**TITLE PAGE**

**Manuscript title:**

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

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**Abstract**

**Objective:** Knee osteoarthritis (OA) is a common problem with increasing prevalence in an ageing population. There are no licensed treatments to modify disease progression. Epidemiological data suggest that low serum 25-hydroxyvitamin D3 (25-OH-D3) levels are associated with radiological progression of knee OA. This study aimed to assess whether vitamin D supplementation can prevent the radiological progression of knee OA.

**Design:** A 3 year, double-blind, randomised, placebo-controlled trial 474 patients aged over 50 with knee OA comparing 800 IU cholecalciferol daily with placebo. The primary outcome was rate of joint space narrowing (JSN) in the medial compartment over three years. Secondary outcomes included WOMAC pain, function and stiffness.

**Results:** Vitamin D supplementation increased 25-OH-D3 from an average of 20·7 (8·9) μg/L to 30·4 (7·7) μg/L, compared to 20·7 (8·1) μg/L and 20·3 (8·1) μg/L in the placebo group. A non-significant decrease of 0.08 mm/year (95% CI -0·14 to 0·29, p=0.49) in the rate of JSN was observed in the treatment group relative to the control. No significant interactions were found between baseline vitamin D levels and treatment effects. There were no significant differences in any of the secondary outcome measures*.*

**Conclusions:**Vitamin D supplementation at a dose sufficient to elevate serum vitamin D3 levels by almost 10 μg/L in one year, when compared with placebo, does not slow the rate of JSN or lead to reduced pain, stiffness or functional loss over a three year period.

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**Introduction**

Knee osteoarthritis (OA) is a chronic, painful disease associated with considerable morbidity, costs and disability [1](#_ENREF_1). In the U.S., it is estimated that over a third of people aged over 60 have radiographic knee OA[2](#_ENREF_2) and over 50% of these with knee OA will go on to have a total knee replacement in their lifetime[3](#_ENREF_3). At present there are no licensed treatments that alter disease progress and management is primarily concerned with symptom control to retain or improve joint function, although a recent randomised controlled trial of strontium ranelate showed promising results [4](#_ENREF_4).

Vitamin D deficiency (defined as 25-hydroxyvitamin D3(25-OH-D3) serum levels below 20ng/mL [5](#_ENREF_5) [6](#_ENREF_6)) 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[7](#_ENREF_7) 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-D3 levels are associated with increased radiological progression of knee OA [8-14](#_ENREF_8). 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 the two skeletal sites over 8-10 years.[8](#_ENREF_8) 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 [13](#_ENREF_13).

Findings from RCTs have thus far not conclusively settled this debate [15-18](#_ENREF_15). 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 [15](#_ENREF_15). 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 [17](#_ENREF_17). A further RCT concluded that calcium plus vitamin D supplementation for two years in post-menopausal women had no effect on the self-reported frequency or severity of joint symptoms [18](#_ENREF_18). 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 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. 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.

*Patients*

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 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-D3 at baseline and 12 months to assess baseline vitamin D status and response to supplementation. Serum vitamin D2 and D3 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 year. Knee X-rays were taken using the MTP technique [19](#_ENREF_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](#_ENREF_20), [21](#_ENREF_21); intra-rater and inter-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] and 0·91 medial [95% CI 0·64 0·97], 0·96 lateral [95% CI 0·83 0·99] respectively

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, 1957, 1963)[22](#_ENREF_22), [23](#_ENREF_23) grade, WOMAC VAS scores (0-100 pain, stiffness, function and total) in the index knee, and Get up and Go test. 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 minimal 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](#_ENREF_24), [25](#_ENREF_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 an analysis plan finalised before the database was locked.

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 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](#_ENREF_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](#_ENREF_27), [28](#_ENREF_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 SI). All statistical analyses were performed using Stata/IC version 12·1.

*Role of the funding source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**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 S1. 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-D3, divided into tertiles, was almost identical in the two groups, with 50% of both groups vitamin D3 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, a number of radiographs from attending patients could not be evaluated accurately and were therefore excluded from the analysis. JSW in the medial compartment of the index knee was missing for a total of 37 patients (8%) at baseline (18 placebo, versus 19 active), 110 patients (23%) at year one (58 placebo versus 52 active) and 183 (39%) at year three (87 placebo versus, 96 active). 38% of the missingness at year one was due to unreadable X-rays (23 placebo and 19 active). 30% of the missingness at year three was due to unreadable X-rays (27 placebo versus 28 vitamin D). The remaining missingness occurred due to withdrawal, death, TKR or loss to follow-up during the trial. Missingness of X-ray data did not vary by treatment arm. 380 patients (189 placebo, 191 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 patients (125 placebo, 117 active) with complete follow-up was also performed.

*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 (average difference 0·08 mm/year, 95% CI -0·14 to 0·29, p=0·49) (figure 2, table 2). Analysis of those with baseline and one year follow-up data also showed no difference. 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 0.31) for the index knee and 1.01 (95% CI 0.80 to 1.27) for the contralateral knee. (table 2). Sensitivity analyses conducted to assess the effect of missing values on the treatment effect produced results no different from the primary analysis (supplementary file eTablesS2 and S3 and eFigureS1). 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 ( 0·71 per year) whereas the vitamin D group showed a decrease of -0.08 per year (table 2, eFigure 2). WOMAC stiffness decreased in both groups (-2·02 and -0·50 per year for vitamin D and placebo groups respectively). WOMAC function increased for both groups (-0·65 per year (95% CI -2·09 to 0·79) for vitamin D compared with placebo). None of the above differences achieved statistical significance. Additional secondary outcomes were assessed and treatment effect estimates can be found in the supplementary file eTable S4. All outcomes at three years are summarised in eTable S5.

*Vitamin D analysis*

At 12 months, serum vitamin D3 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 g/L) fell to 7% in the vitamin D group but rose to 54% in the placebo group. No interaction between baseline vitamin D status and treatment effect () was found (<20 µg/L,  0·06 [-0·20 to 0·32]; 20 µg/L to 30 µg/L,  0·05 [-0·20 to 0·29]; >30 µg/L,  0·05 [-0·30 to 0·40]) (Figure 3, 4).

*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 or in the rates of occurrence of hypercalcaemia (five placebo, three vitamin D)or hypercalciuria (24 placebo, 46 vitamin D).

**Discussion**

Our results show that vitamin D, at a dose of 800 IU cholecalciferol daily, had no effect on the rate of structural worsening of knee OA over a 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 almost 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](#_ENREF_8), however others have shown no association [12](#_ENREF_12), [13](#_ENREF_13), [15](#_ENREF_15), [29-31](#_ENREF_29). These studies vary in methodology and were also subject to a number of important biases. The ideal way to address this issue is through RCTs.

McAlindon performed a two year RCT of 2000 IU/day oral cholecalciferol for patients with vitamin D insufficiency. The primary outcomes were MRI assessed cartilage thickness, radiographic JSN and pain. The population studied had similar baseline concentrations of vitamin D but greater baseline JSW (approximately 5mm vs. 3.5mm). The results demonstrated that despite 63% of patients achieving target concentrations of vitamin D, there were no significant improvements 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](#_ENREF_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 insufficient to be deemed clinically important [32](#_ENREF_32).

The results from our study, which is substantially larger than the previous studies, are consistent with the above results. The VIDEO trial additionally 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 this 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](#_ENREF_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](#_ENREF_4), [25](#_ENREF_25), it is important to measure JSN in the lateral compartment to ensure disease progression is not missed [33](#_ENREF_33). We looked at the association of the treatment effect with baseline [25-OH-D3] 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 [34](#_ENREF_34).

*Strengths and potential limitations*

The radiographs from the screening visits were read by the PI at each centre. A clinical orthopaedic fellow re-read all the 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, the boundary is particularly subjective. The imbalance 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.

This study included 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 [35](#_ENREF_35), 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 participants started the study with vitamin D insufficiency (<20 μg/L) at baseline. Furthermore, when analysis of treatment effect on JSN was broken down by baseline vitamin D level, 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.

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](#_ENREF_4), [17](#_ENREF_17), [25](#_ENREF_25), [36](#_ENREF_36) . 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 and detailed sensitivity analyses to assess the impact of missing data (described in SI) were consistent with the primary analysis. We do not feel therefore that this affected the results of the trial.

*Conclusions*

Despite correcting vitamin D deficiency in the majority of participants, vitamin D supplementation at a dose of 800 IU/day made no significant difference in any of the radiological or functional outcomes. Vitamin D supplementation at a dose sufficient to elevate serum vitamin D3 levels by almost 10 μg/L in one year, when compared with placebo, does not slow the rate of JSN or lead to reduced pain, stiffness of functional loss over a three year period. On the basis of these findings, vitamin D supplementation has no role in the management of knee OA.

**Contributors**

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.

**Declaration 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.

Researchers were independent from funders and sponsors.

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**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](mailto:nigel.arden@ndorms.ox.ac.uk).

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**Figures**

Figure 1. Consort flow diagram for the VIDEO study

Figure 2 Mean Joint Space Width in the medial compartment of the index knee with 95% CI’s by treatment group

Detailed legend: (N = 474 All available readings were included in primary analysis and multiple imputation was used to impute missing values, assuming all missing outcome values were missing at random, conditional on treatment and the covariates included in the imputation model. Both centre and baseline BMI were included in the imputation model.

Figure 3 Scatterplot of 12 month change in Vitamin D3 against three year change in Joint Space Width (N = 402).

Figure 4 Scatter plot of 3 year change in Joint Space Width against 12 month change in vitamin D3 for patients who are vitamin D deficient at baseline, defined as serum 25-OH-D3 < 20 μg/L (N=194).

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | 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/m2) | 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)  Index knee: | 234/236 |  |  |
| 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 |  | 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) |

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] |
| Medial compartment index knee | -0.01 | -0.08 | 0.08 [-0.14 to 0.29] |
| 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] |
| 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 go test per year | 1.00 | 1.04 | 0.96 [0.73 to 1.27] |

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.

**Table 3 Vitamin D3 and Vitamin D2, at baseline and 12 months.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | N vitamin D /  N Placebo | Vitamin D | Placebo |
| Baseline Vitamin D3: | 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 D3 (inµg/L) |  | 20.7 (8.9) | 20.7 (8.1) |
|  |  |  |  |
| Baseline Vitamin D2: | 232/231 |  |  |
| <2.2 µg/L |  | 228 (98%) | 218 (94%) |
| ≥2.2 µg/L |  | 4 (2%) | 13 (6%) |
| Baseline Vitamin D2 (in µg/L)\* | 4/13 | 5.0 (2.7) | 3.8 (1.7) |
|  |  |  |  |
| 12 month Vitamin D3: | 206/206 |  |  |
| <20 µg/L |  | 14 (7%) | 111 (54%) |
| 20 µg/L to 30 inµg/L |  | 97 (47%) | 67 (32%) |
| >30 µg/L |  | 95 (46%) | 28 (14%) |
| 12 month Vitamin D3 (inµg/L) |  | 30.4 (7.7) | 20.3 (8.1) |
|  |  |  |  |
| 12 month Vitamin D2: | 206/206 |  |  |
| <2.2 µg/L |  | 203 (99%) | 193 (94%) |
| ≥2.2 µg/L |  | 3 (1%) | 13 (6%) |
| 12 month Vitamin D2 (in µg/L)\* | 3/11 | 3.3 (0.76) | 4.2 (2.3) |
|  |  |  |  |
| 12 month change Vitamin D3 (µg/L) | 201/201 | 9.4 (8.3) | -0.8 (5.7) |

\*Vitamin D2reported in µg/L for patients with Vitamin D2 ≥2.2 µg/L. Data presented as mean(sd) or number (%) for categorical variables.