Review

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Exploring the impact of vitamin D on tendon health: a comprehensive review

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Abstract: Tendons are vital components of the musculoskeletal system, facilitating movement and supporting mechanical loads. Emerging evidence suggests that vitamin D, beyond its well-established role in bone health, exerts significant effects on tendon physiology. The aim of this manuscript is to review the impact of vitamin D on tendons, focusing on its mechanisms of action, clinical implications, and therapeutic applications. A comprehensive search of scientific electronic databases was conducted to identify articles on the effects of vitamin D on tendon health. Fourteen studies were included in this review. Five studies were performed *in vitro*, and nine studies were conducted *in vivo*. Despite some conflicting results, the included studies showed that vitamin D regulates collagen synthesis, inflammation, and mineralization within tendons through its interaction with vitamin D receptors. Epidemiological studies link vitamin D deficiency with tendon disorders, including tendinopathy and impaired healing. Supplementation with vitamin D shows promise in improving tendon strength and function, particularly in at-risk populations such as athletes and the elderly. Future research should address optimal supplementation strategies and explore the interplay between vitamin D and other factors influencing tendon health. Integrating vitamin D optimization into clinical practice could enhance tendon integrity and reduce the burden of tendon-related pathologies.

Keywords: vitamin D; tendon health; tendinopathy; tendon injury; tendon healing; rotator cuff

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Introduction

Tendon disorders encompass tears and chronic diseases, representing a very common musculoskeletal issue [1]. Tendon pathologies frequently affect athletes due to overuse and involve several anatomical sites such as the rotator cuff, the long head of the brachial biceps, the extensors/flexors of the wrist in the upper limbs, thigh adductors, patellar tendon, posterior tibia tendon, and the Achilles tendon in the lower limbs [1–3]. At least 50 % of tendon issues is related to overload [3].

Tendon tears (partial or complete) can occur after an acute traumatic stress or as a consequence of a chronic degenerative condition [4–6]. The term “tendinopathy” instead includes all the situations in which there are chronic clinical conditions characterized by pain, swelling, and functional limitations of tendons and nearby structures [1, 7, 8]. Both intrinsic and extrinsic factors play a key role in the pathogenesis of tendinopathy; age and gender are the most prominent nonmodifiable factors, while excessive and/or improper loading, disuse, drugs, and smoking habit are the most influent modifiable factors [7, 9–13]. Although the term “tendinitis” is often associated with the concept of tendinopathy, in recent years, it has been shown that the inflammatory process only affects the initial stages of the disease, while degenerative and apoptotic phenomena prevail afterward because of long-lasting overuse condition related to work and/or sports [8, 14–16]. Tendinopathy can be viewed as a failure of the cell matrix to adapt to a variety of stresses as a result of an imbalance between matrix degeneration and synthesis [17–19].

During the initial inflammatory response of tendinopathy, proinflammatory cytokines and mediators such as cyclooxygenase-2 (COX-2), prostaglandin-2 (PGE2), metalloproteinases-1 and -9 (MMP-1 and -9), and interleukin-1β (IL-1β) are released, leading to destruction and modification of the extracellular matrix (ECM) and reduced collagen synthesis [13].

Vitamin D, a prohormone that major sources are the sun exposure and foods (especially dairy products), is the essential precursor of the calcitriol that classically regulates

calcium and phosphate metabolism and that plays a key role for maintaining a balanced bone turnover and a healthy bone microenvironment [20] (Figure 1).

Furthermore, vitamin D is an important regulator of MMP-9, varying inversely with the inflammatory factor [21, 22]. An imbalance between MMPs and their inhibitors (tissue inhibitors of metalloproteinase, TIMPs) has been associated with tendinopathies and large tears of the rotator cuff [23–28]. Furthermore, vitamin D can stimulate p38 pathways and extracellular signal-regulated kinases (ERK) hindering proinflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha (TNF-alpha) [29] (Figure 2).

Altered MMP/TIMP balance has been associated with an increased risk of postoperative complications in arthroscopic rotator cuff repair (RCR) (especially re-tears), which vitamin D may influence [22, 30, 31]. Anyway, this association is still under debate, since some studies did not find any correlation [32, 33].

Animal models have demonstrated that impaired healing of rotator cuff tears (RCTs) in rats fed a vitamin D deficient diet [34].

To date, although the negative effects of serum vitamin D deficiency on muscle and bones health have been thoroughly studied worldwide, only few studies have analyzed whether there is a correlation between low levels of circulating vitamin D and tendon ailments.

The aim of this narrative comprehensive review is to summarize the findings about the effects of vitamin D on tendon health.

Materials and methods

A comprehensive search of scientific databases, including PubMed, Scopus, and Web of Science, was performed by two independent authors (D.T. and R.M.) to collect relevant articles on the topic. All kinds of articles were included, with no limitation of time.

Two independent reviewers (D.T. and R.P.) extracted and evaluated the data. The included articles reported on the effects of vitamin D on tendon health including studies on animal or human tenocytes, tendon ailments (tears and tendinopathies), and the eventual correlation with increased risk of RCTs and poor postoperative outcomes or need for revision in case of RCR. Articles that reported outcomes about the effects of vitamin D not specifically on tendons but on surrounding tissues (such as muscles) were discussed in the Discussion section.

The authors also evaluated the reference lists of the included articles but eventually found no extra articles to be included.

Specific keywords including “vitamin D,” “vitamin D AND tendons,” “vitamin D AND tendon pathology,” “vitamin D AND tendon tear,” and “vitamin D AND tendinopathy” were used during the search.

To facilitate the understanding of the results, we categorized the results into the following sections: studies *in vitro* and *in vivo* about the effects of vitamin D on the rotator cuff (as a risk factor for RCT and its effects on postoperative

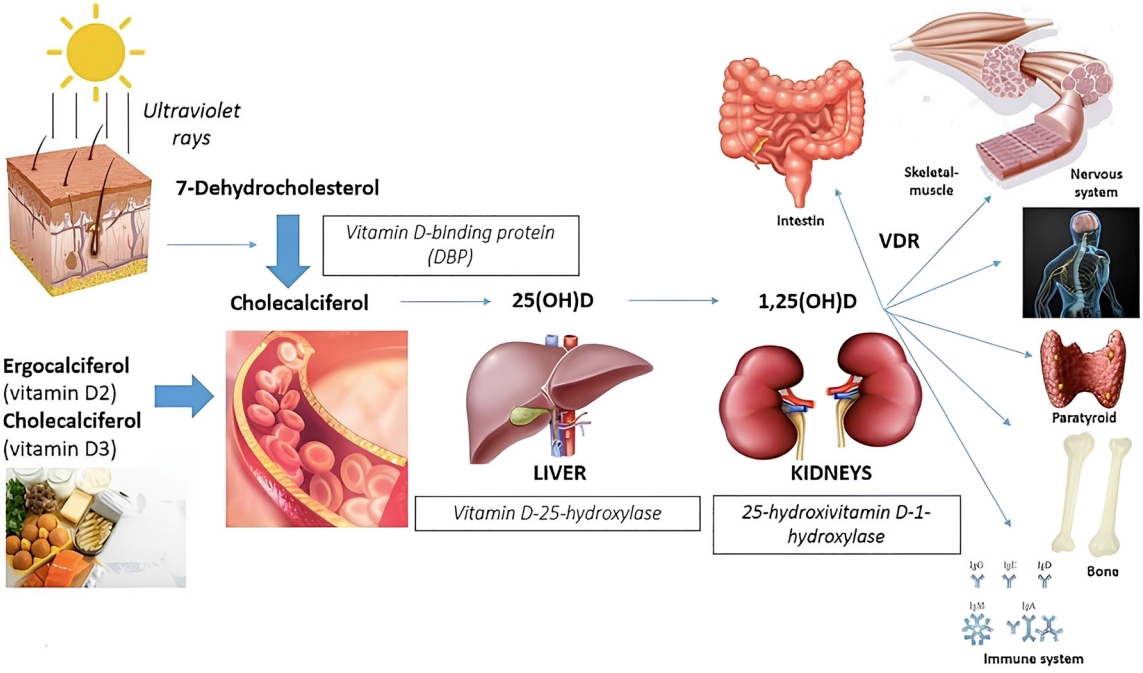

Figure 1: The effects of vitamin D on target organs.

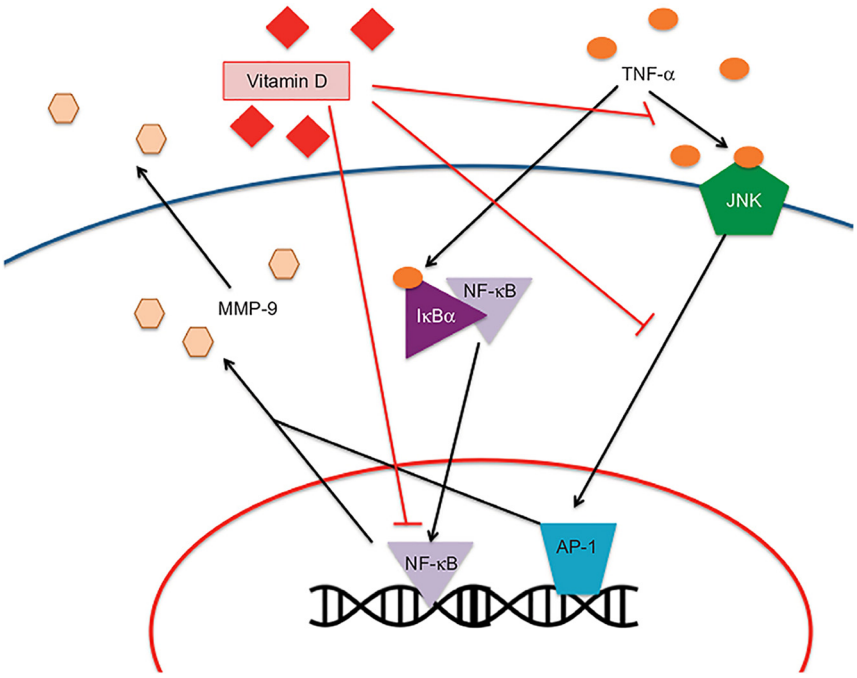

Figure 2: Potential effects of vitamin D on tendon inflammation and healing.

outcomes) and studies *in vitro* and *in vivo* about the effects of vitamin D on tendon healing and tendinopathies.

Results

Fourteen studies met the inclusion criteria and were included in the results below. Five studies were conducted *in vitro*, while nine studies were conducted *in vivo*. A summary of the outcomes of the selected studies is reported in Table 1.

Effects of vitamin D on rotator cuff *in vitro*

In a controlled laboratory study from 2014, Angeline et al. [34] analyzed the effect of vitamin D deficiency on the structure of the healing tendon–bone interface comparing, after 6 weeks of vitamin D deficient diet and ultraviolet light

Table 1: A summary of the outcomes of the selected studies.

Study and authors	Type of study	Cell sample or population	Intervention	Findings
Angeline et al. (2014)	Controlled laboratory study	Vitamin D deficient (exp.) vs. non vitamin D deficient rats	Unilateral detachment of the supraspinatus tendon from the greater tuberosity followed by repair using bone tunnel suture fixation; then, histological analysis on specimens	↓ Load to failure (exp.) ↓ Less bone formation (exp.) ↓ Less collagen fiber organization (exp.)
Maman et al. (2016)	Laboratory study	Tendon-derived cells from rat SSP	Cells treated with estradiol-17β (E2), soy isoflavones, raloxifene and estrogen receptors α and β agonists and antagonists, less-calcemic vitamin D analog, parathyroid hormone	↑ Tendon-derived cells proliferation via estrogen receptor α and VDR ↓ SCX and COL-1 expression
Kim et al. (2023)	Controlled laboratory study	Vitamin D deficient (exp.) vs. non–vitamin D deficient patients with RCT	Histological analysis on SSP muscle, deltoid muscle, and SSP tendon samples	↑ Proinflammatory cytokines (IL-1β and IL-6) in the rotator cuff muscles (exp.)
Lee et al. (2021)	Retrospective study	Patients who underwent arthroscopic RCR for a full-thickness RCT	Preoperative vitamin D assessment	44.3 % hypovitaminosis D ↑ Vitamin D serum levels in the elderly ↓ Vitamin D serum levels in young and indoor workers

Table 1: (continued)

Study and authors	Type of study	Cell sample or population	Intervention	Findings
Liu et al. (2022)	Prospective cross-sectional study	Patients with RCTs only vs. RCTs+OP (exp.) who need arthroscopic RCR	Vitamin D assessment	↓ Vitamin D serum levels (exp.)
Ryu et al. (2015)	Cohort study	Patients who underwent arthroscopic RCR for a full-thickness RCT	Preoperative vitamin D assessment	88 % hypovitaminosis D No relationship with postoperative structural integrity and functional results
Degen et al. (2016)	Prospective study	Vitamin D deficient vs. non–vitamin D deficient who underwent arthroscopic RCR for an RCT	Preoperative vitamin D assessment	43 % hypovitaminosis D No significant differences between groups in terms of re-tear rates and functional outcome scores or muscular strength testing
Harada et al. (2019)	Retrospective study	Vitamin D deficient (exp.) vs. non–vitamin D deficient patients who underwent arthroscopic RCR	Known preoperative vitamin D levels	↑ Risk of postoperative stiffness requiring need for future RCR revision (exp.)
Cancienne et al. (2019)	Retrospective cohort study	Vitamin D deficient (exp.) vs. vitamin D sufficient vs. non–vitamin D deficient patients who underwent arthroscopic RCR	Perioperative serum vitamin D assessment	↑ Rate of revision after RCR (exp.)
Chen et al. (2022)	Cohort study	Vitamin D deficient (exp.) vs. non–vitamin D deficient patients who underwent arthroscopic RCR for a full-thickness RCT	Preoperative vitamin D assessment	↑ Re-tear rate (exp.) ↑ Pain and SSP fatty infiltration at 1 and 3 months after surgery (exp.)
Min et al. (2019)	Laboratory study	Human damaged tenocytes treated with Dex	Tenocytes exposure to vitamin D and 1-α hydroxylase	↑ Cell proliferation ↑ Expression of COL-1 and TNMD
Kim et al. (2022)	Laboratory study	Human damaged tenocytes treated with TNF-α Rats with collagenase-induced tendinopathy	Tenocytes exposure to Vit D@Gel/T80 Vit D@Gel/T80 injection	↓ NF-κB expression ↓ Proinflammatory cytokines (COX-2 and IL-6) ↓ TNC and COL-3 ↑ SCX, TNMD, and COL-1A1 ↓ Proinflammatory cytokines (TNF-α, COX-2, and NF-κB)
Cavalli et al. (2010)	Cohort study	Patients with rotator cuff calcific tendinopathy treated with two-needle US-guided percutaneous treatment	Phospho-calcium metabolism markers (including vitamin D) assessment	93 % hypovitaminosis D ↑ Calcitriol serum levels =/↑ PTH serum levels (upper limits)
Yaka et al. (2022)	Retrospective study	Patients with LE (exp.) vs. patients without LE	Serum vitamin D assessment	↓ Vitamin D serum levels (exp.)

exp, experimental group; VDR, vitamin D receptor; SSP, supraspinatus; RCT, rotator cuff tear; RCR, rotator cuff repair; OP, osteoporosis; Dex, dexamethasone; US, ultrasound; LE, lateral epicondylitis.

restriction, vitamin D deficient rats with control rats who underwent unilateral detachment of the supraspinatus tendon from the greater tuberosity followed by repair using bone tunnel suture fixation. The effects were assessed 2 and 4 weeks after the treatment. The conducted experiment showed no correlation between low vitamin D concentration and total mineral density and fraction of cortical bone volume, whole, or spongy bone 4 weeks after surgery. Biomechanical testing demonstrated a significant decrease in load to failure in the experimental group compared with controls at 2 weeks. Histological analysis showed less bone formation and less collagen fiber organization in the vitamin D deficient specimens at 4 weeks as compared with control. Results demonstrated that low vitamin D levels may negatively impact early healing of RCR sites, so vitamin D may have a key role in the tendon-to-bone healing process by increasing bone mineral density and strengthening skeletal muscles. The authors emphasized that more research is needed to identify the mechanism by which vitamin D influences tendon healing and whether vitamin D supplementation can effectively influence rotator cuff healing and reduce the incidence of relapses.

The influence of vitamin D on tendons was later studied by Maman et al. [35] in 2016 on tendon-derived cells from rat supraspinatus treated with estradiol-17β (E2), soy isoflavones (daidzein, genistein, biochainin A), raloxifene and estrogen receptors α and β agonists and antagonists, less-calcemic vitamin D analog, and parathyroid hormone (PTH). Cell proliferation and mRNA expression of estrogen receptor α and β, vitamin D receptor (VDR), scleraxis (SCX), and collagen (COL)-1 were assessed. The authors found that vitamin D promoted tendon-derived cells proliferation via estrogen receptor α and VDR, not estrogen receptor β. Amplified cell proliferation was not associated with increased SCX and COL-1 expression that was found to be decreased by vitamin D.

A recent (2023) controlled laboratory study by Kim et al. [36] aimed to assess the relationship between vitamin D deficiency and various gene expression patterns in patients with rotator cuff tears. The authors collected, during arthroscopic surgery, samples from the supraspinatus muscle, deltoid muscle, and supraspinatus tendon from patients with vitamin D deficiency and patients with sufficient vitamin D levels. Their results showed that in patients with rotator cuff tears, vitamin D deficiency was observed to be associated with increased levels of proinflammatory cytokines (IL-1β and IL-6) in the rotator cuff muscles, without significant changes in gene expression related to myogenesis or muscle atrophy. Anyway, the supraspinatus tendon tissue did not show any significant differences in any gene expression evaluated.

Effects of vitamin D on rotator cuff *in vivo*

Two studies evaluated the role of vitamin D as a risk factor for rotator cuff tears.

A retrospective study by Lee et al. [37] in 2021 investigated the prevalence of hypovitaminosis D in patients with rotator cuff tears. One hundred seventy-six patients who underwent arthroscopic RCR for a full-thickness tear were enrolled in the study, and preoperative serum vitamin D levels were measured. The results showed that the prevalence of hypovitaminosis D in all patients with rotator cuff tears was 44.3 %. Among 176 patients, the 29.0 % were vitamin D sufficient (>30 ng/mL), the 26.7 % were vitamin D insufficient (20–30 ng/mL), and the 44.3 % were vitamin D deficient (<20 ng/mL). Interestingly, a higher serum level of vitamin D was significantly associated with older age, while young age and indoor working were independent risk factors for hypovitaminosis D in patients with rotator cuff tears. Therefore, the authors concluded that the possibility of hypovitaminosis D should be considered for young and indoor working patients who have rotator cuff tears.

A more recent (2022) single-center, prospective cross-sectional study by Liu et al. [38] investigated the role of vitamin D on rotator cuff tears with osteoporosis. The authors recruited 104 cases of patients who underwent rotator cuff injury and need arthroscopic RCR along with the diagnosis of osteoporosis. Their results revealed that low serum vitamin D level was an independent risk factor for patients with rotator cuff tears and osteoporosis, thus establishing that vitamin D level may be valuable prognostic biomarkers that reflect the combined effect of vitamin D on the progression of RCTs and osteoporosis.

Five studies evaluated the effects of vitamin D on postoperative outcomes after rotator cuff repair (RCR).

A cohort study from 2015 by Ryu et al. [32] evaluated the prevalence of vitamin D deficiency among patients who underwent arthroscopic repair for a full-thickness RCT, the relationship of vitamin D level with severity of RCT, and surgical outcomes after repair. They recruited 91 patients which preoperative serum vitamin D levels were analyzed to detect correlations with the features of a preoperative RCT as well as postoperative structural and functional outcomes. The authors found that preoperative vitamin D levels resulted deficient in the 88 % of subjects, insufficient in the 9 %, and normal in only 3 % of the subjects. However, no correlation was detected between preoperative tear size, degree of fatty infiltration of each muscle, global fatty infiltration index, and extent of retraction and, moreover, no remarkable relationship with postoperative structural integrity and functional results was reported. Thus, the authors stated that low vitamin D serum levels do not represent a risk factor for the severity of rotator cuff pre-/postarthroscopic repair.

One year later (2016), Degen et al. [33] conducted a prospective study to determine the effect of vitamin D deficiency in the healing of surgically repaired rotator cuff tears. Sixty-one patients undergoing arthroscopic RCR were enrolled, and the serum vitamin D levels were collected at baseline. The 43 % of the enrolled patients were identified as vitamin D deficient based on preoperative serum values below 30 ng/mL, while the remnant 57 % of patients had values within the normal range. Anyway, no statistically significant differences between the vitamin D deficient and normal groups were found in terms of re-tear rates and functional outcome scores or muscular strength testing following arthroscopic rotator cuff repair. As for Ryu et al., the authors concluded that vitamin D does not affect RCR postoperative outcomes.

Harada et al. [30] in 2019 conducted a retrospective study on patients who underwent arthroscopic RCR, testing the correlation between preoperative vitamin D levels and postoperative complication. One thousand eight hundred eighty-one subjects with known preoperative vitamin D levels were identified and stratified into vitamin D sufficient or deficient groups; then, these patients were supervised for

the eventual onset of postoperative complications. The 12.2 % of the enrolled patients was found to be vitamin D deficient in the 90 days preceding surgery. The authors determined that vitamin D deficiency was associated with a greater risk of postoperative stiffness requiring need for future RCR revision.

Another retrospective cohort study conducted in 2019 by Cancienne et al. [39] examined any association between perioperative serum vitamin D levels and failure of arthroscopic RCR requiring revision surgery. The authors included 982 patients who underwent arthroscopic RCR with perioperative serum vitamin D levels recorded. Patients were stratified into vitamin D deficiency (12 %), insufficiency (33 %), or sufficient (55 %). The rate of revision after RCR was significantly higher in patients whose serum vitamin D was deficient (5.88 %) compared with those whose serum vitamin D was sufficient (3.7 %). Patients with serum vitamin D deficiency (5.88 %) also had a significantly higher incidence of revision surgery compared with patients with serum vitamin D insufficiency. There was no significant difference in the incidence of revision surgery in the serum vitamin D insufficient group (4.97 %) compared with the serum vitamin D sufficient control group (3.7 %). The authors concluded that although a significant statistical association between serum vitamin D deficiency and insufficiency and the rate of revision rotator cuff surgery after primary arthroscopic RCR was found, the absolute differences of these revision rates were minimal and were accompanied with overlapping confidence intervals limiting the clinical significance of their findings.

Lastly, a recent (2022) cohort study by Chen et al. [40] investigated the correlation between preoperative vitamin D deficiency and the re-tear rate and pain after arthroscopic RCR. Eighty-nine patients with full-thickness rotator cuff tears who underwent arthroscopic RCR were enrolled and divided into a control group with serum vitamin D level≥20 μg/L and a deficiency group (vitamin D level<20 μg/L). The authors found that the re-tear rate was significantly lower in the control group than in the deficiency group (9.09 vs. 26.67 %, respectively). Furthermore, pain and supraspinatus fatty infiltration at 1 and 3 months after surgery were higher in the vitamin D deficient group, while vitamin D levels were not found related to age, symptom duration, tear size, extent of retraction, VAS pain score preoperatively and at 6 and 24 months postoperatively, or any function scores.

Effects of vitamin D on tendon healing *in vitro*

In 2019, Min et al. [41] investigated the effects of vitamin D on tenocytes in their experimental histological study on human damaged tenocytes. Human tenocytes were treated with dexamethasone (Dex) leading to cell damage. Expression of the tenocyte-related markers such asmohawk (MKX), SCX, tenomodulin (TNMD), tenascin C (TNC), and COL-1 and -3 was evaluated. Then, the tenocytes were exposed to vitamin D and 1-α hydroxylase to investigate vitamin D receptors. With 10 μM Dex, the growth of tenocytes was noticeably reduced, and the gene expression of the markers was also diminished. When tenocytes, instead, were cotreated with vitamin D, cell proliferation resumed in a dose-dependent mode and the expression of COL-1 and TNMD enhanced. The modulation of ERK and p38 pathways combined with the antioxidant effect due to the decrease of reactive oxygen species could explain the protective effect of the vitamin D on tenocytes. Moreover, the authors stated that tenocytes had 1-α hydroxylase and vitamin D receptors, and they interact with it given the conspicuous presence of VDR and 1-α hydroxylase in tenocytes, suggesting a positive effect of vitamin D on tendons in addition to bones and muscles.

In 2022, Kim et al. [42], who also participated in the study by Min et al., formulated a vitamin D delivery system with a cross-linked hyaluronic acid (HA) (which is one of the major components of the ECM that has anti-inflammatory and wound-healing properties) hydrogel (Gel) and surfactant Tween 80 (T80), realizing a possible new regeneration drug for the treatment of tendinopathy. In their study, the combined product Vit D@Gel/T80 reduced TNF-α induced damage to human tenocytes *in vitro* through the down-regulation of NF-κB expression, inhibition of ERK and p38 pathway phosphorylation, and reduction of proinflammatory cytokines such as COX-2 and IL-6. Furthermore, Vit D@Gel/T80 reduced TNC and COL-3 expression, then showing tenocyte regeneration properties. In the same study, the Vit D@Gel/T80 preparation was administered in rats with collagenase-induced tendinopathy. At 4 weeks following injection, the treated tendons restored their original clear glossy appearance, which was like that of native tendons. Furthermore, inflammation-related genes (TNF-α, COX-2, and NF-κB) and apoptosis-related gene expressions (BAK and BID) were reduced, while mRNA expressions of tendon-related genes (SCX, TNMD, and COL-1A1) significantly increased.

Effects of vitamin D on tendinopathies *in vivo*

One study conducted by Cavalli et al. in 2010 [27] evaluated the phospho-calcium metabolism markers (including vitamin D) of a group of 30 subjects with rotator cuff calcific tendinopathy treated with two-needle ultrasound (US)-guided percutaneous treatment. Twenty-eight patients showed a low level of vitamin D, calcitriol (that is the active form of vitamin D, normally produced in the kidney) at or

above the upper limits, and PTH concentration in line with the vitamin D levels, most frequently at the upper normal limits (PTH increases in case of low vitamin D levels). The authors stated that a transient hyperparathyroidism secondary to vitamin D deficiency may be at the origin of heterotopic calcifications in patients with rotator cuff tendinopathy, so the administration of vitamin D, by reducing transient increases of PTH and directly acting on connective tissue cells, could probably reduce this pathology or even prevent it.

Yaka et al. [28] in 2022 published a single-center, retrospective study exploring the possible correlation between low vitamin D serum levels and lateral epicondylitis (LE). They enrolled patients with LE as the study group and patients without LE as the control group. The vitamin D levels were assessed in both groups, and the authors found that vitamin D levels of the LE group were significantly lower than the control group ($p<0.001$). Moreover, 77.5 % of the subjects with LE had vitamin D deficiency, 10 % vitamin D insufficiency, and 12.5 % normal vitamin D levels. In the control group, only 43.9 % reported vitamin D deficiency, while 25.8 % had normal vitamin D levels. These findings supported that low vitamin D could be considered as risk factor for the onset of LE.

Discussion

The results of the *in vitro* studies included in this review highlighted the positive effect of vitamin D in reducing inflammation and tenocyte apoptosis and promoting tissue regeneration mechanisms, tendon-derived cells proliferation, collagen neo-apposition in tendon fibers, thus improving tendon-to-bone healing. The included *in vivo* studies mainly concerned the effects of vitamin D on rotator cuff and only two addressed tendinopathies. Most of the *in vivo* studies on rotator cuff showed the importance of serum vitamin D levels as a protective factor that reduces the likelihood of developing rotator cuff tears or any postoperative complications after arthroscopic RCR, while regarding tendinopathies, vitamin D deficiency was found to increase the likelihood of developing calcific rotator cuff tendinopathy and lateral epicondylitis.

Vitamin D deficiency is extremely common worldwide, with over one billion people being estimated to be deficient [26, 43]. Prevalence of vitamin D deficiency is 36–47 % in general population in the United States and European adults [44] and 58–76 % in patients with hip fracture [45–49]. Vitamin D deficiency is usually regarded as serum levels≤20 ng/mL (50 nmol/L) [50, 51]. Advanced age, degree of sun exposure, nonwhite race, low education level, poor diet, high and low body mass index (BMI) have all been reported to affect the prevalence of hypovitaminosis D [37, 43, 44, 51–55]. Vitamin D deficiency has also been linked to low physical performance and elderly falls [56–60].

The outcomes of the studies included in this review highlighted the importance of vitamin D on some key aspects of tendon healing. All the *in vivo* studies unanimously showed that vitamin D can reduce proinflammatory cytokines as well as promoting tendon-derived cell proliferation.

However, while the study by Min et al. [41] reported that vitamin D is able to increase the expression of COL-1, Maman et al. [35] found that COL-1 expression is significantly reduced by vitamin D, while both studies found that SCX levels were not changed by vitamin D. The difference in COL-1 expression may be due to the origin of tenocytes, since in the study by Maman et al., they were collected from rats, while in the study from Min et al. from humans. Furthermore, the tenocytes treated with vitamin D in the study by Min et al. were firstly damaged with the use of Dex, while in the study by Maman et al., a simple exposure of tenocytes to vitamin D was performed. Histological analysis of human and rat tendons showed how Dex decreases COL-1 expression: for this reason, a possible initial damage to tendons due to Dex could affect the ability of vitamin D to restore COL-1 expression [61, 62].

Regarding the *in vivo* studies on rotator cuff, the included studies that evaluated vitamin D deficiency as a risk factor for RCTs agreed that patients with low serum vitamin D levels has an increased likelihood of developing RCTs. In the study by Lee et al. [37], more than half patients with RCTs had vitamin D deficiency or insufficiency. In the study by Liu et al. [38] osteoporosis, a common disease defined primarily by a low bone mass, which seems to be positively correlated with low calcium intake and vitamin D deficiency [63], was found to increase the risk of RCTs, as already reported in previous studies [64, 65]. Furthermore, Entezari and Lazarus [51] reported that osteoporosis leads to a deficient bone mineralization with a significant negative impact on the bone mineral density of the greater tuberosity of the shoulder and, consequently, on the postoperative outcomes following arthroscopic RCR.

The *in vivo* studies that examined the role of vitamin D in postoperative healing and its deficiency as a potential risk factor for postoperative complications showed conflicting results.

Ryu et al. [32] and Degen et al. [33] found no association between vitamin D and RCR postoperative outcomes, while Harada et al. [30], Cancienne et al. [39], and Chen et al. [40] found a correlation between vitamin D deficiency and postoperative complications such as re-tear rate and need for revision. As stated by Cancienne et al., these discrepancies may be due to small sample size in some studies if compared to others (such as in the study by Ryu in which 91 patients were evaluated versus the 982 of the study of Cancienne) that may

result in inadequate statistical power, or due the research conditions. For example, unlike the study by Ryu et al. [32], the study by Chen et al. [40] excluded massive tears and only assessed the degree of supraspinatus fatty infiltration, which may have reduced statistical errors. A higher degree of fatty degeneration of the muscles of the rotator cuff was also reported in the study by Oh et al. [31] in patients with RCTs and low serum vitamin D levels. In the same study, a positive correlation between vitamin D and isokinetic muscle torque was also found. This correlation indicating that the serum level of vitamin D is related to general muscle function was also supported in other studies reporting that sufficient vitamin D supplementation can increase upper and lower body muscle strength [66], especially that vitamin D insufficiency was associated with rotator cuff muscle strength in professional volleyball athletes [67]. However, Degen et al. [33] found no correlation between serum vitamin D levels and muscle strength following arthroscopic RCR.

Although the role of vitamin D in the development of postoperative complications is unclear at this time, the included studies suggest the possibility that preoperative repletion could have a role in mitigating adverse outcomes. Considering the known high prevalence of vitamin D deficiency in the orthopedic sports medicine population and the frequency at which RCRs are performed, it is of high clinical significance to explore hypovitaminosis D as a risk factor for RCR failure [39, 68, 69]. However, the studies conducted *in vivo* that evaluated the role of vitamin D on rotator cuff are mainly level III studies, so we cannot state with certainty that low serum vitamin D levels can lead to an increased risk of postoperative poor outcomes.

Strengths and limitations

This review has some limitations. First, the narrative nature of this review may not have the same impact and scientific rigor as a systematic one. However, given the low quality of the included studies (mainly level III studies among the *in vivo* ones), the narrative approach was regarded as the most suitable one. Given the low level of evidence and the related risk of bias of the included studies, the reported outcomes should be interpreted with caution.

Another important limitation is represented by the small number of relevant studies found in the scientific literature, especially regarding tendinopathies of the lower limbs.

However, to the best of our knowledge, this is the first review to explore in a comprehensive way the effects of vitamin D on tendon health, reporting insights on the importance of vitamin D not only for muscles and bones but also for tendons.

Clinical implications

Given the beneficial effects of vitamin D on tendons reported by the studies included studies despite their low level of evidence, since vitamin D is easy to administer and prescribe, as well as being inexpensive, its serum level should be periodically checked, and its intake dosed according to the serum levels.

Conclusions

The studies included in this review highlighted the role of vitamin D on tendons, showing anti-inflammatory, anti-apoptotic, and antiproliferative properties. The conflicting results examining the relationship between vitamin D and rotator cuff healing in basic science level studies to human translation studies highlight the lack of understanding the mechanism of how vitamin D acts on the rotator cuff and the need for further research. For this reason, more high-quality research should be performed for further understanding of the beneficial effects of vitamin D on tendon health, since there is still too little knowledge about its effectiveness, especially on tendinopathies.

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