

Vitamin D and Osteoarthritis: An Updated Clinical Summary and Review

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ABSTRACT

BACKGROUND: Osteoarthritis remains the most widespread disabling musculoskeletal condition affecting the wellbeing of many older adults.

AIM: This work aimed to update and document findings published in the English language concerning what is known about vitamin D and osteoarthritis disease manifestations and progression, an area of research that has produced confusing results.

QUESTIONS: Specifically examined were: (1) Whether the presence of inadequate serum vitamin D levels predisposes an older adult to more profound osteoarthritis disability than adequate levels; and (2) Whether applying vitamin D as a supplement to older adults

with osteoarthritis and coexisting vitamin D deficiencies is likely to ameliorate osteoarthritis disability in some way.

METHODS: To achieve the current aims, all relevant English language research reports published in the last 40 years, with an emphasis on data from January 1, 2018 up until January 16 2021, and located in the major data bases of PUBMED, Scopus, and Web of Science, were sought. A narrative depiction and synthesis of the key points that emerged from this diverse body of literature was then undertaken.

RESULTS: Findings showed that regardless of study type, a vitamin D deficit that may prevail in a fair proportion of older osteoarthritis cases may produce less than favorable results if the deficiency is not compensated for. However, very few studies are sufficiently well-designed and a number show no uniform consensus in this regard.

CONCLUSION: More well-designed research may help to more firmly establish the possible protective, reparative or aversive role of vitamin D in mediating osteoarthritis and whether supplementation is desirable in vitamin D deficient cases.

Key words: Aging Adults; Disability; Osteoarthritis; Outcomes; Supplementation; Vitamin D

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INTRODUCTION

Despite years of study, the joint disease known as osteoarthritis, a health condition affecting a high proportion of older adults continues to produce large scale personal and social costs, including immense pain, job losses or limitations, and a wide array of functional and psychosocial challenges. Strongly associated with destructive processes of one or more freely moving joints such as the knee and hip joints, the condition is often accompanied by various degrees of joint inflammation, muscle weakness, joint instability, and joint stiffness. In addition, obesity, cardiovascular and metabolic health

comorbid health conditions, poor mental health including depression and anxiety, as well as low life quality and frailty alone or in tandem may prevail in older adult populations with osteoarthritis of one or more joints^[1-3]. As well as being more prone to multi morbidities than healthy older adults, more recent evidence shows older adults with osteoarthritis are found to be at risk not only for functional disability but for acute respiratory disease manifestations in the face of the current COVID-19 pandemic and lockdown situations, including service shutdowns^[4].

In a search for strategies to retard, prevent, or ameliorate one or more features of osteoarthritis disability, which has become more pressing than ever in efforts to minimize COVID-19 susceptibility and adverse outcomes, as well as the extent of the osteoarthritis disease itself, the role of vitamin D, a vital steroid hormone and mediator of bone and cartilage metabolism, as well as the immune system that is not manufactured by the body, has recently been discussed as a possible highly influential factor in this regard^[4-6], but with no definitive conclusion being reached^[7,8].

Since there is no prevailing remedy for successfully reversing osteoarthritis disability, and many cases requiring treatment may now have to be placed on hold during pandemic lockdowns, and lockdowns may limit vitamin D sunlight exposure sources in their own right, efforts to explore options other than traditional pharmacologic and surgical approaches to mitigating this condition, such as vitamin D supplementation appear warranted and supported at this time^[9-17]. However, since contradictory evidence prevails, this present report strove to further examine what we know as of the onset of 2021 about vitamin D and osteoarthritis as a disease mediator.

Unfortunately, while several groups have tried previously to synthesize the knowledge gained on this topic, the topic remains unresolved, despite its possible promise for advancing our adjunctive intervention approaches. To avoid overlooking salient clinically relevant facts or evidence that may have emerged recently, an update on what we know at the start of 2021 was hence deemed to be of value.

METHODS

To obtain the desired evidence base, the key search terms currently applied were *Vitamin D* and *Osteoarthritis*. The currently accepted sources of information included clinical studies with cross-sectional designs, controlled studies, or those based on prospective research designs. The key database consulted was **PUBMED**.

While the search included data from 1980 onwards, the current search focused primarily on the retrieval and examination of data extending from January 1, 2018, to mid January, 2021 as a prior study surveying the years before then had been conducted recently. Articles selected were largely clinical or preclinical reports, rather than those that were surgically oriented. Due the diverse themes that emerged from the search, the data addressing the review questions were examined in a narrative descriptive format, rather than any systematic format. Readers are referred elsewhere for recent systematic reviews on this topic, however^[8,13,18,19].

Excluded were all data that failed to address the current review questions in some way, studies where vitamin was co-administered with other compounds, vitamin D and cognitive functions, hypertension, and obesity, plus arthroplasty-related studies. All forms of osteoarthritis were examined collectively given the limited data on forms other than the hip and knee joints. Only English based articles were deemed acceptable. To avoid any confusion in discussing and comparing studies given the prevailing array of diverse vitamin D

terminologies in this body of data, this review elected to employ the generic term 'vitamin D' to represent any related set of facts.

RESULTS

Among the 469 publications listed on **PUBMED** as of January 30, 2021 that refer to vitamin D and osteoarthritis, more than 70% did not address any of the current questions in a meaningful way or were excluded because they were proposals, or conference summaries. Among the 115 studies selected, a number of prevailing cellular and in vitro laboratory studies on animals largely show results suggesting highly meaningful reproducible associations between vitamin D and a variety of osteoarthritic-like joint tissue manifestations, even if these are not all in concordance^[19-25]. However, many of the same themes are not commonly examined or readily testable in the clinic, and those reasonably well-designed clinical studies that prevail are few in number, and largely observational studies that do not always concur with either lab findings or findings of other clinical researchers. Indeed, even though available lab studies show fairly unanimous observations that extend to the benefits of vitamin D repletion on a variety of structural and functional joint measures^[26-34], these observations are not readily replicated in the clinical realm. Thus while empirically-oriented explanations for the observed favorable clinical studies do exist-which is often not the case- observations conducted in the clinical setting are not currently comparable to those conducted in the various lab settings and osteoarthritis models, nor universal in agreement about their observations.

For example, while some who have focused on vitamin D deficits imply these may be linked to osteoarthritis in some way^[15-17], supplementary vitamin D may have no meaningful clinical benefits^[35,36], and may increase osteoarthritis pathology if serum levels are considered 'excessive' according to some^[37]. On the other hand, it seems that a high percentage of hip or knee osteoarthritis cases are likely to exhibit low- rather than adequate- vitamin D serum levels^[38-41]. They may also incur a greater risk for osteoarthritis progression^[42], osteoarthritis disability, and pain as observed by some^[38,43] but not others^[44,45].

This is potentially confusing because consistent with a wide array of laboratory based observations^[19-34], Wang et al^[46] observed that the administration of a high monthly dose of supplementary vitamin D appeared to successfully allay joint swelling in cases with knee osteoarthritis, as well as predicting the extent of any cartilage loss^[43]. Men with hip osteoarthritis are also shown more likely than not to exhibit vitamin D deficiencies^[47], a situation that may arguably increase rather than decrease or fail to have an effect on the rate of disease progression and joint space narrowing^[48-50]. On the other hand, Ding et al^[51] who assessed a broad range of vitamin D levels, rather than any predefined cut-off points, were able to conclude that achieving vitamin D sufficiency may prevent and/or retard cartilage loss in cases of knee osteoarthritis, a conclusion that concurred with that of Chaghanti et al^[47]. Yoshimura et al^[52] on the other hand, observed no clinically relevant linkage between vitamin D levels and those knee osteoarthritis variables they assessed.

Emerging evidence also show that^[60] cases undergoing joint revision surgery for end stage osteoarthritis and who are found to have low vitamin D levels are more likely to experience 90-day complications as well as periprosthetic joint infections after surgery than those with adequate levels, a situation that may affect up to 84% of surgical candidates^[26]. They may suffer several independent overlapping osteoarthritis related problems as well^[68-78], especially the risk of excess suffering and joint dysfunction^[11,79]. Consequently,

efforts to ensure vitamin D levels are adequate, but not excessive, while at the same time, examining the premises behind the delivery of recommended doses that may be too low^[80], may help to mitigate osteoarthritis progression both within a joint as well as the ‘spread’ of osteoarthritis from one joint to the next^[29]. It may also lessen excess pain sensitization to the extent that opioids could be discontinued or surgery delayed, even in cases where only a single joint is affected, despite negative findings of Cakar et al^[81] who found subjective pain measures of 149 knee osteoarthritis cases, were not affected by degrees of vitamin D presence, although most cases studied were deficient in this vitamin. In addition to muscle related benefits^[5,20,82], vitamin D may help prevent pain^[83] and inflammation^[84], muscle function and sensitivity, plus life quality^[85-91]. Moreover, conceivably, even if vitamin D does not alter structural features of osteoarthritis, if its presence maintains the status quo, or helps to maximize strength capacity^[86], this alone could be considered beneficial in the context of this progressive degenerative disease.

Other benefits that should not be overlooked include a lower falls prevalence rate that may help avert the onset or increase of prevailing osteoarthritic joint damage, plus lower than desired levels of outdoor activity and sunlight exposure^[87]. In addition, recent work further shows that cases with severe knee osteoarthritis and co existing diabetes can yet experience better glycemic control over time in response to either 800IU or 2000IU of vitamin D3 applied over a period of two years^[92]. These beneficial findings and others may be important to examine further, because it is also possible that osteoarthritis exacerbates the availability of adequate vitamin D serum levels in its own right, for example due to its impact on weight gain and subsequent development of obesity where fat cells are found to ‘attract’ vitamin D and reduce its availability^[29]. Obesity, plus associated low levels of vitamin D, may in turn, promote, rather than inhibit inflammation, pain, and muscle weakness, thus producing more unwarranted and extensive progression of any prevailing cartilage and bone damage^[93]. For similar reasons, it may be shown that adults with osteoarthritis who live in climates that are quite sunny, may still be vitamin D deficient in the event their pain and disability renders them depressed, sedentary, and home bound. Low levels of vitamin D are also linked to COVID-19 risk, as well as cardiovascular related syndromes, that can further preclude outdoor activities for protracted periods, while heightening muscle weakness and mobility challenges, thus reducing the general circulation of prevailing vitamin D within the body. Those cases advised to use sunscreen, masks, braces, splints, or gloves, plus those using wheelchair devices, or protective clothing might also be subject to lower than desirable vitamin D sunlight exposure^[16], and its potential for fostering adverse muscle and bone health consequences^[94].

In sum, while several researchers imply there is no added value to recommending vitamin D supplementation in the context of osteoarthritis pathology, even if vitamin D levels are deficient^[112], and that such an approach may even do more harm than good, this conclusion is not universal. On average, however, even if this is only due to publication bias, the numbers of important clinically relevant findings that do exist appear to outweigh the negative or null results that prevail. In addition, unlike many areas of osteoarthritis intervention research, a fairly strong rationale and body of preclinical as well as clinical evidence prevails to support hypothesizing a contributory, moderating or mediating association between vitamin D and osteoarthritis joint damage, and its possible severity amelioration, at least in some cases, if not all. Indeed, even though very few joints have been studied as a whole, this linkage between vitamin D and some aspect of the osteoarthritis pain cycle, the

symptom of most concern to patients, is especially hard to refute in light of the prevailing data and the nature of methods used to discern pain attributes. Another understudied correlate is muscle strength and performance.

Specific confounding factors at present are: (1) Discrepant and/or arbitrary follow-up periods in prospective studies; (2) Failure to control for presence, number, and type of chronic conditions; (3) Unknown medication usage rates, and types of medication usage; (4) Supplement usage; (5) Degree of outdoor activity; (6) Numbers and types of affected joints; (7) Extent of and type of any co-interventions; (8) Disparate and/or insensitive outcome assessment measures; (9) Limited attempts to measure biomechanical disease correlates objectively.

In particular, very few studies have carefully examined the presence of any associated joint inflammation or effusion, the prevailing sleep quality of the individual, the extent of any centralized pain, depression, muscle dysfunction or balance problems, obesity, frailty and falls history, or whether any of these overlapping aspects of osteoarthritis pathology were improved, or regressed consequent to vitamin D supplementation as can be argued might well be highly influential.

Consequently, even if vitamin D has no direct role in producing osteoarthritis, and does not appear to correlate with radiographic structural features of an osteoarthritic joint readily^[95], suboptimal serum levels of vitamin D may still be instrumental in increasing the magnitude of the disability, including the intensity of knee and hip pain^[27], health correlates that are detrimental to joint status, such as cardiovascular disease, and the negative effects of mechanically loading the diseased joint^[96]. Conversely, even if vitamin D measures take time to implement and process, and are not favored by all^[35,97], more specific attention by practitioners to routinely assess their patient’s prevailing serum vitamin D status is expected to be more helpful than not in efforts to attenuate a measurable degree of their musculoskeletal disability^[98,99] and possibly even to their symptomatic as well as structural pathologies^[100]. In particular, older persons with comorbid conditions that involve the kidneys, liver, skin, and gastrointestinal pathways who may be at higher risk than younger persons with no similar comorbid conditions, and unresponsive to recommended levels of oral vitamin D or sunlight exposure might be preferentially targeted. In addition, inquiring whether they are likely to be exposed to sunlight or not, whether they are able to obtain vitamin D food related levels of the vitamin, and efforts to stress the importance of consistent daily exposure or optimal vitamin D supplementation will also be more helpful than not in all likelihood, as may the delivery of optimal methods of vitamin D supplementation, and periodic serum vitamin D level assessments.

DISCUSSION

This work, which attempts to update prior work, has observed the findings of prior work to remain the same, with few exceptions. That is, very little progress has been made of late, and thus the merits of most of the research conducted for 40 years has still not resulted in better clinical practices or osteoarthritis outcomes for this progressive disease. While the hypothesis that on balance, that more good than harm can come from supplementing deficient vitamin D cases^[85], this is not main stream or accepted practice. Contributing here are possible vitamin D fluctuations due to poor patient adherence, as well as differences in joint and mobility, alterations in health and mental health status^[90], the fact that obese cases may need higher doses of supplementation^[101], coupled with the persistent use of subjective

measurement approaches, very limited array of measures employed, and arbitrary vitamin D cutoff points^[11]. As such, and reiterated by Garfinkel et al^[96] and Heiden and Babaie^[102] the role of vitamin D supplementation in the treatment or prevention of osteoarthritis must remain uncertain. This is unfortunate because it is apparent that vitamin D supplements could yet offer a safe adjunctive treatment approach for older osteoarthritis cases with vitamin D deficiencies or severe joint disease that cannot be treated traditionally. Indeed, in accord with Sowers^[57], the aforementioned studies as well as those shown in Table 1, while not all in concordance, do appear to implicate several possible pathways of interacting influence on osteoarthritis pathology that warrant exploration, including: (1) Cartilage structure and function^[96]; (2) Muscle and bone properties^[15,82,88-90,105,106-108,111]; (3) Cardiovascular disease and obesity^[16,80,101]; (4) Depressive symptoms^[103]; (5) Inflammatory processes^[29,56,93,116] and Immune function^[14,68]; (6) Improved physical performance^[56,93] and gait^[115]; (7) Injury and frailty prevention^[115]; (8) Pain and life quality^[56,64,77,81,104].

In this regard, given that osteoarthritis affects the whole joint, as well as other possible body systems and function, deficient or insufficient vitamin D levels can be hypothesized to have multiple widespread negative joint and general health implications that must surely command attention as outlined in Figure 1.

Other data show osteoarthritis benefits in terms of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis, and physical function^[54] and that vitamin D supplementation may help to some degree in osteoarthritis cases with deficient vitamin D levels^[109], as well post surgery^[110]. However, based on multiple methodological differences, possible design and interpretation flaws that exist in the somewhat limited data sets, and the fact that not all authors agree^[97,112,113], more carefully designed research efforts in this sphere appear warranted.

In particular, careful efforts to clearly define and measure vitamin D adequacy levels for different demographic and age categories and to monitor vitamin D intake or vicarious exposure over time, especially if surgery is indicated^[114], along with efforts to study adequate representative samples with varying degrees of pathology appears warranted. As well as the use of validated markers of cartilage pathology, biomechanical measures, and those that can examine muscle strength and structure, balance capacity, and whether correcting 'deficient' vitamin D levels yields changes in one or more of these osteoarthritis correlates are indicated. What the optimum level of vitamin D should be at different disease stages-what modes of delivery are most likely to yield adequate vitamin D levels, and how often these should be applied clearly also warrants attention, as does some concerted universal consensus across or within countries, and Health Agencies, along with agreement on what constitutes the best method of measuring vitamin D intake and presence and the desired duration for retesting this^[28]. In addition, comorbid conditions that might affect vitamin D absorption, and changes to or reduced function of the vitamin D receptors that regulate vitamin D uptake and signaling should be acknowledged in any future exploration as noted by Brennan-Speranza et al.^[101].

Deleterious outcomes and their causes should also be sought, and counter-hypotheses generated and tested, especially in studies where very high supplementary vitamin D doses are administered on a single occasion. Determining how long it would take to impact any aspect of osteoarthritis pathology, and applying different supplementary doses, over varying time periods, followed by salient outcome tests might be especially helpful as well.

In the interim, notwithstanding the highly commendable recent attempts to examine vitamin D as a correlate of osteoarthritis, as

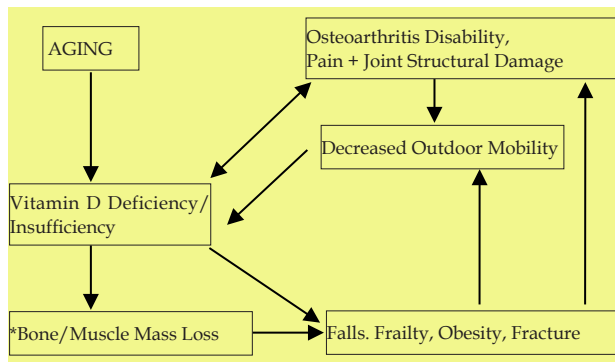


Figure 1 Hypothetical link between the impact of vitamin D deficiency/insufficiency and osteoarthritis showing many pathways involved in vitamin D mediated functions that can directly or indirectly impact articular cartilage and the overall disease process. Accordingly, interventions focusing on vitamin D sufficiency may be necessary for optimal prevention and treatment of osteoarthritis.

articulated by Mabey and Honsawek^[102] and Cao et al.^[103] conducting further research in this realm that can better establish if vitamin D status is a correlate or mediating factor of osteoarthritis outcomes appears to be not only strongly justified, but highly necessary. Moreover, since only the knee joint has been studied to any degree, the question of how vitamin D interacts with other forms of osteoarthritis, requires study to eliminate misconceptions that could be costly if benefits are overlooked, or harm is caused inadvertently. Crafting more comparable carefully controlled and adequately powered research studies across different laboratories and settings, especially the community setting, and focusing on muscle responses to vitamin D may help immensely to uncover important clinically relevant intervention and prevention implications. To this end, more basic research that examines the impact of vitamin D on osteoarthritis joint structures other than articular cartilage, along with trials that examine varying degrees of structural integrity and how the degree of pathology influences the findings, may help clarify the importance of vitamin D across the various stages of the highly debilitating osteoarthritis pain and disability cycle, or explain the reasons for failure as well as successes in supplementation studies.

In the interim gaps in the literature include: (1) Efforts to examine reasons for conflicting study results depicted in Table 1 and others.; (2) Lack of efforts to examine age, gender, pain, frailty, chronic inflammation, extent and degree of activity, musculoskeletal and health status, body mass impact osteoarthritis vitamin D -associations.

At the same time, special attention to the extent of any prevailing biomechanical derangement, the role of vitamin D receptors (VDR), injurious work-related or daily activities and others, and bone health status issues, along with degree of exposure to sunlight and foods containing vitamin, are indicated. Moreover, careful efforts to monitor adherence to any self-administered vitamin D supplements, and overall health recommendations is equally essential.

CONCLUSION

Even if discounted by some, a role for vitamin D in the osteoarthritis pain cycle cannot be ruled out at present with any degree of confidence. As well, promising results from prospective studies as well as a host of observational studies prevail.

Maintaining optimal vitamin D levels is more likely than not to offset both excess osteoarthritis disability as well as its COVID-19 linkage among older adults, commonly at high risk for low serum vitamin D levels.

Table 1 Table depicting most representative clinical investigations conducted prospectively over time in the context of examining linkages between vitamin D and osteoarthritis (OA) and showing little variability in type of osteoarthritis studied, but high variability in sample sizes, and conclusions among the studies [*=no or adverse vitamin D-osteoarthritis effect demonstrated].

Researchers	Study Approach	Study Sample	Key Findings
*Arden et al. [36]	3 year double blinded randomized placebo controlled trial performed at 5 UK hospitals	474 bilateral knee OA patients received 800 IU oral vitamin D or placebo daily for one year	Found radiographic progression over 3 years in the 'contralateral' knee, pain, stiffness, function were not improved
Bassiouni et al. [65]	Prospective 12 months study	38 subjects with and without knee OA matched for age, gender, and body mass were observed	Vitamin D levels were significantly decreased in the subjects with knee OA Medial meniscal deterioration was seen in patients with low vitamin D levels Vitamin D deficiency may play a role in the progression of medial compartment knee OA
Bergink et al. [70]	Prospective cohort study	1248 cases of knee OA underwent baseline, vitamin D dietary intake assays and serum levels measures After a mean follow-up of 6.5 yrs, knee OA incidence + progression was assessed by radiography	Low dietary vitamin D intake increases the risk of progression of knee OA Improving the vitamin D status in the elderly could protect against the development/worsening knee OA, especially in those with low bone mineral density
Chaganti et al. [47]	Prospective study conducted over a 4.6 year time period	1104 elderly men with hip OA were followed Logistic regression was used to assess associations of serum vitamin D levels with prevalent radiographic hip OA	Men with vitamin D deficiencies are at high risk for hip OA, and twice as likely to have prevalent hip OA Vitamin D therapy is warranted for augmenting health in the elderly
Felson et al. [64]*	Examined vitamin D levels in subjects longitudinally In the first, subjects in 1993-1994 were examined again in 2002-2005 In the second, subjects were studied at baseline and at 15 + 30 months.	There were 715 subjects in one study and 277 from another who were examined for vitamin D levels and radiographic worsening, but most knees had no evidence of OA at baseline	Vitamin D status was unrelated to the risk of joint space narrowing or loss of knee joint cartilage
Hussain et al. [37]*	Prospective multiyear study	9135 adults who had vitamin D levels assessed in 1999-2000 and were 40 years or older undergoing hip arthroplasty for OA between 2002-2011	Increasing serum vitamin D levels were associated with an increased risk of hip arthroplasty in males, but not in females
Jin et al. [35]*	2 year randomized controlled trial, where 209 subjects received monthly oral vitamin D treatments; 204 with knee OA did not	There were 413 completers of the study, all with initial low 25-hydroxyvitamin D levels, who had symptomatic knee OA	Monthly treatment with oral vitamin D (50,000units) does not produce significant clinical or cartilage volume structural differences in vitamin D deficient knee OA cases over time Results do not support vitamin D supplementation to prevent pain or cartilage loss
Konstari et al. [74]*	Prospective Finnish based multi year study	805 healthy participants with no hip or knee OA underwent baseline and follow-up clinical examinations at intervals of 20-23 years Knee and hip OA were diagnosed using a standardized clinical examination at baseline and follow-up. Covariates, included age, sex, season of blood draw, education, body mass index Serum vitamin D concentrations were determined from baseline serum samples kept frozen at -20°C.	There is no association between serum vitamin D levels and the risk of incident knee or hip OA. However, there is a significant interaction between season of blood draw and serum vitamin D The relative odds of developing definite knee OA in the winter season was 1.57 (1.10-2.27), whereas for the summer season it was 0.53 (0.28-1.00)
Konstari et al. [45]	10 year prospective cohort study	5274 participants in a national health examination survey who had no knee or hip OA at baseline were studied During the follow-up of 10 years (50 134 person-years), 127 subjects developed incident, physician-diagnosed OA in the knee and 45 in the hip joint	After adjusting for age and gender, serum vitamin D levels were found significantly associated with known risk factors for OA except injuries In the fully adjusted model, low serum vitamin D levels did not predict increased incidence of knee and hip OA Use of physician diagnosed OA may have been problematic
Lane et al. [49]	8 year prospective cohort study	237 female participants of a fracture study	After 8 years-those with vitamin D were 3x more likely to develop hip OA; and an increased risk for progression of knee OA, but this depended on measurement or definitions of OA employed
Manoy et al. [56]	Prospective study with 6 month follow up	175 cases with knee OA and low vitamin D levels received 40, 000 IU orally weekly for 6 months	Pain decreased, life quality increased, grip strength and physical performance increased
Sanghi et al. [77]	1 year randomized controlled trial pilot study	Results of 126 revision total joint arthroplasty patients between 2010 and 2014 were examined	There is a small clinical benefit to using vitamin D as regards pain and subjective functioning
Wang et al. [46]	Prospective 24 months randomized trial	1384 cases with osteoporosis or OA were followed for 3 years	Effusion-synovitis volume remained stable in vitamin D group; but increased in placebo group

Yoshimura et al. [52]*	3 year follow up study	418 knee OA patients	Higher serum vitamin D levels do not prevent knee OA or lumbar spondylosis based on survey responses
Zhang et al. [48]	Prospective	413 knee OA cases, divided into 3 groups, of vitamin D; insufficiency [<50 nmol/L at 3+24 months], fluctuating [> 50 nmol/L at either 3/24 months], and sufficient levels [>50 nmol/L at 3+24 months]. In addition to vitamin D measures at 3 + 24 months, pain measures, effusion-synovitis and various cartilage and bone measures were conducted	Approximately 16% sample had low vitamin D levels. Between baseline and follow-up 15% progressed in joint space narrowing score responses Individuals deficient in vitamin D have an increased risk of knee OA progression compared with those with greater vitamin D serum concentrations
Zheng et al. [54]	Prospective 24 month cohort study-secondary analysis	209 knee osteoarthritis cases with vitamin D deficits received 50,000 oral IU for 24 months	Sufficient vitamin D levels benefit cartilage loss, effusion-synovitis, and physical function compared to the consistently insufficient group
Zheng et al. [87]*	Post-hoc analysis of a 24 month intervention trial	200 participants from one site mean age 63.1 years , were randomly selected for measurement of serum levels of inflammatory and metabolic biomarkers at baseline and 24 months using immunoassays	There were no systemic metabolic or anti-inflammatory effects of note at any vitamin D level in the vitamin D deficient cohort or sufficient cohorts

REFERENCES

- Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. *Postgrad Med* 2020; **132(4)**: 377-384. [DOI: 10.1080/00325481.2020.1730669]; [PMID: 32100608]
- Thinuan P, Siviroj P, Lertrakarnnon P, Lorga T. Prevalence and potential predictors of frailty among community-dwelling older persons in Northern Thailand: a cross-sectional study. *Int J Environ Res Public Health* 2020; **17(11)**: 4077. [DOI: 10.3390/ijerph17114077]; [PMID: 32521642]; [PMCID: PMC7312471]
- Park HM, Kim HS, Lee YJ. Knee osteoarthritis and its association with mental health and health-related quality of life: a nationwide cross-sectional study. *Geriatr Gerontol Int* 2020; **20(4)**: 379-383. [DOI: 10.1111/ggi.13879]; [PMID: 32037727]
- Khoury M, Cuenca J, Cruz FF, Figueroa FE, Rocco PRM, Weiss DJ. Current status of cell-based therapies for respiratory virus infections: applicability to COVID-19. *Eur Respir J* 2020; **4**: 55(6): 2000858. [DOI: 10.1183/13993003.00858-2020]; [PMID: 32265310]; [PMCID: PMC7144273]
- George J. Vitamin D supplementation and progression of knee osteoarthritis. *JAMA* 2016; **316(3)**: 347-348.
- Heidari B, Javadian Y, Babaei M, Yousef-Ghahari B. Restorative effect of vitamin D deficiency on knee pain and quadriceps muscle strength in knee osteoarthritis. *Acta Med Iran* 2015; **53(8)**: 466-470.
- Park CY. Vitamin D in the prevention and treatment of osteoarthritis: from clinical interventions to cellular evidence. *Nutrients*. 2019; **11(2)**: 243. [DOI: 10.3390/nu11020243]; [PMID: 30678273]; [PMCID: PMC6413222]
- Gao XR, Chen YS, Deng W. The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. *Int J Surg* 2017; **46**: 14-20. [DOI: 10.1016/j.ijisu.2017.08.010]
- Thomas JE, Bhat AK, Rao M, Guddattu V, Sekhar M S. Use of vitamin D supplements in osteoarthritis: an observational study in a tertiary health care facility. *J Am Coll Nutr*. 2019; **38(3)**: 227-234. [DOI: 10.1080/07315724.2018.1494641]; [PMID: 30485164]
- Koeckhoven E, van der Leeden M, Roorda LD, van Schoor NM, Lips P, de Zwart A, et al. The association between serum 25-hydroxy vitamin D level and upper leg strength in patients with knee osteoarthritis: results of the Amsterdam osteoarthritis cohort. *J Rheumatol* 2016 May 15. pii: jrheum.150751.
- Hung M, Bounsanga J, Voss MW, Gu Y, Crum AB, Tang P. Dietary and supplemental vitamin C and D on symptom severity and physical function in knee osteoarthritis. *J Nutr Gerontol Geriatr* 2017; **36(2-3)**: 121-133. [DOI: 10.1080/21551197.2017.1317315]; [PMID: 28557644]; [PMCID: PMC6088727]
- Glover TL, Goodin BR, King CD, Sibille KT, Herbert MS, Sotolongo AS, et al. A cross-sectional examination of vitamin D, obesity, and measures of pain and function in middle-aged and older adults with knee osteoarthritis. *Clin J Pain* 2015; **31(12)**: 1060-1067. [DOI: 10.1097/AJP.0000000000000210]
- Glover TL, Horgas AL, Fillingim RB, Goodin BR. Vitamin D status and pain sensitization in knee osteoarthritis: a critical review of the literature. *Pain Manag* 2015; **5(6)**: 447-453. [DOI: 10.2217/pmt.15.43]
- Vanherwegen AS, Gysemans C, Mathieu C. Regulation of immune function by vitamin D and its use in diseases of immunity. *Endocrinol Metab Clin North Am* 2017; **46(4)**:1061-1094. [DOI: 10.1016/j.ecl.2017.07.010]
- Levinger P, Begg R, Sanders KM, Nagano H, Downie C, Petersen A, Hayes A, Cicuttini F. The effect of vitamin D status on pain, lower limb strength and knee function during balance recovery in people with knee osteoarthritis: an exploratory study. *Arch Osteoporos* 2017; **12(1)**: 83. [DOI: 10.1007/s11657-017-0378-4]
- Manoy P, Anomasiri W, Yuktanandana P, Tanavalee A, Ngarmukos S, Tanpowpong T, Honsawek S. Elevated serum leptin levels are associated with low vitamin D, sarcopenic obesity, poor muscle strength, and physical performance in knee osteoarthritis. *Biomarkers* 2017; **22(8)**: 723-730. [DOI: 10.1080/1354750X.2017.1315615]; [PMID: 28374624].
- Fayed HL, Saleh AH. Frequency of vitamin D among Saudi males visiting a rheumatology outpatient clinic of a tertiary hospital in Al-Qassim region: effect of vitamin D supplementation. *Egyptian Rheumatologist* 2017; **39**: 249-254.
- Yu Y, Liu D, Feng D, Zhao J. Association between vitamin D and knee osteoarthritis: a PRISMA-compliant meta-analysis. *Z Orthop Unfall* 2020 Mar 9. English. [DOI: 10.1055/a-1098-8815]; [PMID: 32150754]
- Li HM, Liu Y, Zhang RJ, Ding JY, Shen CL. Vitamin D receptor gene polymorphisms and osteoarthritis: a meta-analysis. *Rheumatology (Oxford)* 2020 Nov 4; keaa644. [DOI: 10.1093/rheumatology/keaa644]; [PMID: 33147632]
- Huhtakangas JA, Veijola J, Turunen S, Karjalainen A, Valkealahti M, Nousiainen T, Yli-Luukko S, Vuolteenaho O, Lehenkari P. 1,25(OH)(2)D(3) and calcipotriol, its hypocalcemic analog, exert a long-lasting anti-inflammatory and anti-proliferative effect in synoviocytes cultured from patients with rheumatoid arthritis and osteoarthritis. *J Steroid Biochem Mol Biol* 2017; **173**: 13-22. [DOI: 10.1016/j.jsbmb.2017.01.017]
- Szychlińska MA, Imbesi R, Castrogiovanni P, Guglielmino C, Ravalli S, Di Rosa M, Musumeci G. Assessment of vitamin D supplementation on articular cartilage morphology in a young healthy sedentary rat model. *Nutrients* 2019; **11(6)**: 1260. [DOI: 10.3390/nu11061260]; [PMID: 31163658]; [PMCID: PMC6628271]
- Schwartz Z, Bonewald LF, Caulfield K, Brooks B, Boyan BD.

- Direct effects of transforming growth factor-beta on chondrocytes are modulated by vitamin D metabolites in a cell maturation-specific manner. *Endocrinol* 1993; **132**(4): 1544-1552.
23. Pascual-Garrido C, Angeline ME, Ma R, Chahla J, Voigt C, Deng XH, Nguyen J, Warren RF, Rodeo SA. Low levels of vitamin D have a deleterious effect on the articular cartilage in a rat model. *HSS J* 2016; **12**(2): 150-157. [DOI: 10.1007/s11420-016-9492-x]; [PMID: 27385944]; [PMCID: PMC4916094]
 24. Malas FU, Kara M, Aktekin L, Ersöz M, Ozçakar L. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. *Clin Rheumatol* 2014; **33**(9): 1331-1334. [DOI: 10.1007/s10067-013-2432-y]
 25. Shen M, Luo Y, Niu Y, Chen L, Yuan X, Goltzman D, et al. 1,25(OH)2D deficiency induces temporomandibular joint osteoarthritis via secretion of senescence-associated inflammatory cytokines. *Bone* 2013; **55**(2): 400-409. [DOI: 10.1016/j.bone.2013.04.015]
 26. Li S, Niu G, Wu Y, Du G, Huang C, Yin X, Liu Z, Song C, Leng H. Vitamin D prevents articular cartilage erosion by regulating collagen II turnover through TGF- β 1 in ovariectomized rats. *Osteoarthritis Cartilage* 2016; **24**(2): 345-353. [DOI: 10.1016/j.joca.2015.08.013]
 27. Kuyucu E, Çabuk H, Güler Y, Çabuk F, Kiliç E, Bülbül M. Can Intra-articular 1 α , 25-Dihydroxyvitamin D3 administration be therapeutic in joint cartilage damage? *Acta Chir Orthop Traumatol Cech* 2020; **87**(2): 90-94; [PMID: 32396508]
 28. Castillo EC, Hernandez-Cueto MA, Vega-Lopez MA, Lavalle C, Kouri JB, Ortiz-Navarrete V. Effects of vitamin D supplementation during the induction and progression of osteoarthritis in a rat model. *Evid Based Complement Alternat Med* 2012; **2012**: 156563. [DOI: 10.1155/2012/156563]
 29. Rai V, Dietz NE, Dilisio MF, Radwan MM, Agrawal DK. Vitamin D attenuates inflammation, fatty infiltration, and cartilage loss in the knee of hyperlipidemic microswine. *Arthritis Res Ther* 2016; **18**(1): 203. [DOI: 10.1186/s13075-016-1099-6]
 30. Ferrándiz ML, Terencio MC, Carceller MC, Ruhí R, Dalmau P, Vergés J, Montell E, Torrent A, Alcaraz MJ. Effects of BIS076 in a model of osteoarthritis induced by anterior cruciate ligament transection in ovariectomized rats. *BMC Musculoskelet Disord* 2015 Apr 17; 16: 92. [DOI: 10.1186/s12891-015-0547-9]
 31. Boyan B, Hyzy S, Schwartz Z, et al. 24R,25-Dihydroxyvitamin D3 protects against articular cartilage damage following anterior cruciate ligament transection in male rats. *Plos One* 2016; **11**(8): 1-23.
 32. Li S, Niu G, Dong XN, Liu Z, Song C, Leng H. Vitamin D inhibits activities of metalloproteinase-9/-13 in articular cartilage in vivo and in vitro. *J Nutr Sci Vitaminol (Tokyo)* 2019; **65**(2): 107-112. [DOI: 10.3177/jnsv.65.107]; [PMID: 31061278]
 33. Hirota Y, Nakagawa K, Mimatsu S, Sawada N, Sakaki T, Kubodera N, Kamao M, Tsugawa N, Suhara Y, Okano T. Nongenomic effects of 1 α ,25-dihydroxyvitamin D(3) on cartilage formation deduced from comparisons between Cyp27b1 and Vdr knockout mice. *Biochem Biophys Res Commun* 2017; **483**(1): 359-365. [DOI: 10.1016/j.bbrc.2016.12.139]
 34. Yamamura K, Ohta Y, Mamoto K, Sugama R, Minoda Y, Nakamura H. Effect of eldelcalcitol on articular cartilage through the regulation of transcription factor Erg in a murine model of knee osteoarthritis. *Biochem Biophys Res Commun* 2018; **495**(1): 179-184. [DOI: 10.1016/j.bbrc.2017.10.155]
 35. Jin X, Jones G, Cicuttini F, Wluka A, Zhu Z, Han W, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. *JAMA* 2016; **315**(10): 1005-1013.
 36. Arden NK, Cro S, Sheard S, Doré CJ, Bara A, Tebbs SA, et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. *Osteoarthritis Cart* 2016 Jun 2. pii: S1063-4584(16)30109-1. [DOI: 10.1016/j.joca.2016.05.020]
 37. Hussain SM, Daly RM, Wang Y, Shaw JE, Magliano DJ, Graves S, Ebeling PR, Wluka AE, Cicuttini FM. Association between serum concentration arthroplasty for osteoarthritis: result from a prospective cohort study. *Osteoarthritis Cart* 2015; **23**: 2134-2140. 10.1016/j.joca.2015.06.006; [PMID: 26093211]
 38. Joseph GB, McCulloch CE, Nevitt MC, Neumann J, Lynch JA, Lane NE, Link TM. Associations between vitamins C and D intake and cartilage composition and knee joint morphology over 4 years: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2020; **72**(9): 1239-1247. [DOI: 10.1002/acr.24021]; [PMID: 31282125]; [PMCID: PMC6946891]
 39. Kong C, Wang C, Shi Y, Yan L, Xu J, Qi W. Active vitamin D activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK-mTOR signaling pathway. *Biochem Cell Biol* 2020; **98**(3): 434-442. [DOI: 10.1139/bcb-2019-0333]; [PMID: 31815524]
 40. Goula T, Kouskoukis A, Drosos G, Tselepis AS, Ververidis A, Valkanis C, et al. Vitamin D status in patients with knee or hip osteoarthritis in a Mediterranean country. *J Orthop Traumatol* 2015; **16**(1): 35-39. [DOI: 10.1007/s10195-014-0322-y]
 41. Malas FU, Kara M, Aktekin L, Ersöz M, Ozçakar L. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. *Clin Rheumatol* 2014; **33**(9): 1331-1334. [DOI: 10.1007/s10067-013-2432-y]
 42. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, Rush D, Wilson PW, Jacques PI. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996; **125**(5): 353-359. [DOI: 10.7326/0003-4819-125-5-199609010-00001]; [PMID: 8702085]
 43. Diao N, Yang B, Yu F. Effect of vitamin D supplementation on knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. *Clin Biochem* 2017; **50**(18): 1312-1316. [DOI: 10.1016/j.clinbiochem.2017.09.001]; [PMID: 28888878]
 44. Gallagher B, Tjoumakaris FP, Harwood MI, Good RP, Ciccotti MG, Freedman KB. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. *Am J Sports Med* 2015; **43**(3): 734-744. [DOI: 10.1177/0363546514533777]
 45. Konstari S, Kaila-Kangas L, Jääskeläinen T, Heliövaara M, Rissanen H, Marniemi J, et al. Serum 25-hydroxyvitamin D and the risk of knee and hip osteoarthritis leading to hospitalization: a cohort study of 5274 Finns. *Rheumatol* 2014; **53**(10): 1778-1782. [DOI: 10.1093/rheumatology/keu178]
 46. Wang X, Cicuttini F, Jin X, Wluka AE, Han W, Zhu Z, Blizzard L, Antony B, Winzenberg T, Jones G, Ding C. Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2017; **25**(8): 1304-1312. [DOI: 10.1016/j.joca.2017.02.804]
 47. Chaganti RK, Parimi N, Cawthon P, Dam TL, Nevitt MC, Lane NE. Association of 25-hydroxyvitamin D with prevalent osteoarthritis of the hip in elderly men: the osteoporotic fractures in men study. *Arthritis Rheum* 2010; **62**(2): 511-514. [DOI: 10.1002/art.27241]
 48. Zhang FF, Driban JB, Lo GH, Price LL, Booth S, Eaton CB, et al. Vitamin D deficiency is associated with progression of knee osteoarthritis. *J Nutr* 2014; **144**(12): 2002-2008. [DOI: 10.3945/jn.114.193227]
 49. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, Nevitt MC. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum* 1999; **42**(5): 854-860. [DOI: 10.1002/1529-0131(199905)42:5<854::AID-ANR3>3.0.CO;2-I]; [PMID: 10323440]

50. Bergink AP, Zillikens MC, Van Leeuwen JP, Hofman A, Uitterlinden AG, van Meurs JB. 25-Hydroxyvitamin D and osteoarthritis: a meta-analysis including new data. *Semin Arthritis Rheum* 2016; **45(5)**: 539-546.
51. Ding C, Cicuttini F, Parameswaran V, Burgess J, Quinn S, Jones G. Serum levels of vitamin D, sunlight exposure, and knee cartilage loss in older adults: the Tasmanian older adult cohort study. *Arthritis Rheum* 2009; **60(5)**: 1381-1389. [DOI: 10.1002/art.24486]
52. Yoshimura N, Muraki S, Oka H, Nakamura K, Kawaguchi H, Tanaka S, Akune T. Serum levels of 25-hydroxyvitamin D and the occurrence of musculoskeletal diseases: a 3-year follow-up to the road study. *Osteoporos Int* 2015 **26(1)**: 151-161. [DOI: 10.1007/s00198-014-2844-9]
53. Grazio S, Naglič ĐB, Anić B, Grubišić F, Bobek D, Bakula M, Kavanagh HS, Kuna AT, Cvijetić S. Vitamin D serum level, disease activity and functional ability in different rheumatic patients. *Am J Med Sci* 2015;**349(1)**:46-9. [DOI: 10.1097/MAJ.0000000000000340]; [PMID: 25310509]
54. Zheng S, Jin X, Cicuttini F, Wang X, Zhu Z, Wluka A, Han W, Winzenberg T, Antony B, Aitken D, Blizzard L, Jones G, Ding C. Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in knee osteoarthritis. *Am J Med* 2017; **130(10)**: 1211-1218. [DOI: 10.1016/j.amjmed.2017.04.038]; [PMID: 28549923]
55. Yazmalar L, Ediz L, Alpacyi M, Hiz O, Toprak M, Tekeoglu I. Seasonal disease activity and serum vitamin D levels in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. *Afr Health Sci* 2013; **13(1)**: 47-55. [DOI: 10.4314/ahs.v13i1.7]
56. Manoy P, Yuktanandana P, Tanavalee A, Anomasiri W, Ngarmukos S, Tanpowpong T, Honsawek S. Vitamin D supplementation improves quality of life and physical performance in osteoarthritis patients. *Nutrients* 2017 Jul 26; **9(8)**. pii: E799. [DOI: 10.3390/nu9080799]
57. Sowers M. Vitamins and arthritis-the roles of vitamin A,C,D, and E. *Rheum Dis Clin N Am* 1999; **25**: 315-316. [DOI: 10.1016/s0889-857x(05)70070-3]
58. Lee A, Chan SK, Samy W, Chiu CH, Gin T. Effect of hypovitaminosis D on postoperative pain outcomes and short-term health-related quality of life after knee arthroplasty: a cohort study. *Medicine (Baltimore)* 2015; **94(42)**: e1812. [DOI: 10.1097/MD.0000000000001812]
59. Zwerina K, Baum W, Axmann R, Heiland GR, Distler JH, Smolen J, et al. Vitamin D receptor regulates TNF-mediated arthritis. *Ann Rheum Dis* 2011; **70(6)**: 1122-1129. [DOI: 10.1136/ard.2010.142331]
60. Nawabi DH, Chin KF, Keen RW, Haddad FS. Vitamin D deficiency in patients with osteoarthritis undergoing total hip replacement: a cause for concern? *J Bone Joint Surg Br* 2010; **92(4)**: 496-499. [DOI: 10.1302/0301-620X.92B3.23535]
61. Robertson MC, Gillespie LD. Fall prevention in community-dwelling older adults. *JAMA* 2013; **309**: 1406-1407. [DOI: 10.1001/jama.2013.3130]; [PMID: 23549586]
62. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, Li P, Davidson KW. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med* 2014; **76(3)**: 190-196. [DOI: 10.1097/PSY.0000000000000044]; [PMID: 24632894]; [PMCID: PMC4008710]
63. Laslett LL, Quinn S, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. *Ann Rheum Dis* 2014; **73(4)**: 697-703. [DOI: 10.1136/annrheumdis-2012-202831]
64. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, Hunter DJ, Amin S, Rogers G, Booth SL. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. *Arthritis Rheum* 2007; **56(1)**: 129-136. [DOI: 10.1002/art.22292]; [PMID: 17195215]
65. Bassiouni H, Aly H, Zaky K, Abaza N, Bardin T. Probing the relation between vitamin D deficiency and progression of medial femoro-tibial osteoarthritis of the knee. *Curr Rheumatol Rev* 2016 Apr 4. [DOI: 10.2174/1573397112666160404124532]; [PMID: 27041085]
66. Jansen JA, Haddad FS. High prevalence of vitamin D deficiency in elderly patients with advanced osteoarthritis scheduled for total knee replacement associated with poorer preoperative functional state. *Ann R Coll Surg Engl* 2013; **95(8)**: 569-572. [DOI: 10.1308/003588413X13781990150374]
67. Alkan G, Akgol G. Do vitamin D levels affect the clinical prognoses of patients with knee osteoarthritis? *J Back Musculoskeletal Rehabil* 2017; **30(4)**: 897-901. [DOI: 10.3233/BMR-160589]
68. Askari A, Naghizadeh MM, Homayounfar R, Abbas S, Afsarian MH, Paknahad A, Kennedy D, Ataollahi MR. Increased serum levels of IL-17A and IL-23 are associated with decreased vitamin D3 and increased pain in osteoarthritis. *Plos One* 2016; **11**: 1-8. [DOI: 10.1371/journal.pone.0164757]; [PMID: 27820818]; [PMCID: PMC5098728]
69. Barker T, Henriksen VT, Rogers VE, Aguirre D, Trawick RH, Lynn Rasmussen G, Momberger NG. Vitamin D deficiency associates with γ -tocopherol and quadriceps weakness but not inflammatory cytokines in subjects with knee osteoarthritis. *Redox Biol* 2014; **2**: 466-474. [DOI: 10.1016/j.redox.2014.01.024]
70. Bergink AP, Uitterlinden AG, Van Leeuwen JP, Burman CJ, Hofman A, Verhaar JA, Pols HA. Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study. *J Clin Rheumatol* 2009; **15(5)**: 230-237. [DOI: 10.1097/RHU.0b013e3181b08f20]
71. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. *Int Orthop* 2011; **35(11)**: 1627-1631. [DOI: 10.1007/s00264-010-1186-2]
72. Jansen JA, Haddad FS. High prevalence of vitamin D deficiency in elderly patients with advanced osteoarthritis scheduled for total knee replacement associated with poorer preoperative functional state. *Ann R Coll Surg Engl* 2013; **95(8)**: 569-572. [DOI: 10.1308/003588413X13781990150374]
73. Maier GS, Maus U, Lazovic D, Horas K, Roth KE, Kurth AA. Is there an association between low serum 25-OH-D levels and the length of hospital stay in orthopaedic patients after arthroplasty? *J Orthop Traumatol* 2016; **17(4)**: 297-302.
74. Konstari S, Paananen M, Heliövaara M, Knekt P, Marniemi J, Impivaara O, Arokoski J, Karppinen J. Association of 25-hydroxyvitamin D with the incidence of knee and hip osteoarthritis: a 22-year follow-up study. *Scand J Rheumatol* 2012; **41(2)**: 124-131. [DOI: 10.3109/03009742.2011.617314]
75. McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA* 2013; **309(2)**: 155-162. [DOI: 10.1001/jama.2012.164487]
76. Muraki S, Dennison E, Jameson K, Boucher BJ, Akune T, Yoshimura N, Judge A, Arden NK, Javaid K, Cooper C. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cart* 2011; **19(11)**: 1301-1306. [DOI: 10.1016/j.joca.2011.07.017]. Epub 2011 Aug 16. [PMID: 21884812]
77. Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, Srivastava RN. Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. *Clin Orthop Relat Res* 2013; **471(11)**: 3556-3562. [DOI: 10.1007/s11999-013-3201-6]
78. Traven SA, Chiaramonti AM, Barfield WR, Kirkland PA, Demos HA, Schutte HD, Drew JM. Fewer complications following revision hip and knee arthroplasty in patients with normal vitamin

- D levels. *J Arthroplasty* 2017; **32(9S)**: S193-S196. [DOI: 10.1016/j.arth.2017.02.038]
79. Veronese N, Maggi S, Noale M, De Rui M, Bolzetta F, Zambon S, Corti MC, Sartori L, Musacchio E, Baggio G, Perissinotto E, Crepaldi G, Manzato E, Sergi G. Serum 25-hydroxyvitamin D and osteoarthritis in older people: the Progetto Veneto Anziani study. *Rejuvenation Res* 2015; **18(6)**: 543-53. [DOI: 10.1089/rej.2015.1671]
 80. Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. *Eur J Clin Nutr* 2020; **74(11)**: 1493-1497. [DOI: 10.1038/s41430-020-0697-1]; [PMID: 32704098]
 81. Cakar M, Ayanoglu S, Cabuk H, Seyran M, Dedeoglu SS, Gurbuz H. Association between vitamin D concentrations and knee pain in patients with osteoarthritis. *Peer J* 2018; **6**: e4670. [DOI: 10.7717/peerj.4670]; [PMID: 29707434]; [PMCID: PMC5922228]
 82. Sanders KM, Scott D, Ebeling PR. Vitamin D deficiency and its role in muscle-bone interactions in the elderly. *Curr Osteoporos Rep* 2014; **12(1)**: 74-81. [DOI: 10.1007/s11914-014-0193-4]
 83. Tu L, Zheng S, Cicuttini F, Jin X, Han W, Zhu Z, Antony B, Winzenberg T, Jones G, Gu J, Wluka AE, Ding C. Effects of vitamin D supplementation on disabling foot pain in patients with symptomatic knee osteoarthritis. *Arthritis Care Res* 2020 Jul 5. [DOI: 10.1002/acr.24371]; [PMID: 32623812]
 84. Ravalli S, Szychlinska MA, Leonardi RM, Musumeci G. Recently highlighted nutraceuticals for preventive management of osteoarthritis. *World J Orthop* 2018; **9(11)**: 255-261. [DOI: 10.5312/wjo.v9.i11.255]; [PMID: 30479972]; [PMCID: PMC6242728]
 85. Kim HJ, Lee JY, Kim TJ, Lee JW. Association between serum vitamin D status and health related quality of life (HRQOL) in older Korean population with radiographic knee osteoarthritis: data from the Korean national health and nutrition examination survey (2010-2011). *Hlth Qual Life Outcomes* 2015; **13**: April 18.
 86. Javadian Y, Adabi M, Heidari B, Babaei M, Firouzjahi A, Ghahhari BY, Hajian-Tilaki K. Quadriceps muscle strength correlates with serum vitamin D and knee pain in knee osteoarthritis. *Clin J Pain* 2017; **33(1)**: 67-70. [DOI: 10.1097/AJP.0000000000000358]; [PMID: 26889621]
 87. Zheng S, Wang B, Han W, Zhu Z, Wang X, Jin X, Antony B, Cicuttini F, Wluka A, Winzenberg T, Aitken D, Blizzard L, Jones G, Ding C. Vitamin D supplementation and inflammatory and metabolic biomarkers in patients with knee osteoarthritis: post hoc analysis of a randomised controlled trial. *Br J Nutr* 2018; **120(1)**: 41-48. [DOI: 10.1017/S0007114518001174]
 88. Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. *Eur J Appl Physiol* 2019; **119(4)**: 825-839. [DOI: 10.1007/s00421-019-04104-x]; [PMID: 30830277]; [PMCID: PMC6422984]
 89. Dzik KP, Skrobot W, Kaczor KB, Flis DJ, Karnia MJ, Libionka W, Antosiewicz J, Kloc W, Kaczor JJ. Vitamin D deficiency is associated with muscle atrophy and reduced mitochondrial function in patients with chronic low back pain. *Oxid Med Cell Longev* 2019; **2019**: 6835341. [DOI: 10.1155/2019/6835341]; [PMID: 31281588]; [PMCID: PMC6589343]
 90. Krasowska K, Skrobot W, Liedtke E, Sawicki P, Flis DJ, Dzik KP, Libionka W, Kloc W, Kaczor JJ. The preoperative supplementation with vitamin D attenuated pain intensity and reduced the level of pro-inflammatory markers in patients after posterior lumbar interbody fusion. *Front Pharmacol* 2019; **10**: 527. [DOI: 10.3389/fphar.2019.00527]; [PMID: 31191300]; [PMCID: PMC6539202]
 91. Dzik K, Skrobot W, Flis DJ, Karnia M, Libionka W, Kloc W, Kaczor JJ. Vitamin D supplementation attenuates oxidative stress in paraspinal skeletal muscles in patients with low back pain. *Eur J Appl Physiol* 2017 Nov 15. [DOI: 10.1007/s00421-017-3755-1]
 92. Grüber MR, Gängler S, Egli A, Bischoff-Ferrari HA. Effects of vitamin D3 on glucose metabolism in patients with severe osteoarthritis: a randomized double-blind trial comparing daily 2000 IU versus 800 IU vitamin D3. *Diabetes Obes Metab* 2020 Dec 28. [DOI: 10.1111/dom.14307]; [PMID: 33368963]
 93. Udomsinprasert W, Manoy P, Yuktanandana P, Tanavalee A, Anomasiri W, Honsawek S. Decreased serum adiponectin reflects low vitamin D, high interleukin 6, and poor physical performance in knee osteoarthritis. *Arch Immunol Ther Exp (Warsz)* 2020; **68(3)**: 16. [DOI: 10.1007/s00005-020-00580-8]; [PMID: 32449055]
 94. Cianferotti L, Bertoldo F, Bischoff-Ferrari HA, Bruyere O, Cooper C, Cutolo M, Kanis JA, Kaufman JM, Reginster JY, Rizzoli R, Brandi ML. Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). *Endocrine* 2017; **56(2)**: 245-261. [DOI: 10.1007/s12020-017-1290-9]
 95. Tripathy SK, Gantaguru A, Nanda SN, Velagada S, Srinivasan A, Mangaraj M. Association of vitamin D and knee osteoarthritis in younger individuals. *World J Orthop* 2020; **11(10)**: 418-425. [DOI: 10.5312/wjo.v11.i10.418]; [PMID: 33134104]; [PMCID: PMC7582112]
 96. Garfinkel RJ, Dilisio MF, Agrawal DK. Vitamin D and its effects on articular cartilage and osteoarthritis. *Orthop J Sports Med* 2017; **5(6)**: 2325967117711376. [DOI: 10.1177/2325967117711376]
 97. Perry TA, Parkes MJ, Hodgson R, Felson DT, O'Neill TW, Arden NK. Effect of vitamin D supplementation on synovial tissue volume and subchondral bone marrow lesion volume in symptomatic knee osteoarthritis. *BMC Musculoskelet Disord* 2019; **20(1)**: 76. [DOI: 10.1186/s12891-019-2424-4]; [PMID: 30764805]; [PMCID: PMC6376763]
 98. Bischoff-Ferrari HA, Zhang Y, Kiel DP, Felson DT. Positive association between serum 25-hydroxyvitamin D level and bone density in osteoarthritis. *Arthritis Rheum* 2005; **53(6)**: 821-826. [DOI: 10.1002/art.21601]; [PMID: 16342101]
 99. Veronese N, La Tegola L, Mattered M, Maggi S, Guglielmi G. Vitamin D intake and magnetic resonance parameters for knee osteoarthritis: data from the Osteoarthritis Initiative. *Calcif Tissue Int*. 2018; **103(5)**: 522-528. [DOI: 10.1007/s00223-018-0448-7]; [PMID: 29943188.100]
 100. Yang T, Sun W, Duan YH, Sun YB, Ren YM, Hou WY, Tian MQ. Vitamin D3 protects articular cartilage by inhibiting the Wnt/ β -catenin signaling pathway. *Exp Ther Med* 2020; **20(2)**: 1775-1781. [DOI: 10.3892/etm.2020.8839]; [PMID: 32742408]; [PMCID: PMC7388321]
 101. Walsh JS, Bowles S, Evans AL. Vitamin D in obesity. *Curr Opin Endocrinol Diabetes Obes* 2017; **24(6)**: 389-394. [DOI: 10.1097/MED.0000000000000371]; [PMID: 28915134]
 102. Heidari B, Babaei M. Therapeutic and Preventive Potential of Vitamin D Supplementation in Knee Osteoarthritis. *ACR Open Rheumatol* 2019; **1(5)**: 318-326. [DOI: 10.1002/acr2.1042]; [PMID: 31777808]; [PMCID: PMC6857993]
 103. Zheng S, Tu L, Cicuttini F, Han W, Zhu Z, Antony B, Wluka A, Winzenberg T, Meng T, Aitken D, Blizzard L, Jones G, Ding C. Effect of Vitamin D supplementation on depressive symptoms in patients with knee osteoarthritis. *J Am Med Dir Assoc* 2019; **20(12)**: 1634-1640.e1. [DOI: 10.1016/j.jamda.2018.09.006]; [PMID: 30401608]
 104. Liberman K, Njemini R, Luiking Y, Forti LN, Verlaan S, Bauer JM, Memelink R, Brandt K, Donini LM, Maggio M, Mets T, Wijers SLJ, Sieber C, Cederholm T, Bautmans I. Thirteen weeks of supplementation of vitamin D and leucine-enriched whey protein nutritional supplement attenuates chronic low-grade inflammation in sarcopenic older adults: the PROVIDE study. *Aging Clin Exp Res* 2019; **31(6)**: 845-854. [DOI: 10.1007/s40520-019-01208-4]; [PMID: 31049877]; [PMCID: PMC6583678]
 105. Montenegro KR, Cruzat V, Carlessi R, Newsholme P. Mechanisms of vitamin D action in skeletal muscle. *Nutr Res Rev* 2019; **32(2)**:

- 192-204. [DOI: 10.1017/S0954422419000064]. 2019 Jun 17. [PMID: 31203824]
106. Dimar JR, Lane JM, Lehman RA Jr, Anderson PA. The basics of bone physiology, healing, and osteoporosis. *Instr Course Lect* 2021; **70**: 527-536. [PMID: 33438933]
107. Tague SE, Clarke GL, Winter MK, McC Carson KE, Wright DE, Smith PG. Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. *J Neurosci* 2011; **31**(39): 13728-38. [DOI: 10.1523/JNEUROSCI.3637-11.2011]; [PMID: 21957236]; [PMCID: PMC3319727]
108. Tague SE, Smith PG. Vitamin D deficiency leads to sensory and sympathetic denervation of the rat synovium. *Neuroscience* 2014; **279**: 77-93. [DOI: 10.1016/j.neuroscience.2014.08.035]; [PMID: 25193239]; [PMCID: PMC4197091]
109. Fuggle NR, Cooper C, Oreffo ROC, Price AJ, Kaux JF, Maheu E, Cutolo M, Honvo G, Conaghan PG, Berenbaum F, Branco J, Brandi ML, Cortet B, Veronese N, Kurth AA, Matijevic R, Roth R, Pelletier JP, Martel-Pelletier J, Vlaskovska M, Thomas T, Lems WF, Al-Daghri N, Bruyère O, Rizzoli R, Kanis JA, Reginster JY. Alternative and complementary therapies in osteoarthritis and cartilage repair. *Aging Clin Exp Res* 2020; **32**(4): 547-560. [DOI: 10.1007/s40520-020-01515-1]; [PMID: 32170710]; [PMCID: PMC7170824]
110. Mabey T, Singhatanadgige W, Yingsakmongkol W, Limthongkul W, Honsawek S. Vitamin D and spine surgery. *World J Orthop* 2016; **7**(11): 726-730. [DOI: 10.5312/wjo.v7.i11.726]; [PMID: 27900269]; [PMCID: PMC5112341]
111. Goltzman D. Functions of vitamin D in bone. *Histochem Cell Biol* 2018; **149**(4): 305-312. [DOI: 10.1007/s00418-018-1648-y]; [PMID: 29435763]
112. Ebell MH. Osteoarthritis: rapid evidence review. *Am Fam Physician* 2018; **97**(8): 523-526. [PMID: 29671497]
113. Orfanidou T, Malizos KN, Varitimidis S, Tsezou A. 1,25-Dihydroxyvitamin D(3) and extracellular inorganic phosphate activate mitogen-activated protein kinase pathway through fibroblast growth factor 23 contributing to hypertrophy and mineralization in osteoarthritic chondrocytes. *Exp Biol Med (Maywood)* 2012; **237**(3): 241-253. [DOI: 10.1258/ebm.2011.011301]. Epub 2012 Mar 5. [PMID: 22393163]
114. Emara AK, Nageeb E, George J, Buttar MA, Higuera C, Piuze NS. Hypovitaminosis D in lower extremity joint arthroplasty: a systematic review and meta-analysis. *J Orthop* 2020; **21**: 109-116. [DOI: 10.1016/j.jor.2020.03.010]; [PMID: 32255990]; [PMCID: PMC7114851]
115. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. *Biomed Res Int* 2015; **2015**: 953241. [DOI: 10.1155/2015/953241. Apr 27]; [PMID: 26000306]; [PMCID: PMC4427016]
116. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. *Inflamm Res* 2014; **63**(10): 803-819. [DOI: 10.1007/s00011-014-0755-z]; [PMID: 25048990]; [PMCID: PMC4160567]