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CLINICAL RESEARCH

Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial

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Abstract

Background Animal, epidemiologic, and human clinical studies suggest a putative role for vitamin D in osteoarthritis (OA). Inadequate sunlight exposure and lower serum levels of 25(OH)D appear in some reports to be associated with an increased risk for progression of knee OA.

Questions/purposes We asked whether treatment with vitamin D would (1) reduce knee pain (WOMAC and VAS), (2) improve function (WOMAC), and (3) change levels of relevant biochemical markers in patients with knee OA with vitamin D insufficiency.

Methods This randomized controlled pilot trial prospectively enrolled 107 patients with knee OA with vitamin D insufficiency (25(OH)D $\leq$ 50 nmol/L) to receive oral vitamin D or placebo. The primary outcome measures were pain and function, and the secondary were biochemical markers. At baseline, the two groups were comparable. The patients were followed for 1 year.

Results At 12 months, knee pain had decreased in the vitamin D group by mean −0.26 (95% CI, −2.82 to −1.43) on VAS and −0.55 (95% CI, −0.07 to 1.02) on the WOMAC, whereas in the placebo group, it increased by mean 0.13 (95% CI, −0.03 to 0.29) on the VAS and 1.16 (95% CI, 0.82 to 1.49) on the WOMAC (effect size = 0.37 and 0.78). Likewise knee function improved in the vitamin D group by mean −1.36 (95% CI, −1.87 to −0.85) over the placebo group which had a mean 0.69 (95% CI, −0.03 to 1.41; effect size = 0.06). There were significant biochemical changes in serum total calcium, 25(OH)D and alkaline phosphatase.

Conclusions The results above suggest there is a small but statistically significant clinical benefit to vitamin D treatment in patients with knee OA, although we recommend a long-term study to determine whether these changes are clinically important and whether they will be sustained with time. Further studies with long-term radiologic evaluations are needed.

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

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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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Introduction

Osteoarthritis (OA) is a degenerative joint disease whose origin is incompletely understood and probably multifactorial [12]. Although the etiology and pathogenesis of OA are largely unknown, OA is primarily a noninflammatory disorder characterized by an imbalance between the synthesis and degradation of articular cartilage leading to classic pathologic change of wearing away and destruction of cartilage [6]. The estimated population prevalence varies from 4% to 30% depending on the age, sex, and disease definition [7]. Risk factors for OA include age, sex, ethnicity, occupation, bone density, obesity, diet, and genetics [15].

OA of the knee is the most frequent reason for joint replacement at a cost of billions of dollars per year. There currently are no effective medical remedies for OA, and the goals of treatment are to minimize patients' symptoms and disability using a combination of physical measures, drug therapy, and, sometimes, surgery. Many nutritional supplements have been used for treatment of OA, but most lack good research data to support their effectiveness and safety. It is hypothesized that vitamin D status has an effect on the risk of the development or progression of OA because vitamin D influences bone quality [20, 23]. It has been estimated that approximately 1 billion people worldwide have vitamin D deficiency or insufficiency [17]. Although vitamin D insufficiency has been linked with osteoporosis and fractures in older women and men, the role of vitamin D insufficiency in the pathogenesis of OA remains controversial [4, 9, 11, 16, 18, 23]. In two epidemiologic studies [20, 22], vitamin D was implicated as having an effect on the radiographic manifestations of OA by observations that low vitamin D serum levels were associated with a higher risk of radiographic knee and hip OA. There is evidence that vitamin D supplementation, a simple and relatively inexpensive intervention, may prove useful in slowing the progression of OA. Even if only modestly effective, it could have a considerable affect on reducing the societal burden in terms of pain and disability leading to work loss, early retirement, and arthroplasty [26]. Therefore, in the interests of public health, the efficacy of vitamin D supplementation as a disease-modifying treatment for OA needs to be evaluated in a rigorous clinical trial.

We therefore asked whether treatment with vitamin D would (1) reduce pain in patients with knee OA (WOMAC and VAS), (2) improve function (WOMAC), and (3) change levels of relevant biochemical markers (including serum calcium (total and ionic), serum phosphorus, serum vitamin D, and serum alkaline phosphatase) in patients with vitamin D insufficiency (25(OH)D $\leq$ 50 nmol/L) with knee OA at short-term followup.

Patients and Methods

This prospective, double-blind parallel, placebo-controlled pilot trial was conducted under the principles of the Helsinki Declaration and approved by the institutional ethics committee (Ref. No. 1989/R.Cell-18, April 12, 2008). Our study consisted of men and women 40 years old or older who were recruited from the outpatient clinic of the department of orthopaedic surgery from April 2008 to April 2010. To meet the eligibility requirements, a patient had to have (1) met the American College of Rheumatology criteria for knee OA (knee pain with osteophyte on radiographs and any one of the following (a) crepitus on knee ROM, (b) age 50 years or older, (c) morning stiffness of short duration [< 30 minutes]) [12]; (2) knee pain for 6 months and WOMAC pain score greater than 4 on the Likert scale (at least 20% of pain dimension on the WOMAC Likert scale); (3) been receiving conventional treatment for OA for at least 6 months; (4) no BMI greater than 30 kg/m^2; (5) no previous fractures of the index knee; (6) no previous surgeries on the index knee; (7) no secondary OA; (8) no allergies to any of the substances used; and (9) been able to understand and agree with the informed consent. The exclusion criteria were: (1) undergoing surgery during the study; (2) patients younger than 40 years; and (3) patients having other chronic disease, eg, asthma, chronic obstructive pulmonary disease, chronic renal failure, and malignancy. During the initial part of the study, 667 prospective participants approached consecutively in the outpatient clinic underwent physician-led clinical and radiologic examinations to verify their eligibility for inclusion. Four hundred thirty individuals with evidence of secondary OA, inflammatory arthritis, obesity, or neurologic conditions were excluded; 57 did not give consent. Therefore, 180 patients with primary knee OA were identified and profiled for serum 25(OH)D status by using the 25-hydroxy vitamin D EIA kit (Immunodiagnostic Systems Ltd, Boldon, Tyne and Wear, UK) based on an ELISA. Of these, approximately 60% were found to have vitamin D insufficiency (25(OH)D $\leq$ 50 nmol/L) [27]. Seven patients did not wish to participate, and finally, 106 subjects were available for parallel and equal randomization (Fig. 1).

The enrolled subjects for the clinical trial were allocated to the placebo and vitamin D groups using a simple randomization procedure. A computer-aided random series program was used to generate the random allocation sequence, which is a list of unique integer random numbers identified as patient code. The unique integer random numbers then were mentioned in respective places (blister pack containing either placebo or vitamin D) as per the random allocation sequence. The random allocation sequence was generated by the study statistician. The entire

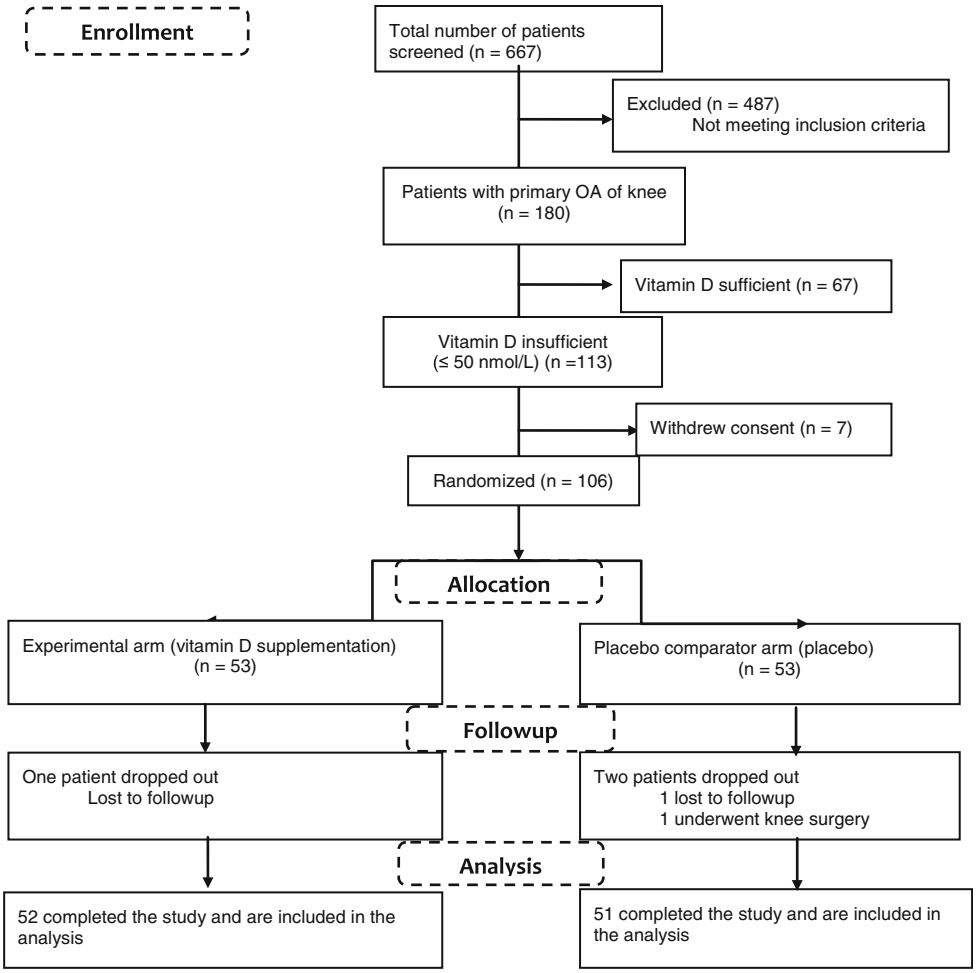

Fig. 1 The flow chart for our study is shown.

process was done in a completely concealed manner and all involved with the study (investigator, participants, and staff) were unaware of the sequence. The participants fulfilling the inclusion and exclusion criteria of the study, and after obtaining written informed consent, were enrolled by the study investigator and subsequently the pharmacist dispensed the study medication to the participants taking into consideration the order of enrollment and the random allocation sequence. The investigator, participants, and pharmacist dispensing the interventions all were blinded to group assignment. The blinding process was maintained until all the data were compiled, confirmed for accuracy, and forwarded to the statistician for analysis.

Along with standard treatment, the vitamin D group (experimental arm) received FDA-approved oral vitamin D (cholecalciferol granules) of 60,000 IU per day for 10 days followed by 60,000 IU once a month for 12 months, and placebo comparator arm participants received one placebo capsule per day for 10 days followed by one capsule once per month for 12 months. Standard treatment included patient education, exercise, appliances (insoles, minimal heel-raise; broad forefoot to allow splaying of the toes during forefoot loading; and deep, soft uppers, sticks and kneebracing when needed), application of heat (eg, hot water bath, paraffin wax bath, and/or short-wave diathermy), NSAIDs, and/or paracetamol (normally not prescribed).

Preparation of the vitamin D capsule and placebo was done in a standard laboratory. Vitamin D granules and sugar were filled in empty capsules to create pills of vitamin D and placebo as described by Griffith [14].

Each study subject was in the study for 12 months. During that time, there were five scheduled study visits (screening months 0, 1½, 3, 6, and 12) and interim safety visits as needed. Anthropometric measurements, clinical assessment (WOMAC and VAS), pill counts, and completion of questionnaires were recorded at all visits. Biochemical (blood) assessments were done at the screening visits at 6 and 12 months. During followup three patients dropped out (two from the vitamin D group and one from the placebo group). Finally, 103 subjects underwent the per protocol analysis (Fig. 1).

The primary outcome measures of our study were knee pain and function and the secondary measures were changes in biochemical parameters (serum calcium [total

and ionic], serum phosphorus, 25 (OH)D, and alkaline phosphatase).

At baseline, the patients were profiled for demographic, clinical, and radiologic features. Age and sex were self-reported. The patients were weighed with a calibrated balance beam scale to the nearest 0.1 kg in the minimum possible clothing, and standing height was measured with a stadiometer in centimeters. BMI was recorded by the Quetelet index. Clinical symptoms related to knee OA were assessed with the WOMAC index [2], which assesses pain, stiffness, function, and interpretation response in terms of a 5-point scale (0 = none to 4 = extreme). Knee pain also was assessed using the VAS, in which higher scores indicate worse status.

At the time of recruitment, weightbearing AP and recumbent lateral knee radiographs were taken using standard procedures. OA was defined as the presence of at least one knee with a Kellgren-Lawrence Grade 2 or greater. As described by Duncan et al. [10], only one knee per individual, the index knee, was analyzed. In patients with unilateral knee pain, the index knee was the painful knee. In patients with bilateral knee pain, the more painful knee was the index knee. When patients reported equal pain for both knees, the index knee was selected at random. All radiographs were first evaluated by two orthopaedic surgeons (AS, SA) to establish a diagnosis and severity by Kellgren-Lawrence grade [19]. In cases of disagreement, the senior author (RNS) gave the final reporting.

Of the 103 participants, 37 were men and 66 were women ranging in age from 40 to 74 years (mean, 54.11 years). Nineteen patients (8 men, 11 women) had a Kellgren-Lawrence grade of 2, 48 (14 men, 34 women) had a grade of 3, and 36 (10 men, 26 women) had a grade 4. The average BMI was 25.02 ± 2.64 kg/m^2. A voluntary written informed consent was signed by all participants. The demographic, clinical, biochemical, and radiologic variables studied at baseline were not significantly different between the groups (Table 1), suggesting the randomization allocated the groups fairly.

Data were summarized as mean ± SD with 95% CI. Two independent groups were compared by independent Student's t-test and discrete (categorical) groups were compared by chi-square test. The changes (from baseline to the end of the study) in outcome measures of the two groups also were compared using an independent Student's t-test. In case of nonnormal or heterogeneous data, the groups were compared by the nonparametric alternative Mann-Whitney U test. A two-tailed ($\alpha = 2$) p less than 0.05 was considered statistically significant. For primary outcome measures, the effect size ([mean 1–mean 2]/pooled SD) also was evaluated. All analyses were performed using STATISTICA software (Version 6.0; Statsoft Ltd, Bedford, England).

Table 1. Baseline characteristics of the placebo and vitamin D groups

General characteristic	Placebo group (n = 51) (%)	Vitamin D group (n = 52) (%)	p value
Age (years)	53.00 ± 7.44 (40–74)	53.24 ± 9.64 (40–70)	0.89
Sex			
Males	21 (40.6%)	16 (30.3%)	0.27
Females	30 (59.4%)	36 (69.7%)	
BMI (kg/m^2)	25.65 ± 2.58	25.86 ± 2.46	0.67
NSAID frequency	1.5 ± 0.87	1.5 ± 0.82	0.99
Serum total calcium (mg/dL)	9.56 ± 0.68	9.44 ± 0.95	0.46
Serum ionic calcium (mg/dL)	4.21 ± 0.60	3.99 ± 0.65	0.08
Serum phosphorus (mg/dL)	3.73 ± 0.77	3.88 ± 0.94	0.35
Serum 25(OH)D (nmol/L)	37.52 ± 7.53	37.03 ± 7.54	0.74
Serum alkaline phosphatase (U/L)	171.67 ± 66.38	176.57 ± 76.51	0.73
WOMAC-pain (0–20)	10.64 ± 2.82	10.94 ± 2.63	0.58
Stiffness (0–8)	2.52 ± 1.30	2.38 ± 1.25	0.58
Physical function (0–68)	23.61 ± 6.51	21.97 ± 6.33	0.20
Total WOMAC (0–96)	37.06 ± 9.06	35.53 ± 8.43	0.38
Kellgren-Lawrence Grades 2, 3, 4	9/25/17	10/23/19	0.89

Values are mean ± SD or number with percentage in parentheses.

Results

Patients randomized to the vitamin D group had less knee pain at 12 months on the WOMAC and on the VAS pain scale than did patients who received the placebo (Table 2). Knee pain on VAS decreased by 0.26 unit (95% CI, −2.82 to −1.43) in the vitamin D group whereas it increased in the placebo group by 0.13 unit (95% CI, −0.03 to 0.29). Similarly WOMAC pain decreased by 0.55 unit (95% CI, −0.07 to 1.02) in the vitamin D group whereas it increased in the placebo group by 1.16 units (95% CI, 0.82 to 1.49). There were significant evident differences between the groups in the pain end point (although of very small effect sizes, 0.78 on WOMAC and 0.37 on VAS).

Patients randomized to the vitamin D group had decreased knee function scores at 12 months on the WOMAC index than did patients who received the placebo (Table 2). Knee function scores decreased by 1.4 units (95% CI, −1.87 to −0.85) in the vitamin D group whereas it increased by 0.7 unit (95% CI, −0.03 to 1.41) in the placebo group. There were significant evident differences

Table 2. Clinical profile changes over the 1-year followup

Variable	Mean (95% CI)			p value
	Vitamin D (n = 52)	Placebo (n = 51)	Between group difference	
VAS pain	−0.26 (−2.82 to −1.43)	0.13 (−0.03 to 0.29)	−0.39 (−0.71 to −0.08)	0.020
WOMAC pain	−0.55 (−0.07 to 1.02)	1.16 (0.82 to 1.49)	−1.70 (−2.28 to 1.12)	< 0.001
WOMAC stiffness	0.15 (0.03 to 0.27)	0.09 (−0.07 to 0.26)	0.06 (−0.15 to 0.26)	0.580
WOMAC physical function	−1.36 (−1.87 to −0.85)	0.69 (−0.03 to 1.41)	−2.05 (−2.92 to −1.19)	< 0.001
WOMAC total	−2.12 (−2.82 to −1.43)	1.41 (0.95 to 1.86)	−3.53 (−4.39 to −2.71)	< 0.001

Table 3. Biochemical parameter changes over the 1-year followup

Variable	Mean (95% CI)			p value
	Vitamin D (n = 52)	Placebo (n = 51)	Between group difference	
Serum calcium (total) (mg/dL)	0.53 (0.33 to 0.73)	−0.14 (−0.24 to −0.04)	0.67 (0.45 to 0.89)	< 0.001
Serum calcium (ionic) (mg/dL)	0.03 (−0.11 to 0.17)	−0.18 (−0.31 to −0.05)	0.21 (0.02 to 0.40)	0.03
Serum phosphorus (mg/dL)	0.05 (−0.12 to 0.22)	0.01 (−0.11 to 0.13)	0.04 (−0.16 to 0.24)	0.70
Serum 25(OH)D (nmol/L)	45.70 (39.29 to 52.12)	2.12 (−0.04 to 4.28)	43.58 (36.85 to 50.312)	< 0.001
Serum alkaline phosphatase (U/L)	60.88 (46.35 to 75.41)	2.94 (−4.52 to 10.40)	57.94 (41.72 to 74.16)	< 0.001

Values are the differences observed between preintervention and postintervention, over 1 year.

between both groups in the knee function scores end point with the minimal effect size of 0.07. Overall WOMAC scores were significantly reduced by 2 units in the vitamin D group whereas in the placebo group it was increased by 1.5 units.

Patients randomized to the vitamin D group had increased serum total and ionic calcium (at 12 months) than did patients who received the placebo (Table 3). Serum total calcium increased by approximately 0.50 unit and ionic calcium by 0.03 unit in the vitamin D group whereas these were decreased in the placebo group by 0.14 and 0.18 units, respectively. Serum 25 (OH)D and alkaline phosphatase increased in both groups, although the change was greater in the vitamin D group (45.7 and 60.8 units) in comparison to the placebo group (2.12 and 2.94 units). There were significant evident differences between both groups in the serum calcium total, 25 (OH)D, and alkaline phosphatase end points, whereas phosphorus did not show any difference between the groups.

Discussion

OA is one of the most frequent causes of pain, loss of function, and disability in the elderly. Knee OA is particularly common in patients in India and there currently is no therapy that can slow its progression. Evidence suggests that vitamin D deficiency plays an important role in development of knee OA [4]; however, it is not known whether correcting a vitamin D deficiency will influence the progress of the disease. Therefore, this study was planned as a pilot study to compare pain, function, and biochemical parameters in patients receiving vitamin D with those receiving a placebo. Pain and functional disability improved slightly in patients receiving vitamin D supplementation, but not sufficiently to reach a minimal clinically improved difference when patients with vitamin D insufficiency with OA were given vitamin D. The changes we observed bordered on being of no difference.

There were several limitations to this study. With the loss to followup, it is possible that even a few patients filling out score sheets differently would have resulted in some differences in statistical findings but the number of patients who dropped out is low (n = 3), so we believe it will not make a major difference in our results. More important limitations of this study were that (1) the effect sizes observed for pain and function were statistically significant but very small (less than 1 mm on VAS pain and 2 points on WOMAC), and because they are so small, we question whether they are clinically important. We believe that these statistically significant findings of a small effect size would be valuable in planning a randomized controlled trial calculating the sample size needed to detect the magnitude of difference between the treatment groups that the study can reliably detect (delta value) [1]. This is a primary issue that needs to be addressed before deciding whether to incorporate, in clinical practice, vitamin D intervention in patients with knee OA and a vitamin D

insufficiency. (2) Another limitation is both pain scales tested showed significance, but more so in the WOMAC pain than in the VAS. This could be attributable to the nature of pain in knee OA which is a chronic slowly progressive disease. VAS was one of the assessment tools we used in this study as it is the most popular outcome measure for pain in different situations, although its reliability has been shown to be better in the acute setting where pain fluctuation might be greater than for chronic pain, as was the case here [5]. The WOMAC is one of the most widely used self-report measures of lower extremity symptoms and function. (3) This is per protocol analysis as we do not have primary outcome data for three patients (one from the vitamin D group and two from the placebo group) because they were lost to followup. We chose not to account for missing data because the small numbers were unlikely to affect the outcome. However we conducted the analysis again (intention-to-treat analysis), giving the two missing patients in the placebo group the highest observed score and the one missing patient in the vitamin D group the lowest observed score in their group. The results supported the original findings of our data. (4) We did not limit the use of analgesics or any other nonpharmacologic treatment. We believe that addition of vitamin D in a conventional treatment does not need exclusion of any other treatment, and we tried to keep both groups as similar as possible. (5) We chose only one knee (index knee) for reporting improvement in clinical scores (WOMAC and VAS) and classified them with the Kellgren-Lawrence grade, even in patients with bilateral knee OA, because it was not possible to ascertain WOMAC scores in individual knees. (6) The sample size of the study is small as it is a pilot study. (7) A followup of 1 year may not be sufficient to monitor radiologic changes in this slowly progressing disease, however, clinical parameters may be predicted.

The strengths of the study included the use of a predefined pain threshold for inclusion, use of outcomes measures consistent with those recommended in the literature [3, 25], and use of a randomized, double-blind design, with a placebo comparison group. Pain on the WOMAC and VAS increased in the placebo group, and decreased minimally in the vitamin D group on the VAS and WOMAC scale. Changes in WOMAC pain between the groups seem to be attributable to worsening in the placebo group and not necessarily to improvements in the vitamin D group. We observed that the vitamin D group did not benefit much over the placebo group regarding pain. Somewhat similar to our findings, another randomized controlled trial of patients with knee OA found that subjects who greatly increased their vitamin D intake had reduced WOMAC pain scores of approximately 2.14 points compared with a reduction of 1.20 points among patients taking placebo but it was insignificant [22]. Moreover, moderate vitamin D deficiency independently predicts incident, or worsening of, knee pain over 5 years and, possibly, hip pain over 2.4 years. Therefore correcting moderate vitamin deficiency may attenuate worsening of knee or hip pain in elderly people but giving supplements to those with a higher 25(OH)D level is unlikely to be effective [21].

Functional disability remained somewhat similar in the placebo group from baseline to the 12-month followup and it was improved only minimally in the vitamin D group. In comparison to the placebo group, functional disability scores decreased but with less effect size in the vitamin D group at last followup. In accordance with our findings, a recent study showed vitamin D supplementation did not reduce knee functional disability in patients with symptomatic knee OA during a 2-year followup [22].

Some biochemical changes were observed in both of our groups. In the vitamin D group, after intervention, serum phosphorus did not show a significant change in contrast to the other three biochemical parameters studied; however, a near normal or nominal increase in comparison to a significant decrease in the placebo group may suggest a putative role of vitamin D in patients with knee OA because ionized calcium is the most important physiologic component of calcium and is controlled by stringent endocrine regulation. Total calcium increased in the vitamin D group and decreased in the placebo group and the difference between the groups was significant. Serum 25(OH)D and alkaline phosphatase increased in the vitamin D group and very nominally increased in the placebo group. The difference between the groups was significant. Once again the point of discord was whether these changes were of any clinical importance looking at no difference in status in the clinical parameters. Although statistically significant, hereto it does not seem to reach minimal clinically important difference. The literature suggested that there is no significant correlation between the bone-specific alkaline phosphatase and pain, physical function, and total scores of the WOMAC [8]. A significant positive correlation was found between bone formation rate and knee stiffness. Our study did not show any significance for knee stiffness.

There has been an increase in studying the role of vitamin D in OA [13, 16, 22, 24], and several clinical trials have ensued and are ongoing. These studies are in the initial stages, and to date and to our knowledge, no strong evidence has been available to establish the role of vitamin D in OA. We believe that a long-term study is needed to validate our preliminary results, including a rigorous evaluation of radiologic changes and an assessment of whether the small differences we observed are clinically important. This short-term randomized controlled trial suggests that there might be a small, but beneficial effect of vitamin D on pain and functional scores in patients with knee OA.

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