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

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SUMMARY

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 & Lawrence grade, Western Ontario and McMaster Universities Osteoarthritis Index (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 (standard deviation (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 3 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% confidence interval (CI) [−0.14–0.29], $P = 0.49$). 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 3-year period. 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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Introduction

Knee osteoarthritis (OA) is a chronic, painful disease associated with considerable morbidity, costs and disability[1]. In the US, 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 (TKR) 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 20 μg/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 fourfold 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 Randomised Controlled Trials (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 2 years had no effect on the structural progression of OA using Magnetic Resonance Imaging (MRI) as the primary outcome[16]. A further *post hoc* analysis of a RCT concluded that calcium plus vitamin D supplementation for 2 years in postmenopausal 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 National Health Service (NHS) hospitals. Participants were randomly assigned to receive either 800 IU of oral cholecalciferol or matched placebo daily. Data from clinical trials indicated that 800 IU/day of cholecalciferol can produce significant increases in serum 25-OH-D_3 levels and that these increases are evident within 1 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, International Standard Registered Clinical/soCial sTudy number (ISRCTN) 94818153, Clinical Trials Agreement (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 General Practioner (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, joint space width (JSW) > 1 mm) and knee pain for most days of the previous month. Reasons for exclusion were: secondary OA, inflammatory arthritis, early morning knee stiffness for >30 min, cod liver oil or vitamin supplementation containing vitamin D > 200 IU, glucosamine or chondroitin use for <3 months, osteoporotic fracture, previous knee surgery or arthroscopy within 6 months, use of bisphosphonates within 2 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 6-month packs. Radiographs and blood sampling were repeated at 12 months and 36 months. Questionnaires (WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index) 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 JSW at baseline in the case of bilateral disease), as measured by the rate of joint space narrowing (JSN) (mm/year) over the 3 years. Knee X-rays were taken using the Metatarsophalangeal (MTP) technique[19] using a foot map to improve accurate repositioning 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% confidence interval (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 contra-lateral knee, K&L[22,23] grade,

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WOMAC visual analogue scale (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 0.22 mm/year in the rate of JSN between treatment groups over 3 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 body mass index (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 > 0.5 mm in the index knee) at 3 years was obtained using a Poisson regression model with robust error estimates. For patients who had a 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 were 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, TX, USA).

Results

In total, 474 participants were recruited between 19/01/2005 and 13/06/2008. Table I shows baseline clinical data and baseline radiographic characteristics. Additional baseline variables can be found in the Supplementary file, eTable 1. The treatment and

Table I
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/m^2)	236/237	30 (5)	29 (5)
Family history of knee or hip OA	236/235	113 (48%)	109 (46%)
Heberden's nodes	237/237	145 (61%)	165 (70%)
Bouchard's 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:	234/236		
0		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 three individuals in the vitamin D group.
† 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.

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Table II
Treatment effect estimates for primary and secondary outcomes

Rate of change of JSW (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]
Clinically significant progression (medial index JSN > 0.5 mm)	39% ($N = 92$)	37% ($N = 88$)	2% [−10% to 14%]*
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 × time OR [95% CI]**
Odds of a higher K&L grade per year index knee	1.32	1.23	1.07 [0.88–1.31]
Odds of a higher K&L grade per year contra-lateral knee	1.19	1.18	1.01 [0.80–1.27]
Odds of higher grade in Get up and Go test per year	1.00	1.04	0.96 [0.73–1.27]

$N = 474$ ($N = 237$ 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. OR, operating room.
* Corresponds to a relative risk of 1.05 [0.77–1.44].

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 III), was almost identical in the two groups, with 50% of both groups vitamin D_3 deficient (<20 μg/L).

As shown in Fig. 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 vs 19/237 active), 110/474 patients (23%) at year one (58/237 placebo vs 52/237 active) and 183/474 (39%) at year three (87/237 placebo vs 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 vs 28 vitamin D). The remaining missingness at year three occurred due to withdrawal 54% (99/183, 49 placebo (three with TKR of index knee at 1 year) and 50 active (one with TKR of index knee at 1 year)), loss to follow-up 10% (18/183, seven placebo and 11 active), TKR of the index knee at year three 5% (9/183, three placebo and six active) or death 1% (2/183, one placebo and one 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

Table III
Vitamin D_3 and vitamin D_2, at baseline and 12 months

	N vitamin D/*N* placebo	Vitamin D	Placebo
Baseline vitamin D_3:	232/231		
<20 μg/L		117 (50%)	115 (50%)
20–30 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%)
20–30 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)

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

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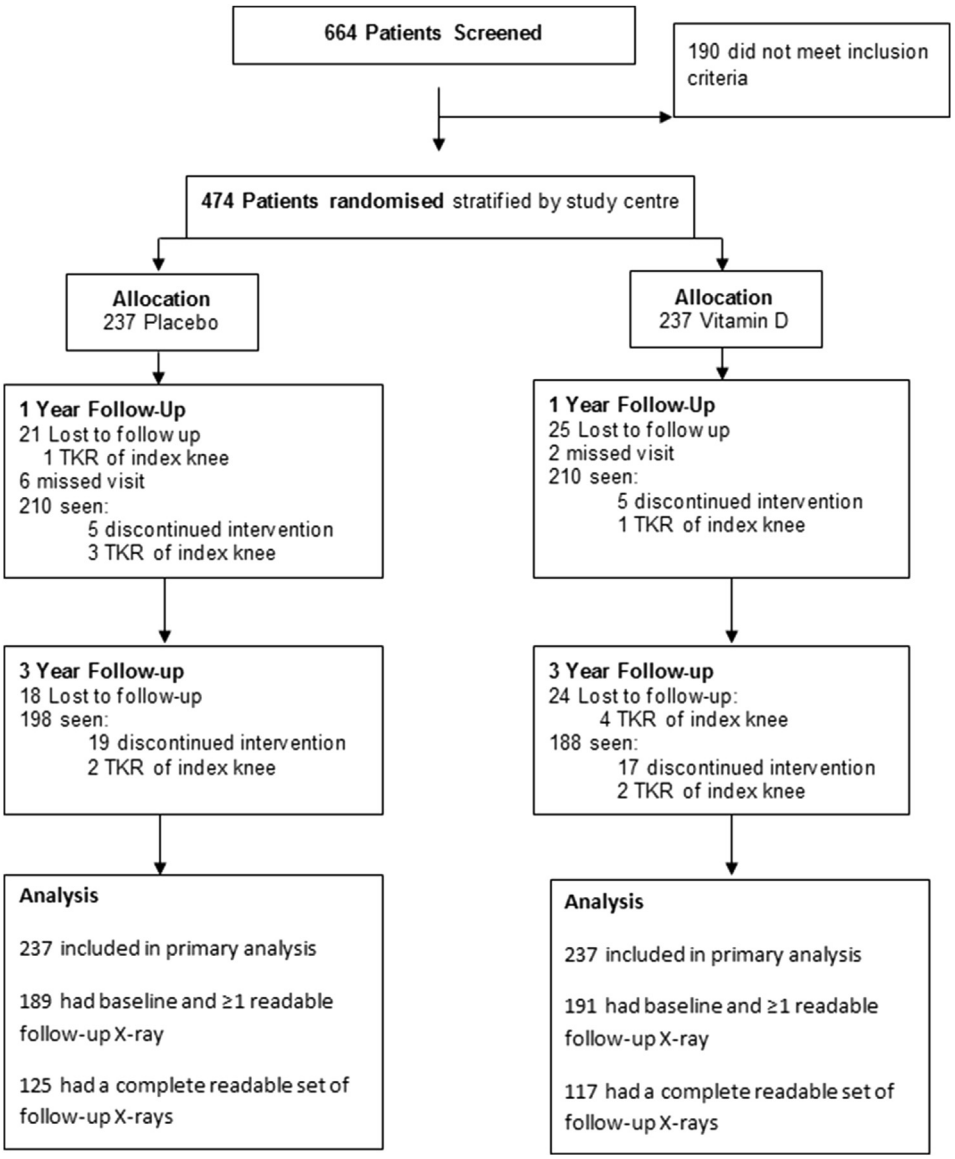

Fig. 1. Consort flow diagram for the VIDEO study.

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 III). 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 3 years in the medial compartment of the index knee between treatment groups (−0.01 mm/year vs −0.08 mm/year for vitamin D and placebo respectively), between group difference 0.08 mm/year, 95% CI [−0.14 to 0.29], $P = 0.49$ (Fig. 2, Table II). 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]; 20–30 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]) (Fig. 3).

There was no difference in the proportion of patients with clinically significant progression of JSN (JSN > 0.5 mm in the index knee) at 3 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 II).

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 vs −0.08 per year, between group difference −0.79, 95% CI [−2.31 to 0.74],

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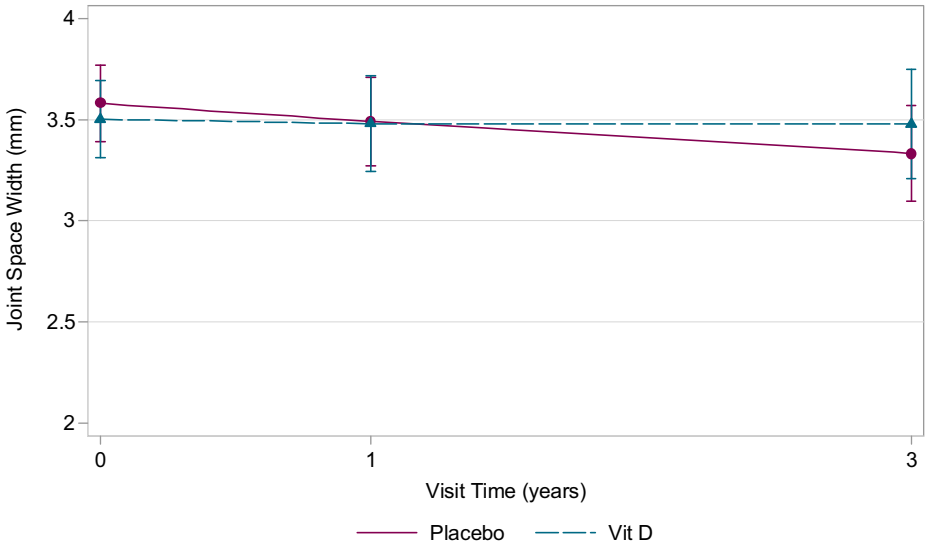

Fig. 2. Mean JSW in the medial compartment of the index knee with 95% CI's by treatment group ($N = 474$). All available readings were included in primary analysis and multiple imputation was used to impute missing values, assuming all missing outcome values were missing at random, conditional on treatment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

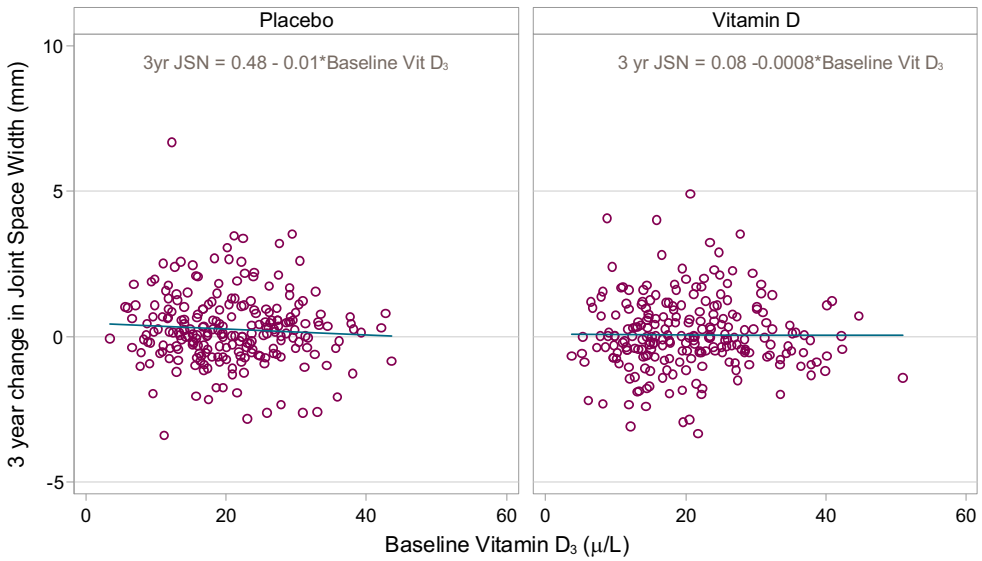

Fig. 3. Scatterplot of baseline vitamin D_3 against estimated 3-year change in JSW by treatment group with linear fit imposed ($N = 463$).

Table II, eFigure 2). WOMAC stiffness decreased in both groups (−2.02 vs −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 vs 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 contra-lateral 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 [0.88−1.31]) for the index knee and 1.01 (95% CI [0.80−1.27]) for the contra-lateral knee (Table II). The odds of a higher Get up and Go test grade per year for vitamin D patients were 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 [0.73−1.27]). Additional secondary outcomes were assessed and treatment effect estimates can be found in the Supplementary file eTable 4. All outcomes at 3 years are summarised in eTable 5.

Adverse events

There was no difference in the proportion of patients experiencing serious adverse event (SAE)'s between the vitamin D (59/237, 25%) and placebo group (64/237, 27%), $P = 0.67$. Only two 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).

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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 3-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 2-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 5 mm vs 3.5 mm). 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 2-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 3-year JSN having been shown in a previous study to be predictive of the incidence of OA related knee surgery[35].

Our results indicate that Vitamin D supplementation at a level of 800 IU daily is safe. Only two 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 5-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 JSW even in subjects who were vitamin D deficient.

We acknowledge limitations. The radiographs from the screening visits were read by the local principle investigator (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 was determined to be K&L grade 1, while the inclusion criteria specified K&L $\geq$ 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 3-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 1 year, did not slow the rate of JSN or lead to reduced pain, stiffness or functional loss over a 3-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.

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.

Conflict of interest

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

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NKA 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.

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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.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2016.05.020.

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