Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review

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Abstract

Objective. To systematically review the evidence for association between serum 25-hydroxyvitamin D (25-(OH)D) and OA and the effect of vitamin D therapy on OA.

Methods. An English Medline, EMBASE and Cochrane Library search for vitamin D and OA from January 1980 to June 2012 was performed. Randomized controlled trials (RCTs), cohort, case-control and cross-sectional studies in adults were included. The methodological quality of the selected studies was assessed and a best-evidence synthesis was used to summarize the results due to the heterogeneity of the studies.

Results. Of the 86 evaluated articles, 2 RCTs and 13 observational studies were included in the final analyses. The number of participants ranged from 64 to 1644 (0-100% women). The RCTs were only reported in abstract form and showed inconsistent results, most likely due to variations in their study design. There was insufficient or limited evidence for associations between 25-(OH)D and hand or hip OA. For knee radiographic OA as assessed by the Kellgren and Lawrence (KL) score, there was moderate evidence showing that low levels of 25-(OH)D were associated with increased progression of radiographic OA. Strong evidence for an association between 25-(OH)D and cartilage loss was apparent when joint space narrowing and changes in cartilage volume were considered collectively as cartilage loss.

Conclusion. 25-(OH)D appears to be implicated in structural changes of knee OA rather than symptoms, and further well-designed RCTs are required to determine whether vitamin D supplementation can slow disease progression. There is insufficient evidence for other sites.

Key words: 25-hydroxyvitamin D, osteoarthritis, systematic review.

Introduction

OA is the most common form of arthritis and is characterized by gradual cartilage loss, eventually resulting in functional failure of synovial joints [1, 2]. OA co-exists frequently with vitamin D deficiency in older people. Vitamin D deficiency, defined mostly as serum 25-hydroxyvitamin D (25-(OH)D) levels of <20 ng/ml, is very prevalent in the community, with a rate ranging from 50% to 80% [3-5]. OA affects all joint structures, including articular cartilage, subchondral bone and periarticular muscle. Disease-modifying OA drugs aim to modify structural changes associated with OA. Vitamin D has multiple biological functions in cartilage, bone and muscle by acting on vitamin D receptors [6-9], and may have beneficial effects on these joint structures in OA [10]. Moreover, low vitamin D may lead to vascular smooth muscle cell proliferation, endothelial cell dysfunction [11], vascular dysfunction [12] and increased inflammation [13, 14]; all of these may play roles in the aetiology of OA [15].
Our previous cohort study demonstrated that higher serum levels of 25-(OH)D predicted reduced loss of cartilage volume over 2 years, and increases in 25-(OH)D levels were associated with further protective association [16]. These suggest that vitamin D supplementation has the potential to modify the disease process of OA [17, 18] in patients with inadequate vitamin D levels. If vitamin D deficiency is confirmed to play a role in the pathogenesis of OA, it will provide a novel strategy for OA intervention.

Several systematic reviews have been published exploring the associations between vitamin D and OA-related conditions, including physical activity [19], muscle strength [20, 21], falls [22], obesity [23], bone density [24], common health outcomes [25] and diabetes [26]; however, no reviews have been performed specifically to investigate the association between vitamin D status and OA outcomes. The aim of this systematic review, therefore, was to systematically examine the evidence for associations between serum 25-(OH)D levels and OA and the effect of vitamin D therapy on OA.

Materials and methods

Literature search and study selection

We electronically searched Medline, EMBASE and the Cochrane Library from January 1980 to June 2012. These databases were searched using all possible terms for vitamin D and osteoarthritis and were limited only to human epidemiological and clinical studies. A detailed search strategy is presented in supplementary Table S1, available at Rheumatology Online. We included studies that met the following criteria: (i) any cohort, case-control or cross-sectional studies examining the association of 25-(OH)D levels with OA outcomes (including symptomatic, radiographic or structural changes) in adults and (ii) randomized controlled trials (RCTs) examining vitamin D supplementation (all forms and all doses) for OA.

Two reviewers (Y.C. and K.N.) independently assessed articles identified by the initial search strategy against the inclusion criteria. Differences of opinion regarding the selection of articles were resolved between the two investigators through discussion.

Assessment of methodological quality of studies

The assessment of the methodological quality of the included observational studies was based on previously used criteria [27, 28] with slight modifications to accommodate our topic. The criteria included 17 items with consideration given to both the internal validity and informativeness of the article (summarized in supplementary Table S2, available at Rheumatology Online) [29]. For each criterion, a rating of (+), (−) or (?) was assigned according to whether it met, did not meet or was unclear based on the descriptors given in supplementary Table S3, available at Rheumatology Online. Quality was independently assessed by two investigators (Y.C. and T.W.). The total score was calculated as a sum of the positive scores (the maximum possible score was 17 for cohort studies and 14 for case-control or cross-sectional studies). Studies were classified into high or low quality, with high quality defined as a methodological quality score >60%. For RCTs, the Cochrane Collaboration Risk of Bias Tool (CCRBT) was used to assess the risk of bias [30, 31]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (supplementary Table S4, available at Rheumatology Online) [32] checklist was used to ensure that all items required for reporting of a systematic review were addressed.

Data extraction and analysis

Data extraction was completed for all included studies by one investigator (Y.C.) and cross-checked by a second investigator (C.D.). Data extracted included the number of participants, gender and age of participants, baseline 25-(OH)D levels, length of investigation/intervention, outcome measures, adjustment for confounders and measures of the association between 25-(OH)D levels and OA. Data on the characteristics and results from the included studies were tabulated. The characteristics comprised first author and publication date, details of the study population, the mean age and percentage of female participants, 25-(OH)D values and study design.

As a result of the substantial heterogeneity in methodology, we chose to perform a best-evidence synthesis rather than statistically pooling the data. The prospective cohort study was considered as the preferred design, followed by the case-control and cross-sectional designs. Studies were also ranked based on their methodological quality score. Level of evidence was then defined using the criteria provided by Lieverse et al. [29]: strong evidence—generally consistent findings in multiple high-quality cohort studies; moderate evidence—generally consistent findings in two high-quality cohort studies, or in one high-quality cohort study and two or more high-quality case-control/cross-sectional studies, or in three or more high-quality case-control/cross-sectional studies; limited evidence—generally consistent findings in a single cohort study, or in two or more case-control/cross-sectional studies; insufficient evidence—finding in single case-control or cross-sectional study; conflicting evidence—conflicting findings (i.e., <75% of the studies reported consistent findings); and no evidence—no studies can be found.

Results

Of the 357 originally identified abstracts, 271 were excluded after initial title and abstract screening (Fig. 1). A further 72 were excluded after full-text review because the disease studied was not OA but another disease (breast cancer, JCA, hip fracture, HOA, RA and osteoporosis) (n = 65) or they were review articles (n = 7). A final library of 14 articles (15 studies) remained for further analyses [16, 33–45].

Characteristics of the included studies

There were 12 articles involving 13 observational studies that reported the associations between vitamin status and
OA. There were two RCTs on vitamin D supplementation for the treatment of OA; however, they were only reported in abstract form [42, 44]. Characteristics of included studies are presented in Table 1. Out of 15 studies, 6 were undertaken in the USA, 2 in Australia and the remaining in countries including Israel, Iran, Kuwait, Finland, the Netherlands, UK and India. The number of participants ranged from 64 to 1644, with ages ranging from 30.0 to 77.2 years and female participants ranging from 0% to 100%.

Of the 13 observational studies, 7 were cohort [16, 33, 35, 39, 40, 43] (one article reported results from two cohort studies [35]), 1 was a case–control [36] and 5 were cross-sectional studies [16, 34, 37, 41, 43]. One article reported both longitudinal and cross-sectional data [16]. The joints studied were hip (3 studies [34, 39, 43]), hand (1 study [38]) and knee (10 studies [16, 33, 35–37, 39–41, 45]).

Various methods were used to examine the changes in disease severity of OA. The Croft score and Altman/Gold atlas were used for hip [43] and hand OA [38], respectively. The Kellgren and Lawrence (KL) scale, which combines assessments of joint space narrowing (JSN) and osteophytes with a score of 0–4, was used to assess knee radiographic OA (ROA) in three studies [33, 40, 41]. Individual radiographic features, i.e. JSN (0–3) [16, 35, 40] and osteophytes (0–3) [16, 35, 40], were also used. For MRI measurement of cartilage loss, a quantitative method to assess cartilage volume [16] and semi-quantitative methods to assess cartilage defects [16, 35] were used.

To measure 25-(OH)D levels, radioimmunoassay was employed in nine studies [16, 33, 35, 37–39, 43, 45], and mass spectrometry [34], protein binding [40], chemiluminescence assay [41] or ELISA [36] were used in other studies. Three studies did not report the inter- and intra-assay coefficients of variation (CVs) [36, 38, 40], but others reported inter-assay CVs from 3.3% [16] to 15.6% [37] and/or intra-assay CVs from 1.8% [16] to 13.2% [35].

Linear or logistic regression models were used to explore the associations between serum 25-(OH)D levels and OA in 13 observational studies. Serum 25-(OH)D levels were analysed as a continuous variable [16, 37, 38, 45] or categorized using tertiles [33, 35, 40, 41, 43], quartiles [39], a cut-point value (20 ng/ml) [35, 38] or values for definition of sufficiency (>30 ng/ml), insufficiency (15.1–50 ng/ml) and deficiency (<15 ng/ml) [34].

Methodological quality assessment for observational studies
The mean score for the methodological quality of the included studies was 73.9%, with a range from 57.1% to 88.2% (supplementary Table S3, available at Rheumatology Online). Most studies (90%) were considered to be of high quality. Of the methodological criteria assessed, most studies scored well on selection of participants and assessment of determinants. The results were adjusted for at least age, sex and BMI in most studies; however, several studies provided insufficient information regarding withdrawals, participation rate or whether assessment of OA [using methods such as KL score or Osteoarthritis Research Society International (OARSI) atlas] was independent of vitamin D status (supplementary Table S3, available at Rheumatology online).

Cross-sectional and case–control studies for the association between 25-(OH)D and OA
Of the five cross-sectional and one case–control studies, five were of high quality (Table 2). Chaganti et al. [34] documented that men with vitamin D deficiency (<20 ng/ml) were twice as likely to have prevalent radiographic hip OA. For the knee, Heidari et al. [36] reported that 25-(OH)D was associated with symptomatic knee OA in patients aged <60 years and Muraki et al. [41] reported that lower tertiles of 25-(OH)D may be associated with increased knee pain rather than radiographic changes. Hunter et al. [37] reported that there were no associations between 25-(OH)D and knee radiographic OA or osteophytes and Al-Jarallah et al. [45] reported no significant associations between 25-(OH)D and JSN or osteophytes. In contrast, Ding et al. [16] documented that vitamin D insufficiency (<20 ng/ml) was associated with increased moderate to severe JSN compared with vitamin D sufficiency in older adults.
<table>
<thead>
<tr>
<th>Author (country, year)</th>
<th>n</th>
<th>Participants</th>
<th>Gender MF (%)</th>
<th>Baseline age (years), mean (S.D.), unless otherwise stated</th>
<th>Baseline 25-(OH)D (ng/ml), mean (S.D.), unless otherwise stated</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter et al. [37] (Australia, 2003)</td>
<td>1644</td>
<td>882 female Caucasian twin pairs from the St Thomas’ UK Adult Twin Registry</td>
<td>0:100</td>
<td>Those with knee osteophytes: 53.3 (7.6); those without knee osteophytes: 53.2 (7.8)</td>
<td>Those with knee osteophytes: 33.1(12.9); those without knee osteophytes: 35.1(13.4)</td>
<td>Cross-sectional study of knee OA</td>
</tr>
<tr>
<td>Chaganti et al. [34] (USA, 2010)</td>
<td>1104</td>
<td>Cohort of osteoporotic fractures in men geographically dispersed across USA</td>
<td>100:0</td>
<td>Baseline: 77.2 (5.3)</td>
<td>Baseline: 23.4(6.7) with hip ROA; 26.0 (7.8) without hip ROA</td>
<td>Cross-sectional study of hip OA</td>
</tr>
<tr>
<td>Kalichman et al. [38] (Israel, 2011)</td>
<td>190</td>
<td>Chuvashians in the Bashkortostan autonomy of the Russian Federation</td>
<td>48:52</td>
<td>Baseline: 45.6 (16.1)</td>
<td>Baseline: 26.1 (7.3) for males; 22.4 (6.8) for females</td>
<td>Cross-sectional study of hand OA</td>
</tr>
<tr>
<td>Muraki et al. [41] (Japan, 2011)</td>
<td>787</td>
<td>Participants in the UK Hertfordshire Cohort Study</td>
<td>51:49</td>
<td>Baseline: 65.6 (2.7)</td>
<td>Baseline: 17.0, IQR (12.3, 22.9) measured in 683 subjects</td>
<td>Cross-sectional study for knee OA</td>
</tr>
<tr>
<td>Heidari et al. [36] (Iran, 2011)</td>
<td>298</td>
<td>148 outpatients and 150 controls in Babol, Iran</td>
<td>Not reported</td>
<td>Knee OA cases: 60.2 (12.9); controls: 60.1 (10.2)</td>
<td>Knee OA cases: 34.1(32.4); controls: 38.5(32.4)</td>
<td>Cross-sectional study of knee OA</td>
</tr>
<tr>
<td>Al-Jarallah et al. [45] (Kuwait, 2012)</td>
<td>99</td>
<td>Patients with primary knee OA recruited from clinics</td>
<td>91:9</td>
<td>Framingham: 56.9(1.1)</td>
<td>Framingham study: 19.7 (7.4); BOKS with radiographic follow-up: 20.2 (8.3); BOKS with MRI follow-up: 20.3 (8.3)</td>
<td>Case-control study of knee OA</td>
</tr>
<tr>
<td>McAlindon et al. [40] (USA, 1996)</td>
<td>556</td>
<td>Population-based Framingham Study</td>
<td>37:63</td>
<td>Framingham: 70.3 (4.5)</td>
<td>Framingham study: 25.0 (6.6) no incidence hip OA: 26.9 (8.0)</td>
<td>Cross-sectional study of knee OA</td>
</tr>
<tr>
<td>Lane et al. [43] (USA, 1999)</td>
<td>237</td>
<td>Population-based listings in four areas of the USA excluded black women</td>
<td>0:100</td>
<td>Framingham: 65.0 (2.5)</td>
<td>Incident hip OA: 25.0 (6.6) no incidence hip OA: 26.9 (8.0)</td>
<td>Cross-sectional study of knee OA</td>
</tr>
<tr>
<td>Ding et al. [16] (Australia, 2009)</td>
<td>880</td>
<td>The Tasmanian Older Adult Cohort Study</td>
<td>50:50</td>
<td>Framingham: 61 (range 51-79)</td>
<td>Framingham study: 19.7 (7.4); BOKS with radiographic follow-up: 20.2 (8.3); BOKS with MRI follow-up: 20.3 (8.3)</td>
<td>Two prospective cohort studies of knee OA</td>
</tr>
<tr>
<td>Bergink et al. [33] (Netherlands, 2009)</td>
<td>1248</td>
<td>The Rotterdam Study: men and women aged &gt;55 years</td>
<td>42:58</td>
<td>Framingham: 62.6 (6.7)</td>
<td>Framingham study: 19.7 (7.4); BOKS with radiographic follow-up: 20.2 (8.3); BOKS with MRI follow-up: 20.3 (8.3)</td>
<td>Prospective cohort study of knee OA</td>
</tr>
<tr>
<td>Konstari et al. [39] (Finland, 2011)</td>
<td>805</td>
<td>Sample from the Mini-Finland Health Examination Survey</td>
<td>45:55</td>
<td>Framingham: 30-39: n = 380; 40-59: n = 276; &gt;50: n = 149</td>
<td>Framingham study: 30-39: 43.4; 40-59: 46.8; &gt;50: 51.4</td>
<td>Prospective cohort study of knee OA</td>
</tr>
<tr>
<td>McAlindon et al. [44] (USA, 2010)</td>
<td>146</td>
<td>Knee SOA with no restriction of 25-(OH)D levels</td>
<td>43:57</td>
<td>Framingham: 62.4 (8.5)</td>
<td>Framingham study: 22.3 (10)</td>
<td>Prospective cohort study of knee OA</td>
</tr>
<tr>
<td>Sanghi et al. [42] (India, 2011)</td>
<td>64</td>
<td>Knee OA subjects with 25-(OH)D levels &lt;20</td>
<td>Not reported</td>
<td>Framingham: 62.4 (8.5)</td>
<td>Framingham study: 22.3 (10)</td>
<td>6-month RCT of knee OA</td>
</tr>
</tbody>
</table>

BOKS: Boston Osteoarthritis of the Knee Study; IQR: interquartile range.
### Table 2 Cross-sectional and case-control studies examining the association between serum 25-(OH)D levels and OA

<table>
<thead>
<tr>
<th>Author</th>
<th>Adjustment for confounders</th>
<th>Assessment of OA</th>
<th>Results [as 25-(OH)D level associated with]</th>
<th>Conclusions</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding et al. [16]</td>
<td>Age, sex, BMI, smoking and other diseases</td>
<td>JSN (0-3), osteophytes (0-3), MRI cartilage volume measurement</td>
<td>25-(OH)D was significantly associated with moderate to severe JSN in the medial tibiofemoral compartment. 25-(OH)D was positively associated with medial and lateral tibial cartilage volume</td>
<td>25-(OH)D was associated with JSN and cartilage volume</td>
<td>85.7</td>
</tr>
<tr>
<td>Hunter et al. [37]</td>
<td>Age and BMI</td>
<td>JSN (0-3) and osteophytes (0-3)</td>
<td>Decreased 25-(OH)D levels in osteophyte group compared with non-osteophyte group, while non-significant after the adjustment</td>
<td>25-(OH)D was not associated with osteophytes after adjustment for age and BMI</td>
<td>85.7</td>
</tr>
<tr>
<td>Chaganti et al. [34]</td>
<td>Age, season at blood withdrawal and clinic sites</td>
<td>JSN (0-4), osteophytes (0-3), modified Croft hip ROA score (0-4)</td>
<td>Vitamin D insufficiency and deficiency in men increased likelihood of radiographic hip OA with OR 2.2 (95% CI 1.2, 4.0) and 2.0 (95% CI 0.8, 4.7), respectively</td>
<td>Men with vitamin D deficiency were twice as likely to have prevalent radiographic hip OA</td>
<td>78.6</td>
</tr>
<tr>
<td>Kalichman and Kobyliansky [38]</td>
<td>Age, sex and BMI</td>
<td>KL scoring, Altman and Gold atlas</td>
<td>No significant association between serum levels of 25-(OH)D and prevalence/severity of hand ROA</td>
<td>25-(OH)D was not associated with hand ROA</td>
<td>78.6</td>
</tr>
<tr>
<td>Muraki et al. [41]</td>
<td>Age, sex, BMI, season of the visit and KL grade</td>
<td>KL grade ≥2 for a definition of knee OA</td>
<td>Not significantly associated with knee ROA, but low tertile of 25-(OH)D level tended to be associated with knee pain compared with high tertile after adjustment (OR 1.5, P = 0.08).</td>
<td>25-(OH)D might be associated with knee pain rather than knee radiographic change</td>
<td>78.6</td>
</tr>
<tr>
<td>Heidari et al. [36]</td>
<td>Age and sex</td>
<td>SOA based on ACR criteria</td>
<td>Significant association between vitamin D deficiency and OA in those aged &lt;60 years (OR 2.3, 95% CI 1.2, 4.4), whereas in patients aged ≥60 years, it was not significant</td>
<td>25-(OH)D was associated with knee SOA in patients aged &lt;60 years</td>
<td>57.1</td>
</tr>
<tr>
<td>Al-Jarallah et al. [45]</td>
<td>Age, sex and BMI</td>
<td>JSN (0-3) and osteophytes (0-3)</td>
<td>No significant association between 25-(OH)D and JSN or osteophytes in the medial tibiofemoral compartment</td>
<td>25-(OH)D was not associated with JSN or osteophytes</td>
<td>57.1</td>
</tr>
</tbody>
</table>

OR: odds ratio.
Longitudinal studies for the association of 25-(OH)D and OA

All seven prospective cohort studies were of high quality (Table 3). Konstari et al. [39] reported no significant association between serum 25-(OH)D levels and the risks of incident knee or hip OA, diagnosed based on clinical examination by a physician. Lane et al. [43] reported that low serum levels of 25-(OH)D were associated with increased incidence of hip JSN. Both McAlindon et al. [40] and Bergink et al. [33] reported that the lowest tertile of 25-(OH)D level was associated with greater knee ROA progression assessed by change in the KL score. Using MRI assessment, Ding et al. [16] demonstrated that lower serum 25-(OH)D levels were associated with greater cartilage volume loss over 2.7 years in older adults; however, Felson et al. [35] reported that vitamin D status was not associated with the risk of cartilage loss, as assessed using an increase in cartilage defect score.

Risk of bias assessment for RCTs

Two RCTs were published only in abstract form, providing limited data for bias and outcome assessments. The seven criteria recommended by CCRBT were used to assess the risk of bias. The number of criteria met from the preliminary assessment was four or five; neither abstract adequately described the specific outcome data or withdrawals. Placebo controls were applied in both trials. In one study, patients were recruited regardless of their 25-(OH)D levels and cartilage structural changes were assessed using MRI. This study reported that supplementation of vitamin D3 2000 U/day had no symptom- or structure-modifying benefits for knee OA over a 2-year period [44]. The other was conducted in vitamin D-insufficient patients and documented a beneficial effect of vitamin D on symptoms of OA but no effect on ROA over 6 months [42] (Table 4).

Best-evidence synthesis for observational studies

We synthesized evidence when outcome measures were highly comparable. These are: (i) symptomatic OA (SOA), including complaints of pain, stiffness or dysfunction, or diagnostic OA based on clinical examination; (ii) osteoarthritis, assessed by standard radiographic atlas; (iii) JSN, assessed by standard radiographic atlas; (iv) ROA, assessed by KL score; and (v) MRI-detected cartilage loss, including loss of cartilage volume or an increase of cartilage defect score. The prevalence, incidence and progression of these five features of OA were addressed. As JSN is a proxy measure of cartilage loss, we also graded the evidence for cartilage loss using incident/progressive JSN in combination with loss of cartilage volume.

Based on the collective examination of all the literature reviewed (Table 5), we conclude that in hand and hip OA:

- There was insufficient evidence for a significant association between serum 25-(OH)D levels and prevalence of SOA [36, 41].
- There was limited evidence for the association of serum 25-(OH)D levels and radiographic hip OA.
- There was strong evidence between 25-(OH)D and radiographic hand OA.
- There was insufficient evidence (single cross-sectional study [38]) for the association between 25-(OH)D and radiographic hand OA.
- There was limited evidence (single cohort study [43]) to suggest that 25-(OH)D was associated with the incidence and progression of hip JSN.

In knee OA:

- There was limited evidence for an association between 25-(OH)D levels and prevalence of SOA (two case-control/cross-sectional studies [36, 41]), and no association between 25-(OH)D and incidence of SOA (single cohort study [39]).
- There was limited evidence (single cohort study [33]) to demonstrate that 25-(OH)D levels were positively associated with the incidence of JSN, whereas there was conflicting evidence (three cohort studies) for the association between 25-(OH)D and the progression of JSN [35, 40] or osteophytes [35, 40].
- There was moderate evidence (two high-quality cohort studies) to suggest that low levels of 25-(OH)D were positively associated with the progression of ROA assessed by KL [33, 40], but not with the incidence of ROA [33, 40].
- There was moderate evidence (two high-quality cohort studies [16, 35]) to demonstrate that 25-(OH)D levels were not associated with MRI-detected change in focal cartilage defects, and limited evidence for a significant association between vitamin D deficiency and loss of cartilage volume [16].
- There was strong evidence between 25-(OH)D and cartilage loss (four high-quality cohort studies [16, 33, 40, 43]) when incident/progressive JSN and changes in cartilage volume were combined as the outcome of cartilage loss.

Discussion

The results of this extensive systematic review demonstrated that while there was limited or conflicting evidence suggesting that serum levels of 25-(OH)D were associated with the incidence and progression of individual features of knee OA, there was moderate evidence suggesting that low 25-(OH)D levels were associated with progression of knee ROA. A strong level of evidence was clearly evident when JSN (incident and progressive) and change in cartilage volume were combined as the outcome of cartilage loss. These indicate that interventions to improve vitamin D level in OA warrant further investigation.

There were different levels of evidence for the association between 25-(OH)D and OA. Evidence was limited or insufficient in hip or hand OA mainly because the number of observational studies was insufficient. Different outcome measures used in knee OA may result in inconsistent results: some had a significant positive association with vitamin D deficiency, whereas others failed to show significant association. These may eventually lead to
<table>
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<th>Author</th>
<th>Adjustment for confounders</th>
<th>Assessment of OA</th>
<th>Results [as baseline 25-(OH)D level associated with]</th>
<th>Conclusions</th>
<th>Follow-up time (years)</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding et al. [16]</td>
<td>Age, sex, BMI, smoking, steps per day, knee pain, cartilage defects, season of blood sampling, tibial bone area, ROA, disease status (cardiovascular disease, asthma and diabetes)</td>
<td>MRI cartilage volume measurement for cartilage loss</td>
<td>Baseline serum 25-(OH)D level were associated with reduced loss of tibial cartilage volume; vitamin D deficiency predicted increased cartilage loss</td>
<td>25-(OH)D levels were associated with decreased knee cartilage loss</td>
<td>2.9</td>
<td>88.2</td>
</tr>
<tr>
<td>Lane et al. [43]</td>
<td>Age, investigational site, weight at age 50, calcaneal BMD, vitamin D supplement use, self-reported health status, kilocalories of exercise per week and hours sedentary per day</td>
<td>Hip JSN (0–3), osteophytes (0–3) and a summary grade of hip ROA</td>
<td>Middle and lowest tertiles of 25-(OH)D were associated with increased incidence of hip JSN (OR 3.2 and 3.3, respectively)</td>
<td>Low 25-(OH)D might increase the risk of incident hip JSN</td>
<td>8</td>
<td>70.6</td>
</tr>
<tr>
<td>McAlindon et al. [40]</td>
<td>Age, sex, BMI, weight change, physical activity index, knee injury, total energy intake and health status</td>
<td>Modified KL score (0–4), JSN (0–3) and osteophytes (0–3)</td>
<td>Lower tertile of 25-(OH)D predicted loss of knee JSN (OR 2.3, 95% CI 0.9, 5.5), osteophyte growth (OR 3.1, 95% CI 1.3, 7.5) and ROA progression (OR 2.9, 95% CI 1.0, 8.3), but not incident ROA</td>
<td>25-(OH)D was associated with an increased risk for progression of ROA</td>
<td>8</td>
<td>70.6</td>
</tr>
<tr>
<td>Bergink et al. [33]</td>
<td>Age, sex, BMI, BMD, smoking status, health status, disability index, fall tendency, baseline joint space narrowing and time of the season</td>
<td>KL scores (0–4), JSN and osteophytosis</td>
<td>Lowest tertile of 25-(OH)D was associated with incidence of JSN in women (OR 2.1, 95% CI 0.9, 4.7) and progression of ROA (OR 2.1, 95% CI 0.6, 7.4)</td>
<td>25-(OH)D seemed to influence the incidence and progression of knee ROA</td>
<td>6.5</td>
<td>70.6</td>
</tr>
<tr>
<td>Konstari et al. [39]</td>
<td>Age, gender, education, BMI, physical workload, smoking, leisure time physical activity, injuries and season of blood draw</td>
<td>KL scoring for ROA; 0–3 scale for JSN and osteophytes; MRI WORMS assessment for cartilage loss</td>
<td>No association between serum 25(OH)D and the incidence of knee or hip OA, but the risk with 25(OH)D increased in winter and decreased in summer</td>
<td>Vitamin D insufficiency did not increase the risk of incidence of OA, but it might have different effects in different seasons</td>
<td>22</td>
<td>70.6</td>
</tr>
<tr>
<td>Felson et al. [35]</td>
<td>Age, baseline BMI, change in weight from baseline to follow-up, sex and baseline KL score</td>
<td>KL scoring for ROA; 0–3 scale for JSN and osteophytes; MRI WORMS assessment for cartilage loss</td>
<td>25-(OH)D was not associated with radiographic worsening (JSN and osteophytes) and cartilage loss</td>
<td>Vitamin D did not increase the risk of ROA or cartilage loss</td>
<td>9.5 or 2.5</td>
<td>64.7</td>
</tr>
</tbody>
</table>

OR: odds ratio.
some moderate and conflicting evidence in the evidence synthesis. Both JSN and osteophytes are key elements of ROA. Although we found moderate evidence for 25-(OH)D and progression of ROA (assessed by KL), evidence for the associations between 25-(OH)D and progression of osteophytes or JSN alone was conflicting. Progression of knee ROA assessed by the KL scoring system is usually defined as an increase of at least 1 grade of JSN in knees with prevalent disease (grade 2 corresponds to the presence of definite osteophytes with possible JSN); therefore progression of ROA actually reflects loss of joint space in those with established osteophytes. The higher level of evidence for the association of 25-(OH)D with progression of ROA than with progression of JSN or osteophytes suggests that vitamin D deficiency may be associated with cartilage loss (reflected by loss of joint space) mainly in those with subchondral bone overgrowth. There was moderate evidence indicating that vitamin D deficiency was not associated with incidence of knee ROA. There was only one cohort study reporting that low 25-(OH)D was not associated with incident hip ROA, so the evidence is limited. Incidence of ROA is defined as the occurrence of definite osteophytes (grade 2) in knees without prevalent disease [2]. However, the evidence for the associations between vitamin D deficiency and incidence of knee ROA assessed by the KL scoring system is usually defined as an increase of at least 1 grade of JSN in knees with prevalent disease [2]. Therefore, the presence of definite osteophytes with possible JSN suggests that vitamin D deficiency may be associated with cartilage loss (reflected by loss of joint space) mainly in those with subchondral bone overgrowth.

Radiographic JSN is a surrogate method used to assess cartilage loss [49]: however, it has been regarded as insensitive to the measurement of changes over time [47]. Loss of cartilage volume and progression of cartilage defects have been used to measure disease activity in knees with symptomatic OA, whereas Ding et al. [16] adopted semi-quantitative whole-organ magnetic resonance imaging scores (WORMS) to score progression of cartilage defects and did not find significant association between serum 25-(OH)D levels and the progression of knee OA. In this systematic review, evidence for the associations between 25-(OH)D and cartilage loss is inconsistent due to different methods used to assess cartilage loss. Felson et al. [35] used a semi-quantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS) to score progression of cartilage defects and did not find significant association between serum 25-(OH)D levels and the progression of knee OA, whereas Ding et al. [16] adopted semi-quantitative whole-organ magnetic resonance imaging scores (WORMS) to score progression of cartilage defects and did not find significant association between serum 25-(OH)D levels and the progression of knee OA. Nevertheless, these two studies were conducted in subgroups with different characteristics, and the inconsistency may be due to different methods used to assess cartilage loss. In addition, the small number of studies with sufficient power and the low quality of evidence may also contribute to the inconsistency. Therefore, further studies with larger sample sizes and higher methodological quality are needed to clarify the association between vitamin D deficiency and progression of cartilage loss in knees with prevalent disease.
findings, Ding et al. [16] reported that 25-(OH)D was not associated with change in cartilage defects either. Evidence regarding 25-(OH)D and MRI-detected cartilage change was therefore controversial. These results suggest that cartilage loss assessed by entire volume change is susceptible to metabolic abnormalities, including vitamin D deficiency, but cartilage loss assessed by progression of focal cartilage defects may be more relevant to non-metabolic factors such as mechanical loading, as we reported for leptin [49].

JSN (incident or progressive) is a later-stage change compared with MRI-evident changes in OA [50]. Nevertheless, JSN and MRI-assessed cartilage volume change both measure cartilage loss and therefore a combination of these outcomes for analysis appears plausible. In that case, there is strong evidence that vitamin D deficiency is positively associated with cartilage loss in OA, as demonstrated by the significant results obtained in four high-quality cohort studies [16, 33, 40, 43], despite one report of no association [35].

In this study, we found limited evidence to support the association between 25-(OH)D levels and the prevalence or incidence of SOA. Theoretically, however, vitamin D has an anti-inflammatory effect through regulation of cytokines and macrophage activity [51], and therefore may have a beneficial effect on inflammatory pain. Recently Laslett et al. [52] reported in abstract form that moderate to severe vitamin D deficiency (25-(OH)D < 10 ng/ml) was associated with greater knee pain over 5 years. On the contrary, a cross-sectional study reported that vitamin D status was associated with chronic widespread pain only in women but not in men [53], and a systematic review suggested that the evidence base for the use of vitamin D for chronic pain in adults is poor [54]. Further studies are required to determine whether 25-(OH)D is associated with symptoms in OA.
More importantly, because of different underlying pathophysiology for various stages of OA and various biases in the observational design, risk factors for progressive OA may be different from those for incident OA [55], therefore discrepancy between the roles of 25-(OH)D for OA progression and for OA incidence would exist in the current study. This could be a reason why we found that 25-(OH)D was associated with the incidence of JSN but the evidence was conflicting for the progression of JSN. It may also explain why moderate evidence was seen for 25-(OH)D in the progression of ROA, but not in the incidence of ROA.

There is no doubt that RCTs are the preferred approach to determine whether interventions to correct vitamin D deficiency will prevent the progression of OA. The results from two RCTs were reported only in abstract form, making interpretation of the findings difficult. It is clear that the trials were performed in discrepant populations, namely vitamin D-deficient participants in one RCT [42] vs non-selective participants in the second study [44]. It is most likely that vitamin D supplementation is effective only in those with vitamin D deficiency, and this can explain the null effect in the second study. X-ray assessment after only a short-term period (6 months) may contribute to the negative finding for radiological progression despite an improvement in symptoms in the first trial [42]. To verify whether correction of vitamin D deficiency is effective in the treatment of OA, future rigorously designed RCTs with careful consideration of variables including vitamin D-deficient participants, not severe disease, sufficient duration and sensitive outcome measures are required. We are now conducting an RCT and the protocol of this trial has been published recently [56]. In this trial, we included patients with moderate and mild vitamin D deficiency but excluded those with severe vitamin D deficiency and severe disease.

There are a number of limitations to our study. First, we were not able to perform a meta-analysis because of the heterogeneity of the studies included in this review, therefore a best-evidence synthesis was performed. Second, there were only 15 relevant studies, with only a few allowing evidence syntheses for each OA outcome. Nevertheless, most studies were of high quality with relatively large sample sizes (n > 200), and moderate to strong levels of evidence for some OA measures could be established. Finally, given that there was only one study that specifically examined the association between 25-(OH)D and loss of cartilage volume, the effect of 25-(OH)D on cartilage loss remains uncertain; however, there is strong evidence for the association between vitamin D deficiency and cartilage loss if both incident and progressive JSN are regarded as measures of cartilage loss.

In summary, 25-(OH)D appears to be implicated in knee OA with regard to structural change rather than symptoms; further well-designed RCTs are required to determine whether vitamin D supplementation can slow disease progression. There is insufficient evidence to determine conclusive associations for hand and hip OA.

**Rheumatology key messages**

- This review is the first to systematically evaluate evidence for associations between 25-(OH)D and OA.
- There was moderate evidence showing that low levels of 25-(OH)D were associated with increased progression of radiographic OA.
- Strong evidence for an association between 25-(OH)D and cartilage loss was apparent when combining different imaging results in knee OA.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**


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