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Effects of vitamin D supplementation on disabling foot pain in patients with symptomatic knee osteoarthritis

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Competing interests

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Abstract

Objectives: This study aims to determine whether vitamin D supplementation or maintaining sufficient vitamin D level reduces foot pain over two years in patients with symptomatic knee OA.

Methods: A post hoc study was conducted from a randomized double-blind placebo-controlled trial named the VItamin D Effect on Osteoarthritis (VIDEO) study. Symptomatic knee OA patients with serum 25-hydroxyvitamin D levels between 12.5 nmol/L to 60 nmol/L were included and randomly allocated to either monthly vitamin D3 or placebo treatment (1:1) for 2 years. Manchester Foot Pain and Disability Index (MFPDI) was used to evaluate foot pain and Disabling foot pain was defined as at least one of the 10 functional limitation items (items 1-9,11) being documented as on 'most/every day(s)' in the last month. A repeated-measure mixed effect model was used to analyze the change of MFPDI scores between groups adjusting for potential confounders.

Results: A total of 413 patients with a mean age of 63.2 years (49.7% males) were enrolled and 340 completed the study. The mean MFPDI score was 22.8±7.3, with 23.7% participants having disabling foot pain at baseline. There were significant differences in MFPDI scores change between groups over 2 years, with more improvements in vitamin D group than in placebo group (-0.03 vs. 1.30, P=0.013) and more improvement in those maintaining sufficient vitamin D levels (n=226) than those who did not (n=114) (-0.09 vs. 2.19, P=0.001).

Conclusion: Vitamin D supplementation and maintenance of sufficient vitamin D levels may improve foot pain in those with knee OA.

Significance and Innovations:

1. Foot pain is common in symptomatic OA patients and vitamin D deficiency is related to chronic pain.
2. This study indicates vitamin D supplementation may be beneficial for foot pain in OA patients.

Introduction

Osteoarthritis (OA) is a chronic disease worldwide characterized by joint pain and deformity. In those over 60 years old, the global prevalence of OA is approximately 10% in men and 20% in women; the financial burden is estimated as high as 1.0%-2.5% of the GDP in Western countries(1). Foot pain, a common musculoskeletal pain, often defined as pain in the foot and/or ankle(2), affects nearly one in five older people in the community(3-7) and has a detrimental impact on health-related quality of life. Foot pain often coexists with knee pain, and concurrent foot pain leads to impairing physical activity, lower quality of life and increased levels of depression in knee OA patients when compared with the general population(4, 5). In addition, in a survey of 8990 older people, most people with knee pain had multiple joint site pain, and the

severity of knee pain and related disability were worse in the presence of pain elsewhere(6). Given that patients with knee OA are more likely to have foot pain and increased severity of foot pain, management of foot pain in OA patients is of priority.

Vitamin D deficiency and insufficiency, which mostly defined as serum 25-hydroxyvitamin D concentration of less than 50nmol/L and between 50 to 75 nmol/L, respectively (8), is common all around the world and the prevalence of it presents in about 45% of adults in Australia(9). Previous epidemiological studies reported that vitamin D deficiency was associated with chronic musculoskeletal pain and depression, but underlying mechanisms were complex and unclear(10-12). Studies exploring the effect of vitamin D supplementation on non-specific chronic pain in the adult population and those with rheumatoid arthritis and osteoporosis have had inconsistent findings(12, 13). Besides, the efficacy of vitamin D supplementation on knee pain in patients with knee OA was also conflicting both for WOMAC pain score and VAS knee pain score(14, 15). To date, there have been no studies exploring the effect of vitamin D supplementation on foot pain in knee OA patients. Therefore, the aim of our study is to explore whether vitamin D supplementation or maintaining sufficient vitamin D level reduces foot pain in patients with symptomatic knee OA, initially deficient in vitamin D.

Methods

Patients and trial design

A post hoc study was conducted from a randomized double-blind placebo-controlled trial named the Vitamin D Effect on Osteoarthritis (VIDEO) study (clinicaltrials.gov identifier: NCT01176344), in which the primary outcomes were tibial cartilage volume and knee pain among patients with symptomatic knee OA(16). Patients who suffered from symptomatic knee OA at least for 6 months, had knee pain of 20-80 mm on a 100-mm visual analog scale (VAS) and serum 25-hydroxyvitamin D levels between 12.5 nmol/L to 60 nmol/L, and aged 50 to 79 years were included. Patients with the Altman and Gold atlas grade 3 radiographic changes, severe knee pain on standing (>80 mm on a 100-mm VAS), other rheumatic diseases such as rheumatoid

arthritis, psoriatic arthritis and lupus, contraindication to MRI, cancer, severe cardiac or renal impairment, hypersensitivity to vitamin D, anticipated knee or hip surgery within the next 2 years and history of taking vitamin D within the previous 1 month were excluded from this study. After signing the written consent, patients were randomly allocated to 24 months' vitamin D or placebo treatment at a ratio of 1:1. A monthly capsule containing 50000IU (1.25mg) vitamin D3 (cholecalciferol) or placebo was given to patients and assessments were conducted at baseline and at month 3, 6, 12 and 24.

Measurements

Manchester Foot Pain and Disability Index Questionnaires

The Manchester Foot Pain and Disability Index (MFPDI) questionnaire was used to measure foot pain of patients at month 0, 3, 6, 12 and 24. The MFPDI was developed to measure foot pain and disability in the elderly(17). It is a proven useful and valid instrument for assessing foot pain in the older population and has been used in both observational studies and randomized controlled trials(18). Each item was scored either 1 (none of the time), 2 (on some days) or 3 (on most days/every day). The total score was calculated by summing the scores of 17 items, with a possible score range of 17 to 54. A higher score indicates greater disability. Disabling foot pain was defined when at least one of the 10 functional limitation items (items 1-9,11) was documented as on 'most/every day(s)' in the last month(18).

Knee structures measurements

Radiographic OA was assessed at baseline by a standing semiflexed anterior-posterior radiograph as per the Altman atlas(19) according to the protocol using the Osteoarthritis Research Society International (OARSI) atlas to score osteophytes and joint space narrowing. MRI scans with a commercial transmit-receive extremity coil at baseline and two years of the study knee were obtained according to a standardized protocol. T2-weighted/proton density-weighted fast spin echo sequences were used to assess cartilage defects and bone marrow lesions (BMLs) and detail are described before in the protocol(20).

WOMAC

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)(21) scale was used to detect knee symptoms at month 0, 3, 6, 12 and 24. The sum of pain (0-500), stiffness (0-200) and physical function (0-1700) subscales is calculated as the total WOMAC score (0-2400).

Serum 25(OH)D measurement and definition of vitamin D status

Serum 25-hydroxyvitamin D levels were assayed using direct competitive chemiluminescent immunoassays at screening, month 3 and month 24. Patients whose serum 25-hydroxyvitmin D level greater than 50 nmol/L at both month 3 and 24 were classified into maintaining sufficient vitamin D group and whose serum 25-hydroxyvitmin D level less than 50 nmol/L at either month 3 and 24 were classified into not maintaining sufficient vitamin D group.

Physical activity

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short version, which was proven to be valid and reliable in monitoring population levels of physical activity among old adults in diverse settings(22). Based on the scoring protocol, we classified physical activity status as insufficiently active, sufficiently active and highly active.

Other measurements

Body height and weight were measured at baseline and body mass index (BMI, in kg/m^2) was calculated. Height was measured to the nearest 0.1 cm (with shoes removed) using a stadiometer (Leicester Height Measure, Invicta Plastics Ltd, Leicester, UK) and weight was measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using electronic scales (Heine S-7307, Heine, New Hampshire, USA).

Statistical analysis

Baseline characteristics between patients with and without disabling foot pain were compared using independent *t* or χ^2 tests. A repeated-measure mixed effect model with terms for treatment, time, treatment by time and adjustment for age, sex, BMI was used to analyse the change in MFPDI scores over 24 months between groups including vitamin D vs. placebo group and maintaining sufficient vitamin D vs. not maintaining sufficient vitamin D group. Multilevel mixed-effect models were used to deal with missing data caused by loss to follow-up and

nonresponses. Subgroup analysis exploring effects of vitamin D supplementation and maintaining sufficient vitamin D level on foot pain relief in patients with disabling foot pain at baseline was performed. All tests were two-sided and P value <0.05 was considered statistically significant. Stata version 12.0 was used to perform statistical analyses.

Results

Baseline characteristics

A total of 413 patients were included and randomized to receive either vitamin D (n=209) or placebo (n=204) treatment. After 24 months, 340 patients completed the trial: there were no significant differences in baseline characteristics between patients who completed the study and who did not. The average age of patients was 63.2 years with a mean BMI of 29.6 kg/m^2, and 49.7% of them were female. The mean MFPDI score was 22.8±7.3. For those reporting foot pain (n=214) at baseline, sites of pain were the toes (74 [34.6%]), 49 (22.9%) reported pain in the ball of foot, 48 (22.4%) reported pain in the arch, 43 (20%) reported in whole feet and 37 (17.3%) reported pain in heel. Disabling foot pain was present in 23.7% (n=98) of patients according to MFPDI case definition. There were also no significant differences in baseline characteristics, MFPDI scores, prevalence of disabling foot pain, knee symptoms and knee structure measurements between vitamin D group and placebo group (Table 1). At the same time, the baseline serum vitamin D level was higher in the maintaining sufficient vitamin D group when compared with not maintaining sufficient vitamin D group (45.2 vs 41.5, *P*=0.01), while other characteristics were similar in two groups.

Vitamin D supplementation and change in MFPDI scores

Over 24 months, MFPDI scores remained largely unchanged in the vitamin D group (-0.03 [95%CI, -0.80 to 0.74]) while worsening in the placebo group (1.30 [95%CI, 0.51 to 2.09]) (Figure 1). There were significant differences in change of MFPDI scores between groups in the mixed-effect model after including all time points adjusted for age, sex and BMI (between-group difference,

-1.32 [95%CI, -2.43 to -0.22]; P=0.013) (Table 2 and Figure 1).

In subgroup analyses, for patients with disabling foot pain at baseline, although those who received vitamin D treatment had lower changes in MFPDI scores compared with placebo group after 24 months, the difference was not statistically significant (Change of -4.86 [95%CI, -6.79 to -2.93] in vitamin D group vs. -2.30 [95%CI, -5.33 to -0.31] in placebo group, between-group difference, -2.56 [95%CI, -5.33 to 0.21]; P=0.07). In patients without disabling foot pain at baseline, the between group difference was smaller and also not statistically significant (change of 1.36 [95%CI, 0.59 to 2.14] in vitamin D group vs. 2.46 [95%CI, 1.66 to 3.25] in placebo group, between-group difference, -1.09 [95%CI, -2.20 to 0.02]; P=0.05) different (Table 2). For females, there was no significant difference between vitamin D group and placebo group in change of MFPDI scores. In male patients, vitamin D supplementation significantly improved MFPDI scores when compared with placebo group (Table 2). However, there was no significant interaction between sex and vitamin D supplementation on change in MFPDI scores.

Maintaining sufficient vitamin D levels and change in MFPDI scores

In *P*ost-hoc analyses comparing patients who maintained sufficient vitamin D to those who did not maintain vitamin D sufficiency MFPDI score decreased in those maintaining sufficient vitamin D group but increased in those not maintaining sufficient vitamin D group over 2 years (-0.09 [95%CI, -0.79 to 0.61] in maintaining sufficient vitamin D group vs. 2.19 [95%CI, 1.21 to 3.18] in not maintaining sufficient vitamin D group, between-group difference, -2.29 [95%CI, -3.49 to -1.08]; P=0.001) after adjusted for age, sex, BMI, serum 25(OH)D level and baseline MFPDI score (Table 3 and Figure 2).

In subgroup analyses, for those with disabling foot pain at baseline, there was a greater decrease in MFPDI score in those maintaining sufficient vitamin D group compared to those not maintaining sufficient vitamin D (-4.63 [95%CI, -6.35 to -2.92] in maintaining vitamin D group vs. -0.14 [95%CI, -2.75 to 2.48] in not maintaining sufficient vitamin D group, between-group difference, -4.49 [95%CI, -7.62 to -1.37]; P=0.005) (Table 3). There were similar findings in

patients without disabling foot pain at baseline (Table 3). For females, there was no significant difference between maintaining sufficient vitamin D and not maintaining sufficient vitamin D in change of MFPDI scores (Table 3). While in males, significant improvement of MFPDI scores was found in maintaining sufficient vitamin D group compared to not maintaining sufficient vitamin D group. However, there was no significant interaction between sex and maintaining sufficient vitamin D on change in MFPDI scores.

Discussion

To the best of our knowledge, this current study is the first to investigate the effects of supplementing vitamin D and maintaining sufficient vitamin D level on foot pain in symptomatic knee OA patients. In this sample, 51.8% of participants with knee OA and vitamin D deficiency reported foot pain. Foot pain and disability (MFPDI) scores decreased more over 24 months in the vitamin D treatment group that maintained sufficient vitamin D than in the placebo group and the group that did not maintain sufficient Vit D. Our results suggest that foot pain is common and that maintaining sufficient vitamin D levels over 24 months may have beneficial effects on foot pain in patients with knee OA.

Foot pain is a common condition in patients with OA. A recent cross-sectional study using data from the Osteoarthritis Initiative (OAI) reported that one quarter of people with knee OA experienced concurrent foot pain with the majority (55%) reporting pain in both feet. Furthermore, knee OA patients with foot/ankle symptoms reported worse scores on all WOMAC subscales including the total score, worse health outcomes and poorer physical function compared with those without foot/ankle symptoms(5). In our study, over half the patients (51.8%) reported foot pain at baseline and patients with foot pain had lower quality of life and higher rates of depression, which was similar to previous studies. In another study, foot/ankle symptoms in either or both feet significantly increased the odds of developing knee symptoms and symptomatic radiographic knee OA in people at risk of the disease(23). Additionally, in patients with symptomatic radiographic knee OA, the presence of foot/ankle symptoms was

associated with increased risk of knee pain over four years(24). Owing to the coexistent relationships between foot/ankle symptoms and knee OA, more attention should be paid to management of foot pain in OA patients and those at risk of knee OA.

Although there is a growing body of evidence suggesting that a low level of vitamin D is associated with chronic pain, no clinical study has been conducted to explore the effect of vitamin D supplementation on foot pain. Furthermore, studies examining whether vitamin D supplementation is beneficial on other musculoskeletal pains are limited and have found conflicting results(10, 12, 25-27), mainly due to variations in participants, outcome measures, sample size, vitamin D dose and follow-up time. A recent secondary analysis of an RCT study with large sample suggested long-term monthly 100,000 IU vitamin D supplementation did not improve pain scores or reduce analgesic dispensing in the general population(27). Similarly, a Cochrane review also concluded that a large beneficial effect of vitamin D on chronic painful conditions across different sites was unlikely(10). However, in the current study, vitamin D supplementation and sufficient Vitamin D reduced MFPDI scores in symptomatic knee OA patients after 24 months compared with the placebo group, particularly in patients with disabling foot pain at baseline. There are a number of reasons as to why our results vary from other studies. Our participants were selected based on low baseline vitamin D levels, we specifically examined foot pain using a validated measure, our vitamin D dose was 50,000IU per month with the potential to improve compliance, and our duration of treatment was 2 years. As reported before in our RCT, 62% of patients in placebo group gained sufficient 25-hydroxyvitamin D level after 24 months. This may dilute the effect of vitamin D supplementation on MFPDI score. On the other hand, consistent results were found when patients were classified into maintaining sufficient vitamin D group and not maintaining sufficient vitamin D group. However, further clinical trials will be needed to determine whether vitamin D supplementation is beneficial for foot pain in patients with knee OA.

Previous studies have found that low levels of vitamin D are associated with chronic pain(12, 28, 29); but there is no previous work linking vitamin D deficiency to foot pain. In one

population-based, cross sectional study of 958 older adults, a lower level of vitamin D was not related to foot pain, but was to back pain(30). In contrast, in our longitudinal study, our population with low Vitamin D levels who maintained vitamin D sufficiency with supplementation had significantly decreased MFPDI scores compared with those did not maintain vitamin D sufficiency between month 3 and 24 suggesting that correction of vitamin D deficiency might reduce foot pain over time.

Several potential mechanisms such as bone demineralization, muscle weakness and pain dysregulation may link vitamin D deficiency to musculoskeletal pain. Vitamin D can modulate a number of inflammatory pathways(31), which are associated with pain sensitization. Low vitamin D level can activate proinflammatory cytokine proliferation, thus alter sensitization of peripheral and central pathways through nociceptive inflammation processing(32, 33), which may be an important contributor to clinical symptoms of knee OA(34). Even so, the underlying mechanisms between vitamin D deficiency and foot pain are still unclear and further investigations are needed.

In OA patients, sex differences existed in the experience of pain, and psychological factors (35) and other factors such as foot and ankle shape, footwear habit, obesity, muscle strength declines with aging and ligamentous laxity may underline the sex difference in pain. In our study, females reported higher MFPDI scores and more disabling foot pain at baseline. Although males experienced significantly improvement in MFPDI scores when treated with vitamin D supplementation and maintaining sufficient vitamin D level, there were no significant interactions between sex and vitamin D supplementation or maintaining sufficient vitamin D on change in MFPDI scores. This suggests that there is no sex difference in effects of vitamin D supplementation or maintaining sufficient vitamin D on change in MFPDI scores.

There are several potential limitations in our study. First, this is a post hoc analysis in which foot pain was the secondary outcome in the original protocol. Second, nearly half of patients reported some foot pain at baseline, only 23.7% of patients had disabling foot pain according to definition we used in this study. Even through the MFPDI score increased less after vitamin D

supplementation in those without disabling foot pain, the clinically significant difference of MFPDI score is unknown. Third, 62% of patients in placebo group reached sufficient vitamin D levels after 24 months' follow-up, which might due to seasonal change, outdoor physical activity or other reasons that may underestimate any benefit of vitamin D. In support of this, beneficial effects of vitamin D were also found in MFDPI scores after patients were divided into consistently and not consistently sufficient vitamin D group.

Conclusion

This is the first study to show that vitamin D supplementation and maintaining sufficient vitamin D levels reduces foot pain over two years in patients with symptomatic knee OA. Vitamin D supplementation and maintaining sufficient vitamin D level may improve foot pain in knee OA patients.

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Contributions

Dr Ding 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. Drs Tu and Zheng contributed equally to this study. Study concept and design: Ding, Jones, Cicuttini, Winzenberg. Acquisition, analysis, or interpretation of data: all authors. Drafting the manuscript: Tu, Shuang, Cicuttini, Jin, Ding. Critical revision of the manuscript for important intellectual content: all authors. Final approval of the article: all authors. Provision of study materials or patients: Ding, Jones, Cicuttini, Winzenberg. Statistical expertise: Tu, Shuang, Han, Zhu, Ding. Administrative, technical, or logistic support: Ding, Jones, Cicuttini. Collection and assembly of data: Ding, Jones, Cicuttini, Winzenberg.

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Ethical approval information

This study was approved by the Ethics Committee in Tasmania and Melbourne (reference number: H1040 and CF10/1182-2010000616, respectively).

Competing interests

Dr Jones reports being the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship. Drs Wluka and Winzenberg report being recipients of NHMRC Career Development Fellowship. Dr Ding reports being the recipient of an Australian Research Council Future Fellowship. No other disclosures were reported.

Table 1. Baseline characteristics of participants between maintaining sufficient vitamin D group and insufficient vitamin D group

	Vitamin D group (N= 209)	**Placebo group (N= 204)**	**P value**
Age, mean (SD), y	63.55±6.88	62.85±7.22	0.32
Female, No. (%)	106(50.72)	102(50)	0.92
Body mass index (BMI), mean (SD)	29.57±5.39	29.64±4.62	0.88
Baseline 25-(OH)D level, mean (SD), nmol/L	43.74±11.79	43.81±12.66	0.95
MFPDI (0-34), mean (SD)	21.85±6.83	22.66±7.49	0.27
Disabling foot pain, No. (%)	101(47.42)	112(52.58)	0.30
Physical activity			
Insufficiently active, No. (%)	38(19.0)	40 (20.83)	0.71
Sufficiently active, No. (%)	82 (41.0)	71 (36.98)	
Highly active, No. (%)	80 (40)	81 (42.19)	
WOMAC score			
Pain (0-500)**,** mean (SD)	137.88±88.82	134.74±83.42	0.71
Function (0-1700)**,** mean (SD)	487.94±318.14	467.59±292.79	0.50

Stiffness (0-200), mean (SD)	61.48±41.53	61.74±40.08	0.95
Knee structures			
Total radiographic OA (0-18)	8.26±5.56	8.31±4.91	0.93
Total cartilage defects (0-24)	14.84±4.08	14.42±3.94	0.29
Total bone marrow lesions (0-45)	3.15±3.22	3.59±3.23	0.17

MFPDI, Manchester foot pain and disability index;

Two-tailed Student's *t* tests were used for differences between means.

χ^2 tests were used for proportions (percentages) and Wilcoxon rank-sum tests were used for differences between medians.

Table 2. Effect of vitamin D supplementation on change in MFPDI over two years

	Mean change, (95% CI)	Between-group difference change, mean (95% CI)	P-value
Whole sample			
Placebo Group (N= 204)	**1.30 (0.51, 2.09)**	**-1.32 (-2.43, -0.22)**	**0.013**
Vitamin D Group (N= 209)	-0.03 (-0.80, 0.74)		
Those without disabling foot pain at baseline			
Placebo Group (N= 153)	**2.46 (1.66, 3.25)**	-1.09 (-2.20, 0.02)	0.05
Vitamin D Group (N=162)	**1.36 (0.59, 2.14)**		
Those with disabling foot pain at baseline			
Placebo Group (N=51)	**-2.30 (-5.33, -0.31)**	-2.56 (-5.33, 0.21)	0.07
Vitamin D Group (N=47)	**-4.86 (-6.79, -2.93)**		
Females			

Placebo Group (N=102)	1.19 (-0.06, 2.43)	-0.97 (-2.65, 0.70)	0.26
Vitamin D Group (N=106)	0.22 (-0.91, 1.34)		
Males			
Placebo Group (N=102)	**1.32 (0.31, 2.33)**	**-1.59 (-3.05, -0.13)**	**0.03**
Vitamin D Group (N=103)	-0.27 (-1.33, 0.78)		

Changes in outcomes are generated from mixed-effect models adjusted for age, sex and body mass index.

Between-group differences were calculated with vitamin D group values minus placebo group values or maintaining sufficient vitamin D group minus insufficient group.

Table 3. Effect of vitamin D status on change in MFPDI over 2 years

	Mean change, (95% CI)	Between-group difference change, mean (95% CI)	P-value
Whole sample			
Not maintaining sufficient vitamin D (N= 114)	**2.19 (1.21 to 3.18)**	**-2.29 (-3.49 to -1.08)**	**0.001**
Maintaining sufficient vitamin D (N= 226)	-0.09 (-0.79 to 0.61)		
Those without disabling foot pain at baseline			
Not maintaining sufficient vitamin D (N= 91)	**2.76 (1.77, 3.74)**	**-1.55 (-2.76, -0.33)**	**0.01**
Maintaining sufficient vitamin D (N= 174)	**1.21 (0.50, 1.93)**		
Those with disabling foot pain at baseline			
Not maintaining sufficient vitamin D (N= 23)	-0.14 (-2.75, 2.48)	**-4.49 (-7.62, -1.37)**	**0.005**

Maintaining sufficient vitamin D (N= 52)	**-4.63 (-6.35, -2.92)**		
Females			
Not maintaining sufficient vitamin D (N= 62)	**1.52 (0.13, 2.91)**	-1.21 (-2.98, 0.56)	0.18
Maintaining sufficient vitamin D (N= 98)	0.31 (-0.79, 1.40)		
Males			
Not maintaining sufficient vitamin D (N= 52)	**2.81 (1.45, 4.17)**	**-2.92 (-4.54, -1.31)**	**0.001**
Maintaining sufficient vitamin D (N= 128)	-0.11 (-0.99, 0.77)		

Changes in outcomes are generated from mixed-effect models adjusted for age, sex, body mass index, serum 25(OH)D level and baseline MFPDI score.

Between-group differences were calculated with vitamin D group values minus placebo group values or maintaining sufficient vitamin D group minus insufficient group.

Figure 1. Change in MFPDI scores in the vitamin D supplementation group and the placebo group

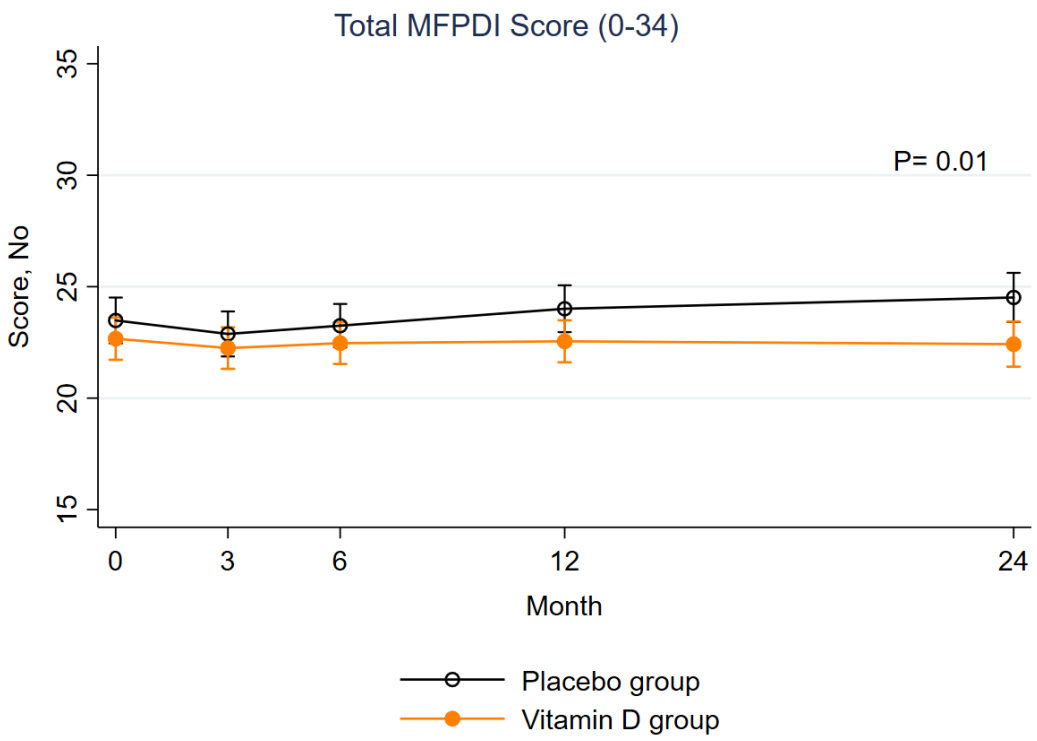

Figure 2. Change in MFPDI scores in groups between maintained and did not maintain vitamin D sufficiency