



■ GENERAL ORTHOPAEDICS

The role of Vitamin D in orthopaedic infection: a systematic literature review

**A. Zargaran,
D. Zargaran,
A. J. Trompeter**

*From King's College
London, London, UK*

Aims

Orthopaedic infection is a potentially serious complication of elective and emergency trauma and orthopaedic procedures, with a high associated burden of morbidity and cost. Optimization of vitamin D levels has been postulated to be beneficial in the prevention of orthopaedic infection. This study explores the role of vitamin D in orthopaedic infection through a systematic review of available evidence.

Methods

A comprehensive search was conducted on databases including Medline and Embase, as well as grey literature such as Google Scholar and The World Health Organization Database. Pooled analysis with weighted means was undertaken.

Results

Pooled analysis of four studies including 651 patients found the mean 25(OH)D level to be 50.7 nmol/l with a mean incidence of infection of 70%. There was a paucity of literature exploring prophylactic 25(OH)D supplementation on reducing orthopaedic infection, however, there was evidence of association between low 25(OH)D levels and increased incidence of orthopaedic infection.

Conclusion

The results indicate a significant proportion of orthopaedic patients have low 25(OH)D levels, as well as an association between low 25(OH)D levels and orthopaedic infection, but more randomized controlled trials need to be conducted to establish the benefit of prophylactic supplementation and the optimum regimen by dose and time.

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Introduction

With the ongoing recovery of surgical services following the cancellations resulting from the COVID-19 pandemic, increased focus is needed on optimizing outcomes from both elective and trauma procedures in orthopaedic surgery. Orthopaedic infection is a potentially serious complication of elective and emergency trauma and orthopaedic procedures, which is costly in terms of both patient outcomes and healthcare resources.^{1,2} Orthopaedic trauma implants, while providing important means of stabilizing fractures, present a possible nidus for biofilm formation and infection to develop. There were 104,622 reported cases of orthopaedic surgery-related osteomyelitis in the UK between April 2013 and January 2017.²

Strategies to mitigate the risk of orthopaedic infection include preoperative antibiotic prophylaxis, as well as other emerging technologies such as silver coating of devices, and antimicrobial and antibiofilm peptide application to the surface of devices.¹ Despite the level of innovation, the issue of orthopaedic infection persists, and new strategies must be explored to help with the prevention of infective complications. Vitamin D (25(OH)D) supplementation represents a simple, yet potentially effective means of preventing infection. Vitamin D possesses immunomodulatory properties, exerting an effect on multiple pathways including the cathelicidin antimicrobial peptide pathway, and the induction of the anti-inflammatory mediator Interleukin-10.^{3,4}

Correspondence should be sent to Alexander Zargaran; email: alexander.zargaran@kcl.ac.uk

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Table 1. Search strategy.

PubMed/MEDLINE	Embase
((("Orthopaedic"[Mesh]) OR ("Orthopaedic"[Mesh]) OR ("Fracture"[Mesh]) OR ("Arthroplasty"[Mesh]) OR ("Arthroscopy"[Mesh]) OR("Orthopaedic") OR ("Orthopaedic") OR ("Fracture") OR ("Arthroplasty") OR ("Arthroscopy"))) AND (((("Vitamin D"[Mesh]) OR ("Ergocalciferols"[Mesh]) OR ("Vitamin D Deficiency"[Mesh]) OR ("Cholecalciferol"[Mesh]) OR ("25-Hydroxyvitamin D 2"[Mesh]) OR ("Calcifediol"[Mesh]) OR ("Vitamin D") OR (Ergocalciferols) OR ("Vitamin D Deficiency") OR (Cholecalciferol) OR ("25-Hydroxyvitamin D 2") OR (Calcifediol) OR ("25-Hydroxyvitamin D")))) AND (("Infection"[Mesh] OR ("Infection") OR ("Osteomyelitis"[Mesh]) OR ("Osteomyelitis") OR ("Inflammation"[Mesh]) OR ("Inflammation")) OR ("Infect"))))	((("Orthopaedic" OR 'Orthopaedic' OR 'Fracture' OR arthroplasty OR 'arthroscopy') AND (vitamin AND d OR ergocalciferols OR vitamin) AND d AND deficiency OR cholecalciferol OR calcifediol OR '25 hydroxyvitamin') AND d2 OR '25 hydroxyvitamin') AND d) AND ('infection' OR 'osteomyelitis' OR 'inflammation'))

In the UK, sufficient Vitamin D levels are considered to be a serum concentration of 25(OH)D > 50 nmol/l, however literature has suggested that levels > 75 nmol/l should be considered as optimal.⁵ In the UK, Vitamin D deficiency is 25(OH)D is < 25 nmol/l and insufficiency is between 25 to 50 nmol/l.⁶ A total of 61% of adults in the UK are thought to have 25(OH)D levels of less than 75 nmol/l during summer and autumn, with that value rising to 87% in winter and spring.⁷ Studies have demonstrated Vitamin D to be protective against respiratory tract infections, influenza A, and sepsis. While thought to be beneficial in prevention of infection, the precise role Vitamin D plays in the prevention and/or pathogenesis of orthopaedic infection remains unclear. This review proposes to expand the evidence base by conducting a comprehensive review of the extent of hypovitaminosis D within orthopaedic patients and exploring the relationship between vitamin D and orthopaedic infection. We also appraise the evidence for supplementation of vitamin D in orthopaedic patients for the prevention of orthopaedic infection.

Methods

This review protocol follows the COSMOS-E Guideline.⁸

Types of studies. Quantitative studies including randomized controlled trials (RCTs), cross-sectional studies, case-control studies, cohort studies, and case series were included. Only human studies were included. Where studies were in different languages, translations from medical professionals were sought for the appraisal process. Primary studies published between 1 January 1949 and 5 April 2020 were included. Qualitative studies and reviews were excluded from analysis.

Population. Only studies that included adult patients undergoing an orthopaedic procedure were included.

Exposure. Orthopaedic infection was defined as a new infection occurring following an orthopaedic procedure. Reporting was variable and did not adhere to a common standard; as such, either clinical evidence such as a new temperature or sepsis, or an acute rise in inflammatory markers such as CRP were used to define infection.

Searches. A variety of search terms were used to capture the full range of studies exploring vitamin D and orthopaedic infection. A copy of the search string can be found in Table 1, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Figure 1. Databases including Medline and Embase were searched, as well as grey literature such as Google Scholar and The World Health Organization Database.

Data extraction, selection, and coding. The software COVidence was used for extraction, selection, and coding of data. Titles and abstracts were screened independently by two reviewers (AZ and DZ). Where the two reviewers disagreed, initially a discussion was held to see if consensus could be reached and, where necessary, a third reviewer (AJT) was consulted. Full-text screening was conducted by AZ and DZ independently. The kappa score for interobserver reliability was 1.0. Data were extracted on study design, age, controlled covariables, mean/median vitamin D levels, and results.

Quality assessment and risk of bias. The NICE Quality appraisal checklist for quantitative studies reporting correlations and associations was used to assess risk of bias and quality.⁹ In line with this, each study was awarded an overall grade for internal validity and external validity. Studies were independently reviewed by AZ and DZ, with discrepancies resolved by discussion.

Results

The search yielded 703 studies, following the removal of 16 duplicates. Nine studies met the inclusion criteria.¹⁰⁻¹⁸ Table II illustrates the salient data from these studies. Countries of study included Germany (n = 3), USA (n = 3), UK (n = 2), and Italy (n = 1). The total number of study participants was 1,417. The majority of studies were observational (n = 8), with one RCT included.

25(OH)D levels in orthopaedic patients. The majority of studies reported serum 25(OH)D levels in ng/ml, and considered hypovitaminosis D to be equivalent to a level < 75 nmol/l in line with their respective national definitions. Studies differed in reporting of levels, with some reporting medians and others reporting means. Due to

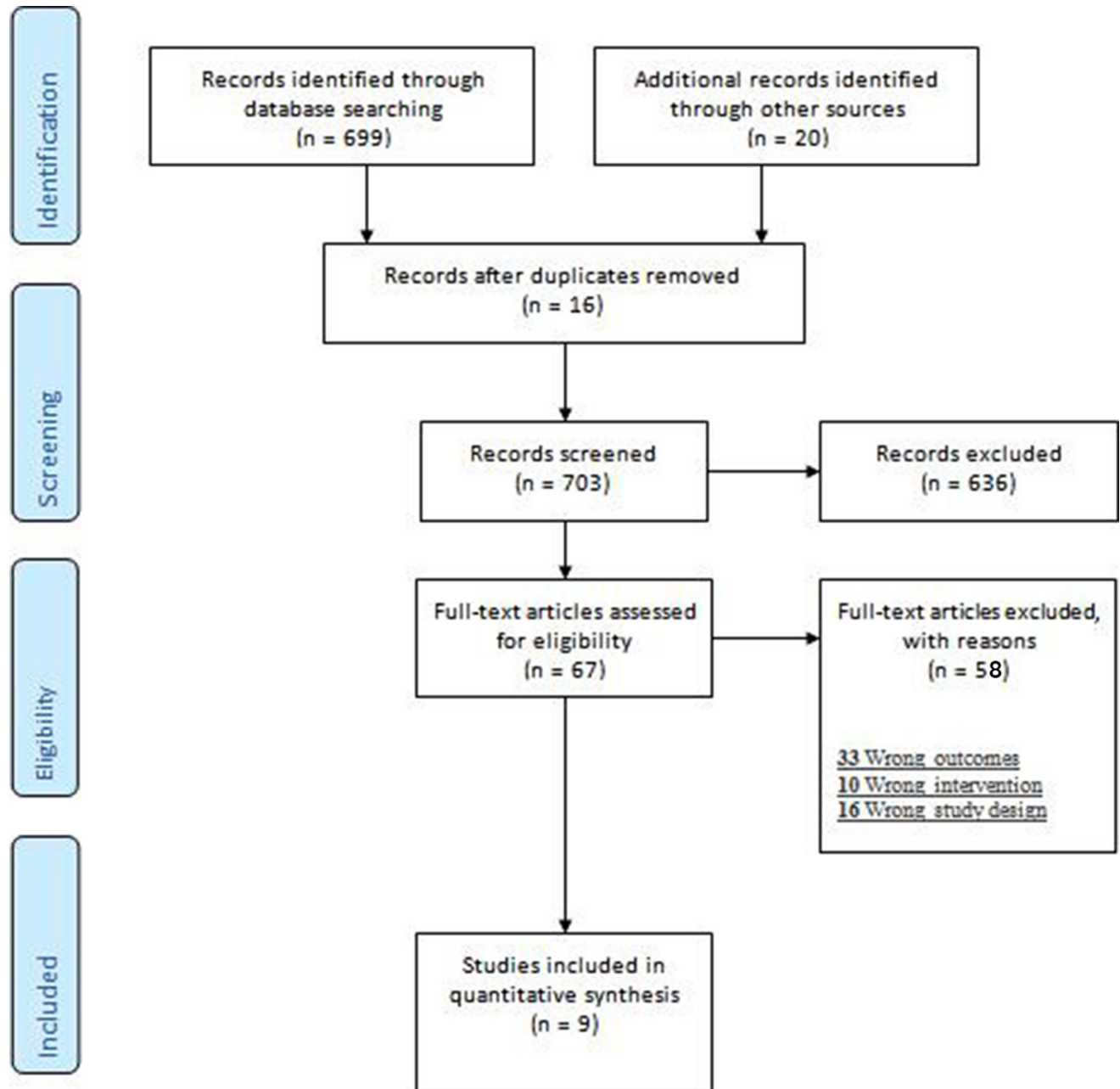


Fig. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

the likely inaccuracies relating from conversion of the medians to means for analysis, and the lack of availability of the necessary data to do this, the analysis was kept separate. The overall mean 25(OH)D level in a pooled analysis of four studies including 615 patients was 50.7 nmol/l with a mean incidence of infection of 70%.^{12,13,15,18}

In a study of 209 patients with hip fractures, Falker et al¹⁰ found a significant association between 25(OH)D and one-year mortality in matched controls. The mean vitamin D level for the cohort was 21 nmol/l, with extrapulmonary infections occurring in 4%. A multivariate

analysis which adjusted for age, sex, BMI, and American Society of Anesthesiologists (ASA)¹⁹ score found 25(OH)D levels to be an independent predictor of postoperative complications, of which infection was a component, but the study did not evaluate whether 25(OH)D levels were independent predictors of infection.

Association between 25(OH)D and orthopaedic infection. Two studies reported that Vitamin D did not have an association with infection. Marschall et al¹³ conducted a retrospective cohort study of 233 patients with osteomyelitis or septic arthritis, and while they found that 75%

Table II. Study characteristics and findings.

Study	Country	Study design	Statistical analysis	Sample size	Key clinical findings	Median baseline 25(OH) D level (nmol/l)	Mean baseline 25(OH) D level (nmol/l)	Incidence of orthopaedic infection (%)	Quality rating
10	Germany	Single-centre prospective cohort study of patients with low-energy medial femoral neck fracture exploring relationship between 25(OH)D, CRP, and postoperative medical complications.	Multiple logistic regression analysis. Spearman correlation.	209	25(OH)D deficiency in 87% of all patients. Correlation between raised CRP and low 25(OH)D (0.245, $p = 0.001$). Hypovitaminosis D identified as independent risk factor for postoperative medical complications, but not specifically infection.	21	N/A	N/A	+
11	USA	Prospective double-blind placebo-controlled single-centre randomized study of emergency presentations of humerus, femur, or tibia fractures. Intervention group given single 100,000 IU dose of Vitamin D3, versus placebo in control group, looking at fracture union.	t -test and Fisher's exact test	113	Hypovitaminosis D in 89% of patients. No significant difference in outcomes including union, fixation failure, and infection between the two groups.	40	N/A	2	++
12	Germany	Single-centre retrospective case-control study of patients scheduled to receive total prosthesis of the hip, knee, or shoulder, looking at the relationship between PJI and hypovitaminosis D.	Independent-samples t -test, ANCOVA, ANOVA	190	Hypovitaminosis D in 64% of patients undergoing primary arthroplasty, 52% of patients with prosthesis loosening and 86% of patients with PJI.	N/A	45	26	+
13	USA	Single-centre retrospective cohort study of patients with a diagnosis of osteomyelitis and/or septic arthritis undergoing treatment, looking at the relationship between hypovitaminosis D and poor clinical outcomes in osteoarticular infections.	Chi-square, Fisher's test, t -test and Mann-Whitney U test as appropriate	223	Hypovitaminosis D in 75% of patients. No significant difference in 25(OH)D levels in patients with and without successful clinical outcomes.	N/A	58	100	N/A
14	UK	Single-centre prospective cohort study of patients undergoing primary arthroplasty due to OA looking at changes in 25(OH)D concentration post-surgery.	Mann-Whitney U test, Spearman's rank correlation.	33	Majority of patients had hypovitaminosis D. Significant decrease in 25(OH)D concentration postoperatively.	40	N/A	N/A	+

Continued

Table II. Continued

Study	Country	Study design	Statistical analysis	Sample size	Key clinical findings	Median baseline 25(OH) D level (nmol/l)	Mean baseline 25(OH) D level (nmol/l)	Incidence of orthopaedic infection (%)	Quality rating
15	Italy	Single-centre retrospective cohort study of patients with prosthetic failure, osteoarticular infections, or other osteoarticular pathologies looking at the relationship between baseline 25(OH) D concentration and subsequent development of infection.	One-way ANOVA, student <i>t</i> -test	78	Hypovitaminosis D in 79% of patients. Significantly higher concentration of 25(OH)D in patients with PJI compared with aseptic loosening.	N/A	41	56	N/A
16	USA	Single-centre retrospective case-control study of patients undergoing rTHA or rTKA, looking at the relationship between complications and 25(OH)D concentration.	Independent-samples <i>t</i> -test, chi-squared and regression analysis	126	Hypovitaminosis D in 55% of patients. Hypovitaminosis D associated with increased risk of 90-day complications and PJI.	N/A	N/A	25	+
17	Germany	Single-centre prospective case-control study of patients with PJIs in hip and knee joints, looking at vitamin D balance.	Chi-squared test, Fisher's test, Mann-Whitney U test	240	High prevalence of hypovitaminosis D in patients with PJIs. Significantly lower concentration of 25(OH)D in patients with acute infection versus chronic infection.	45	N/A	25	+
18	UK	Single-centre prospective case-control study of orthopaedic patients, looking at relationship between 25(OH) D concentration and incidence of orthopaedic infection.	Independent-samples <i>t</i> -test, odds ratios and bivariate correlation analysis	205	High overall prevalence of hypovitaminosis D. Correlation between low concentrations of 25(OH)D and increased rate of orthopaedic infection.	N/A	59	56	+

ANCOVA, analysis of covariance; ANOVA, analysis of variance; N/A, not applicable; OA, osteoarthritis; PJI, periprosthetic joint infection; rTHA, revision total hip arthroplasty; rTKA, revision total knee arthroplasty.

of patients had Vitamin D levels < 75 nmol/l, they found that Vitamin D levels had no significant impact on success of treatment of infection. The study only included patients who had an orthopaedic infection, and as such, a comparison was not possible with a control group.

Zajonz et al¹⁷ carried out a prospective matched case-control study of 240 patients after total hip and total knee arthroplasties, comparing vitamin D levels in patients with acute periprosthetic joint infections (PJIs) versus chronic PJIs. There were three different groups, which included the standard group of patients with infections in their hip or knee implants, control group I with primary implants, and control group II with aseptic loosening. The median 25(OH)D level in the total population was reported at 45

nmol/l. Patients who developed acute PJIs had a median 25(OH)D level of 21 nmol/l, which was 33 nmol/l lower than patients who developed chronic infection. While all acute PJIs showed low vitamin D levels, there was no significant difference noted between the three groups.

Signori et al¹⁵ reported that higher levels of vitamin D were associated with lower levels of infection. They performed a retrospective cohort study of 78 orthopaedic patients, who were divided into four groups including those with prosthetic revision due to PJI, aseptic loosening, osteoarticular infections without prosthesis, and other osteoarticular pathologies.

The overall study population mean 25(OH)D level was insufficient at 41 nmol/l. They identified that patients

who presented with PJIs had significantly higher concentrations of 25(OH)D than patients who presented for aseptic loosening, with a difference of 12.25 nmol/l ($p < 0.05$). The authors posit that the difference between their study and other findings in the literature was likely due to the fact that their study measured 25(OH)D levels at the time of confirmed diagnosis of orthopaedic infection, rather than a baseline. As such, it is possible that dynamic fluctuations in serum 25(OH)D concentrations may be observed with the onset of infection, or peri-procedurally. Furthermore, in this study, the groups were not controlled for or matched on independent risk factors for infections such as age, sex and other comorbidities.

Reid et al¹⁴ carried out an observational cohort study where 33 patients who underwent elective primary knee arthroplasty had vitamin D levels taken preoperatively, at six to 12 hours, every day for the first five days, and finally at three months after the procedure. The study explored the relationship between acute markers such as CRP, estimated glomerular filtration rate (e-GFR), calcium, parathyroid hormone (PTH), and albumin with Vitamin D. While it did not quantify the incidence of clinical infection, it found a significant decrease in serum 25(OH)D levels of 19% over the course of the study ($p = 0.003$), while CRP increased by 14% ($p = 0.122$), though there was no significant relationship between the two. The overall median 25(OH)D level for the population was 40 nmol/l.

A cohort study of 190 patients,¹² with three different cohorts of primary arthroplasty, PJI, and aseptic loosening of prosthesis, found that patients with PJIs (25(OH)D = 33 nmol/l) had significantly lower levels of vitamin D than patients undergoing primary arthroplasty (49 nmol/l; $p < 0.001$) and aseptic prosthesis loosening (51.3 nmol/l; $p < 0.001$). *Staphylococcus aureus* was grown in 52% of patients with PJI.

A retrospective case-control study of 126 patients undergoing either revision total hip arthroplasty or revision total knee arthroplasty identified fewer complications in patients with normal Vitamin D levels.¹⁶ Patients were divided into two groups: a group with vitamin D levels < 75 nmol/l and another group with vitamin D levels > 75 nmol/l. Absolute 25(OH)D concentrations were not reported, but the study found that 23.9% more patients undergoing revision surgery for PJI had low vitamin D levels compared to patients undergoing surgery for aseptic indications ($p = 0.016$) and they also had a 17.5% higher chance of PJI ($p < 0.001$). Zargaran et al¹⁸ identified a positive correlation between higher serum 25(OH)D concentrations and lower incidence of orthopaedic infection in a case-control study of 205 patients.¹⁸

Haines et al¹¹ completed a randomized double-blind placebo-controlled trial of 113 adults with long-bone fractures, where patients in the intervention group were given a single dose of 100,000 IU of vitamin D orally

within two weeks of their injury found that infection occurred in 2% of the control group ($n = 1/50$) and none of the intervention group.

Discussion

The majority of studies included in the literature were observational rather than interventional, making it difficult to infer causation. Every study included reported suboptimal levels of 25(OH)D in the orthopaedic patient population, raising the question of whether orthopaedic patients should be started on 25(OH)D supplementation regardless of its impact on orthopaedic infection, due to the other known benefits including reduced risk of respiratory tract infections and sepsis. This corresponds to studies in other populations, including patients in critical care, the obstetric population, as well as a recent cross-sectional study of 588 professional football players where vitamin D deficiency or insufficiency was the most common medical condition, occurring in 89%.²⁰ The majority of studies included benchmark low vitamin D levels as < 75 nmol/l, while the normal range within the UK is above 50 nmol/l. Given the international consensus regarding that target in the included studies, increasing the lower limit of normal from 50 nmol/l to 75 nmol/l should be explored.

Correlations between 25(OH)D concentrations and reduced incidence of orthopaedic infection were noted, and are consistent with studies in other fields that demonstrate vitamin D repletion as protective against infection.^{21,22} Sample sizes were limited, with further limitations in methodology. However, correlations between higher 25(OH)D levels and lower incidence of infection were observed across a number of the studies, suggesting that prophylactic supplementation of vitamin D may improve outcomes.

In terms of methodology, studies were inconsistent with respect to when 25(OH)D levels were measured, with certain studies only evaluating at the point of diagnosis of infection, while others reported baseline levels instead. A more comprehensive overview including baseline 25(OH)D levels, post-procedure serial levels, and long-term levels would provide a greater insight into the benefit of vitamin D.

The impact of supplementation was inadequately explored, and this review includes a RCT which explores this as part of its primary focus of the effect of Vitamin D supplementation of fracture union. The reported 2% increase in incidence of infection in the control group was not statistically significant, and is accounted for by a single case of infection. Further RCTs are needed to explore whether supplementation of vitamin D prophylactically reduces the risk of orthopaedic infection and improves patient outcomes. Furthermore, studies should explore when supplementation is most effective: does a single dose of Vitamin D immediately before a procedure

provide the body with enough time for vitamin D to exert its immunoprotective effects, or does supplementation need to be over a longer period of time, thus conferring greater benefit to elective patients?

Based off the appraisal of studies within this review, there is evidence in the literature that higher levels of vitamin D are associated with lower rates of orthopaedic infection. However, it is clear that there is a lack of high-quality studies exploring this important question, and more research needs to be done to better elucidate the potential value of vitamin D supplementation for reducing orthopaedic infection. This review provides a foundation for RCTs to explore and establish whether supplementation of vitamin D is protective against orthopaedic infection.

In conclusion, orthopaedic patients have suboptimal levels of 25(OH)D, and there is a correlation between higher vitamin D levels and a lower incidence of orthopaedic infection. Further research is needed to explore the impact of supplementation of vitamin D on orthopaedic infection in the form of RCTs of supplementation to determine whether there is benefit, as well as the optimum dose and timing of prophylactic supplementation.



Take home message

- A significant proportion of orthopaedic patients have low 25(OH)D levels.
- There is an association between low 25(OH)D levels and orthopaedic infection.
- More randomized controlled trials need to be conducted to establish the benefit of prophylactic supplementation and the optimum regimen by dose and time.

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Author information:

- A. Zargarán, MBBS, BSc (Hons), FHEA, Academic Foundation Doctor, King's College London, London, UK; Guy's and St Thomas' NHS Foundation Trust, London.
- D. Zargarán, MBBS, BSc (Hons), FHEA, MRCS, Registrar in Plastic Surgery, Imperial College London, London, UK.
- A. J. Trompeter, MBBS, BSc, FRCS (Tr&Orth), Consultant Trauma & Orthopaedic Surgeon, Orthopaedics and Trauma, St George's Hospital, London, UK.

Author contributions:

- A. Zargarán: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft.
- D. Zargarán: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—review & editing.
- A. J. Trompeter: Conceptualization, Methodology, Supervision, Validation, Writing—review & editing.

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