Osteoarthritis and Cartilage 24 (2016) 1858–1866

Osteoarthritis and Cartilage

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

N.K. Arden † ‡ § *, S. Cro ||, S. Sheard †, C.J. Doré ||, A. Bara ||, S.A. Tebbs ||, D.J. Hunter † ¶, S. James #, C. Cooper † ‡, T.W. O'Neill †† ‡‡, A. Macgregor §§, F. Birrell |||, R. Keen ¶¶ ##

† *Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Oxford OX3 7LD, UK*
‡ *MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK*
§ *Arthritis Research UK Centre of Excellence for Sport, Injury, and Osteoarthritis, UK*
|| *MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, Aviation House, 125 Kingsway, London WC2B 6NH, UK*
¶ *Chromatic Innovation Limited, Leamington Spa, UK*
# *St Richard's Hospital, Chichester, UK*
†† *Arthritis Research UK Centre for Epidemiology, Institute of Inflammation and Repair, Faculty of Medical and Human Sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK*
‡‡ *NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK*
§§ *Norwich Medical School, University of East Anglia, Norwich, UK*
||| *Institute of Cellular Medicine, Newcastle University, UK*
¶¶ *Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK*
Institute of Orthopaedics and Musculoskeletal Science, University College London, London, UK

ARTICLE INFO

Article history:
Received 10 December 2015
Accepted 23 May 2016

Keywords:
Vitamin D
Knee
Randomised placebo-controlled trial
Osteoarthritis

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.
© 2016 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

* Address correspondence and reprint requests to: N.K. Arden, Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Nuffield Orthopaedic Centre, Windmill Road, Oxford OX3 7LD, UK. Tel: 44-0-1865-737859; Fax: 44-0-1865-227966.
E-mail addresses: Nigel.Arden@ndorms.ox.ac.uk (N.K. Arden), s.cro@ucl.ac.uk (S. Cro), sally.sheard@isis.ox.ac.uk (S. Sheard), caroline.dore@ucl.ac.uk (C.J. Doré), a.bara@ucl.ac.uk (A. Bara), susan.tebbs@ucl.ac.uk (S.A. Tebbs), d.j.hunter@gmail.com (D.J. Hunter), samjames1@nhs.net (S. James), cc@mrc.soton.ac.uk (C. Cooper), terence.o'neill@manchester.ac.uk (T.W. O'Neill), A.Macgregor@uea.ac.uk (A. Macgregor), fraser.birrell@newcastle.ac.uk (F. Birrell), Richard.Keen@rnoh.nhs.uk (R. Keen).

http://dx.doi.org/10.1016/j.joca.2016.05.020
1063-4584/© 2016 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

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,

Download English Version:

https://daneshyari.com/en/article/5669348

Download Persian Version:

https://daneshyari.com/article/5669348

Daneshyari.com