TITLE PAGE

Manuscript title:

The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial

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Running title: Vitamin D in knee osteoarthritis

Abstract

Objective: Epidemiological data suggest low serum 25-hydroxyvitamin D_3 (25-OH-D_3) levels are associated with radiological progression of knee osteoarthritis (OA). This study aimed to assess whether vitamin D supplementation can slow the rate of progression.

Method: A 3 year, double-blind, randomised, placebo-controlled trial of 474 patients aged over 50 with radiographically evident knee OA comparing 800 IU cholecalciferol daily with placebo. Primary outcome was difference in rate of medial joint space narrowing (JSN). Secondary outcomes included lateral JSN, Kellgren and Lawrence grade, WOMAC pain, function, stiffness and the Get up and Go test.

Results: Vitamin D supplementation increased 25-OH-D_3 from an average of 20·7 (SD 8·9) µg/L to 30·4 (SD 7·7) µg/L, compared to 20·7 (SD 8·1) µg/L and 20·3 (SD 8·1) µg/L in the placebo group. There was no significant difference in the rate of JSN over three years in the medial compartment of the index knee between the treatment group (average -0.01 mm/year) and placebo group (-0.08 mm/year), average difference 0.08 mm/year, (95% CI [-0·14 to 0·29], p=0.49). No significant interaction was found between baseline vitamin D levels and treatment effect. There were no significant differences for any of the secondary outcome measures.

Conclusion: Vitamin D supplementation did not slow the rate of JSN or lead to reduced pain, stiffness or functional loss over a three year period. On the basis of these findings we consider that vitamin D supplementation has no role in the management of knee OA.

Abstract word count: 240/250

Key words: Vitamin D, knee, randomized placebo controlled trial, osteoarthritis

Introduction

Knee Osteoarthritis (OA) is a chronic, painful disease associated with considerable morbidity, costs and disability [1]. In the U.S., it is estimated that over a third of people aged over 60 have radiographic knee OA[2] and over 50% of these with knee OA will go on to have a total knee replacement in their lifetime[3]. At present there are no licensed treatments that alter disease progression and management is primarily concerned with symptom control to retain or improve joint function.

Vitamin D deficiency (defined as 25-hydroxyvitamin D_3(25-OH-D_3) serum levels below 20µg/mL [4 5]) is common in the UK with estimates of over 12% for people living in private households and 30% of care home residents in the over 65s. There has been considerable interest in the association between vitamin D deficiency and OA incidence and progression. Vitamin D has a number of important biological functions in bone, cartilage and muscle[6] which has led to the hypothesis that vitamin D supplementation may prevent the progression of OA. There is evidence from a number of, but not all, epidemiological studies suggesting that low dietary intake of vitamin D and low serum 25-OH-D_3 levels are associated with increased radiological progression of knee OA [7-13]. Epidemiological data from the Framingham Study demonstrated that low vitamin D intake was associated with a three to four-fold increased risk of radiographic progression at two skeletal sites over 8-10 years.[7] Further analysis of a separate cohort of patients in the Framingham study, along with another cohort from the Boston Osteoarthritis of the Knee Study (BOKS) found no association between vitamin D status and joint space or cartilage loss in knee OA [12].

Findings from RCTs have thus far not conclusively settled this debate [14-17]. A 12 month trial of vitamin D in 107 vitamin D insufficient subjects with knee OA found a small but statistically significant improvement in pain [14]. A trial of 146 subjects with symptomatic knee OA found that vitamin D

supplementation for two years had no effect on the structural progression of OA using MRI as the primary outcome [16]. A further post hoc analysis of a RCT concluded that calcium plus vitamin D supplementation for two years in post-menopausal women had no effect on self-reported frequency or severity of joint symptoms [17]. As these trials were heterogeneous in terms of patients recruited, sample sizes and some also used calcium in addition to vitamin D supplements, it is important to have a large RCT with a prolonged follow up to provide further clarity on the role of vitamin supplementation in patients with knee OA.

Aim

The primary aim of this trial was to determine whether vitamin D supplementation can reduce the rate of structural progression of knee OA as measured by change in medial joint space assessed on a weight-bearing radiograph over a 3-year period. Secondary outcomes included changes in pain and function.

Methods

Study design

The VIDEO study was a double-blind, randomised, placebo-controlled trial performed at five UK NHS hospitals. Participants were randomly assigned to receive either 800IU of oral cholecalciferol or matched placebo daily. Data from clinical trials indicated that 800IU/day of cholecalciferol can produce significant increases in serum 25-hydroxyvitamin D_3 levels and that these increases are evident within one month of starting treatment[18]. The protocol was approved by the Scotland A Research Ethics Committee and the trial was registered with EudraCT: ref. 2004-000169-37,

ISRCTN94818153, CTA No. 11287/0001/001. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Participants were identified from GP lists, patient referrals to hospitals and via radio advertisements. Patients were eligible if they: were aged >50 years, ambulatory, had radiological evidence of knee OA at medial tibio-femoral knee compartment (Modified Kellgren & Lawrence (K&L) score 2/3, JSW >1mm) and knee pain for most days of the previous month. Reasons for exclusion were: secondary OA, inflammatory arthritis, early morning knee stiffness for >30 minutes, cod liver oil or vitamin supplementation containing vitamin D >200 IU, glucosamine or chondroitin use for <three months, osteoporotic fracture, previous knee surgery or arthroscopy within six months, use of bisphosphonates within two years. Eligible participants were invited to a screening appointment. Informed consent was taken along with knee radiographs, which were assessed by the local clinician to determine eligibility.

Randomisation and blinding

Eligible participants were randomised centrally by the UK Medical Research Council Clinical Trials Unit (MRC CTU) via telephone to receive either oral vitamin D or matching placebo tablets (1:1) by computer-generated randomisation with stratification by recruitment centre. Treatment allocation was concealed from the patients, clinicians, outcome assessors and investigators. Both the active treatment and placebo were manufactured by Thompson and Capper Ltd, and packed by Bilcare Global Clinical Supplies (Europe) Ltd.

Trial procedures

At the baseline visit knee bilateral radiographs and blood samples were taken, and the assigned drug dispensed in six month packs. Radiographs and blood sampling were repeated at 12 months and 36 months. Questionnaires (WOMAC) were completed at 6-monthly intervals until the final visit. Blood was drawn to measure serum 25-OH-D_3 at baseline and 12 months to assess baseline vitamin D status and response to supplementation. Serum vitamin D_2 and D_3 concentrations were assayed at King's College Hospitals NHS Foundation Trust via mass spectrophotometry using the MassChrom reagent kit (Chromsystems Instruments & Chemicals GmbH).

Outcome measures

The primary outcome measure was radiological progression of knee OA in the medial joint compartment of the index knee (knee with the smallest joint space width (JSW) at baseline in the case of bilateral disease), as measured by the rate of JSN (mm/year) over the three years. Knee X-rays were taken using the MTP technique [19] using a foot map to improve accurate re-positioning at follow up visits.

All joint space measurements were performed by a single reader. Reproducibility was excellent, and comparable to previous results using the same software package [20, 21]; intra-rater intra-class correlation coefficients (ICCs) were: 0·96 medial 95% CI [0·88-0·98], 0·98 lateral 95% CI [0·94 0·99].

Secondary outcomes measures included: rates of change in minimum JSW of the lateral compartment, and of the medial and lateral compartments of the contralateral knee, Kellgren and Lawrence (K&L)[22, 23] grade, WOMAC VAS scores (0-100 pain, stiffness, function and total) in the index

knee, and Get up and Go test. Baseline and follow-up X-rays were graded for K&L grade by a Clinical Orthopaedic Fellow, with an intra-reader Kappa of 0·68.

Sample size

The study was designed to detect a clinically important mean difference of 0·22mm/year in the rate of JSN between treatment groups over three years, assuming a standard deviation of 0·7 mm [24, 25], with 80% power at the 5% significance level. Allowing for 32% drop-out rate, the total sample size required was 470.

Statistics

Analysis was conducted following the intention-to-treat principle and in accordance with a pre-specified analysis plan which was finalised prior to database lock and breaking the blind.

To assess JSN a longitudinal analysis was performed using a linear mixed regression model with fixed effects for treatment, time, treatment by time and adjustment for: baseline JSW, centre, gender, glucosamine or chondroitin use, age and BMI. To allow for between patient differences the model included a random patient intercept. The central parameter of interest was the treatment by time interaction, which represents the average difference in the rate of JSN/year between the treatment groups. Continuous secondary outcomes were analysed similarly. Changes in ordinal outcomes over time were analysed using ordinal logistic regression models with robust Huber-White sandwich estimators of standard errors. The effect of treatment on the proportion of patients with clinically significant progression (JSN>0·5mm in the index knee) at three years was obtained using a Poisson

regression model with robust error estimates. For patients who had a total knee replacement (TKR) in the index knee during the trial, clinically significant progression was assumed.

Mean imputation was used to deal with missing covariate values [26]. For patients who had TKR during the trial, data before surgery was included and data after surgery assumed to be missing. All missing outcome values were assumed to be missing at random and multiple imputation by chained equations was used [27, 28]. Sensitivity analyses, including analysis of the complete cases and a range of missing not at random mechanisms, were performed to assess the robustness of the primary results to the effect of missing data (for full details see supplementary file eTable 2 and eFigure 1). All statistical analyses were performed using Stata/IC version 12·1 (StataCorp, College Station, TC, USA).

Results

In total, 474 participants were recruited between 19/01/2005 and 13/06/2008. Table 1 shows baseline clinical data and baseline radiographic characteristics. Additional baseline variables can be found in the supplementary file, eTable 1. The treatment and placebo groups were well matched for clinical characteristics and showed a similar distribution of radiographic characteristics. The distribution of serum 25-OH-D_3, divided into tertiles (table 3), was almost identical in the two groups, with 50% of both groups vitamin D_3 deficient (<20µg/L).

As shown in Figure 1, 198 of participants in the placebo group (84%) and 188 of those in the treatment group (79%) attended the 3-year follow-up visit. Six patients in the placebo group and seven in the vitamin D group received a TKR of the index knee during the follow up period. Due to a combination of technical and logistic reasons, including poor positioning and quality a number of radiographs from attending patients, including baseline, could not be evaluated for JSW accurately. JSW in the medial compartment of the index knee was missing for a total of 37/474 patients (8%) at

baseline (18/237 placebo, versus 19/237 active), 110/474 patients (23%) at year one (58/237 placebo versus 52/237 active) and 183/474 (39%) at year three (87/237 placebo versus, 96/237 active). 38% of the missingness at year one (42/110) was due to unreadable X-rays (23 placebo and 19 active). 30% of the missingness at year three (55/183) was due to unreadable X-rays (27 placebo versus 28 vitamin D). The remaining missingness at year three occurred due to withdrawal 54% (99/183, 49 placebo (3 with TKR of index knee at one year) and 50 active (1 with TKR of index knee at one year)), loss to follow-up 10% (18/183, 7 placebo and 11 active), TKR of the index knee at year three 5% (9/183, 3 placebo and 6 active) or death 1% (2/183, 1 placebo and 1 active). Missingness of X-ray data did not vary by treatment arm. 380/474 patients (189/237 placebo, 191/237 active) had baseline and at least one follow up JSW reading available and were analysed separately as a sensitivity analysis. A separate analysis of the 242/474 patients (125/237 placebo, 117/237 active) with complete follow-up was also performed along with additional sensitivity analysis to assess the impact of missing data (supplementary file eTable 2 and eFigure 1).

Vitamin D analysis

At 12 months, serum vitamin D_3 levels had increased from an average of 20·7 (8·9) μg/L at baseline to 30·4 (7·7) μg/L in the vitamin D group. Levels decreased for those receiving placebo from 20·7 (8·1) μg/L at baseline to 20·3 (8·1) μg/L at 12 months (table 3). The number of patients with vitamin D deficiency (<20 μg/L) fell to 7% in the vitamin D group but rose to 54% in the placebo group.

Radiographic results

There was no significant difference in the rate of JSN over three years in the medial compartment of the index knee between treatment groups (-0.01mm/year versus -0.08mm/year for vitamin D and placebo respectively), between group difference 0·08 mm/year, 95% CI [-0·14 to 0·29], p=0·49 (figure 2, table 2). Sensitivity analyses conducted to assess the effect of missing values on the estimated treatment effect produced results no different from the primary analysis (supplementary file eTable 2 and eFigure 1). No interaction between baseline vitamin D status and treatment effect (Δ) was found (<20 μg/L, Δ 0·06, 95% CI [-0·20 to 0·32]; 20 μg/L to 30 μg/L, Δ 0·05, 95% CI [-0·20 to 0·29]; >30 μg/L, Δ 0·05, 95% CI [-0·30 to 0·40]) (Figure 3).

There was no difference in the proportion of patients with clinically significant progression of JSN (JSN>0.5mm in the index knee) at three years between the vitamin D group (39%) and placebo group (37%). The absolute risk difference was 2% (95% CI [-10% to 14%], p = 0.76) (Table 2).

We explored the hypothesis that there may be an interaction between treatment effect and baseline JSN. The interaction did not reach significance (p=0·86, N = 474).

Secondary outcomes

The placebo group showed an increase in WOMAC pain whereas the vitamin D group showed a small decrease (0.71 versus -0.08 per year, between group difference -0.79, 95% CI [-2.31 to 0.74], table 2, eFigure 2). WOMAC stiffness decreased in both groups (-2·02 versus -0.50 per year for vitamin D and placebo groups respectively, between group difference -1.52, 95% CI [-3.24 to 0.21]). WOMAC function increased for both groups (0.42 versus 1.07 per year for vitamin D and placebo, between group difference -0·65, 95% CI [-2·09 to 0·79]) . None of the above differences achieved statistical significance.

Odds ratios of a higher K&L grade per year were calculated as 1.32 (Vitamin D) and 1.23 (placebo) for the index knee and 1.19 (Vitamin D) and 1.18 (placebo) for the contralateral knee. This gave a treatment by time odds ratio, which represents the increase in odds of a higher K&L grade per year for vitamin D patients relative to placebo, of 1.07 (95% CI [0.88 to 1.31]) for the index knee and 1.01 (95% CI [0.80 to 1.27]) for the contralateral knee (Table 2). The odds of a higher get up and go test grade per year for Vitamin D patients was 1.00 and 1.04 for placebo patients. There was no significant difference in the odds of a higher get up and go test grade over time between the treatment groups (OR = 0.96, 95% CI [0.73 to 1.27]). Additional secondary outcomes were assessed and treatment effect estimates can be found in the supplementary file eTable 4. All outcomes at three years are summarised in eTable 5.

Adverse events

There was no difference in the proportion of patients experiencing SAE's between the vitamin D (59/237, 25%) and placebo group (64/237, 27%), p = 0.67. Only 2 SAE's were classified as possibly related to treatment (one placebo with pancreatitis and one vitamin D with calculus ureteric), the remaining SAE's were classified as unrelated to treatment. There were no differences in the rates of occurrence of hypercalcaemia (five placebo, three vitamin D) or hypercalciuria (34 placebo, 46 vitamin D).

Discussion

There is no clear evidence that vitamin D supplementation, at a dose of 800 IU cholecalciferol daily, had an effect on the progression of knee OA over the three year period, as measured by changes in JSW, or on knee pain, function or stiffness. This is despite the fact that participants had high rates of vitamin D deficiency at trial entry, and the level of supplementation was sufficient to increase serum vitamin D levels by 10 µg/L on average in the first year of treatment, reducing the proportion of participants with deficiency by over 80%.

Previous research has not provided a consensus on the effect of vitamin D on the progression of knee OA, with observational studies and RCTs generating conflicting findings. Several high quality epidemiologic studies have demonstrated an association between low serum vitamin D and /or vitamin D intake and the risk of either OA incidence or progression [8-11], however others have shown no association [12, 13, 15, 29-31]. These studies vary in methodology and were also subject to a number of important biases.

McAlindon performed a two year RCT of 2000 IU/day oral cholecalciferol for patients with symptomatic knee OA. The primary outcomes were knee cartilage volume loss measured by MRI and knee pain by WOMAC. The population studied had similar baseline concentrations of vitamin D but greater baseline JSW (approximately 5mm vs. 3.5mm). The results demonstrated that despite 61.3% of patients achieving target concentrations of vitamin D, there were no significant improvements over placebo in any of the outcomes. Sanghi *et al* performed a 12 month RCT of vitamin D supplementation in patients with knee OA and vitamin D deficiency [15]. They demonstrated a statistically significant reduction in pain and increase in physical function in a group taking vitamin D compared with placebo, however the difference between the two groups was not deemed to be clinically important [32]. Jin *et al* performed a two year RCT of vitamin D supplementation, also in patients with knee OA and low vitamin D levels. The primary outcomes were knee cartilage volume loss measured by MRI and knee pain by WOMAC. No reduction in knee cartilage volume loss of pain was observed[33].

The results from our study, which in comparison to the previous studies is the largest pragmatic trial with inclusion of non-vitamin D deficient patients, are consistent with the above results. The VIDEO trial contributes several new findings. Firstly, we measured JSN and K&L grade in the contra-lateral knee. This is important as pathogenic mechanisms may be different in the contra-lateral joint compared with the index knee which exhibits later stage disease in patients with bilateral OA, as suggested in the Doxycycline trial by Brandt *et al* [25]. In addition, we measured JSN in the medial and lateral compartments individually. Although medial compartment disease is far more prevalent, and the majority of previous studies focus only on joint space changes in the medial compartment [4, 25], it is important to measure JSN in the lateral compartment to ensure disease progression is not missed [34]. We looked at the association of the treatment effect with baseline [25-OH-D_3] concentration and the change in vitamin D concentration after 12 months of treatment. This study has a longer follow-up period than previous trials, with three year JSN having been shown in a previous study to be predictive of the incidence of osteoarthritis related knee surgery [35].

Our results indicate that Vitamin D supplementation at a level of 800 IU daily is safe. Only 2 SAE's were classified as possibly being related to treatment (one placebo with pancreatitis and one vitamin D with calculus ureteric). All other recorded SAE's were unrelated to treatment. Rates of occurrence of hypercalcaemia and hypercalciuria were comparable across treatment arms.

Strengths and potential limitations

A key strength of VIDEO was the inclusion of patients who were not biochemically vitamin D deficient. Laslett *et al* found that vitamin D deficiency was associated with incident or worsening of knee pain over a five year period [36], suggesting that vitamin D supplementation would be effective in

attenuating the progression of knee pain only in those who already show moderate deficiency. However, 50% of VIDEO participants had vitamin D insufficiency (<20 μg/L) at baseline.

When analysis of treatment effect on JSN was broken down by baseline vitamin D status, no significant interactions with the treatment effect were found. Vitamin D supplementation had no effect on the change in joint space width even in subjects who were vitamin D deficient.

We acknowledge limitations. The radiographs from the screening visits were read by the local PI at each centre to establish eligibility into the trial. A clinical orthopaedic fellow re-read all the baseline x-rays for the final analysis. This explains why a proportion of the baseline radiographs were determined to be K&L grade 1, while the inclusion criteria specified K&L ≥2. The difference between the definitions of the two grades relates to a possible *vs.* definite osteophyte, this boundary being particularly subjective. The distribution however was similar between the two groups and would be unlikely to bias the results of the trial. Of interest, it allowed us to assess the effect of vitamin D in very early OA.

The proportion of participants lost to follow-up by the three year visit (16% placebo group, 21% treatment group) could be considered a limiting factor. This rate of loss is consistent with other OA trials [4, 17, 25, 37] and the sample size calculation allowed for 32% loss to follow up. An additional number of x-rays were unevaluable for JSW due to technical and logistic reasons. However, there was no evidence of a differential loss to follow up or unevaluable X-rays between treatment arms and detailed sensitivity analyses to assess the impact of missing data (described in supplementary file) were consistent with the primary analysis.

Conclusions

Vitamin D supplementation, at a dose sufficient to elevate serum vitamin D_3 levels by 10 µg/L in one year, did not slow the rate of JSN or lead to reduced pain, stiffness or functional loss over a three year period, when compared with placebo. On the basis of these findings we consider that vitamin D supplementation has no role in the management of knee OA.

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Author Contributions

RK, NKA, FB, TWON, AM, CC, CJD contributed to the design of the work and acquisition of the data. AB and SAT contributed to the acquisition of the data. SC, CJD, SS, DJH, SJ contributed to the analysis of the data.

All authors contributed to drafting the work or revising the content critically and all authors have approved the final version.

NKA had 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.

Role of the funding source

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Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare the following interests:

NA reports consultancy work for Merck, Roche, Smith & Nephew, Q-Med, Nicox, Flexion, payment for lectures from Bioiberica and Servier, outside of the submitted work.

CC reports personal fees from Servier, personal fees from Amgen, personal fees from Eli Lilly, personal fees from Merck, personal fees from Medtronic, personal fees from Novartis, outside the submitted work.

Ethics statement

The trial was registered with EudraCT: ref. 2004-000169-37, ISRCTN94818153, CTA No. 11287/0001/001, and the protocol received full approval from the Scotland A Research Ethics Committee (NHS REC Application Reference: 04/MRE10/30). The full protocol can be accessed at http://www.ctu.mrc.ac.uk/our_research/research_areas/other_conditions/studies/video/.

Data sharing statement

Anonymised patient level data and statistical code available from the corresponding author at nigel.arden@ndorms.ox.ac.uk.

References

1. Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. Curr Opin Rheumatol. 2006; 18(2): 147-56.

2. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010; 26(3):355-69
3. Weinstein AM, Rome BN, Reichmann WM, Collins JE, Burbine SA, Thornhill TS, et al. Estimating the Burden of Total Knee Replacement in the United States. J Bone Joint Surg Am. 2013; 95A(5):385-92.
4. Hirani V, Primatesta P. Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey. Age and Ageing. 2005; 34(5): 485-91.
5. Bruyere O, Slomian J, Beaudart C, Buckinx F, Cavalier E, Gillain S, et al. Prevalence of vitamin D inadequacy in European women aged over 80 years. Archives of Gerontology and Geriatrics. 2014; 59(1): 78-82.
6. Bikle DD. Vitamin D and bone. Curr Osteoporos Rep. 2012; 10(2): 151-9.
7. McAlindon TE, Felson DT, Zhang YQ, Hannan MT, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med. 1996; 125(5): 353-9.
8. Ding C, Cicuttini F, Parameswaran V, Burgess J, Quinn S, Jones G. Serum Levels of Vitamin D, Sunlight Exposure, and Knee Cartilage Loss in Older Adults The Tasmanian Older Adult Cohort Study. Arthritis Rheum. 2009; 60(5): 1381-9.
9. Bergink AP, Uitterlinden AG, Van Leeuwen JPTM, Buurman CJ, Hofman A, Verhaar JAN, et al. Vitamin D Status, Bone Mineral Density, and the Development of Radiographic Osteoarthritis of the Knee The Rotterdam Study. Jcr-J Clin Rheumatol. 2009; 15(5): 230-7.
10. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. Int Orthop. 2011; 35(11): 1627-31.
11. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis - A longitudinal study. Arthritis Rheum. 1999; 42(5): 854-60.

12. Felson DT, Niu JB, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis - Results of two longitudinal studies. Arthritis Rheum. 2007; 56(1): 129-36.
13. Zhang FF, Driban JB, Lo GH, Price LL, Booth S, Eaton CB, et al. Vitamin D Deficiency Is Associated with Progression of Knee Osteoarthritis. J Nutr. 2014; 144(12): 2002-8.
14. Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, et al. Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial. Clin Orthop Relat R. 2013; 471(11): 3556-62.
15. Sanghi D, Srivastava RN, Mishra A, Natu S, Mishra R, Agarwal S. ROLE OF VITAMIN D IN OSTEOARTHRITIS KNEE: A SIX MONTH DOUBLE BLIND, RANDOMIZED, PLACEBO CONTROL TRIAL. Osteoarthr Cartilage. 2013; 21: S28-S9.
16. McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, et al. Effect of Vitamin D Supplementation on Progression of Knee Pain and Cartilage Volume Loss in Patients With Symptomatic Osteoarthritis A Randomized Controlled Trial. Jama-J Am Med Assoc. 2013; 309(2): 155-62.
17. Chlebowski RT, Pettinger M, Johnson KC, Wallace R, Womack C, Mossavar-Rahmani Y, et al. Calcium Plus Vitamin D Supplementation and Joint Symptoms in Postmenopausal Women in the Women's Health Initiative Randomized Trial. Journal of the Academy of Nutrition and Dietetics. 2013; 113(10): 1302-10.
18. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999; 69: 842-856.
19. Duddy J, Kirwan JR, Szebenyi B, Clarke S, Granell R, Volkov S. A comparison of the semiflexed (MTP) view with the standing extended view (SEV) in the radiographic assessment of knee osteoarthritis in a busy routine X-ray department. Rheumatology (Oxford). 2005; 44(3): 349-51.

20. Leyland KM, Judge A, Bottomley N, Gill R, Hart D, Javiad MK, et al. Bezier curves for measuring joint space on knee radiographs - reproducibility and validity. Osteoarthritis and Cartilage. 2011; 19: S180-S181.
21. Leyland KM, Judge A, Hunter D, Spector T, Hart D, Javiad MK, et al. Joint space narrowing predicts future knee replacements up to 15 years later. British Society of Rheumatology; 2013; 52: 152-152.
22. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. Annals of the Rheumatic Diseases. 1957; 16(4): 494-502.
23. Kellgren JH, Bier F, Lawrence JS. Genetic Factors in Generalized Osteo-Arthrosis. Annals of the Rheumatic Diseases. 1963; 22(4): 237-&.
24. Bingham CO, Buckland-Wright JC, Garnero P, Cohen SB, DougadoS M, Adarni S, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee - Results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006; 54(11): 3494-507.
25. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, et al. Effects of doxycycline on progression of osteoarthritis - Results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum. 2005; 52(7): 2015-25.
26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011; 30(4): 377-99.
27. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons; 1987.
28. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999; 18(6): 681-94.

29. Konstari S, Paananen M, Heliovaara M, Knekt P, Marniemi J, Impivaara O, et al. Association of 25-hydroxyvitamin D with the incidence of knee and hip osteoarthritis: a 22-year follow-up study. Scandinavian Journal of Rheumatology. 2012; 41(2): 124-31.
30. Muraki S, Dennison E, Jameson K, Boucher BJ, Akune T, Yoshimura N, et al. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. Osteoarthr Cartilage. 2011; 19(11): 1301-6.
31. Jagannath D EMH, Parsons C, Litwic A, Cooper C, Dennison E. Serum Vitamin D Does Not Influence Rate of Progression of Knee Osteoarthritis Over 10 Years: Results from the Hertfordshire Cohort Study Rheumatology. 2014; 53(Supplement 1).
32. Stratford PW, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. Osteoarthr Cartilage. 2007; 15(3): 266-72.
33. Jin X, Jones G, Cicuttini F, Wluka A, Zhu Z, Han W, et al. Effect of vitmain D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis, a randomized trial. Jama-J Am Med Assoc. 2016; 315(10): 1005-1013.
34. Felson DT, Nevitt MC, Yang M, Clancy M, Niu J, Torner JC, et al. A new approach yields high rates of radiographic progression in knee osteoarthritis. Journal of Rheumatology. 2008; 35(10): 2047-54.
35. Bruyere O, Richy F, Reginster JY. Three year joint space narrowing predicts long term incidence of knee surgery in patients with osteoarthritis: an eight year prospective follow up study. Annals of the Rheumatic Diseases. 2005; 64(12): 1727-30.
36. Laslett LL, Quinn S, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. Annals of the Rheumatic Diseases. 2014; 73(4): 697-703.
37. Spector TD, Conaghan PG, Buckland-Wright JC, Garnero P, Cline GA, Beary JF, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK

randomized, controlled trial ISRCTN01928173. Arthritis Research & Therapy. 2005; 7(3): R625-R33.

564 **Figure Legends**

565

566 Figure 1. Consort flow diagram for the VIDEO study

567

568 Figure 2. Mean Joint Space Width in the medial compartment of the index knee with 95% CI's by
569 treatment group (N = 474). All available readings were included in primary analysis and multiple
570 imputation was used to impute missing values, assuming all missing outcome values were missing at
571 random, conditional on treatment and the covariates included in the imputation model. Both centre
572 and baseline BMI were included in the imputation model.

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574 Figure 3. Scatterplot of baseline Vitamin D_3 against three year change in Joint Space Width by
575 treatment group with linear fit imposed (N = 463).

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582 **Table 1 Baseline Clinical and radiographic Characteristics as mean (sd) or number (%).**

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	N vitamin D / N Placebo	Vitamin D	Placebo
Age (yrs)	237/237	64 (8)	64 (8)
Sex: (% Female)	237/237	144 (61%)	145 (61%)
Index knee: % Right	237/237	136 (57%)	146 (62%)
BMI (kg/m^2)	236/237	30 (5)	29 (5)
Family history of knee or hip OA	236/235	113 (48%)	109 (46%)
Heberdens nodes	237/237	145 (61%)	165 (70%)
Bouchards nodes	237/237	71 (30%)	83 (35%)
CMC joint OA	237/237	105 (44%)	101 (43%)
% Bilateral knee OA	237/237	169 (71%)	166 (70%)
% Taking analgesics	237/237	104 (44%)	98 (41%)
% Taking glucosamine or chondroitin	237/237	109 (46%)	104 (44%)
% Taking cod liver oil	236/236	73 (31%)	78 (33%)
WOMAC pain score	236/232	33 (18)	31 (19)
WOMAC function score	236/232	36 (21)	35 (20)
WOMAC stiffness score	236/231	47 (24)	43 (24)
WOMAC total score	236/232	36 (19)	35 (19)
Worst K&L grade$^+$ (of medial/lateral)	234/236		
Index knee:			
0		3 (1%)	3 (1%)
1		62 (26%)	59 (25%)
2		86 (37%)	92 (39%)

3		70 (30%)	66 (28%)
4		13 (6%)	16 (7%)
Worst K&L grade[+] (of medial/lateral)			
Contra-lateral knee:			
0	234/236	2 (1%)	2 (1%)
1		77 (33%)	87 (37%)
2		65 (28%)	70 (30%)
3		54 (23%)	43 (18%)
4		29 (12%)	26 (11%)
TKR Contra-lateral knee		7 (3%)	8 (3%)
Medial JSW index knee (mm) [†]	218/219	3.49 (1.48)	3.58 (1.47)
Lateral JSW index knee (mm) [†]	222/219	5.27 (1.95)	5.42 (1.87)
Medial JSW Contra-lateral knee [†] (mm)	214/213	3.40 (1.69)	3.62 (1.60)
Lateral JSW Contra-lateral knee[†] (mm)	216/212	5.38 (2.07)	5.22 (1.90)
Baseline Vitamin D_3 (in µg/L)		20.7 (8.9)	20.7 (8.1)

[+]Baseline X-rays were missing for 3 individuals in the vitamin D group. 1 placebo patients X-ray disc was corrupt therefore could not be read. Due to X-ray quality issues, including poor positioning, the numbers of readable JSW measures vary by region and by knee.

Table 2 Treatment effect estimates for primary and secondary outcomes

Rate of change of Joint Space width (mm/year)	Vitamin D	Placebo	Difference [95% CI]
Primary Outcome:			
Medial compartment index knee	-0.01	-0.08	0.08 [-0.14 to 0.29]
Secondary Outcomes:			
Lateral compartment index knee	-0.11	-0.18	0.07 [-0.19 to 0.33]
Medial compartment contra-lateral knee	-0.03	0.03	-0.06 [-0.26 to 0.13]
Lateral compartment contra-lateral knee	-0.10	-0.07	-0.03 [-0.27 to 0.21]
	Vitamin D	Placebo	Difference [95% CI]
Clinically significant progression (Medial index JSN>0.5mm)	39%(N=92)	37%(N=88)	2% [-10% to 14%][1]
Rate of change per year	Vitamin D	Placebo	Difference [95% CI]
WOMAC pain	-0.08	0.71	-0.79 [-2.31 to 0.74]
WOMAC stiffness	-2.02	-0.50	-1.52 [-3.24 to 0.21]
WOMAC function	0.42	1.07	-0.65 [-2.09 to 0.79]
WOMAC total	0.11	0.84	-0.72 [-1.92 to 0.48]
	Vitamin D	Placebo	Treatment x Time OR [95% CI]
Odds of a higher K&L grade per year index knee	1.32	1.23	1.07 [0.88 to 1.31]
Odds of a higher K&L grade per year contra-lateral knee	1.19	1.18	1.01 [0.80 to 1.27]
Odds of higher grade in Get up and	1.00	1.04	0.96 [0.73 to 1.27]

go test per year

N=474 (N=237 Vitamin D, N = 237 Placebo). WOMAC scores range from 0 to 100, 0 = no pain/disability, 100 = extreme pain/disability. Get up and Go test graded 1 - normal to 6 – abnormal.

[1]Corresponds to a relative risk of 1.05 [0.77 to 1.44].

600 **Table 3 Vitamin D_3 and Vitamin D_2, at baseline and 12 months.**

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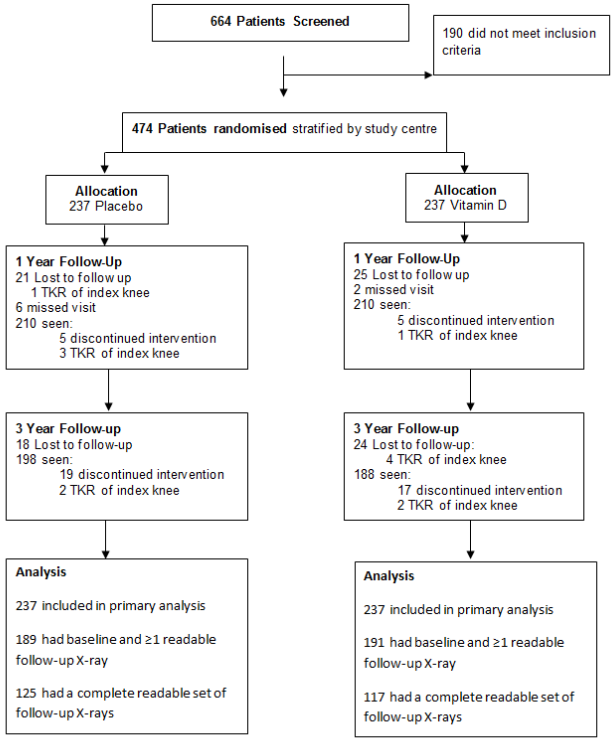
	N vitamin D / N Placebo	Vitamin D	Placebo
Baseline Vitamin D_3:	232/231		
<20 µg/L		117 (50%)	115 (50%)
20 µg/L to 30 µg/L		79 (34%)	87 (38%)
>30 µg/L		36 (16%)	29 (12%)
Baseline Vitamin D_3 (in µg/L)		20.7 (8.9)	20.7 (8.1)
Baseline Vitamin D_2:	232/231		
<2.2 µg/L		228 (98%)	218 (94%)
≥2.2 µg/L		4 (2%)	13 (6%)
Baseline Vitamin D_2 (in µg/L)*	4/13	5.0 (2.7)	3.8 (1.7)
12 month Vitamin D_3:	206/206		
<20 µg/L		14 (7%)	111 (54%)
20 µg/L to 30 in µg/L		97 (47%)	67 (32%)
>30 µg/L		95 (46%)	28 (14%)
12 month Vitamin D_3 (in µg/L)		30.4 (7.7)	20.3 (8.1)
12 month Vitamin D_2:	206/206		
<2.2 µg/L		203 (99%)	193 (94%)
≥2.2 µg/L		3 (1%)	13 (6%)
12 month Vitamin D_2 (in µg/L)*	3/11	3.3 (0.76)	4.2 (2.3)

12 month change Vitamin D_3 (μg/L)	201/201	9.4 (8.3)	-0.8 (5.7)

*Vitamin D_2 reported in μg/L for patients with Vitamin D_2 ≥2.2 μg/L only. Data presented as mean(sd) or number (%) for categorical variables. Vitamin D_3 and Vitamin D_2 were not available at baseline for 5 vitamin D and 6 placebo patients and at 12 months for 31 vitamin D and 31 placebo patients, for reasons unknown.



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615 Figure 1. Consort flow diagram for the VIDEO study

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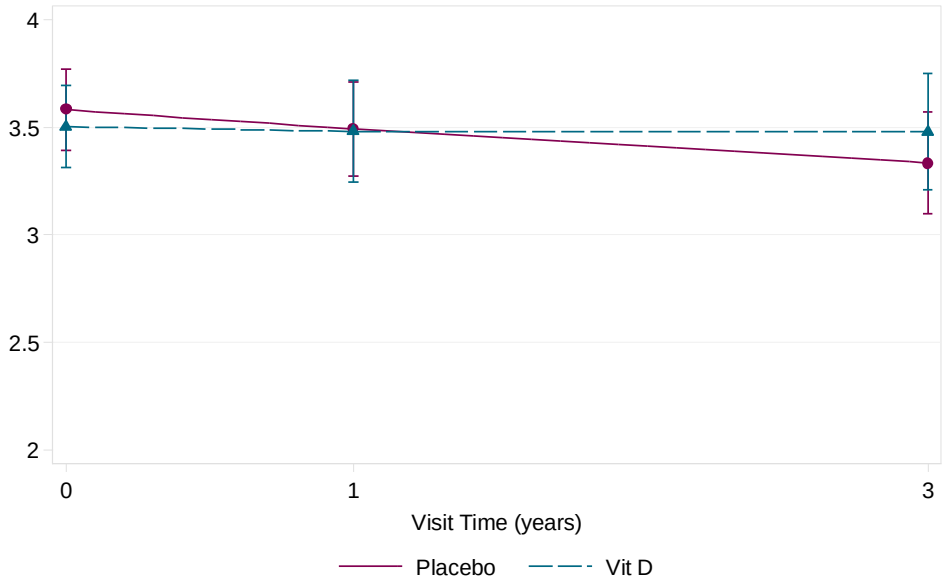

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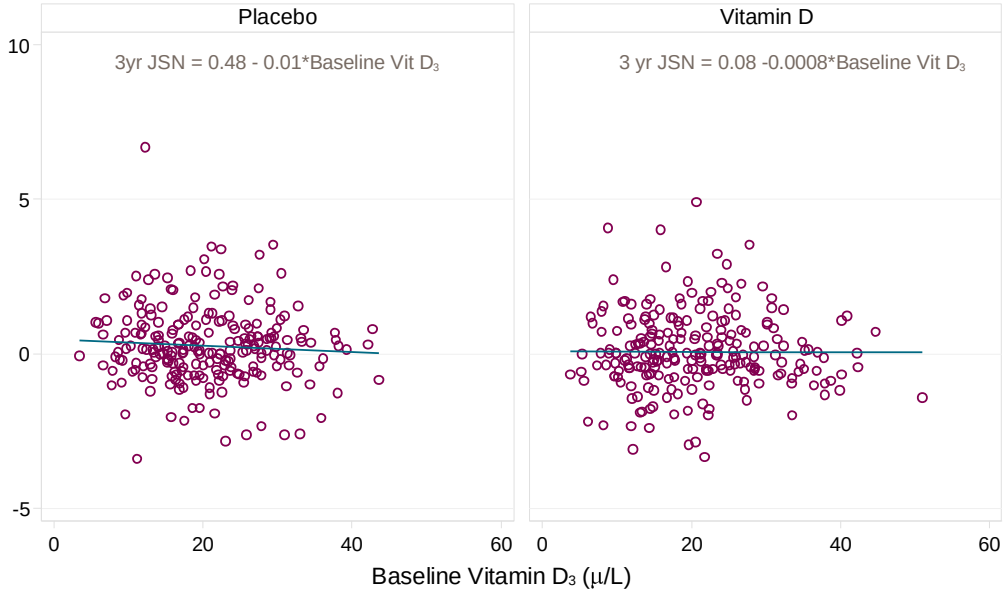

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