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# Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis

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SUMMARY

*Objective:* To develop a measure of knee joint effusion-synovitis volume and to examine the effect of vitamin D supplementation on effusion-synovitis in people with knee osteoarthritis (OA) and low vitamin D levels over 24 months.
*Method:* Symptomatic knee OA patients with low 25-(OH)D levels (12.5–60 nmol/l) were recruited for a multi-centre, randomised, placebo-controlled and double-blind trial. Participants (age 63 ± 7 years, 208 females) were allocated to either 50,000 IU monthly vitamin $D_3$ ($n = 209$) or placebo ($n = 204$) for 24 months. Knee effusion-synovitis volume in suprapatellar and other regions was measured on magnetic resonance imaging (MRI) using OsiriX software. The intra-class correlation coefficients (ICCs) were used to test inter- and intra-rater reliabilities. The least significant change criterion was used to define the increase/decrease in effusion-synovitis volume.
*Result:* The reproducibilities of effusion-synovitis volume measurement were high with ICCs ranging from 0.93 to 0.99. Over 24 months, effusion-synovitis volume remained stable in the vitamin D group but increased in placebos with a significant between-group difference (−1.94 ml, 95% confidence interval (CI): −3.54, −0.33). This effect was evident in those with baseline effusion-synovitis and with suprapatellar effusion-synovitis. The proportion with an increase in effusion-synovitis volume was lower in the vitamin D group than placebo (risk ratio (RR): 0.87, 95% CI: 0.77, 0.97).
*Conclusion:* This highly reproducible effusion-synovitis volume measurement could be a promising outcome measure in OA trials. Vitamin D supplementation could retard the progression of effusion-synovitis which can potentially benefit people with an inflammatory OA phenotype.


## Introduction

Osteoarthritis (OA) was generally thought of as a 'non-inflammatory' type of arthritis; however, localised low-grade inflammation is now known to be an important factor in OA pathogenesis[1–3]. The development of chronic inflammation in OA following joint injury or metabolic dysfunction may contribute to the formation of a cycle of local tissue lesions, inflammation and repair[4]. Notably, synovial activation (effusion and/or synovitis) has been considered as a precursor of OA outcomes such as radiographic changes and total knee replacement[5,6]. It is independently associated with clinical symptoms, such as knee pain and physical function[7,8]. Studies have demonstrated the link between synovial inflammation and structural changes of knee OA[9–12], suggesting that reducing synovial inflammation may be a potential avenue for slowing disease progression in knee OA. This is extremely important, as there are no proven treatment options to modify disease progression in OA so far.

Joint effusion-synovitis (a magnetic resonance imaging (MRI) marker of synovial inflammation) has been assessed using MRI with high reproducibility and validity, but the scoring methods were often semi-quantitative and subjective even for experienced professionals[13,14]. This may be one of reasons why inconsistent

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findings regarding the association of structural alterations with severity of synovitis have been reported[15–17]. Quantitative measures of synovial membrane inflammation had been shown better correlated with clinical signs and histopathologic parameters in inflammatory arthritis[18]. Currently, very few studies have investigated effusion/synovitis volume using MRI in OA[19,20], and no study has yet practically investigated it as an outcome measure in clinical trials.

Importantly, compared to articular and bony alterations, synovial inflammation has a greater potential to regress or resolve[21] which creates a treatment opportunity. Pharmaceutical managements such as non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroid injection have been recommended for OA patients particularly for those with joint effusion[22]; however, these treatments can result in side-effects and drug intolerance during long-term use[23,24]. It is therefore important to identify safer and more cost-effective interventions targeting synovial inflammation in OA[25].

In observational studies vitamin D deficiency has been associated with cartilage loss and pain[26,27]. In animal models, vitamin D supplementation has a protective effect in OA by reducing the expression of pro-inflammatory cytokines[28]. Furthermore, an exercise-interventional study has found that vitamin D sufficiency increases anti-inflammatory cytokine response to muscular injury[29]. So far, randomised controlled trials (RCTs) on the efficacy of vitamin D supplementation for knee OA is limited and inconsistent. While one study suggested it had beneficial effects on symptoms[30], another showed no effects on symptoms and cartilage loss[31]. In our recent Vitamin D Effect on Osteoarthritis (VIDEO) study in patients with knee OA and low serum vitamin D levels, vitamin D supplementation over 24 months had no significant effect on knee pain or cartilage morphology but might have modest effects on knee function loss and bone marrow lesions[32]. However, none of these studies has investigated the effects of vitamin D on synovial inflammation. We hypothesised that vitamin D could reduce synovial inflammation in patients with knee OA.

The aims of this study were, therefore, to develop a measure of knee joint effusion-synovitis volume and to examine the effect of vitamin D supplementation over 24 months on effusion-synovitis as a post-hoc analysis in the VIDEO study.

## Methods

### *Trial design*

The VIDEO study was a randomised, double-blind, placebo-controlled clinical trial[32]. Participants were recruited in Tasmania and Victoria, Australia, using a combined strategy, including working with general practitioners, specialist rheumatologists and orthopaedic surgeons, and advertising through media and community groups. Eligible participants were randomly allocated to either treatment or matching placebo group in a 1:1 ratio. A telephone pre-screen assessed knee pain, anticipated knee and hip surgery, participation in other studies and comorbidities. Eligible participants were subsequently screened in a clinic visit including knee radiographs and a blood test for serum 25-(OH)D level.

### *Participants*

Eligible participants were aged between 50 and 79 years with symptomatic knee OA for at least 6 months and pain of at least 20 mm on a 100 mm on a visual analogue scale (VAS) and were recruited from August 2010 to December 2011. All individuals were assessed according to the American College of Rheumatology (ACR) criteria for symptomatic knee OA[33]. Participants also had an ACR function class rating of I, II and III[34] and relatively good health, with a score of 0–2 on a 5-point Likert scale (from 0 indicating very good health to 4 indicating very poor health) according to the global investigator assessment of disease status. Participants were included if their serum 25-(OH)D levels >12.5 nmol/l or <60 nmol/l. Ethics approval was received from the Tasmania Health and Human Medical Research Ethics Committee (reference number H1040) and Monash University Human Research Ethics Committee (reference number CF10/1182-2010000616). Informed written consent was obtained from all participants.

Exclusion criteria included grade 3 radiographic knee OA according to Altman's atlas[35], contraindication to MRI, rheumatoid or psoriatic arthritis, lupus, cancer, severe cardiac or renal impairment, hypersensitivity to vitamin D, conditions affecting oral drug absorption, anticipated knee or hip surgery within the next 2 years, history of significant trauma of knees (e.g., arthroscopy or injury to ligaments or menisci within 1 year preceding the study) and history of taking vitamin D or an investigational drug within the last 30 days.

### *Interventions*

Participants in the intervention group were given a monthly capsule of 50,000 IU (1.25 mg) vitamin $D_3$ (cholecalciferol) orally for 24 months[36]. The vitamin $D_3$ compound was purchased from Nationwide Compounding Pharmacy, Melbourne, Australia. Participants in the control group received an identical inert placebo provided by the same company. Serum 25-(OH)D was assayed by Liaison method utilizing a direct competitive chemiluminescent immunoassays (DiaSorin Inc., Stillwater, Minnesota, USA). The intra-assay and inter-assay coefficients of variation were 3.2% and 6.0%.

### *Randomisation*

Participants were allocated to either vitamin D or placebo arm at a ratio of 1:1 based on computer-generated random numbers. Allocation concealment was ensured by a central automated allocation procedure with security in place to ensure allocation data could not be accessed or influenced by any person from the investigative team.

### *Blinding*

Participants, research coordinators and investigators were all blinded to treatment assignment. The blinding procedure was maintained until all the data were collected, cleaned, confirmed for accuracy and statistical analyses were performed.

### *Outcome measures*

The co-primary efficacy endpoint measures of the trial were MRI assessment of knee cartilage volume changes from baseline to month 24, as well as the Western Ontario and McMaster Universities Index of OA (WOMAC) score as have been reported[32]. This post-hoc analysis examined outcomes of volume of knee effusion-synovitis. The knee that met the inclusion/exclusion criteria was selected as the study knee for outcome measures. When both knees met the criteria, the less severe one was studied as it has more cartilage volume at baseline which would enable to observe the effect on loss of cartilage volume (the primary outcome) as large as possible.

### *MRI and image processing*

MRI of the study knee was acquired with a 1.5 T whole-body magnetic resonance unit (Picker, Cleveland, OH, USA) using a commercial transmit-receive extremity coil. Image sequence