institution that is a major referral center for medically complex patients, which may further impact the generalizability of our findings. Another potential limitation is related to the fact that the 25OHD assessments and UCLA activity scale scores were not necessarily performed on the same day. However, the majority of results were obtained within 2 weeks of each other and it is very unlikely that 25OHD levels or functional activity changed significantly during this time. Additionally, we were unable to control for amount of sunlight exposure among patients in the analytic cohort. Moreover, we did not control for the use of vitamin D supplementation (only 11 patients had a specifically documented use of vitamin D supplements and in those taking a multivitamin it was unclear how much vitamin D was in each formulation), NSAIDs (there was too large a variation in terms of specific drugs, doses, and frequency of use), and glucosamine/chondroitin supplements (only 9 patients had a documented use of these supplements). The use of these medications may indeed have influenced pre-operative activity in this cohort of patients. These issues will need to be addressed by future studies in order to replicate and extend our findings.

CONCLUSION

Our results suggest that vitamin D status may be a modifiable risk factor for loss of functional mobility in OA patients. We hypothesize that ideal 25OHD levels are associated with improved musculoskeletal health, which in turn, allows for greater physical activity. Optimal vitamin D status likely attenuates the age-related loss of muscle mass (which supports joint mobility and function),[16] slows down the natural thinning of articular cartilage,[32] and improves musculoskeletal pain via several mechanisms beyond its potent anti-inflammatory effects.[18] Larger studies are needed to validate our findings, to assess the potential benefit of optimizing pre-operative 25OHD levels in patients considering TKR or THR, and to identify the mechanism by which vitamin D may reduce the need for or delay the time to surgery in OA patients with symptomatic knee or hip pain.

WHERE WORK WAS PERFORMED

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DISCLOSURE OF INTERESTS

None of the authors declare any financial conflicts of interest. Dr. Quraishi maintained an uncompensated position on the Board of Directors for the Vitamin D Council during the conduct of this study.

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