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PII: S0002-9343(17)30506-5

DOI: 10.1016/j.amjmed.2017.04.038

Reference: AJM 14098

To appear in: *The American Journal of Medicine*

Received Date: 30 November 2016

Revised Date: 22 February 2017

Accepted Date: 17 April 2017

Please cite this article as: Zheng S, Jin X, Cicuttini F, Wang X, Zhu Z, Wluka A, Han W, Winzenberg T, Antony B, Aitken D, Blizzard L, Jones G, Ding C, Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in knee osteoarthritis, *The American Journal of Medicine* (2017), doi: 10.1016/j.amjmed.2017.04.038.

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# Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in knee osteoarthritis

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**Word count:** 2716

**Funding:** Australian National Health and Medical Research Council Grant (Project Code 605501)

**Conflict of Interest Disclosures:** No COPETING interests were reported.

**Contribution:** Dr Ding has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SZ and CD designed and carried out data analyses, interpreted the results and drafted the manuscript. XJ, FC, XW, ZZ, AEW, WH, TW, BA, DA, LB and GJ were involved in collecting the data, designing the data analyses, interpreting the results, and revising the manuscript for important intellectual content. All authors approved the final version for submission.

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**Abstract**

**Background:** To describe whether maintaining sufficient serum vitamin D levels in people with knee osteoarthritis and baseline vitamin D insufficiency has an association with change in knee structures and symptoms over two years.

**Methods:** Participants (n=413, age 63.2) with symptomatic knee osteoarthritis and vitamin D insufficiency were enrolled in a clinical trial. 340 participants (82.3%) completed the study with 25-hydroxyvitamin D [25(OH)D] measurements at month 0, 3 and 24. Participants were classified as consistently insufficient (serum 25(OH)D≤50nmol/l at month 3 and 24, n=45), fluctuating (25(OH)D>50nmol/l at either point, n=68) and consistently sufficient (25(OH)D>50nmol/l at month 3 and 24, n=226) groups. Knee cartilage volume, cartilage defects, bone marrow lesions and effusion-synovitis volume were assessed using MRI at baseline and month 24. Knee symptoms were assessed at baseline, month 3, 6 12 and 24 using Western Ontario and McMaster Universities Arthritis Index (WOMAC).

**Results:** The consistently sufficient group had significantly less loss of tibial cartilage volume (β: 2.1%, 95 CI%: 0.3%, 3.9%), less increase in effusion-synovitis volume (β: -2.5ml, 95 CI%: -4.7, -0.2) and less loss of WOMAC physical function (β: -94.2, 95% CI: -183.8, -4.5) compared to the consistently insufficient group in multivariable analyses. In contrast, there were no significant differences in these outcomes between the fluctuating and consistently insufficient groups. Changes in cartilage defects, bone marrow lesions and knee pain were similar between groups.

**Conclusion:** This post hoc analysis suggests beneficial effects of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis and physical function in people with knee osteoarthritis.

**Keyword:** Vitamin D; post-hoc; knee osteoarthritis; MRI

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**Background**

Osteoarthritis and vitamin D deficiency are very common conditions worldwide, often co-existing, especially in the aging population[1 2]. Osteoarthritis is a major cause of chronic pain and impaired physical function in older adults and has contributed substantially to an increased economic burden and imposed huge challenges on health systems worldwide[3 4].

The ideal treatment for osteoarthritis is to reduce symptoms and slow disease progression. These may, in turn, reduce the impact of osteoarthritis on patients' mobility and quality of life, with a consequent reduction in the need for the joint replacement surgery and the health care costs in the long term[5]. In experimental studies, sufficient vitamin D can protect against increased bone turnover and cartilage degradation[6-8]. While there is increasing epidemiological evidence suggests that insufficient serum vitamin D status is associated with the progression of osteoarthritis and worsening in its symptoms, the results have been inconsistent[9].

In the Vitamin D Effect on Osteoarthritis (VIDEO) randomised controlled trial, we reported that vitamin D supplementation did not prevent tibial cartilage loss or improve knee pain as assessed using the Western Ontario McMaster Osteoarthritis Index (WOMAC), but had significant but small effects on visual analog scale (VAS) knee pain, total WOMAC score and WOMAC function in post-hoc analyses in participants with symptomatic knee osteoarthritis and insufficient vitamin D levels[10]. Although the level of 25-hydroxyvitamin D (25(OH)D) increased much more in the vitamin D group (40.6 nmol/L) than in the placebo group (6.7 nmol/L) over two years, 62% participants in the placebo group still reached a sufficient level of serum 25(OH)D (>50nmol/l) at month 24 (unpublished data). Thus the high proportion of participants achieving sufficient 25(OH)D level in the placebo group may have masked the beneficial effects of vitamin D supplementation.

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Therefore, we conducted a post-hoc analysis of the VIDEO study to describe whether maintaining sufficient serum vitamin D levels in people with knee osteoarthritis and baseline vitamin D insufficiency had an association with change in knee structures and symptoms over two years.

## Methods

***Participants*** This study is a post-hoc analysis of the VIDEO study. VIDEO was a multicentre, randomized, double-blind, placebo-controlled clinical trial in Tasmania and Victoria, Australia, which aimed to evaluate the effect of vitamin D supplementation over two years on knee pain and knee cartilage volume in people with symptomatic knee osteoarthritis combined with low 25(OH)D levels. Trial design, inclusion and exclusion criteria have been described in the published protocol[11]. Participants had symptomatic knee osteoarthritis (assessed using American College of Rheumatology, ACR criteria[12]) at least for 6 months and had the pain of >20 mm on a 100-mm VAS with low levels of 25(OH) D (between 12.5 and 60 nmol/L). Participants with severe radiographic changes (grade 3 of Altman and Gold Atlas[13]), severe knee pain on standing (>80mm on a 100-mm VAS), contraindications to magnetic resonance imaging (MRI), rheumatoid or psoriatic arthritis, lupus, cancer, severe cardiac or renal impairment, hypersensitivity to vitamin D, conditions affecting oral drug absorption, anticipated knee or hip surgery within the next 2 years, history of significant trauma of knees (e.g. arthroscopy or injury to ligaments or menisci within one year preceding the study) and history of taking vitamin D or an investigational drug within the last 30 days were excluded[11]. 413 participants aged 63.2 years old were included and 340 completed the study with serum 25(OH)D levels measured at month 3 and 24.

***Vitamin D measurement and groups***

Serum 25(OH)D was measured at baseline, month 3 and 24 utilizing direct competitive chemiluminescent immunoassays (DiaSorin Inc.). The intra-assay and inter-assay coefficients of variation were 3.2% and 6.0%, respectively[10]. Serum 25(OH)D levels of ≤50 nmol/l was defined as vitamin D deficient, and of >50 nmol/l defined as vitamin D sufficient[14 15]. Participants for the current analysis were classified into three groups based on the levels of 25(OH)D at month 3 and 24: consistently insufficient (serum 25(OH)D≤50nmol/l at both month 3 and 24), fluctuating (serum 25(OH)D>50nmol/l at either point) and consistently sufficient (serum 25(OH)D>50nmol/l at both month 3 and 24) vitamin D groups.

***Assessment of knee structural changes***

MRI scans of the study knee were obtained according to a standardized protocol using a 1.5 T whole-body MRI unit with a commercial transmit-receive extremity coil at baseline and two years. The sequences used for cartilage volume assessment were sagittal fat saturated T1-weighted spoiled gradient echo. Cartilage defects, bone marrow lesions and effusion-synovitis volume were assessed using T2-weighted/proton density–weighted fast spin echo sequences. MRIs were assessed by trained readers blinded to treatment allocations according to methods described previously[11 16 17].

Cartilage volume was determined using the previously described image processing techniques[11]. The volumes of individual cartilage plates (medial tibial and lateral tibial) were isolated by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis then resampled using bilinear and cubic interpolation for final three-dimensional rendering using OsiriX imaging software (32-bit version 5.9, Pixmeo SARL). The coefficient of variation was 2.1% for medial tibia and 2.2% for the lateral tibia.

Cartilage defects (0-4) were graded using a modification of the Outerbridge classification system at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, with details described in the protocol[18]. A total score of the tibiofemoral compartment was calculated as the total of 2 subregional scores (medial tibial and femoral, lateral tibial and femoral, 0-8). Intra-observer reliability expressed as an intra-class correlation coefficient ranged from 0.77 to 0.94.

Bone marrow lesions, defined as discrete areas of increased signal adjacent to the subcortical bone, were measured using a modification of the classification system of Whole-Organ Magnetic Resonance Imaging Score (0 =none, 1 ≤25% of the subregion, 2 =25%-50%, and 3≥ 50%)[17]. A total score of the tibiofemoral compartment was calculated as the total of 12 subregional scores (0-36). The intra-class correlation coefficient of this bone marrow lesions measurement ranged from 0.93 to 0.98.

Effusion-synovitis volume at 4 regions (suprapatellar pouch, central portion, posterior femoral recess and subpopliteal recess) were isolated from the total volume selecting each region of interest according to the intra-articular fluid-equivalent signal on a section-by-section basis and then resampled by means of bilinear and cubic interpolation for final 3D rendering using OsiriX software[19 20]. The intra-class correlation coefficient were from 0.96 to 0.97.

Change in cartilage volume and effusion-synovitis volume were calculated as follows:

Absolute change (ml) = (follow-up volume) – (baseline volume);

Percentage change per annum (% p.a.) = [(absolute change)/ (baseline volume)]/ (time interval between 2 scans in years) x 100.

Change in cartilage defects and bone marrow lesions were calculated as follow:

Cartilage defects change = (follow-up cartilage defects) – (baseline cartilage defects);

Bone marrow lesions change = (follow-up bone marrow lesions) – (baseline bone marrow lesions).

### *Assessment of symptomatic changes*

Knee symptoms were assessed at baseline and months 3, 6, 12, and 24 using WOMAC and the VAS[21 22]. The total WOMAC score (0-2400) is the sum of subscale scores including pain (0-500), stiffness (0-200), and physical function (0-1700).

### *Anthropometrics and questionnaires*

Height was measured to the nearest 0.1 cm (with shoes removed) using a stadiometer (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK). Weight was measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using electronic scales (Heine S-7307, Heine, New Hampshire, USA). Body mass index ($kg/m^2$) was calculated. We also recorded use of nonsteroidal anti-inflammatory drugs in VIDEO study.

## Statistical Analysis

The one-way ANOVA or Kruskal-Wallis rank tests were used to compare differences in baseline characteristics (age, sex, body mass index, cartilage volume, cartilage defects, bone marrow lesions, effusion-synovitis volume, VAS scores and WOMAC scores) among three vitamin D groups. To take into account missing data, we assumed data were missing at random and used a weighted estimating equation method[23 24]. We estimated the probability of a participant remaining in the study during follow-up by fitting a logistic regression model using the baseline characteristics age, sex, body mass index and level of 25-(OH)D as predictors, for which complete data were available. In subsequent analyses, completed cases were weighted by the inverse of their estimated probabilities of being observed. Univariable and multivariable linear regressions were used to examine the difference in the changes in cartilage volume, cartilage defects, bone marrow lesions and effusion-synovitis volume between vitamin D groups before and after adjustment for age, sex, body mass index, change in season of blood sampling. The difference in changes of symptoms between different vitamin D groups was analysed using a repeated-measures mixed model with terms for age, sex, body mass index and season of blood sampling. The correlation between the repeated measures was addressed by using individual participant identification as a random effect. The differences between groups were further adjusted for use of nonsteroidal anti-inflammatory drugs. We used Stata 12.0 for Windows (Stata Corp LP) for all analyses. A p-value < 0.05 (two-tailed) was regarded as statistically significant.

**Results**

**Participants and Groups** 413 participants (mean age 63.2 years, 50% women) with symptomatic knee osteoarthritis and low vitamin D levels were enrolled in the VIDEO study from June 2010 to December 2011. 340 (82.3%) participants completed the study with 25(OH)D measurements at month 3 and 24. At baseline, participants who did not complete the study were more likely to be female and had lower tibial cartilage volume than those who completed, but there were no other significant differences in baseline characteristics between these groups[10]. Baseline characteristics of participants in three vitamin D status groups are showed in Table 1. Forty-six participants were classified as consistently insufficient (mean age 62.6, 52.2% females), 68 as fluctuating (mean age 62.9, 55.9% females) and 226 as consistently sufficient (mean age 63.5, 43.4% females) vitamin D groups. There were no significant differences in baseline characteristics among groups.

**Change in knee joint structures** There was a dose-response relationship between the status of serum vitamin D and change in total tibial cartilage volume (Figure 1). Participants with consistently sufficient vitamin D experienced significantly less loss of total tibial cartilage volume per year than participants with consistently insufficient vitamin D (Table 2, Figure 1). The differences between these two groups and among three groups remained significant after adjustment for age, sex, body mass index and change in season of blood sampling. A similar pattern was seen for medial and lateral tibial cartilage volume but the trend did not reach statistical significance in adjusted analyses (all $P \leq 0.10$) (data not shown). Similarly, participants with consistently sufficient vitamin D had significantly less increases in effusion-synovitis volume (absolute and percentage per year) compared with participants with consistently insufficient vitamin D (Table 3, Figure 2). The differences between these two groups and among three groups remained significant after adjustment for age, sex, body mass index and season of blood sampling (Table 3). In contrast, there were no significant differences in change in cartilage volume or effusion-synovitis volume between the fluctuating and consistently insufficient vitamin D groups. Additionally, there were no significant differences in changes in total cartilage defects and bone marrow lesions between and among groups (Table 2 and Table 3). We further adjusted for use of nonsteroidal anti-inflammatory drugs and found that the results remained largely unchanged (data not shown).

**Changes in knee symptoms** Changes in WOMAC scores over 24 months are shown in Table 4. There were significant differences in WOMAC physical function between consistently sufficient and consistently insufficient vitamin D groups in the mixed-effect models, adjusted for age, sex, body mass index and change in season of blood sampling (Table 4). Physical function improved time-dependently in consistently sufficient vitamin D group while fluctuated in other two groups over 24 months (Figure 3). The differences in total WOMAC score and physical function were significant among three groups (Table 4). There were no significant differences in WOMAC pain and stiffness between or among groups (Table 4). After further adjustment for nonsteroidal anti-inflammatory drugs use, the results remained largely unchanged (data not shown).

## Discussion

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To the best of our knowledge, this study is the first describing the differences in disease progression and symptoms among people with knee osteoarthritis by vitamin D status over time. It demonstrated that participants who maintained sufficient serum 25(OH)D levels over two years had decreased loss of tibial cartilage volume and less increase in effusion-synovitis volume comparing with those who did not. In addition, WOMAC physical function in participants with persistent vitamin D sufficiency improved significantly more than those with persistent vitamin D insufficiency. However, we did not find significant differences in changes in cartilage defects, bone marrow lesions or knee pain between groups.

Results from previous randomised controlled trials have been mixed and do not provide consistent results[10 25-27]. McAlindon et al reported no effect of vitamin D supplementation (vitamin D3 2000 IU/day over two years, n=146) on cartilage volume loss or knee pain in patients with knee osteoarthritis[26]. However, the major limitations of this study were small sample size, the inclusion of participants with both vitamin D sufficiency and insufficiency, and the inclusion of participants with severe disease[28]. Participants with sufficient vitamin D may not benefit from vitamin D supplementation and patients with severe disease are unlikely to respond to any treatment[28]. Furthermore, a recent trial reported that vitamin D supplementation for three years (800IU per day for three years, n=474) did not slow progression of joint space narrowing (JSN) or reduce WOMAC pain, stiffness and function in knee osteoarthritis [25]. However, the researchers used a radiographic measurement as the outcome, which is less sensitive for change. In contrast, another randomised controlled trial reported that vitamin D supplement at a high dose (60,000 IU per day for 10 days followed by 60,000 IU once a month for a year, n=106) reduced knee pain and improved function in knee osteoarthritis, but this study was limited by its small sample size, short follow-up period and not examining structural change[27]. The VIDEO study aimed to overcome some of the limitations of previous studies but still had consistent negative results for the primary

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outcomes. In the secondary analyses, we found that the intervention group had small but statistically significant improvements in VAS knee pain and WOMAC function when compared with the placebo group[10]. In addition, 62% participants achieved a higher level of 25(OH)D (>50 nmol/l) at month 24 in the placebo group (unpublished data), which was thought in part to result from changes in lifestyle (e.g., sun exposure), dietary supplementation, supplementation of vitamin D outside the trial and seasonal variation.

We hypothesised that the high proportion of sufficient vitamin D level in the placebo group might dilute a beneficial effect of vitamin D supplementation. Thus we performed a post-hoc analysis to examine if maintaining sufficient vitamin D levels over time was associated with beneficial effects on joint structural and symptomatic changes in knee osteoarthritis patients in VIDEO study. Those patients who maintained sufficient serum vitamin D levels over two years had less loss of total tibial cartilage volume per year than those who did not. Furthermore, there was a dose-response relationship between the status of serum vitamin D (consistently insufficient, fluctuating and consistently sufficient) and change in total tibial cartilage volume. In contrast, changes in cartilage defects and bone marrow lesions were not significantly different between and among groups. These results were largely consistent with the findings from two high-quality cohort studies[29 30]. Felson et al[30] reported that low 25(OH)D status was not associated with change in cartilage defects in knee osteoarthritis patients while we reported that high serum 25(OH)D levels were associated with decreased knee cartilage volume loss over 2.7 years in older adults[29].

The relationship between vitamin D status and joint effusion-synovitis in knee osteoarthritis patients is unknown. In the VIDEO study, we recently reported that vitamin D supplementation significantly reduced the increase in effusion-synovit volume compared with placebo in patients with knee osteoarthritis particularly those with baseline effusion-synovitis[31]. The results from this study were consistent with this. The current study found that

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persistent vitamin D sufficiency was associated with improvement in physical function and total WOMAC score, but not with WOMAC pain and WOMAC stiffness. Again, these results were largely consistent with the findings from the VIDEO trial [10].

Overall, our results suggest that maintaining sufficient serum vitamin D may have a small but beneficial effect on retarding cartilage loss, reducing joint inflammation and improving physical function in knee osteoarthritis patients. The analyses in the current study have enabled us to use the actual serum vitamin D levels to define groups, which can reduce the potential confounding effect from those who achieved sufficient vitamin D levels in the placebo group during the trial. However, these data were post hoc and data-driven and need to be confirmed by further clinical trials. Further, loss of follow-up bias would exist; however, the retention rate in this trial was high (82%), and we used inverse probability weighting to count the impact of the missing values. In addition, we defined consistent vitamin D sufficiency or deficiency using 25(OH)D levels at only month 3 and 24, but the course of 25(OH)D levels between these measurements were unknown.

## Conclusions

This post hoc analysis suggests beneficial effects of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis and physical function in people with symptomatic knee osteoarthritis.

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Table 1, Baseline Characteristics in Groups with Different Serum Vitamin D Concentrations

| | Consistently insufficient (N=46) | Fluctuating (N=68) | Consistently sufficient (N=226) | ***P* value** |
|---|---|---|---|---|
| Sex, Female, No. (%) | 24 (52.2%) | 38 (55.9%) | 98 (43.4%) | 0.15 |
| Age, y | 62.6 (8.0) | 62.9 (6.1) | 63.5 (7.2) | 0.68 |
| Body Mass Index | 30.6 (4.6) | 29.0 (4.5) | 29.4 (4.9) | 0.21 |
| *Cartilage Volume, cm$^3$* | | | | |
| Later Tibial | 2.0 (0.7) | 2.0 (0.6) | 2.1 (0.7) | 0.32 |
| Medial Tibial | 1.4 (0.5) | 1.5 (0.5) | 1.6 (0.5) | 0.12 |
| Total Tibial | 3.4 (1.1) | 3.5 (0.9) | 3.7 (1.1) | 0.15 |
| *Tibiofemoral Cartilage Defects, Scores (0-8)* | | | | |
| Lateral | 4.4 (1.8) | 4.4 (1.7) | 4.3 (1.9) | 0.80 |
| Medial | 5.2 (2.0) | 4.9 (2.1) | 4.7 (2.1) | 0.29 |
| *Tibiofemoral Bone Marrow Lesions, Scores (0-18)* | | | | |
| Lateral | 0.6 (1.0) | 0.9 (1.4) | 0.9 (1.4) | 0.48 |
| Medial | 1.7 (2.7) | 1.6 (2.6) | 1.3 (2.2) | 0.55 |
| Effusion-Synovitis Volume, cm$^3$ | 5.7 (5.6) | 8.0 (9.5) | 8.4 (8.5) | 0.14 |
| WOMAC Score System | | | | |
| Pain (0-500) | 144.2 (99.0) | 130.0 (77.4) | 133.8 (86.6) | 0.91 |
| Stiffness(0-200) | 66.9 (44.8) | 61.5 (39.1) | 59.6 (39.4) | 0.64 |
| Function(0-1700) | 524.2 (307.0) | 440.7 (269.1) | 461.8 (308.5) | 0.37 |

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| | | | | |
|---|---|---|---|---|
| Nonsteroidal anti-inflammatory drugs use, No. (%) | 13 (28.3%) | 19 (27.9%) | 70 (31.0%) | 0.86 |

Values are mean (SD) unless otherwise stated.

One-way ANOVA or Kruskal-Wallis rank test was used for the comparisons.

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Table 2, Associations between maintaining vitamin D sufficiency and changes in cartilage volume and cartilage defects over 24 months

| | Univariable | | Multivariable* | |
|---|---|---|---|---|
| | β (95%CI) | P Value | β (95%CI) | P Value |
| **Total tibial Cartilage Volume Change (%/y)** | | | | |
| Consistently insufficient | *Reference* | | *Reference* | |
| Fluctuating | 1.7 (-0.3, 3.6) | 0.10 | 1.5 (-0.5, 3.5) | 0.15 |
| Consistently sufficient | **2.2 (0.4, 4.0)** | **0.02** | **2.1 (0.3, 3.9)** | **0.03** |
| P for trend | | **0.02** | | **0.02** |
| **Change in Total Tibiofemoral Cartilage Defects** | | | | |
| Consistently insufficient | *Reference* | | *Reference* | |
| Fluctuating | -0.3 (-0.8, 0.3) | 0.40 | -0.2 (-0.8, 0.4) | 0.42 |
| Consistently sufficient | -0.4 (-0.9, 0.1) | 0.16 | -0.4 (-0.9, 0.1) | 0.15 |
| P for trend | | 0.16 | | 0.15 |

The dependent variables are percentage change in cartilage volume per year or absolute change in cartilage defects over 24 months;

*Adjusted age, sex and body mass index and change in season of blood sampling;

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Table 3, Association between maintain vitamin D sufficiency and change bone marrow lesions and effusion-synovitis volume over 24 months

| | Univariable | | Multivariable* | |
|---|---|---|---|---|
| | β (95%CI) | P Value | β (95%CI) | P Value |
| **Change in Total Tibiofemoral bone marrow lesions** | | | | |
| Consistently insufficient | *Reference* | | *Reference* | |
| Fluctuating | 0.6 (-0.5, 1.6) | 0.28 | 0.6 (-0.5, 1.6) | 0.30 |
| Consistently sufficient | 0.5 (-0.4, 1.4) | 0.25 | 0.5 (-0.4, 1.4) | 0.25 |
| P for trend | | 0.36 | | 0.33 |
| **Effusion-Synovitis Absolute Volume Change (ml)** | | | | |
| Consistently insufficient | *Reference* | | *Reference* | |
| Fluctuating | 0.5 (-2.8, 3.8) | 0.77 | 0.7 (-2.5, 3.9) | 0.66 |
| Consistently sufficient | **-2.4 (-4.5, -0.2)** | **0.03** | **-2.5 (-4.7, -0.2)** | **0.03** |
| P for trend | | **0.01** | | **<0.01** |
| **Effusion-Synovitis Volume Change (%/y)** | | | | |
| Consistently insufficient | *Reference* | | *Reference* | |
| Fluctuating | -9.5 (-118.4, 99.3) | 0.86 | 2.2 (-112.2, 116.6) | 0.97 |
| Consistently sufficient | **-69.5 (-133.4, -5.6)** | **0.03** | **-61.8 (-121.9, -1.7)** | **0.04** |
| P for trend | | **0.01** | | **0.01** |

The dependent variables are absolute change in bone marrow lesions or percentage change per year/absolute change in effusion-synovitis volume over 24 months;

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*Adjusted for age, sex, body mass index and change in season of blood sampling;

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Table 4, Associations between maintaining vitamin D sufficiency and changes in clinical symptoms over 24 months

| | Change<br>Mean (95%CI) | Multivariable*<br>β (95%CI) | P<br>Value |
|---|---|---|---|
| **Total WOMAC Score** | | | |
| Consistently insufficient | -123.2 (-236.1, -10.4) | *Reference* | |
| Fluctuating | -111.4 (-194.8, -28.0) | 11.8 (-128.5, 152.1) | 0.87 |
| Consistently sufficient | -240.4 (-298.4, -182.5) | -117.2 (-244.1, 9.6) | 0.07 |
| P for trend | | | **<0.01** |
| **Pain** | | | |
| Consistently insufficient | -34.7 (-66.6, -3.0) | *Reference* | |
| Fluctuating | -31.7 (-54.7, -8.8) | 3.0 (-36.2, 42.3) | 0.88 |
| Consistently sufficient | -50.2 (-63.7, -36.6) | -15.4 (-49.9, 19.2) | 0.38 |
| P for trend | | | 0.11 |
| **Stiffness** | | | |
| Consistently insufficient | -11.7 (-25.1, 1.6) | *Reference* | |
| Fluctuating | -16.5 (-27.1, -6.0) | -4.7 (-21.7, 12.3) | 0.59 |
| Consistently sufficient | -20.3 (-26.4, -14.2) | -8.5 (-23.2, 6.1) | 0.25 |
| P for trend | | | 0.17 |
| **Function** | | | |
| Consistently insufficient | -76.0 (-153.6, 1.6) | *Reference* | |
| Fluctuating | -61.9 (-118.5, -5.3) | 14.8 (-82.6, 112.2) | *0.77* |
| Consistently sufficient | -170.8 (-212.8, -128.8) | *-94.2 (-183.8, -4.5)* | ***0.04*** |
| P for trend | | | **<0.01** |

WOMAC: Western Ontario McMaster Osteoarthritis Index; VAS: Visual Analog Scale;

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Mixed effect model adjusted for age, sex, body mass index and change in season of blood sampling;

Change in WOMAC scores results are generated from mixed models adjusted for age, sex, body mass index and change in season of blood sampling;

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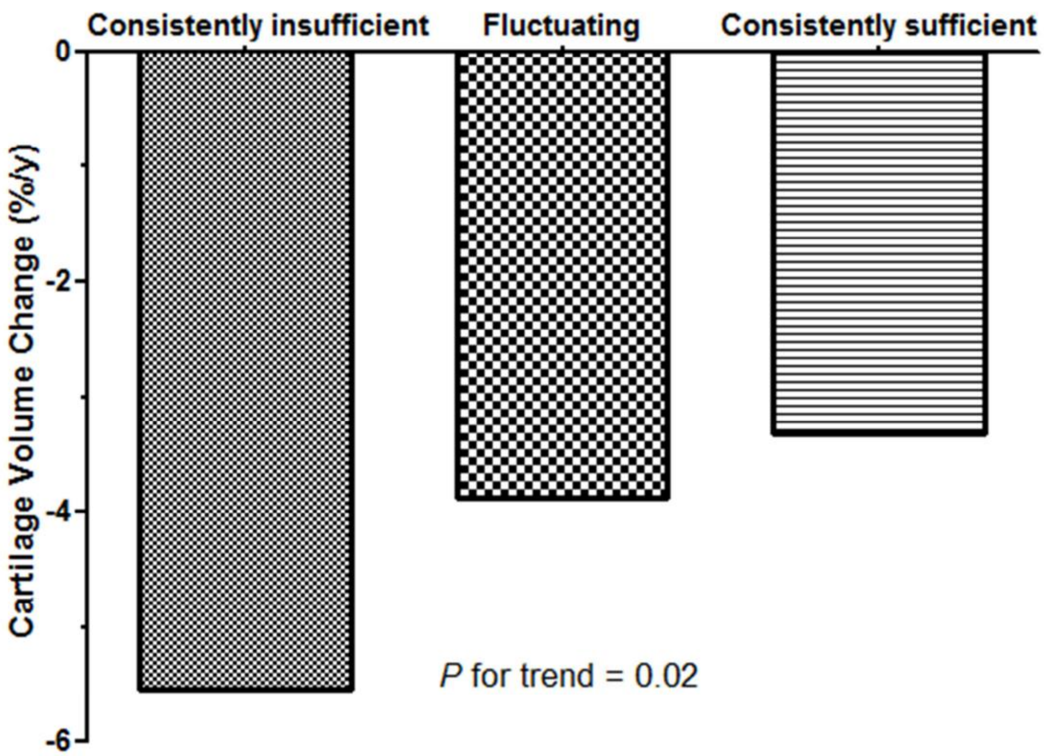
Figure 1, Tibial Cartilage Volume Change (%/y) in knee OA patients with or without sufficient serum vitamin D levels over 24 months.




Consistently insufficient vitamin D group: serum 25-OHD≤ 50nmol/l at both month 3 and 24;

Fluctuating vitamin D group: serum 25-OHD> 50nmol/l at either time point;

Consistently sufficient vitamin D group: serum 25-OHD> 50nmol/l at both month 3 and 24.

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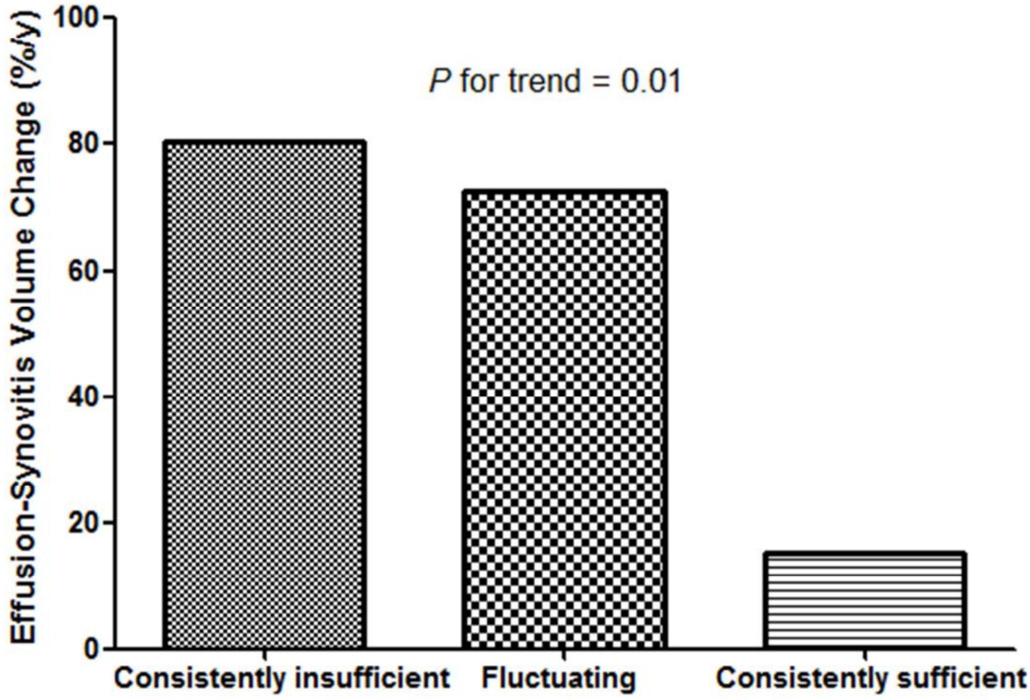
Figure 2, Effusion-Synovitis Volume Change (%/y) in knee OA patients with or without sufficient serum vitamin D levels over 24 months.




Consistently insufficient vitamin D group: serum 25-OHD≤ 50nmol/l at both month 3 and 24;

Fluctuating vitamin D group: serum 25-OHD> 50nmol/l at either time point;

Consistently sufficient vitamin D group: serum 25-OHD> 50nmol/l at both month 3 and 24.

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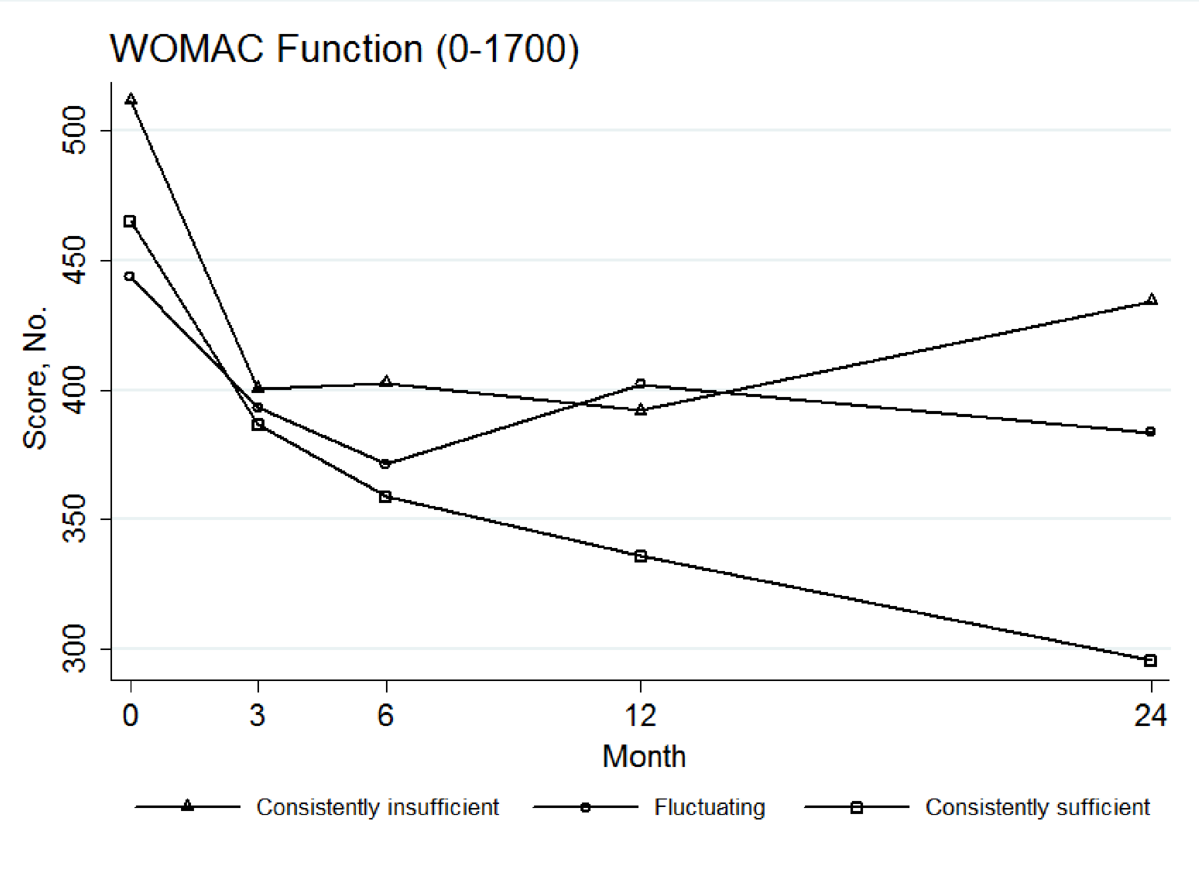
Figure 3, Changes in WOMAC Function in knee OA patients with or without sufficient serum vitamin D levels over 24 months.




Consistently insufficient vitamin D group: serum 25-OHD≤ 50nmol/l at both month 3 and 24;

Fluctuating vitamin D group: serum 25-OHD> 50nmol/l at either time point;

Consistently sufficient vitamin D group: serum 25-OHD> 50nmol/l at both month 3 and 24.

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Clinical Significance

- The evidence of whether vitamin D supplementation is an effective treatment for osteoarthritis is contradictory.
- Patients who are maintaining vitamin D sufficiency had significantly less loss of tibial cartilage volume, less increase in effusion-synovitis volume and less loss of WOMAC physical function compared with those who did not maintain vitamin D sufficiency in patients with symptomatic knee osteoarthritis.
- Maintaining vitamin D sufficiency may have beneficial effects in knee osteoarthritic patients.

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