Recovery after unilateral knee replacement due to severe osteoarthritis and progression in the contralateral knee: a randomised clinical trial comparing daily 2000 IU versus 800 IU vitamin D

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ABSTRACT

Objective To test whether daily high-dose vitamin D improves recovery after unilateral total knee replacement.

Methods Data come from a 24-month randomised, double-blind clinical trial. Adults aged 60 and older undergoing unilateral joint replacement due to severe knee osteoarthritis were 6–8 weeks after surgery randomly assigned to receive daily high-dose (2000 IU) or standard-dose (800 IU) vitamin D. The primary endpoints were symptoms (Western Ontario and McMaster Universities Arthritis Index pain and function scores) assessed at baseline, 6, 12, 18 and 24 months in both knees, and the rate of falls over 24 months. The secondary outcomes were sit-to-stand performance, gait speed, physical activity and radiographic progression in the contralateral knee.

Results We recruited 273 participants, 137 were randomised to receive 2000 IU and 136 were randomised to receive 800 IU vitamin D per day. 2000 IU vitamin D increased 25-hydroxyvitamin D levels to 45.6 ng/mL and 800 IU vitamin D to 37.1 ng/mL at month 24 (p<0.0001). While symptoms improved significantly in the operated knee and remained stable in the contralateral knee over time, none of the primary or secondary endpoints differed by treatment group over time. The rate of falls over 24 months was 1.05 with 2000 IU and 1.07 with 800 IU (p=0.84). 30.5% of participants in the 2000 IU and 31.3% of participants in the 800 IU group had radiographic progression in the contralateral knee over 24 months (p=0.88).

Conclusions Our findings suggest that a 24-month treatment with daily 2000 IU vitamin D did not show greater benefits or harm than a daily standard dose of 800 IU among older adults undergoing unilateral total knee replacement.

INTRODUCTION

Osteoarthritis (OA) is the leading cause of disability in later age,1 and approximately 30% of individuals aged 65 and older today have symptomatic OA marked by pain in the affected joint.2,3 Despite its frequency, OA is a condition that is poorly understood, with no specific treatments to prevent or reverse the condition.4 Therefore current interventions in patients with OA are limited to symptomatic pain relief. This is initially achieved by the use of pain medication, and later with total joint replacement.5–7 However, joint replacement does not fully restore function in most individuals.8,9 Further, adults aged 65 and older have a more than 50% chance of the disease on the contralateral joint10–12 which often progresses rapidly10 and likely impacts negatively on recovery after total joint replacement.

One promising secondary prevention strategy in older individuals with symptomatic knee OA may be oral vitamin D supplementation. Epidemiological studies suggest that increased vitamin D intake and higher 25-hydroxyvitamin D (25(OH)D) levels may be a strategy to prevent structural progression of knee OA.13–15 The potential benefit has been attributed to a direct effect of vitamin D on cartilage cells based on preliminary studies and in vitro findings.15–17 However, all three recent clinical trials that assessed radiographic progression among patients with
symptomatic knee OA found no benefit on MRI-based tibial cartilage volume or X-ray-based joint space narrowing with vitamin D supplementation compared with placebo. Alternatively, vitamin D may have a beneficial effect on muscle surrounding the OA-affected joint. This is supported by the presence of the vitamin D receptor in adults aged 65+ at risk of vitamin D deficiency improves lower extremity function and reduces the risk of falls and related fractures. Given that vitamin D deficiency is common among individuals with knee OA and symptomatic knee OA has been shown to double the risk of falls and hip fractures, vitamin D supplementation may have clinical relevance in these patients. Notably, one smaller clinical trial of 107 patients suggested a significant improvement in both pain and function among middle-aged adults treated with vitamin D compared with placebo.

To our knowledge, no clinical trial has been performed to test the benefit of vitamin D on fall prevention or recovery after unilateral knee replacement among patients with severe knee OA. Therefore, our primary goals were to examine whether 2000 IU vitamin D improved symptoms (pain and function) in the operated knee, reduced falls and slowed the progression of symptoms in the contralateral knee, relative to a standard dose of 800 IU vitamin D. Notably, the study did not include a placebo group as the ethical commission at the time requested that the comparator should be standard-dose 800 IU vitamin D to allow compliance with current recommendations given the high risk of falls and hip fractures among seniors with knee OA. The high dose of 2000 IU vitamin D was chosen because it was previously found to be more effective than the standard 800 IU vitamin D in shifting most individuals to a target therapeutic range of 24–30 ng/mL, where a maximum benefit with regard to knee OA disease progression as well as fall and fracture prevention was expected.

METHODS

Trial design
This is a single-centre, double-blind randomised trial. All participants gave written informed consent for participation in the trial. The trial was registered at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/results/NCT00599807. Clinical visits were performed by all participants at baseline (6–8 weeks after unilateral total knee replacement surgery), and at months 6, 12, 18 and 24 after baseline. Between clinical visits, the study nurses called the participants every 2 months to assess falls, adverse events and adherence to study medication.

Setting and locations
The study was performed at the Center on Aging and Mobility at the University Hospital Zurich, with the first patient enrolled in the study in January 2008 and the last patient follow-up visit in March 2014.

Participants and screening procedures
Participants were recruited from two large hospital centres (Schulthess Clinic Zurich, Triemli City Hospital) with a multistep screening process (see also figure 1). Those who were eligible based on the prescreening questionnaire and gave their preconsent to participate in the trial filled out the Western Ontario and McMaster Universities Arthritis Index (WOMAC; score 0–100) prior to their surgery. This instrument was used to capture presurgery symptoms, and later to stratify randomisation. Those who met all the inclusion and exclusion criteria and gave written informed consent (n=273) were enrolled in the trial at 6–8 weeks after surgery.

Inclusion and exclusion criteria
Eligible patients were aged 60 years and older, underwent unilateral total knee replacement due to severe knee OA and did not plan bilateral knee replacement within the next 2 years. Further eligibility criteria included willingness to stop current vitamin D and calcium supplements during the trial, fluent oral and written language skills in
German, and a score of at least 24 (of 30) points in the Mini-Mental State Examination cognitive test. Key exclusion criteria were history of inflammatory arthritis and inability to walk at least 3 m with or without a walking aid (for additional exclusion criteria, see online supplementary appendix 1).

**Interventions**
Participants were randomised to either one capsule containing 2000 IU vitamin D₃/day or one capsule containing 800 IU vitamin D₃/day. Vitamin D capsules were produced by the cantonal pharmacy of Zurich and had identical appearances and taste, and assays confirmed the expected contents (eight assessments of individual batches varied between 2017 and 2115 IU for the high-dose group, and between 797 and 864 IU for the standard-dose group). All participants received a 500 mg supplement of calcium per day (calcium carbonate; Sandoz Switzerland).

**Outcomes**

**Primary outcomes**
WOMAC symptoms were assessed for the operated and the contralateral knee (function and pain subscales range from 0 to 100, with 0 indicating optimal function and no pain). The rate of falls was assessed over 24 months by diary and by phone calls every 2 months. Falls were defined as ‘unintentionally coming to rest on the ground, floor, or other lower level’; coming to rest against furniture or a wall was not counted. The primary endpoints, WOMAC pain and function scores, were assessed at baseline, 6, 12, 18 and 24 months in both knees, and the rate of falls over 24 months.

**Secondary outcomes**
Repeated sit-to-stand test performance and 4 m normal gait speed were assessed at all clinical visits. Physical activity was measured at baseline, 12 and 24 months by a seven consecutive day ankle-worn ambulatory activity...
monitor (StepWatch Step Activity Monitor, Cyma, Seattle, Washington)\textsuperscript{37,38} (see online supplementary appendix 1 for additional details on the physical activity assessment and analysis). Radiographic progression in the contralateral knee was assessed at baseline and at 24-month follow-up (see section above) and is detailed in online supplementary appendix 1. In short, we used the Multicentre Osteoarthritis Study (MOST) study centre standardised X-ray assessment procedures,\textsuperscript{39} and X-rays were evaluated by two blinded expert readers using two published approaches detecting changes in radiographs due to OA.\textsuperscript{40,41}

**Randomisation–blinding–treatment allocation**

Randomisation lists were computer-generated by the trial statistician (EJO), with separate lists stratified by presurgery WOMAC function score (<52 vs ≥52\textsuperscript{35} in the operated knee, presence of OA in the non-operated knee and recruitment centre). Each list was blocked in groups of 4 to assure balance. The randomisation lists were sent directly and exclusively to the cantonal pharmacy in Zurich, Switzerland, which carried out the blinding and labelling of the study medication. This pharmacy was located outside the study centre with no access for study team members. The participants and all trial staff were blinded to treatment allocation.

**Vitamin D and other laboratory assessments**

Fasting blood and urine (second voiding) samples were taken between 08:00 and 09:30 at all clinical visits. The 25(OH)D serum concentrations were measured by a sensitive high-performance liquid chromatography mass spectrometry with multiple steps of mass spectrometry selection (HPLC-MS/MS) method\textsuperscript{42,43} included in the National Institute of Standards and Technology/National Institutes of Health Vitamin D Metabolites Quality Assurance Program\textsuperscript{44} at baseline, 6 months and 24 months. Intact parathyroid hormone (iPTH), serum calcium and creatinine, and urinary calcium to creatinine ratio were measured at baseline and at months 6, 12, 18 and 24 using the cobas 8000 system and assays from Roche Diagnostics (Rotkreuz, Switzerland) c501 machine.

**Sample size analysis**

Our study was designed to enrol 287 patients in order to detect a 38% relative difference in the rate of falls between the two intervention groups. For the rate of falls, our power calculation is based on a conservative estimate from a European trial data on ambulatory older women, which suggested a 46% difference in the rate of falls between the vitamin D group and the control group over a 12-month follow-up.\textsuperscript{45} We reduced the expected rate difference to 38% as our trial included men and women.\textsuperscript{46} Assuming full 24-month follow-up on 220 of the patients and at least 12-month follow-up on 234 of the patients, we would have had a power of 80% (two-sided alpha=0.05). During the trial, we recruited slightly fewer patients (273), but more of them (226) completed the full 24-month protocol, providing adequate power for our analyses.

**Statistical analyses**

A longitudinal linear regression with random intercepts for each patient was used to account for correlation over time (baseline, 6, 12, 18 and 24 months) for continuous variables. The primary predictors in each model were categorical time, intervention group, and the interaction between intervention and time. These models were run initially with no adjustment covariates. The models for primary and secondary outcomes adjusted for design stratification covariates (preoperative WOMAC function score (<52 vs ≥52\textsuperscript{35} in the operated knee, presence of OA in the contralateral knee and recruitment centre) as well as four prechosen covariates considered to be clinically important (baseline age, gender, body mass index (BMI) and Charlson Comorbidity Index). Since five primary outcomes were specified in our protocol (pain and function over time in the operated and contralateral knee and rate of falls), a Bonferroni-adjusted p value of <0.01 should be considered evidence of significance. For the rate of falls, we used a simple Poisson regression model, including the number of months of follow-up as an offset. For the percentages of patients with any falls, we used a logistic regression model and included a patient’s follow-up time as a covariate in all models.

Each of the analyses was an intention-to-treat analysis. Predefined subgroup analyses included gender, preoperative WOMAC function score (<52 vs ≥52\textsuperscript{35} in the operated knee and presence of OA in the contralateral knee). We first added a three-way interaction term between each of these characteristics, time and intervention group to the model. If that term was significant at p<0.10, we examined the intervention effect within each subgroup.

**RESULTS**

**Participants**

Figure 1 shows the conduct of the trial. Because of slow accrual, the study closed before the last 27 subjects reached their 24-month follow-up visits. These participants were included in all analyses. Notably, of the actual 20 dropouts, 4 were deaths, and thus the true dropout rate was 5.8% (16 of 273). At baseline, all variables but weight and BMI were balanced between the treatment groups (table 1).

**Adherence to study medication and changes in 25(OH)D and iPTH serum concentrations by treatment groups and biochemical safety**

Based on 2-monthly phone-based assessments, 93% of participants in the 800 IU group and 92% in the 2000 IU group were at least 80% adherent to the vitamin D study medication. Changes in 25(OH)D serum concentrations are shown in table 2. After adjustment for all covariates, 800 IU vitamin D per day increased 25(OH)D to 40.4 ng/mL at 6 months and to 37.1 ng/mL at 24 months. With 2000 IU vitamin D, 25(OH)D levels increased to 47.0 ng/
Table 1  Baseline characteristics by treatment

|                          | Total participants | 800 IU vitamin D₃ | 2000 IU vitamin D₃ | Difference (p values) |
|--------------------------|--------------------|-------------------|-------------------|-----------------------|
| Participants, n (%)      | 273 (100)          | 136 (49.8)        | 137 (50.2)        | 0.30                  |
| Women, n (%)             | 146 (53.5)         | 77 (56.6)         | 69 (50.4)         | 0.67                  |
| Age (years)              | 70.3 (6.4)         | 70.5 (6.0)        | 70.2 (6.8)        | 0.20                  |
| Patients ≥70 years, n (%)| 130 (47.6)         | 70 (51.5)         | 60 (43.8)         | 0.98                  |
| Low preoperative WOMAC function score, n (%)* | 50 (18.3) | 25 (18.4) | 25 (18.3) | 0.98                  |
| Osteoarthritis also on the other knee, n (%) | 223 (81.7) | 112 (82.4) | 111 (81.0) | 0.78                  |
| Height (cm)              | 168.4 (9.2)        | 167.7 (9.1)       | 169.2 (9.3)       | 0.17                  |
| Weight (kg)              | 77.5 (14)          | 75.4 (14.3)       | 79.5 (13.4)       | 0.02                  |
| Body mass index (kg/m²)  | 27.2 (3.9)         | 26.7 (4.1)        | 27.7 (3.8)        | 0.04                  |
| Charlson Comorbidity Index (score 0–37) | 0.5 (0.9) | 0.5 (1) | 0.5 (0.8) | 0.82                  |
| Mini-Mental State Examination (score 0–30) | 28.0 (1.5) | 28.1 (1.2) | 27.8 (1.6) | 0.21                  |
| Baseline 25-hydroxyvitamin D (ng/mL) | 27.3 (12.4) | 27.2 (12.7) | 27.3 (12.2) | 0.96                  |
| Pain operated knee       | 28.5 (15.0)        | 28.3 (15.9)       | 28.7 (14.1)       | 0.81                  |
| Pain non-operated knee   | 4.7 (8.1)          | 4.7 (7.6)         | 4.7 (8.7)         | 0.96                  |
| Function operated knee   | 25.8 (13.8)        | 25.3 (14.3)       | 26.2 (13.3)       | 0.58                  |
| Function non-operated knee | 4.2 (8.0)       | 4.2 (7.9)         | 4.3 (8.1)         | 0.98                  |
| Repeated sit-to-stand test (score 0–4) | 3.4 (1.0) | 3.4 (0.9) | 3.4 (1.0) | 0.88                  |
| Gait speed, 4 m (s)      | 4.4 (0.9)          | 4.3 (1.0)         | 4.4 (0.8)         | 0.33                  |
| Physical activity (min MVPA/day) | 42.1 (22.5) | 42.2 (22.0) | 41.9 (23.2) | 0.92                  |
| Kellgren-Lawrence grades, n (%), contralateral knee | 57 (21.1) | 29 (21.3) | 28 (20.9) | 0.66                  |
| 1                        | 62 (23.0)          | 33 (24.3)         | 29 (21.6)         | 0.66                  |
| 2                        | 54 (20.0)          | 25 (18.4)         | 29 (21.6)         | 0.66                  |
| 3                        | 73 (27.0)          | 34 (25.0)         | 39 (29.1)         | 0.66                  |
| 4                        | 24 (8.9)           | 15 (11.0)         | 9 (6.8)           | 0.66                  |

Data (n=273) are crude mean (±SD) or n (%). Differences between treatment groups (800 vs 2000 IU vitamin D₃) were assessed using Student’s t-test and Wilcoxon test for continuous variables and χ² test for categorical variables. P values are two-sided; statistical significance was set at p<0.05.

*Preoperative WOMAC function score in the operated knee ≤52.

MVPA, medium-to-vigorous physical activity; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

mL at 6 months and 45.5 ng/mL at 24 months. Adjusted levels for iPTH did not differ by treatment, although there was a significant increase over time in the 800 IU group (table 2).

Primary endpoints: symptoms (pain and function) and falls

Both treatment groups experienced a significant functional improvement and pain reduction from baseline (6–8 weeks after unilateral knee replacement) across the operated knee (p<0.0001), while symptoms remained unchanged over time in the contralateral knee (see table 3A and figure 2). In both knees, symptoms did not differ by treatment at any time point, nor over the whole follow-up across 24 months.

Over 24 months 158 of 273 participants sustained 307 falls, of which 157 occurred in the 800 IU group and 150 in the 2000 IU group. Fourteen participants had more than four falls (nine with standard-dose and five with high-dose), which according to protocol were truncated to four for the analyses in table 3A. The adjusted mean number of falls was similar in both treatment groups over the 24 months of follow-up (1.07 falls in the standard vs 1.05 in the high-dose vitamin D group, p=0.84). A similar
**Table 2** Change in serum 25(OH)D and iPTH concentration at 6-month and 24-month follow-up by treatment

|                      | Standard-dose | High-dose       | P value* difference by time point | P value† difference over time |
|----------------------|---------------|-----------------|----------------------------------|-----------------------------|
|                      | 800 IU vitamin D₃ (n=136) | 2000 IU vitamin D₃ (n=137) |                                  |                             |
| 25(OH)D (ng/mL)      |                |                 |                                  |                             |
| Baseline             | 26.8 (24.9 to 28.7) | 27.7 (25.8 to 29.6) | 0.51                             | <0.0001                     |
| 6 months             | 40.4 (38.4 to 42.3) | 47.0 (45.1 to 49.0) | <0.0001                          |                             |
| 24 months            | 37.1 (35.1 to 39.2) | 45.5 (43.5 to 47.6) | <0.0001                          |                             |
| **P over time †**    | <0.0001        | <0.0001         |                                  |                             |
| iPTH (ng/L)          |                |                 |                                  |                             |
| Baseline             | 49.8 (46.8 to 52.9) | 48.7 (45.7 to 51.7) | 0.62                             | 0.22                        |
| 6 months             | 50.5 (47.4 to 53.5) | 47.8 (44.8 to 50.9) | 0.22                             |                             |
| 12 months            | 52.7 (49.6 to 55.8) | 48.5 (45.4 to 51.6) | 0.06                             |                             |
| 18 months            | 53.5 (50.4 to 56.6) | 49.5 (46.4 to 52.6) | 0.07                             |                             |
| 24 months            | 52.4 (49.3 to 55.6) | 48.8 (45.7 to 52.0) | 0.11                             |                             |
| **P over time †**    | 0.004          | 0.59            |                                  |                             |

Data show LSM (95% CI) of repeated measurements of serum 25-OH(D) and iPTH concentration by treatment group from multivariable repeated-measures models. Models included an indicator variable for treatment, visit, and the interaction between treatment and visit, and were adjusted for preoperative Western Ontario and McMaster Universities Arthritis Index. Function score (<52 vs ≥52 in the operated knee), presence of osteoarthritis in the non-operated knee, hospital site, and baseline age, gender, body mass index and Charlson Comorbidity Index (score 0–37). P values are two-sided. Statistical significance was set at p<0.05.

*P value for the difference in 25(OH)D and iPTH concentration by treatment group at baseline and individual follow-up time points.
†P value for the overall treatment effect across the repeated measurements of 25(OH)D and iPTH concentration.
‡P value for the change in 25(OH)D and iPTH concentration within treatment groups over time.

25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; LSM, least-square means.

Pattern was seen over the first 12 months of follow-up (see table 3A). Although not a primary endpoint, we also compared the percentage of patient who fell and found no difference between the arms (see table 3A).

**Secondary endpoints: lower extremity function, physical activity and radiographic progression in the contralateral knee**

Both treatment groups experienced a significant gain in lower extremity function from baseline (6–8 weeks after unilateral knee replacement) to 6, 12, 18 and 24 months of follow-up (p<0.0001; see table 3B). For both lower extremity function test sit-to-stand (STS) and gait speed, the difference between treatment groups approached significance (p=0.09 for each), with a possibly more pronounced improvement in the 2000 IU group. StepWatch-based physical activity also increased significantly over time, but not differentially so by treatment group (p=0.84; see table 3B).

Based on standardised X-rays of the contralateral knee, 31.3% of participants in the standard-dose and 30.5% of participants in the high-dose group progressed from baseline to 24 months, but again with no difference between the treatment groups (p=0.88; see table 3B).

**Subgroup analyses**

As predefined in the study protocol, we tested three interactions with treatment for the primary endpoints: by gender, by WOMAC function in the operated knee prior to surgery (<52 vs ≥52) and by OA in the contralateral knee at baseline (see online supplementary appendix 2). One interaction with treatment was found for gender, suggesting that high-dose vitamin D may improve WOMAC pain in the operated knee among men but not among women. The other interaction was found for treatment and function prior to surgery, where seniors with a lower function may have an increased chance to fall with high-dose vitamin D.

**Biochemical safety**

Regarding biochemical safety (see online supplementary appendix 3), mean serum calcium, and creatinine levels and mean urinary calcium excretion did not differ by treatment group at baseline and at 6, 12, 18 and 24 months of follow-up. There were few cases (between 0 and 4) of mild hypercalcaemia (>2.6 mmol/L) balanced between the treatment groups at all time points. At none of the time points were there any cases of overt hypercalcaemia >3.0 mmol/L (see online supplementary appendix 3).

**DISCUSSION**

Our study shows that among patients aged 60 and above, a higher dose of 2000 IU daily vitamin D supplementation compared with a standard dose of 800 IU daily vitamin D supplementation does not improve outcomes after total unilateral knee replacement. This includes pain and function in the operated and contralateral knees, as well as the rate of falls. While this strongly suggests that a
Table 3  (A) Primary and secondary endpoints — by treatment

(A) Primary endpoints

|                        | Standard-dose 800 IU vitamin D₃ n=136 | High-dose 2000 IU vitamin D₃ n=137 | P values* |
|------------------------|-------------------------------------|-----------------------------------|-----------|
| **WOMAC function, operated knee** | P=0.94                             |                                   |           |
| Baseline               | 25.0 (23.3, 26.8)                   | 26.3 (24.6, 28.1)                 | 0.31      |
| 6 months               | 9.9 (8.1, 11.6)                     | 10.8 (9.0, 12.5)                  | 0.49      |
| 12 months              | 7.9 (6.1, 9.6)                      | 8.2 (6.4, 9.9)                    | 0.82      |
| 18 months              | 7.2 (5.4, 9.0)                      | 8.0 (6.2, 9.8)                    | 0.56      |
| 24 months              | 6.6 (4.8, 8.5)                      | 7.0 (5.2, 8.9)                    | 0.77      |
| P across time†         | <0.0001                             | <0.0001                           |           |
| **WOMAC pain, operated knee** | P=0.97                             |                                   |           |
| Baseline               | 28.0 (26.1, 29.9)                   | 28.9 (27.0, 30.7)                 | 0.54      |
| 6 months               | 9.1 (7.2, 11.0)                     | 10.0 (8.0, 11.9)                  | 0.52      |
| 12 months              | 6.2 (4.3, 8.1)                      | 6.8 (4.9, 8.7)                    | 0.66      |
| 18 months              | 5.7 (3.8, 7.7)                      | 6.3 (4.3, 8.3)                    | 0.70      |
| 24 months              | 6.4 (4.4, 8.4)                      | 6.2 (4.2, 8.2)                    | 0.92      |
| P across time‡         | <0.0001                             | <0.0001                           |           |
| **WOMAC function, contralateral knee** | P=0.36                             |                                   |           |
| Baseline               | 4.2 (2.8, 5.6)                      | 4.3 (2.9, 5.7)                    | 0.94      |
| 6 months               | 6.1 (4.7, 7.5)                      | 4.6 (3.2, 6.0)                    | 0.15      |
| 12 months              | 5.1 (3.7, 6.6)                      | 4.7 (3.2, 6.1)                    | 0.67      |
| 18 months              | 5.3 (3.9, 6.8)                      | 5.3 (3.8, 6.7)                    | 0.94      |
| 24 months              | 4.1 (2.6, 5.6)                      | 4.6 (3.1, 6.1)                    | 0.68      |
| P across time‡         | 0.63                                | 0.06                              |           |
| **WOMAC pain, contralateral knee** | P=0.59                             |                                   |           |
| Baseline               | 4.7 (2.9, 6.4)                      | 4.6 (2.9, 6.4)                    | 0.98      |
| 6 months               | 6.9 (5.1, 8.6)                      | 5.2 (3.5, 7.0)                    | 0.20      |
| 12 months              | 6.4 (4.6, 8.2)                      | 5.2 (3.5, 7.0)                    | 0.37      |
| 18 months              | 6.5 (4.7, 8.3)                      | 5.5 (3.7, 7.3)                    | 0.44      |
| 24 months              | 6.5 (3.6, 7.3)                      | 5.8 (3.9, 7.6)                    | 0.84      |
| P across time‡         | 0.19                                | 0.80                              |           |
| **Rate of falls (mean)** |                                   |                                   |           |
| Baseline to 12 months  | 0.53 (0.32, 0.83)                   | 0.45 (0.27, 0.72)                 | 0.27      |
| Baseline to 24 months  | 1.07 (0.92, 1.23)                   | 1.05 (0.90, 1.21)                 | 0.84      |

(B) Secondary endpoints

| Secondary endpoints | Least-square means | P values† |
|---------------------|--------------------|-----------|
| Standard-dose 800 IU vitamin D₃ | High-dose 2000 IU vitamin D₃ | P values† |
| **Sit-to-stand performance in seconds** | P=0.09 |
| Baseline | 10.7 (10.2, 11.2) | 11.1 (10.6, 11.6) | 0.28 |
| 6 months | 9.7 (9.2, 10.1) | 9.3 (8.8, 9.8) | 0.32 |
| 12 months | 9.2 (8.7, 9.7) | 9.2 (8.7, 9.7) | 0.90 |
| 18 months | 9.2 (8.7, 9.7) | 9.0 (8.5, 9.5) | 0.48 |

Continued
higher dose of 2000 IU is not necessary for recovery after unilateral total knee replacement, we cannot determine the degree of efficacy of the 800 IU dose without a pure control group.

The only significant dose-differential findings were identified in predefined subgroup analyses by gender and by function prior to surgery. Based on these, we cannot exclude the possibility that men may benefit from 2000 IU superior to 800 IU vitamin D with respect to a significantly greater pain reduction in their operated knee. On the other hand, we also cannot exclude the possibility that 2000 IU vitamin D may increase fall risk significantly among patients who are most limited in their WOMAC function at the index knee prior to surgery.

Our trial is the fifth in a recent series of double-blind randomised controlled trials on vitamin D supplementation among patients with symptomatic knee OA. Compared with the prior trials, we targeted somewhat older adults with a mean age of 70 years versus aged 53–64 and not yet at the stage of surgery in the previous four trials. Unique to our trial is also the concept of targeting WOMAC symptoms individually for the operated and the contralateral non-operated knee.47 For the latter, we anticipated10–12 and confirmed a high 57% prevalence of radiographic OA in the contralateral knee at baseline. However, contrary to our expectations, we did
not find rapid disease progression\textsuperscript{10} in the contralateral knee, both clinically and radiographically. In fact, for symptoms, the majority of participants in both treatment groups remained stable.

One explanation may be that 800 IU vitamin D may have been sufficient to stop symptomatic progression in the contralateral knee. Supporting such a benefit, in three\textsuperscript{18,19,31} of the four prior trials, a benefit of vitamin D on WOMAC function could not be excluded, and one\textsuperscript{31} of the four prior trials found a significant improvement in WOMAC pain. However, regarding structural disease progression, none of the prior trials support such a benefit.

We confirm the high risk of falling in this patient group.\textsuperscript{48} However, the adjusted mean number of falls over 24 months was similar between the treatment groups. Only in the subgroup with most pronounced functional limitations prior to surgery more falls occurred with 2000 IU vitamin D compared with 800 IU vitamin D. This is consistent with one prior trial among 173 patients with hip fracture, where a possible increase of falls with 2000 IU vitamin D/day vs 800 IU/day could not be excluded (+28%; 95% CI −4% to +68%).\textsuperscript{34}

A limitation of our study is the lack of a pure control group, which is why our trial cannot establish a benefit of daily 800 IU vitamin D over placebo. However, at the time of the trial (start in 2007), the safe upper intake of vitamin D was still 2000 IU, and the ethical commission at the time requested that the comparator should be the standard-dose 800 IU vitamin D to allow compliance with current recommendations given the high risk of falls and hip fractures among seniors with knee OA.\textsuperscript{30} Also, contrary to our expectations,\textsuperscript{39} only 31.4% of participants were vitamin D-deficient at baseline, and the achieved 25(OH)D levels only differed by 6.6 ng/mL at 6 months and 8.4 ng/mL at 24 months.\textsuperscript{34}

In conclusion, our findings suggest that daily 800 IU vitamin D may be sufficient for recovery after unilateral total knee replacement due to severe knee OA. However, despite the observed improvement in symptoms among participants of both treatment groups in our trial, we cannot determine the degree of efficacy of the 800 IU dose without a pure control group. More research is needed to clarify the potential benefit of vitamin D on OA symptoms.
Contributors HAB-F designed the trial, is the guarantor, received funding for the trial, wrote the analysis plan, performed statistical analyses and wrote the first draft of the paper. EJO codeigned the trial, supervised the analyses as the head biostatistician and contributed to the first draft of the paper. AE was the coordinating study MD of the trial, contributed to data cleaning and contributed to the first draft of the paper. BD-H contributed to the design of the trial and contributed to the first draft of the paper. KF cleaned the data set, contributed to the first draft of the Methods and Results sections, and reviewed the final draft of the paper. HBS contributed to the design of the trial, was an advisor on the falls outcome and reviewed the final draft of the paper. RF contributed to the design of the trial, was an advisor on the WOMAC pain and function outcomes, and reviewed the final draft of the paper. HHS contributed to the design of the trial and reviewed the final draft of the paper. JH collaborated on the radiological assessment of knee OA in the trial, advised on the radiological outcome and reviewed the final draft of the paper. AVG advised and performed the laboratory analyses and reviewed the final draft of the paper. GF advised on the analyses and adjudication of falls and reviewed the final draft of the paper. UM cleaned the data set, contributed to the first draft of the Methods section and reviewed the final draft of the paper. TG advised on the participant selection for the trial, supervised recruitment at the largest recruitment site and reviewed the final draft of the paper. PB contributed to the design of the trial, was an advisor on 25-hydroxyvitamin D measurements and reviewed the final draft of the paper. AV advised on the analyses of comorbidity conditions and reviewed the final draft of the paper. PC-B contributed to data cleaning, advised on the statistical analyses and reviewed the final draft of the paper. RT contributed to the design of the trial and the first draft of the paper. WC contributed to the design of the trial and the first draft of the paper. DF contributed to the design of the trial, is guarantor, coordinated the radiological assessment and contributed to the first draft of the paper. All authors reviewed and approved the final draft of the paper.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study protocol was approved by the ethical committee of the Canton of Zurich and the Swiss Agency for Therapeutic Products (Swissmedic, regulatory agency of Switzerland).

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