



Review article

Current concepts in vitamin D and orthopaedic surgery

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ABSTRACT

Introduction: Vitamin D plays an important role in the musculoskeletal system of the human body. Here, we review the most current literature on vitamin D as it relates to orthopaedic surgery and the musculoskeletal system, focusing largely on non-fracture applications.

Materials and methods: A literature review was performed on the basic science of vitamin D metabolism, epidemiology of vitamin D levels, role of vitamin D within the musculoskeletal system, and the correlation of vitamin D with injuries and orthopaedic surgical outcomes.

Results: The existing literature suggests vitamin D plays multiple roles in the musculoskeletal system. Recent research has shed light on the importance of vitamin D in the setting of soft tissue healing and recovery in addition to affecting postoperative outcomes after common orthopaedic procedures.

Conclusions: Given the widespread prevalence of vitamin D deficiency, orthopaedic surgeons should be aware of the current evidence regarding clinical implications in patients with musculoskeletal complaints.

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1. Introduction

Vitamin D plays an important role in the musculoskeletal system of the human body. Traditionally, much of the focus on vitamin D has been placed on the regulation of bone health and fracture healing. However, recent growing evidence has shed light on the importance of vitamin D and its relation to soft tissue healing and function. Despite recent research, there continues to remain confusion about the role of vitamin D. Here, we review the most current literature on vitamin D as it relates to orthopaedic surgery and the musculoskeletal system, focusing largely on non-fracture applications. We outline the basic science of vitamin D metabolism, epidemiology of vitamin D levels, roles vitamin D serves within the musculoskeletal system, and the correlation of vitamin D with injuries and surgical outcomes.

2. Background

2.1. Sources of vitamin D

Vitamin D is biologically synthesized using ultraviolet B (UVB) rays from the sun. Solar UVB rays transform 7-dehydrocholesterol

to pre-vitamin D₃ at the skin level (Fig. 1). Pre-vitamin D₃ is also acquired in small quantities through the consumption of liver, cod liver oil, fatty fish, and egg yolks [1–3]. From the skin, pre-vitamin D₃ is attached to vitamin D binding protein and transported to the liver where it is converted to 25-hydroxyvitamin D₃ (25 OHD), also known as calcifediol [1,3]. Through an additional hydroxylation step, predominantly in the kidneys, 25 OHD is converted to 1,25-dihydroxyvitamin D₃ or calcitriol, the active form of vitamin D [1,3,4].

2.2. Basic mechanisms

Vitamin D is a secosteroid with direct hormonal interactions with over 200 genes in the human genome [5]. Vitamin D receptors (VDR) on target cell nuclear membranes facilitate the endocrine and autocrine functions of vitamin D in multiple tissues [1]. The endocrine function of vitamin D is largely present in the small intestine where it is instrumental in regulating serum calcium and phosphate absorption. This modulation of serum calcium and phosphate is intertwined with the actions of parathyroid hormone (PTH) and, consequently, bone mineralization [1,3]. Additionally, it stimulates osteoblasts causing osteoclast activation, a crucial step in calcium mobilization and bone remodeling [6].

In addition to the endocrine effects of vitamin D, it plays many important roles in muscular development and function. This includes regulating phosphate accumulation in myocytes, aiding in

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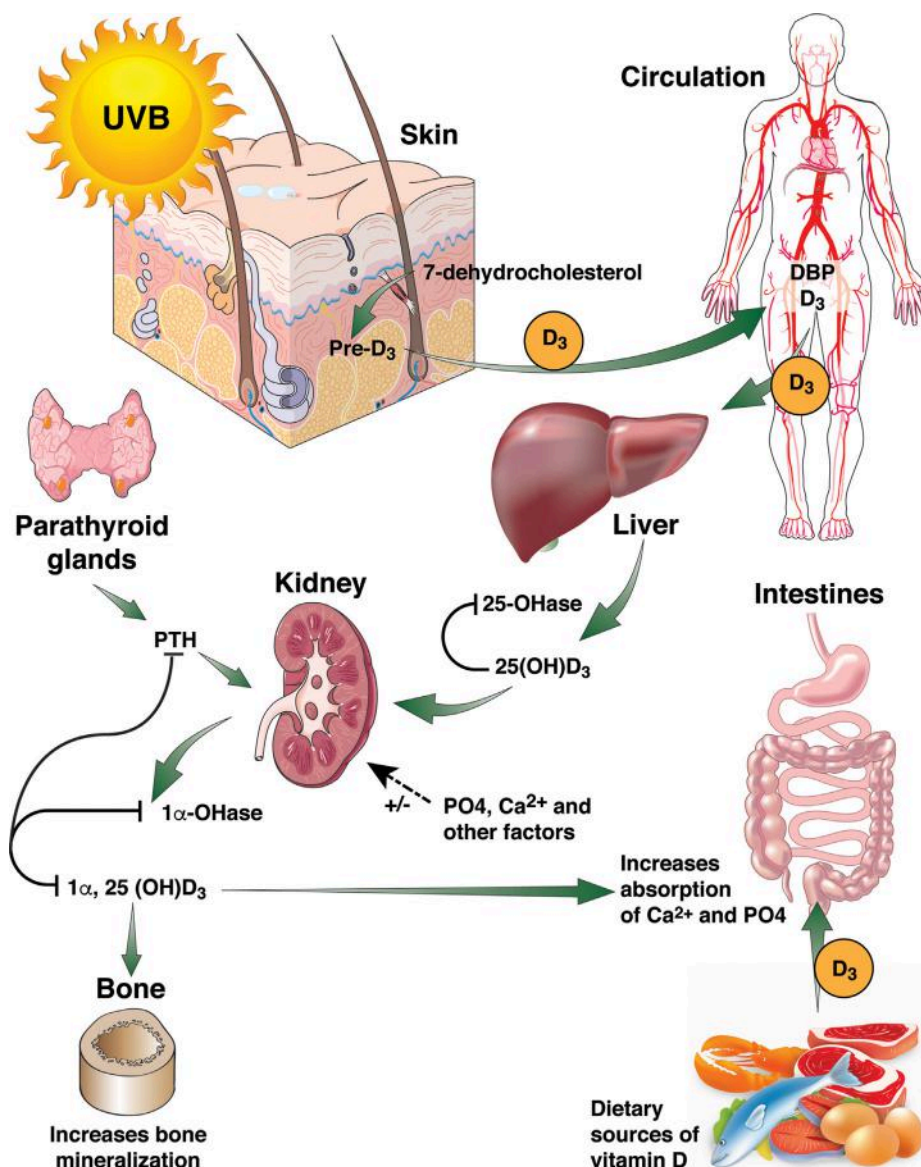


Fig. 1. Vitamin D pathway.

muscle function, and metabolism after conversion to creatine phosphate. It is also theorized to play a direct role in protein synthesis and growth.³ Vitamin D has been found to alter myocyte responsiveness to insulin, indirectly improving muscle recovery and construction. Lastly, it has been theorized that type II muscle fibers have a greater amount of VDRs than type I, leading to type II proliferation when a hypovitaminosis D individual increases their serum vitamin D concentration [7]. Cartilage and joint capsular tissues have also been evaluated for their relationship to vitamin D. One theory is that the vitamin D metabolite 24R,25-dihydroxyvitamin D₃ plays a role in stimulating extracellular matrix proliferation by chondrocytes. Through these effects, vitamin D plays an important role in optimizing mechanical loading [8].

2.3. Vitamin D levels

There is considerable debate as to the level of serum 25 OH D that designates a person as vitamin D deficient, insufficient, or sufficient, and there has been no minimal clinically important value established for vitamin D. The Vitamin D Council reports deficient as 0–30 ng/mL, insufficient as 31–39 ng/mL,

and sufficient as 40–80 ng/mL [1]. The Endocrine Society reports deficient as 0–20 ng/mL, insufficient as 21–29 ng/mL, and sufficient as 30–100 ng/mL [9]. The Food and Nutritional Board Institute of Medicine reports deficient as 0–11 ng/mL, insufficient as 12–20 ng/mL, and sufficient as greater than 20 ng/mL [10,11]. Thus, further studies are needed to help standardize normal ranges for vitamin D. In addition, levels categorized as deficient or insufficient should be clinically important and correlate with injury and healing variables.

2.4. Vitamin D supplementation

Vitamin D supplementation is available in the form of vitamin D₃ (cholecalciferol), or vitamin D₂ (ergocalciferol). Although there is some debate, vitamin D₃ appears to be preferable for supplementation, with varying ranges of recommended dosages [9–14]. According to the Institute of Medicine, the recommended daily allowance (RDAs) for vitamin D is 600 IU for ages 1–70, and 800 IU for ages 71 and older, while the tolerable upper level (UL) is 4000 IU per day for ages 9 and older [10,11]. Treatment dosages for low vitamin D levels are varied, with ranges between 400–1000 IU

per day [13]. Recommended dosages for patients with 25OHD levels between 25–30 ng/mL are 2000–4000 IU D₃ daily, and 50,000 IU once a week of D₂ for 8 to 12 weeks for those with serum 25OHD levels < 25 ng/mL [9,13].

3. Epidemiology

The National Center for Health Statistics estimates that up to 32% of Americans are deficient in vitamin D, and up to 1 billion people worldwide are estimated to be insufficient or deficient [1]. Prevalence of vitamin D deficiency is likely to increase due to time spent indoors and increased use of sunscreen for skin cancer prevention. Risk factors for hypovitaminosis D include latitudinal location, winter season, skin melanin abundance, clothing coverage, kidney disease, and Crohn's disease [1,3,15].

3.1. Athletes

Recently, there have been numerous studies evaluating the prevalence of abnormal vitamin D concentrations in the athletic population at both the collegiate and professional levels. In 2012, Villacis et al. found that 33.6% division I athletes at the University of Southern California had abnormal vitamin D levels [16]. Specifically, males, African-Americans, Hispanics, and those with a darker skin complexion were at increased risk for having low vitamin D levels. Barcal et al. showed that 74% of collegiate wrestlers had levels < 32 ng/mL in the fall, which increased to 94% in the winter and spring seasons [17]. They also found an association between low vitamin D levels and higher adiposity. The changes in vitamin D levels on a seasonal basis are well documented. Vitale et al. performed a prospective cohort study analyzing vitamin D levels in 152 professional Italian alpine skiers over the course of 3 full years in order to evaluate fluctuations in vitamin D [18]. Fifty one percent of these athletes at one point were vitamin D insufficient and 30% were deficient at one point over the course of three seasons. Most athletes' vitamin D levels peak in the summer and are lowest in the winter.

At the professional level in the United States, the prevalence of low vitamin D levels has been studied in the National Basketball Association (NBA), National Football League (NFL) and National Hockey League (NHL). In a study by Fishman et al., 90 (32.3%) of the 279 NBA players at the NBA combine from 2009–2013 were vitamin D deficient, while 131 (47.0%) were vitamin D insufficient [19]. The mean vitamin D level in this cohort was 25.6 ± 10.2 ng/mL. Similarly, Angeline et al. found that 30% of NFL players on a single NFL team were vitamin D deficient (< 20 ng/mL), while 51% were vitamin D insufficient (20 to 31 ng/mL) [20]. In this cohort, lower vitamin D levels were associated with muscle injury. Maroon et al. found that African-American NFL players were more likely than white players to be vitamin D deficient [21]. In contrast, Mehran et al. found a low prevalence of vitamin D insufficiency (20–31.9 ng/mL) in the NHL, with a rate of only 13.3% in 105 hockey players across 3 NHL teams [22]. However, there were major differences in racial composition in these cohorts, with a higher percentage of white athletes in the NHL cohort compared to the NFL study. 3.8% of athletes were black and 96.2% of athletes were white in the NHL study cohort, while 84% of athletes were black in the study by Maroon et al. [21,22] Some authors espouse a 25-OH vitamin D level > 40 ng/mL as ideal in athletes.

3.2. Orthopaedic patients

Many studies have evaluated the deficiency of vitamin D in patients undergoing orthopaedic procedures. Observational cohort studies in the United States and internationally have demonstrated a high prevalence hypovitaminosis D in these patients [23–25].

Additionally, recent studies have demonstrated high rates of vitamin D insufficiency and deficiency in pediatric orthopaedic patients and adult patients undergoing foot and ankle, spine, joint replacement, and orthopaedic trauma surgeries [26,6,27–29]. Inkrott et al. retrospectively reviewed vitamin D levels in 218 patients undergoing shoulder arthroplasty and found that 43% of patients were vitamin D insufficient (< 30 ng/mL) and 11% were vitamin D deficient (< 20 ng/mL) [29]. In this study, low vitamin D levels were associated with increased BMI (≥ 30 kg/m²), similar to the study by Barcal et al. [21].

4. Musculoskeletal systems

4.1. Intra-articular cartilage

Recent studies have specifically investigated the effects of vitamin D on cartilage health. A systematic review by Garfinkel et al. about vitamin D and cartilage found that patients with decreased articular cartilage thickness were more likely to be vitamin D insufficient and concluded that low levels of vitamin D is a risk factor for the development of osteoarthritis (OA) [30]. Using a rodent model, Pascual-Garrido et al. found that low vitamin D levels had deleterious effects on articular cartilage as determined by histological analysis and micro-CT [31]. Castillo et al. conducted a rat study investigating the relationship between vitamin D and the biochemical mechanisms of cartilage loss, inflammation, and OA progression and found that vitamin D supplementation had a protective effect during the initial stages of OA but not during the chronic stage [32]. In another rat study by Li et al. using ovariectomized rats, the authors found that vitamin D prevented cartilage loss through the regulation of type II collagen turnover [33]. Rai et al. evaluated the role of vitamin D in inflammation, fatty infiltration, and cartilage loss in the knee in microswine fed a high-cholesterol diet and found increased inflammation in knee joint tissues, increased fatty infiltration in the soft tissue, and increased chondrocyte clustering in the articular cartilage, a hallmark of OA, in the vitamin D deficient and sufficient groups compared to the group supplemented with vitamin D [34].

4.2. Muscle function

Tomlinson et al. conducted a meta-analysis assessing the effects of vitamin D supplementation on upper and lower body muscle strength [35]. Results showed that there was a significant increase in muscle strength when healthy adults ages 18–40 received vitamin D₃ supplementation. Rebolledo et al. performed a retrospective cohort study on the 214 athletes at the 2015 NFL combine to assess vitamin D levels and lower extremity and core muscle strains [36]. Fifty percent of athletes reported a lower extremity muscle strain or core muscle injury. Athletes who reported a history of injury has significant lower levels of vitamin D compared to those who reported no injuries ($p=0.03$). Additionally, athletes with inadequate levels of vitamin D had 3.61 higher odds ($p<0.001$) of a hamstring strain compared to those with normal levels. However, the study was retrospective and authors did not account for seasonal changes of vitamin D levels. Dawson-Hughes reviewed the relationship between vitamin D and muscle function and found that older adults with 25 OHD < 40 nmol/L were most likely to improve their muscle performance on strength testing with supplementation (dosing of 800–1000 IU/day) [8]. Conversely, in a randomized control trial by Saha et al. assessing the effect of calcium and vitamin D supplementation on testosterone levels and muscle strength in young males (age 20.2 ± 2.2), there was no statistically significant evidence suggesting a positive relationship with supplementation, testosterone, and muscle strength after 6 months [37].

4.3. Falls in the elderly

In the elderly, one notable area of investigation is the relationship between vitamin D and physical performance, including falls, a major cause of morbidity and mortality in this population. In reviewing the literature on the effect on vitamin D on falls and physical performance, Dhaliwal et al. found that there may be an association in older adults, although the existing literature is inconsistent [38]. However, excessive vitamin D supplementation and high serum 25 OHD levels can also increase the risk of falls in the elderly. Smith et al. conducted a double blind randomized clinical trial with elderly women given 1 of 7 possible oral vitamin D₃ doses or placebo [39]. It was found that medium dosing (1600–3200 IU/per) showed the greatest reduction in falls compared to low (400–800 IU/day) or high dosing (4000–4800 IU/day). Interestingly, this study found that fall rates increased in patients with serum 25 OHD levels above 40–45 ng/mL, although the reason for this remains unclear. Duque et al. showed that vitamin D supplementation appeared to improve muscle strength and decrease falls in older patients who have low baseline levels of 25 OHD (< 30 nmol/L) [40]. Antoniuk et al. conducted a meta-analysis relating vitamin D supplementation and falls in older adults found that supplementation of vitamin D decreased the risk of falls in older individuals when combined with resistance exercise [41]. In summary, vitamin D supplementation appears to be beneficial in the elderly when baseline levels of 25 OHD are low (< 30 nmol/L).

5. Outcomes after orthopaedic surgeries

5.1. ACL reconstruction

Barker et al. studied the effects of vitamin D on strength gains after an ACL injury and subsequent reconstruction [42]. This retrospective analysis was conducted in a group of 18 Caucasian males who underwent ACL reconstruction compared to 11 control subjects without ACL injury by measuring single leg isometric strength, vitamin D, and cytokine levels 2 weeks prior to surgery and 3 months postoperative. Cytokines were elevated in the study group compared to the control group in both pre- and postoperative blood samples. Results showed that isometric leg strength increases postoperative were significantly lower in participants whose vitamin D levels were < 30 ng/mL. The authors concluded that low vitamin D levels might impair strength recovery after ACL reconstruction.

In another rat model study, Boyan et al. looked at the effects of intra-articular vitamin D injections on in vivo ACL transections [9]. Compared to placebo injections, the rats receiving vitamin D injections post in vivo ACL transections showed less articular damage and lower levels of inflammatory mediators. These findings point towards some potential clinical implications on trauma induced osteoarthritis, but human clinical studies are needed to further investigate these potential correlations.

5.2. Rotator cuff injury

In a controlled laboratory study, Angeline et al. compared vitamin D deficient rats with vitamin D sufficient control rats who underwent unilateral detachment of the supraspinatus tendon from the greater tuberosity followed by repair using bone tunnel suture fixation [43]. Results demonstrated that low vitamin D levels may negatively impact early healing of rotator cuff repair sites. It is theorized that vitamin D may have an important role in the tendon-to-bone healing process by increasing bone mineral density and strengthening skeletal muscles. However, more data is needed to determine the clinical relevance of these biochemical effects.

Oh et al. examined the relation between vitamin D levels and its effect on rotator cuff health in a retrospective study comparing vitamin D levels in patients with shoulder injuries and healthy patients with no shoulder injury [44]. The mean age this population was 61.3 years (range, 43–80). Results showed that low vitamin D levels were associated with significant fatty degeneration of the rotator cuff muscles. Furthermore, vitamin D levels were positively correlated with isokinetic muscle torque of the shoulder.

In a clinical study evaluating the relationship of vitamin D in patients undergoing arthroscopic rotator cuff repairs for full-thickness rotator cuff tears, Ryu et al. found that low vitamin D levels were not related to outcomes after arthroscopic repair of rotator cuff muscles [45]. In this cohort, 80 patients (88%) were vitamin D insufficient, 8 (9%) were vitamin D deficient, and 3 (3%) were vitamin D sufficient. The authors concluded that low vitamin D levels had no correlation with size of the tear, fatty infiltration in cuff muscles or the extent of the retraction, or functional outcomes as measured by the University of California, Los Angeles (UCLA) score, Constant score, and American Shoulder and Elbow Society (ASES) score at 1 year postoperatively. A major limitation of this study, however, was that only 3 patients were vitamin D sufficient. The study thus lacked power to definitely state the relationship between vitamin D and rotator cuff repair outcomes. Furthermore, the authors did not re-test vitamin D levels at final follow up to adjust for variations.

5.3. Osteoarthritis

The existing literature on vitamin D levels in patients with osteoarthritis (OA) has been inconsistent. In a randomized controlled trial investigating 800 IU daily vitamin D supplementation versus placebo in 474 patients with knee OA, Arden et al. found that vitamin D supplementation did not have any effect on joint space narrowing, pain, stiffness, or functional loss [46]. This is consistent with other randomized controlled trials demonstrating no reduction in knee pain or cartilage volume loss in patients with symptomatic knee OA and low vitamin D levels [47,48].

In contrast, Zheng et al. found that vitamin D sufficiency had a beneficial effect on cartilage loss, effusion-synovitis, and physical function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [49]. A randomized controlled trial by Sanghi et al. demonstrated a small but statistically significant benefit of vitamin D use in patients with knee OA and vitamin D insufficiency as measured by the visual analogue scale (VAS) and WOMAC [50]. Levinger et al. found that patients with knee OA and vitamin D insufficiency (≤ 50 nmol/L) had worse knee function during balance recovery, increased pain, and locomotor dysfunction as measured by the WOMAC [51]. Similarly, Manoy et al. found that vitamin D supplementation improved quality of life, handgrip strength, physical performance, and decreased pain and oxidative protein damage in patients with OA, as measured by the WOMAC and VAS scales [52].

Several meta-analyses of vitamin D and OA have demonstrated significant associations between low vitamin D levels and knee OA, including joint space narrowing and structural changes in the knee [53,54]. Regarding vitamin D supplementation in knee OA, a meta-analysis by Gao et al. found supplementation improved WOMAC pain and function, but had no effect on the prevention of tibial cartilage loss [55]. Conversely, a meta-analysis by Diao et al. found supplementation had no clinically significant effect on pain relief or joint structure improvement in patients with knee OA [56]. Despite the extensive literature on relationship between vitamin D and OA, further longitudinal studies are needed to reconcile these discrepancies in the literature.

5.4. Arthroplasty

There are several studies evaluating vitamin D status in patients undergoing arthroplasty surgeries. Shin et al. conducted a prospective cohort study with patients undergoing total knee arthroplasty (TKA) and found that early post-operative outcomes following TKA were affected by patients' preoperative vitamin D status [57]. Using a cut-off value of < 12 ng/mL to define deficiency, they found that those in the vitamin D-deficient group had significantly worse outcomes as assessed by the functional American Knee Society Score (KSS), the alternative step-test, and the six-meter walk test. These findings are supported by several other studies investigating vitamin D levels and pre-/post-operative functional scores in patients undergoing TKA [58–60]. In contrast, Lee et al. investigated vitamin D levels in patients undergoing TKA and found there was no effect of vitamin D levels on total WOMAC ($p=0.22$) postoperatively, although there was an increased risk of moderate-to-severe pain in patients with low vitamin D [61]. They concluded that hypovitaminosis D was not associated with worse health-related quality of life at 3 months postoperatively following TKA.

Nawabi et al. evaluated vitamin D levels and Harris hip scores in 62 Caucasian patients undergoing THA for OA and found that vitamin D deficient patients had lower preoperative Harris hip scores ($p=0.018$) and were less likely to have an excellent outcome postoperatively ($p=0.038$) [62]. In contrast, Unnanuntana et al. investigated vitamin D levels and short-term functional outcomes in 219 patients following THA and found no associations between THA and functional outcomes at 6 weeks postoperatively as measured by the WOMAC, Short Form-36, 2-minute walk test, and timed get up-and-go tests [63]. Additionally, the same authors investigated vitamin D levels in a separate cohort of 200 THA patients and found no associations between vitamin D levels and in-hospital milestones, length of hospital stay, or perioperative complications [64].

In a prospective observational study by Maier et al. assessing the effect of low vitamin D levels and length of hospital stay in 1083 patients after elective hip or knee arthroplasty, patients with low vitamin D levels stayed on average 4.3 days longer post-arthroplasty than patients with adequate vitamin D levels [65]. Eighty-six percent of these patients were vitamin D insufficient, and over 60% were vitamin D deficient. Future randomized controlled clinical trials are necessary to clarify the conflicting evidence in the current literature regarding vitamin D and outcomes in total joint arthroplasty.

Recent studies have investigated postoperative complications associated with low vitamin D levels in patients undergoing arthroplasty procedures. Traven et al. retrospectively evaluated 126 revision TJA patients and found a prevalence of 55% vitamin D deficiency in this population [66]. They found that low vitamin D was associated with an increased risk of 90-day complications, including an increased risk of periprosthetic joint infection as the reason for revision surgery. These findings are supported by a study by Maier et al. [67]. A high percentage of patients requiring revision surgeries due to aseptic loosening (52%) and periprosthetic joint infection (86%) had vitamin D levels < 20 ng/mL. These results suggested an association between periprosthetic joint infection and vitamin D deficiency. Using an intra-articular knee implant mouse model, Hegde et al. found that vitamin D deficient mice had increased bacterial burden and neutrophil infiltration at the knee joint [68]. Furthermore, they found that replenishing the vitamin D deficient mice with supplemental vitamin D₃ could reverse this effect. Further studies are needed to investigate the potential association between low vitamin D levels and increased risk of periprosthetic joint infection. Vitamin D supplementation could potentially represent a low-cost adjunct for infection prophylaxis after total joint arthroplasty (Table 1).

Table 1
Vitamin D and orthopaedic procedures.

ACL reconstruction	Low vitamin D levels (< 30 ng/mL) may delay muscle strength recovery after ACL reconstruction [42] Decreased articular damage & inflammatory mediators in rats given intra-articular vitamin D injections post- in vivo ACL transections [9]
Rotator cuff	Low vitamin D levels may negatively affect early healing of rotator cuff repair sites in rats [43] Low vitamin D levels (< 30 ng/mL) associated with fatty degeneration of rotator cuff [44] Vitamin D levels positively correlated with isokinetic muscle torque of the shoulder [44] Clinically, low vitamin D levels showed no correlation with outcomes (UCLA, CS, ASES) following rotator cuff repair [45]
Arthroplasty	Low vitamin D levels may result in longer hospital stays following TJA [65] High prevalence of low vitamin D levels in TJA patients [66] Low vitamin D levels (< 20 ng/mL) associated with increased risk of postoperative complications, including periprosthetic joint infection [66,67]
Knee arthroplasty	Vitamin D deficient (< 12 ng/mL) patients undergoing TKA have significantly worse outcomes (KSS, alternative step-test, six-meter walk test) [57–60] Vitamin D deficient mice with intra-articular knee implants have increased bacterial burden and increased neutrophil infiltration in knee joint, reversible with vitamin D ₃ supplementation [68]
Hip arthroplasty	Lower pre- & postoperative Harris hip scores in vitamin D deficient THA patients [62] No association between vitamin D levels in THA patients & short-term postoperative outcomes (in-hospital milestones, length of stay, perioperative complications, WOMAC, SF-36, 2-minute walk test, & timed get up-and-go tests) [63,64]
Shoulder arthroplasty	High prevalence of low vitamin D levels in shoulder arthroplasty patients [29]

UCLA: University of California, Los Angeles; CS: Constant score; ASES: American Shoulder and Elbow Society; KSS: American Knee Society Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SF-36: Short-Form-36; TJA: total joint arthroplasty; TKA: total knee arthroplasty; THA: total hip arthroplasty.

6. Practice guidelines

6.1. Testing and dosages

When a patient presents, deciding whether serum 25 OHD levels need to be measured is the initial step. Aspray et al. summarized the Vitamin D Guideline put forth by the National Osteoporosis Society. Patients with bone disease that can potentially be improved with vitamin D treatment or need vitamin D deficiency corrected prior to specific treatment should have levels measured. Those with musculoskeletal symptoms, for example myopathy, caused by known or suspected vitamin D deficiency or osteomalacia should also be tested. Finally, testing is appropriate when deficiency can affect co-prescribed medication although there is weak evidence to support this practice. In contrast, those with osteoporosis or fragility fracture(s) being co-prescribed vitamin D and an oral antiresorptive treatment do not need routine testing. Testing is not justified when vitamin D supplement is simply co-prescribed as in asymptomatic patients with bone-protecting agents [69].

Oral cholecalciferol (D₃) is generally the recommended form for dosing [70]. Patients with symptomatic deficiency or those requiring prophylactic treatment prior to receiving a potent antiresorptive agent (e.g. zoledronate, denosumab, etc.) should receive a

Table 2
Dosages for specific indications.

Indication	Recommended vitamin D dosage (IU/day)	Comments
Fragility fracture	800–100,000	Higher doses were more efficacious in increasing vitamin D levels [71]
Traumatic fracture	2000	Note that a study by Haines et al. Bone Joint J (2017) reported that union rate may be independent of vitamin D3 supplementation [72,73]
Stress fracture	General: 800 Age < 50: 400–800 Age > 50: 800–1000	Higher dosages up to 4000 IU may be necessary and calcium co-supplementation is recommended [74,75]
Athletes	2000–4000	4000 has positive effect on recovery of force after damaging eccentric exercise [76] Prescribe if sunlight exposure (35% of body) limited to < 20 min/day or resides < 30° or > 60° N and Dark skinned, 25 OHD < 75 nmol/L or cannot test for levels Light skinned and free 25 OHD < 2 ng/mL
Osteoporosis	700–1000	Reported to bring 50% of adults up to 75–100 nmol/L 2000 IU (safe upper limit defined by National Academy of Science) may shift distribution so only 10–15% of individuals are < 75 nmol/L [77]
Prior to grafting surgery	1200 IU (Rat study)	Rats with vascularized bone allograft given the equivalent of 1200 IU had higher bone mineral density and union than those who did not [78]

loading dose beforehand of 300,000 IU over 6 to 10 weeks, followed by maintenance doses of 800–2000 IU (occasionally up to 4000 when appropriate) daily to maintain appropriate vitamin D levels. In less urgent cases (chronic disease, mild hypovitaminosis D) and in cases where vitamin D is co-prescribed with an oral antiresorptive agent, a loading dose is not necessary, and the maintenance regimen can be started [69].

Table 2 describes dosages for specific indications including fragility fracture [71], traumatic fracture [72,73], stress fracture [74,75], athletics [76], osteoporosis [77], and prior to grafting [78]. In general, the literature reports a wide range of acceptable doses for each indication. The recommendations are standard although there is data that supports higher doses in order to more successfully achieve target vitamin D levels. At the same time, for pathologies like osteoporosis, only prescription for patients with specific risk factors for vitamin D deficiency is warranted and general preventative widespread use is inappropriate [79].

7. Conclusion

The existing literature suggests vitamin D plays multiple roles in the musculoskeletal system. Historically, much of the research has focused on vitamin D and its relation to fracture healing, but more recent research has shed light on the importance of vitamin D in the setting of soft tissue healing and recovery in addition to affecting postoperative outcomes after common orthopaedic procedures. Nonetheless, there remains conflicting evidence and future prospective randomized studies are needed to elucidate the role of vitamin D in the musculoskeletal system.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

For this type of study formal consent is not required.

Disclosure of interest

Brent Ponce holds stock/stock options with Help Lightning, is a paid consultant/presenter/speaker for Tornier, and has IP royalties with Wright Medical Technology, Inc.

The other authors declare that they have no competing interest.

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Authors' contribution

Andrew Moon – Project design, data collection and analysis, manuscript writing.

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Eugene W. Brabston – Advisor, final edits, data analysis.

Brent A. Ponce – Project design, project oversight, advisor, final edits.

Amit M. Momaya – PI, project design, overall coordination and oversight.

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