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The effect of vitamin D supplementation on outcomes following total hip or knee arthroplasty surgery: a rapid systematic review of current evidence

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- *Purpose:* Vitamin D deficiency has been linked to poorer outcomes following hip (THR) and knee (TKR) replacement. We review the effect of peri-operative supplementation on clinical and patient-reported outcomes following THR/TKR.
- *Methods:* This study was registered with PROSPERO (CRD42021238086). Searches of electronic databases were performed from inception to March 2021. All randomised, cohort, or case-controlled studies reported in English of adults undergoing THR/TKR where vitamin D supplementation was given peri-operatively and at least one outcome was reported were included. Studies reporting on vitamin D in relation to osteoporosis and hip fracture were excluded, as were conference abstracts and those involving preclinical models. Risks of bias were performed using the RoB-2 and ROBINS-I tools.
- *Results:* Three studies comprising 413 TKR patients were identified; two were randomised controlled trials and one was a prospective cohort study. No studies meeting the inclusion criteria reported on the outcomes following THR. Supplementation was associated with a statistically significant reduction in the IL6:IL10 ratio at 24- and 48h following surgery, but no effect was noted on Western Ontario and McMaster Universities Osteoarthritis Index scores or the rates of falls. All studies were judged to be limited by bias, with heterogeneity in the supplementation dose and timing of administration, as well as the reported outcome measures used.
- *Discussion:* Further adequately powered randomised-controlled trials using vitamin D supplementation and a specific clinically relevant or patient-reported outcome measure are required to assess if pre-operative vitamin D insufficiency is a modifiable risk factor to improve outcomes following THR/TKR.

Keywords
- vitamin D
- PROMs
- THR
- TKR
- arthroplasty

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Purpose

Vitamin D is a secosteroid produced in the skin in response to sunlight and regulates calcium and phosphate levels. Insufficiency is common due to limited sun exposure, poor dietary intake, or as a consequence of gut malabsorption or failure to metabolise vitamin D to its active form (1). In the United Kingdom, supplementation is recommended for all adults during the winter months and year-round for those deemed at higher risk of deficiency (2).

Inadequate vitamin D levels have been associated with a range of adverse post-operative outcomes (3), and there is a high incidence of deficiency reported in patients undergoing total hip (THR) or knee (TKR) arthroplasty (4). Previous systematic reviews (4, 5, 6, 7) have described an association between deficiency and poorer outcomes following THR/TKR, although two meta-analyses (4, 6) allude to the inclusion of retrospective and non-randomised studies with significant heterogeneity. No systematic review has yet addressed the role of peri-operative supplementation. We aim to review if optimising vitamin D status with supplementation in adult patients before arthroplasty surgery improves clinical or patient-reported outcomes, compared to those with ongoing insufficiency.

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Methods

This review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (8). It was prospectively registered on 1st March 2021 with the PROSPERO International Register of Systematic Reviews, reference CRD42021238086 (9).

Systematic searches of Medline, Embase, and PubMed were independently performed from database inception to March 2021 by two authors (RJMM and WFF). The search terms and Boolean operators used were 'THR' <OR> 'THA' <OR> 'hip replacement' <OR> 'hip arthroplasty' <OR> 'TKR' <OR> 'TKA' <OR> 'knee replacement' <OR> 'knee arthroplasty' <AND> 'vitamin D' <OR> 'cholecalciferol' <OR> 'ergocalciferol' <OR> '25-hydroxy vitamin D'. These keywords were also used to search The Cochrane Library, ISRCTN Registry, ClinicalTrials.gov, and the International HTA Database for the same time period.

All randomised, cohort, or case-controlled studies of adult patients undergoing hip or knee replacement where vitamin D supplementation was given in the peri-operative period and where at least one post-operative outcome was reported were included in this review. Post-operative outcomes were either clinical or patient reported (via either a procedure-specific or general-health outcome questionnaire). Studies reporting on vitamin D in relation to osteoporosis and hip fracture were excluded, as were conference abstracts, preclinical models, and studies that were not reported in English.

Two authors (RJMM and WFF) independently screened the titles and abstracts of retrieved articles for eligibility. Following discussion and consensus, a final list of studies was agreed upon, and the full text of these records was retrieved and read independently. The reference sections of these retrieved studies were also reviewed to capture any further relevant studies.

Data extraction was performed by a single author (RJMM) and checked by another WFF). Extracted data included study design, number of patients, age, gender, vitamin D assay method, definition of vitamin D levels, supplementation dose, timing, and route, as well as the timing of and study outcome used as the primary outcome measure.

Risks of bias for all eligible studies were performed according to the Cochrane Handbook for Systematic Reviews of Interventions (10) using the RoB 2 tool for randomised studies (11), and the ROBINS-I tool for non-randomised studies of interventions (12). One author (RJMM) performed the assessment, with checking and agreement by a second (WFF).

Due to the heterogeneity in reported clinical outcomes, a meta-analysis or sub-group analysis was not possible. The data is therefore presented as a narrative synthesis of the retrieved studies.

Results

Study retrieval

Following identification and screening, three studies comprising 413 patients in total, fulfilled the criteria for offering supplementation of vitamin D in the peri-operative period, and reporting on at least one post-operative outcome (Fig. 1). One study was an randomised controlled trial (RCT) comparing a multivitamin tablet to placebo (13), one was an RCT comparing two different strengths of vitamin D supplementation on two primary endpoints (14), and the last was a non-randomised prospective cohort study (15). All retrieved studies involved patients undergoing TKR, with no studies reporting the outcome following THR. A summary of key trial characteristics, patient demographics, intervention details, and outcome measures for each study are included in Table 1.

Bias

Using the RoB-2 criteria to assess the two randomised trials, one was judged to be at 'high risk' of bias, and there were 'some concerns' of bias with the other (Table 2).

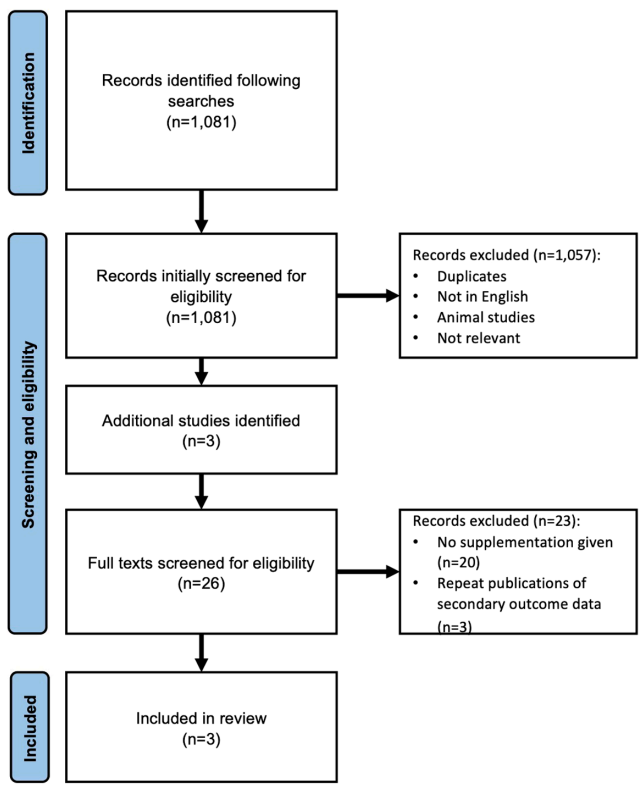

Figure 1
PRISMA flow diagram presenting the systematic review process used.

Table 1 Summary data of retrieved manuscripts.

Reference	Design	*n*	Supplement dose	Supplement timing	Vitamin D status definition, mean level per group	Age (years)	Gender (*n*, % female)	Vitamin D Assay	Outcome(s) Reported	Time of Measurement	Findings
Barker *et al.* (13)	RCT	20 TKR	900 IU /day as part of multivitamin tablet vs placebo	Daily from 6 weeks pre-op	Not defined; MV: 70 nmol/L; PL: 78 nmol/L	MV:62; PL: 63	MV: 5 (50%); PL: 6 (55%)	Not recorded	IL-6:IL-10 ratio	Baseline 24 and 48 h post-op	Multivitamin reduces IL-6:IL-10 ratio post-op at 24 h (effect size 0.64) and 48 h (effect size 0.48)
Bischoff-Ferrari *et al.* (14)	RCT	273 TKR	800 IU vs 2000 IU	Daily from 6 weeks post-op	Not defined; 800 IU: 68nmol/L; 2000 IU: 68nmol/L	800 IU: 71; 2000 IU: 70	800 IU: 77 (57%); 2000 IU: 69 (50%)	HPLC-MS/MS	Rate of falls, WOMAC	Baseline (6-weeks post-op), 6, 12, 18, and 24 months post-op	No difference at any measured timepoint for primary or secondary outcomes between 800 IU and 2000 IU; Power calculation was based on rate of falls
Maniar *et al.* (15)	Retrospective review of prospectively collected data	120 TKR	20 IU for all patients	Daily from 2 weeks post-op for 4 weeks	Def:<75 nmol/L (53%); Suff: >75 nmol/L (47%)	Def: 67; Suff: 69	Def: 50 (78%); Suff: 47 (84%)	Not recorded	WOMAC; SF-12; KSS	Pre-op; 3 months post-op	Deficient group had worse pre-op WOMAC scores (48.3 vs 42.3, $P=0.04$), but no difference post-op (17.6 vs 15.8, $P=0.362$); No difference in pre- or post-op KSS or SF-12 scores.

Def, deficient; HPLC-MS/MS, high performance liquid chromatography tandem mass spectrometry; IU, international units; KSS, Knee Society Score; MV, multivitamin; PL, placebo; RCT, randomised controlled trial; Suff, sufficient; SF-12, 12-item Short Form Survey; TKR, total knee replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Using the ROBINS-I tool, the only non-randomised study included in this review was deemed to be at 'serious risk' of bias (Table 3).

Inflammatory response outcome

A pilot study RCT from a single centre in the US randomised 22 adult patients to receive either a daily multivitamin (containing 900 IU of vitamin D) or placebo tablet from 6 weeks prior until 6 months following TKR surgery (13). There was a non-significant increase in the measured vitamin D level in those receiving the multivitamin, and both groups were noted to have a lower vitamin D level at 48 h following surgery compared to pre-operatively. A statistically significant reduction in the IL6:IL10 ratio was seen in those patients receiving the multivitamin compared to placebo at 24- and 48 h following surgery, with a reported effect size of 0.64 and 0.48, respectively.

Falls and WOMAC score outcomes

In a double-blinded RCT between January 2008 and March 2014, 273 patients 60 years and older undergoing TKR due to OA at a single centre in Switzerland, were randomised to receive either 800 IU or 2000 IU vitamin D supplement per day from 6 weeks following TKR (14). The primary outcomes were the WOMAC scores for both operated and non-operated knees, and the rate of falls over 24 months. Secondary outcomes included a sit-to-stand test, 4-m normal gait speed, activity level, and radiographic progression in the contralateral knee. No difference was seen between the two groups at 24 months for any of the outcomes measured.

Patient reported outcome measures – WOMAC, KSS, and SF-12 scores

Maniar *et al.* (15) report on 120 patients undergoing TKR by a single surgeon in India. All patients were given 20 IU of vitamin D daily for 4 weeks, beginning 2 weeks following surgery. Those patients with vitamin D deficiency at baseline (53% of patients had vitamin D levels <75 nmol/L) had worse pre-operative WOMAC scores compared to those with sufficiency (48.3 vs 42.3, $P=0.04$), however, there was no difference in post-operative scores at three months (17.6 vs 15.8, $P=0.362$). Furthermore, no difference was noted in pre-operative or post-operative Knee Society Score and SF-12 scores between the two groups.

Due to differences in definitions of vitamin D sufficiency, supplement dose, timing, and duration, as well as the variation in the reported outcomes measures used, meta-analysis of the retrieved studies was not possible.

Table 2 RoB-2 bias assessment for each domain of randomised trials.

	D1	D2	D3	D4	D5	Overall
Barker *et al.* (13)	+	+	!	+	-	-
Bischoff-Ferrari *et al.* (14)	+	+	+	+	!	!

D1, randomisation process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result.
+, low concern of bias; !, some concern of bias; -, high risk of bias.

Discussion

We have demonstrated a paucity of evidence exists for whether vitamin D supplementation prior to TKR has any benefit on clinical or patient-reported outcomes, with no evidence reported for those undergoing THR. Further studies are required to address this.

Vitamin D was given prior to surgery in only one study where patients were randomised to receive either a multivitamin tablet containing 900 IU of vitamin D or placebo (13). The remaining two studies started vitamin D supplementation for all patients 2 weeks following surgery, and neither used a placebo nor compared to a control group who did not receive supplementation (14, 15).

Barker *et al*. (13) demonstrated a reduction in serum vitamin D levels at 48 h following surgery in both treatment and placebo arms but noted that the administration of a multivitamin significantly modulated the post-operative inflammatory response, as indicated by a reduction in the Il-6:Il-10 ratio. As a multivitamin was used in this study then the authors are unable to conclude that the impact is solely related to vitamin D, but it does suggest that if supplementation is to be effective to modulate the inflammatory response then it should be given prior to surgery.

Bischoff-Ferrari *et al*. (14) present a well-conducted RCT with pre-published primary and secondary endpoints. They showed no difference in WOMAC scores or rate of falls at 24 months between patients receiving 800 IU or 2000 IU, although the study was powered for falls rather than WOMAC score. All patients were given vitamin D at one of two strengths, and as no placebo group was used, the authors acknowledge that the efficacy of vitamin D versus no treatment could not be assessed.

Table 3 ROBINS-I bias assessment for the non-randomised trial (15).

Domain	Bias assessment
Bias due to confounding	Serious
Bias in selection of participants into the study	Low
Bias in classification of interventions	Low
Bias due to deviations from intended interventions	Low
Bias due to missing data	Low
Bias in measurement of outcomes	Low
Bias in selection of the reported result	Low
Overall bias	Serious

Of the 15 pre-defined secondary outcomes reported in the main paper, three subsequent publications have addressed glucose metabolism (16), cognitive performance (17), and total blood pressure reduction (18) at 24 months, with no difference between groups reported. We excluded these subsequent papers from analysis as they appeared to be 'salami-sliced' secondary outcome publications of the main trial. Furthermore, their focus was on the difference between 800 and 2000 IU of vitamin D on the outcome of interest, rather than in relation to the role of vitamin D in influencing patients' post-surgical outcomes.

Maniar *et al.* (15) reported lower pre-operative WOMAC scores in those with deficiency, and although this was statistically significant, the clinical relevance is questioned as the baseline difference between groups was lower than the reported minimal clinically important difference (MCIDs) for the WOMAC score (19, 20, 21). Low-dose vitamin D was given to all patients after surgery, whether deficient or not, but there was no post-operative vitamin D level check to determine the influence supplementation had on serum levels. No difference in post-operative scores was noted between the two groups. Furthermore, the lack of a control group who did not receive supplementation prevents any conclusions on the role of vitamin D to be made.

During our search we identified and read the full manuscripts of 23 studies reporting the relationship between vitamin D level and a post-operative outcome, although these were excluded from analysis as no peri-operative intervention with vitamin D supplementation was offered. Some studies have found no association between vitamin D level and post-operative outcomes (22, 23, 24, 25, 26), with one study even concluding that higher vitamin D levels were associated with an increased risk of prosthetic joint infection (PJI) (27). In contrast, others have linked insufficiency with worse pain scores (28), lower pre-operative (29, 30, 31, 32) or post-operative (32, 33, 34, 35) functional scores, longer length of stay (36), differences in gait kinematics and kinetics (37), an increased risk of developing post-operative complications (38, 39), and a greater need for revision surgery and PJI (40). Authors therefore suggest that perioperative supplementation should be offered to address these adverse outcomes, despite having no evidence for this, as correlation does not prove causation. As the majority of natural vitamin D is obtained through sunlight, then deficiency may be a marker of the inability to get outdoors, whether due to comorbidity or functional limitations from advanced joint disease. Worse pre-operative function has been shown to be related to poorer post-operative outcomes (41, 42, 43, 44, 45). Whether altering vitamin D status with supplementation enables those with deficiency to achieve the same outcomes as those who

have a 'naturally' sufficient status remains to be seen, and future appropriately powered studies are required to answer this.

This review has focussed on the impact of supplementation in the peri-operative period to determine the effect on post-operative outcomes. There have been four previous systematic reviews on the relationship between vitamin D level and hip and knee arthroplasty outcomes, and one on outcomes following surgery in general, but none have focussed on the role of peri-operative supplementation.

The strengths of this review are that it was prospectively registered, with a clearly defined search question. All types of interventional studies, whether prospective or retrospective, were included, as were all types of post-operative outcomes. However, we acknowledge that as this was a rapid review then there may be limitations in that not all literature sources, such as 'grey literature' or conference proceedings were searched. We did review the reference lists of retrieved studies and previous systematic reviews to ensure we had not missed key papers.

Conclusion

To date, there are only three studies that have reported on the perioperative administration of vitamin D and its influence on a measured outcome following TKR. None have reported on patients undergoing THR. All studies included in this review were judged to be limited by bias, and there was heterogeneity in the reported outcome measures, supplementation dose, and timing of administration. We recommend further adequately powered randomised-controlled trials using vitamin D supplementation and a specific PROM are required to assess if pre-operative vitamin D insufficiency is a modifiable risk factor to improve outcomes following THR/TKR.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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