Vitamin D and Osteoarthritis: What is the Consensus?

Article · February 2018

DOI: 10.17554/j.issn.2311-5106.2018.05.267

1 author:

Ray Marks
Teachers College
194 PUBLICATIONS **3,345** CITATIONS

SEE PROFILE

International Journal of Orthopaedics

Online Submissions: http://www.ghrnet.org/index.php/ijo
doi:10.17554/j.issn.2311-5106.2018.05.267

Int. J. of Orth. 2018 February 28; 5(1): 849-862
ISSN 2311-5106 (Print), ISSN 2313-1462 (Online)

EDITORIAL

Vitamin D and Osteoarthritis: What is the Consensus?

Ray Marks

Ray Marks, Department of Health, Physical Education, Gerontological Studies and Services, School of Health Sciences and Professional Studies, City University of New York, York College, NY 11451, United States, and Department of Health and Behavior Studies, Teachers College, Columbia University, NY 10027, the United States

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Ray Marks, Department of Health and Behavior Studies, Teachers College, Columbia University, Box 114, 525W, 120th Street, New York, NY 10027, the United States.
Email: rm226@columbia.edu
Telephone: +1-212-678-3445
Fax: +1-212-678-8259

Received: February 27, 2018
Revised: February 28, 2018
Accepted: February 28 2018
Published online: February 28, 2018

ABSTRACT

BACKGROUND: Osteoarthritis, a painful irreversible disabling joint disease, and one that predominantly affects the cartilage tissue lining freely moving joints is rapidly increasing in prevalence among older populations.

QUESTIONS: This work aimed to critically explore and document all published data in the English language pertaining to the questions of: 1) Whether vitamin D is an important correlate to consider in the context of future attempts to ameliorate or prevent osteoarthritis; and 2) Whether applying vitamin D as a supplement can potentially ameliorate the many functional problems and pain associated with osteoarthritis in some way, where deficiencies of the product are evident.

METHODS: A comprehensive overview of all relevant English language research reports published over the last 50 years and located in the major data bases of PUBMED, Scopus, and Web of Science, was undertaken. Relevant data sought were those addressing the questions above and included basic as well as clinical studies, regardless of research design. A narrative depiction of the key points that emerged from this diverse body of literature was then undertaken, rather than any systematic review.

RESULTS: Findings showed that regardless of study type, no clear conclusion can currently be forged with respect to question one. However, sufficient data, coupled with prevailing study flaws, imply more research in this realm is warranted.

CONCLUSION: While no consensus prevails concerning any area of the research on this topic, more research to delineate the possible protective, reparative or aversive role of vitamin D in mediating articular cartilage and overall joint status appears highly desirable and will likely prove of immense clinical utility in the future.

Key words: Articular Cartilage; Disability; Intervention; Osteoarthritis; Pain; Vitamin D

Marks R. Vitamin D and Osteoarthritis: What is the Consensus? *International Journal of Orthopaedics* 2018; **5(1)**: 849-862 Available from: URL: http://www.ghrnet.org/index.php/ijo/article/view/2288

INTRODUCTION

Osteoarthritis, a highly prevalent disabling joint disease affecting older as well as younger adults produces incalculable personal and social costs, including immense pain, job losses or limitations, and a wide array of functional and psychosocial challenges. Strongly associated with progressive lesions of the cartilaginous tissue lining

freely moving joints such as the knee and hip, as well as varying degrees of underlying bone pathology, this irreversible progressively disabling condition is often accompanied by various degrees of joint inflammation, muscle weakness and obesity along with cardiovascular and metabolic health comorbidities. In a search for strategies to retard, prevent, or ameliorate one or more features of osteoarthritis disability, the role of vitamin D, a key mediator of bone, and cartilage metabolism, has recently been discussed as a possible highly influential factor[1-6], but with no definitive conclusion being reached[7].

Since no prevailing remedy for alleviating osteoarthritis has been proven efficacious for effectively treating or preventing this condition, and some research favors a role for vitamin D in influencing its pathology, it was felt an effort to re-examine the potential role of vitamin D in the context of osteoarthritis might yet prove valuable. To this end, this present report focuses on conclusions by various research groups concerning vitamin D, an hormonal compound of high potential relevance in the context of factors that could impact directly or indirectly on the onset and progression of osteoarthritis disability[8-17].

While only true experiments can provide definitive evidence of a causal relationship between the factors of interest, most current meta-analyses of these types of studies offer no clear consensus as to whether vitamin D levels are definitively related in some way to osteoarthritis and its outcomes. Indeed, while some refute a role for vitamin D in the osteoarthritis pain cycle, others suggest vitamin D supplementation alleviates individual suffering, whereas vitamin D deficiencies correlate with greater impairments in overall life quality, pain, and functional disability[16].

To better understand if differences in research approaches, as well as flaws in these, are likely to explain the present variations as to the extent to which vitamin D is relevant in the osteoarthritis disability cycle, this present review examined the degree to which there is apparent support for a role for vitamin D in predicting or influencing the extent or rate of cartilage synthesis and/or degradation as is found in osteoarthritis, either directly or indirectly. To avoid overlooking salient facts or evidence provided by research approaches, other than randomized trials, this present report specifically sought to include, rather than omit cross-sectional studies and others as some related research questions are clearly better addressed by non-experimental designs or may serve as templates for future study.

In any event, and to avoid any confusion that might arise from in comparing studies due to terminology differences, this review employs the term vitamin D, simply as a generic term to describe the active form of the vitamin [$1,25(OH)_2D_3$]. In consideration of the diverse terms used in the prevailing literature in this respect, and a general lack of any discernible standardized or universally accepted formulaic approaches in this respect, the levels of vitamin D sufficiency or deficiency described in this review follow those definitions actually used by the individual authors.

METHODS

Using the search terms *Articular Cartilage and Vitamin D*, and *Osteoarthritis and Vitamin D*, accepted sources of information included meta-analyses, basic, cross-sectional and prospective studies. Databases consulted were PUBMED, Scopus, and the Web of Science consolidated data base. To establish the nature of any ongoing clinical research projects in this area, current listings of clinical trials in progress were sought from the United States ClinicalTrials.gov website.

To ensure a comprehensive report, a very careful search and selection process was undertaken, articles selected were read several times, and then carefully categorized into basic versus clinical study categories. These data were documented in a narrative format, rather than by applying any systematic approach, since the literature uncovered was extremely broad and highly heterogeneous and challenging to effectively aggregate. Readers are referred elsewhere for recent systematic reviews on this topic, however[7].

In this respect and as of January 6, 2018, we found PUBMED to house 86 articles dating back to 1963 when applying the terms *Articular Cartilage and Vitamin D*, with 21 being published in the last 5 years. Scopus had 135 articles; 27 in the last 5 years and Web of Science 214 since 1959. Using the key words *Osteoarthritis and Vitamin D* yielded 345 articles in PUBMED, 153 in last 5 years. There were 869 articles in Scopus using these key words; 278 in last 5 years. In the Web of Science cumulative data base there were 920 articles, although many were not relevant. To ascertain trends in joints studied over time separate searches were made for joints most affected by osteoarthritis.

After reviewing the possible review material, all data that did not address the current review themes in some way were excluded. 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.

Table 1 Chief features of the various in vitro studies that have attempted to examine vitamin D attributes in the context of osteoarthritis pathology.

Substrate	Model	Finding
Boyan *et al*[31]	Rat ligament transaction model	Protects against OA
Cantona *et al*[32]	Murine + collagen-induced model	Prevents progression OA
Castillo *et al*[28]	Rat model	Protects against early OA
Chen *et al*[18]	Rat chondrosarcoma chondrocytes	Might foster cartilage erosion
Hansen *et al*[19]	Human OA related chondrocytes	Yields negative results
Hirota *et al*[33]	Mouse model	Influences cartilage formation
Huhtakangas *et al*[20]	OA synovial stromal cells	Reduces inflammation
Li *et al*[26]	Ovariectomized rats	Has protective effects
Pascual-Garrido *et al*[27]	Rat model	Deficiency has negative effect
Rai *et al*[29]	Swine OA model	Attenuates inflammation
Shen *et al*[25]	Murine TMJ model	Prevents OA regression
Yamamura *et al*[34]	Murine knee OA model	Reduces articular degenertion early on

OA = osteoarthritis.

Table 2 Table depicting general overview of most representative clinical investigations conducted over the last 40 years 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, approaches, and conclusions among the studies across time (Observational outcomes 11/12 positive as regards a pathological or intervention effect or both; Prospective study outcomes 13/18 positive).

Authors	Study design	Sample	FINDING + LIMITATIONS*
Abu el Maaty *et al*[88]	*Cross-sectional study	36 women and 10 men with knee OA were screened for vitamin D status	Suboptimal vitamin D levels are associated with knee OA incidence among Egyptian post-menopausal women
Alkan and Akgol [67]	*Cross-sectional 2 group comparison study	100 knee OA cases, divided into vitamin D levels-present or absent were examined on a variety of salient endpoints and correlates	Vitamin D deficiency exacerbates pain, dysfunction, and poorer life quality in knee OA cases, but not radiographic disease stage
Askari *et al*[68]	Case-control study	131 cases with OA and 262 healthy controls had serum vitamin D and interleukin levels tested	Interleuken levels were higher in OA cases and vitamin D3 levels were lower. Interleuken levels, pain, and vitamin D3 serum were positively correlated
Arden *et al*[36]	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	Radiographic progression over 3 years in the 'contra-lateral' knee, pain, stiffness, function were not improved-however on average 50% were already 'vitamin D sufficient' at baseline and WOMAC total scores were not identical numerically speaking post treatment; placebo group experienced higher levels of vitamin D deficiency over time-and an increase in WOMAC pain scores. What/whether other interventions were pursued; whether adherence to the 'active' regimen was optimal; what occurred between years 1 and 3; what occurred in the 'ipsilateral' knee; vitamin D levels at 3 years were not published; and reasons for substantive dropout rates or why many had unreadable x-rays was unclear
Barker *et al*[69]	Observational study	56 subjects, av. age 48yr, with knee OA, 17 deficient, 21 insufficient, 18 vitamin D sufficient	Vitamin D deficiency impairs quadriceps function, and could play an anti-inflammatory role in cases of vitamin D sufficiency. Subjects were quite young, a small sample was studied, and no other micronutrients were examined
Bassiouni *et al*[65]	Prospective study	38 subjects with and without knee OA were observed over a 12 month period	Vitamin D (25(OH) 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 radiographically	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 and worsening of 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; covariates included age, clinic site, season at time of blood withdrawal, self-reported hip pain for >30 days, timed 6-meter walk, presence of at least 1 coexisting condition, and self-rated health status	Men with vitamin D deficiencies (15.1-30 ng/ml) are at high risk for hip OA, and twice as likely to have prevalent hip OA if they are vitamin D deficient. Men with higher vitamin D levels (above 30ng/ml) were less likely to have hip arthritis. Vitamin D therapy is warranted for augmenting health in the elderly
Felson *et al*[64]	Examined vitamin D levels in subjects longitudinally	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, and were average were 19.7+7.4 ng/ml was unrelated to the risk of joint space narrowing or loss of knee joint cartilage
Goula *et al*[40]	*Observational uncontrolled cohort study	164 patients with knee or hip OA scheduled for joint replacement in Greece were examined one week before surgery	A large percentage of patients were vitamin D deficient (81.7%); 15.2% were vitamin D insufficient, only 3% were vitamin D sufficient though Greece is a 'sunny' country. Male gender and vitamin D levels were positively correlated

Grazio *et al*[53]	*Observational study of 120 patients with psoriasis, rheumatoid and osteoarthritis (OA)	In OA cases, 97% subjects had serum vitamin D deficiencies	Prophylactic supplementation with vitamin D is recommended for OA patients
Heidari *et al*[71]	*Observational study	148 cases knee OA; 150 controls, mean ages 60.2 and 60.1 years, respectively	Significant associations exist between levels of serum vitamin D and knee osteoarthritis in patients less than 60 years of age
Huhtakangas *et al*[20]	Examined effects of vitamin D3 and calcipotriol on synoviocytes from OA patients	Exposure to either product produced long-lasting inhibition of cell proliferation and cytokine production	Results warrant further exploration of the anti inflammatory properties of the vitamin D active form and its analog
Hussain *et al*[37]	Prospective	9135 adults who had vitamin D levels assessed in 1999-2000 and were 40 years or older than 40 years undergoing hip arthroplasty for OA between 2002-2011	Increasing serum 25-hydroxyvitamin D levels were associated with and increased risk of hip arthroplasty, but not females. Reasons for hip arthroplasty may not all be correctly diagnosed as being primary OA related, especially in young cohorts; other factors such as involvement in contact sports, occupational stresses, and motor vehicle crashes were not examined or added to the regression model; there are no vitamin D measures over time that could determine status over time, and whether these were low, high, or adequate
Jansen and Haddad [72]	*Cross sectional	Examined elderly cases with advanced knee OA awaiting surgery	A high prevalence of vitamin D deficiencies was evident
Javadian *et al*[8]	*Observational	40 knee OA cases	Vitamin D levels correlate with pain, and muscle strength
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 (50,000 units) did not produce significant clinical or cartilage volume structural differences in the 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 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 (BMI). 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]	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]	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
Levinger *et al*[17]	*Observational	24 cases with knee OA	Cases with vitamin D insufficiency showed poorer function during balance recovery, more pain, and walking problems, as well as muscle power dysfunction
Maier *et al*[73]	Observational	Vitamin D levels were measured in 1083 patients admitted for elective hip or knee arthroplasty. Comparisons were performed using Chi square or Student's t test, followed by univariate and multiple linear regression analysis adjusting for possible confounders	There was a high frequency of hypovitaminosis D among patients Low vitamin D levels showed a significant inverse association to the length of stay in the unit. Patients with vitamin D levels in the target range were hospitalized 4.3 days less than patients with hypovitaminosis D.

Malas *et al*[24]	Investigated the association between vitamin D levels and distal femoral cartilage thickness in healthy subjects	80 women in an outpatient clinic who had musculoskeletal complaints other than the knee and classified into 3 subgroups according to vitamin D levels; <10, 10-20, and >20 ng/mL	The severe deficiency group had thinner femoral cartilage thickness, and it was concluded low vitamin D levels affect femoral cartilage thickness negatively. Only women were studied, and results relied on ultrasound measures
Manoy *et al*[56]	Prospective study with 6 month follow up	175 knee OA cases with low serum vitamin D received supplementary doses of 40,000 IU per week for six months	Patient quality of life and pain improved after six months as did mean serum levels of vitamin D, although 42.9% still exhibited vitamin D deficiency. Knee OA cases improved their grip strength and function, gait speed, balance, and walking endurance and showed reduced oxidative protein damage. Were mean body weight status also declined significantly, as did fat mass, and percentage of fat. There was no true control group, the sample size was small, and 8.37% of patients were lost to follow-up
McAlindon *et al*[75]	Prospective randomized double-blind single-centre study	146 cases with knee OA received 2000 IU orally with altered doses at 4, 8, and 12 months	There was a 4% cartilage loss in the experimental as well as the control group. Gender ratios were not the same in the 2 groups at baseline; pain was more intense in experimental group; function was also worse numerically speaking; both groups were vitamin D 'sufficient' on average at baseline; cartilage volume was numerically lower in the experimental group
Muraki *et al*[76]	*Cross sectional study	787 knee OA cases in the United Kingdom, mean age 65.6 years	Vitamin D may be more strongly associated with pain measured on a questionnaire than radiographic change according to a general estimating equation
Sanghi *et al*[77]	1 year RCT	106 knee OA cases considered vitamin D insufficient {< 50 nmol/L) were randomized and experimental group received 60,000 IU vitamin D for 10 days, followed by 60,000 once a month for 12 months	There is a small clinical benefit to using vitamin D as regards pain and subjective functioning. The criterion for vitamin D insufficiency was not defined, cases and controls were younger than expected for primary knee OA, the allocated vitamin D regimen was not a dosage commonly applied or discussed in the mainstream literature. The 45.70 nmol/L vitamin D serum change in experiment group– if denoting an increase, may have raised the serum level by an excessive amount in one year
Traven *et al*[78]	Retrospective review of post-operative cases followed over a 4 year period	126 total joint arthroplasty revision cases conducted between 2010-2014 were examined	Low vitamin D is not associated with risk of 30-day readmission, but is associated with an increased risk of 90-day complications as well as periprosthetic joint infection as the reason for revision surgery. Preoperative vitamin D level should be considered a modifiable risk factor for complications following revision arthroplasty
Veronese *et al*[79]	Cross-sectional study	Examined the relationship between vitamin D levels and presence of OA and pain in a cohort of older people. 2756 subjects (1102 males and 1654 females) with a mean age of 74.2±7.1 years. OA and OA-related pain were defined using a standardized algorithm	Logistic regression showed those in the lowest quartile had significantly higher odds of OA involving the hands, and pain. Similar results were found for the hip. For the knee, low vitamin D levels were associated with the presence of OA and OA related pain in the sample as a whole, particularly when the hand and hip were involved
Wang *et al*[46]	Prospective 24 months RCT	413 cases 209-active vitamin D; 204 to placebo group	Effusion-synovitis volume remained stable in vitamin D group; but increased in placebo group
Yoshimura *et al*[52]	Prospective	1384 cases with osteoporosis or OA were followed for 3 years and assessed radiographically using the Kellgren-Lawrence rating scale	Higher serum 25-hydroxy vitamin D levels do not prevent knee OA or lumbar spondylosis based on survey responses; cases with knee OA had higher vitamin D levels than those without the disease. Some did not complete follow-up assessments and dropout rate may have skewed or obviated salient findings. Knee OA was associated with risk of femoral fractures for which low vitamin D was considered a risk factor
Zhang *et al*[48]	Prospective	418 knee OA patients	Approximately 16% sample had low vitamin D levels. Between baseline and follow-up 15% progressed in joint space narrowing score response. 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	413 knee OA cases were divided into 3 groups of vitamin D; insufficiency [<50 nmol/L, 3 + 24 months], fluctuating [> 50 nmol/L at either 3/24 months], and sufficient levels [>50 nmol/L at 3+24 months]. In addition, pain, effusion-synovitis and various cartilage and bone measures were made at 3 and 24 months	Sufficient vitamin D levels benefited cartilage loss, effusion-synovitis, and physical function compared to the consistently insufficient group. It is not clear how the functional improvements occurred in this progressively degenerating disease because no data on other interventions or whether vitamin D supplementation was applied were reported. At baseline, effusion-synovitis was lower than that of the consistently sufficient group even though deemed comparable

RESULTS

Laboratory based studies

Among the diverse strategies employed in the laboratory to examine the nature of any possible clinically important association between vitamin D and osteoarthritis pathology are cell culture studies, as well as explants or various simulations of the osteoarthritis process. As outlined in Table 1, which provides but a very brief synopsis of the substrate studied and the conclusions reached by the study group, as arranged alphabetically, rather than in any hierarchy, it can be seen that most found some type of association between the presence or absence of optimal vitamin D levels and one or more osteoarthritis correlates that could prove of potential clinical import, with the exception of Chen *et al*[18]. Contrary to the findings of most other groups, this research group observed that the presence of vitamin D stimulated metalloproteinase 3 expression-a pro inflammatory agent-in a dose and time dependent manner. It also inhibited type II collagen and aggrecan expression, findings that would be contrary to the idea that vitamin D supplementation may be beneficial in some way in averting or minimizing osteoarthritis degenerative processes. Indeed, both the specific form of enzymatic expression, and the decrease in aggrecan expression that was observed would be extremely harmful to the integrity of articular cartilage, the tissue of most concern in osteoarthritis. Hence, contrary to having a favorable therapeutic impact, this research implied vitamin D might activate the expression of harmful chondrocyte products, rather than any beneficial response, a speculation raised by both Chen *et al*[18] and Hansen *et al*[19]. However, the substrates examined by Chen *et al*[18] and Hansen *et al*[19], namely, potentially 'healthy' dedifferentiated human cartilage cells from osteoarthritis cases may not have emulated the in situ responses of actual intact osteoarthritic chondrocytes relative to vitamin D applications at all adequately. Even if they did, the non physiological vitamin D concentrations and unnatural experimental situations may have produced or induced the observed destructive quality of the vitamin D in the context of the cartilage cells and tissue examined, but this was not discussed to any degree.

These aforementioned results were also diametrically at odds with those of others, such as Huhtakangas *et al*[20] who found 24-48 hour cartilage exposures to vitamin D reduced cytokine production and synovial cell proliferation significantly. Early work by Corvol[21] in the rabbit chondrocyte along with that by Schwartz[22] also found vitamin D [24, 25-$(OH)_2D_3$] to stimulate proteoglycan synthesis in "mature" chondrocytes, while the 1, 25-$(OH)_2D_3$ form of vitamin D increased chondrocyte DNA polymerase activities during the logarithmic division phase.

As well, Dean *et al*[23] found that neutral metalloproteinase and plasminogen activator activity in cartilage matrix vesicles tended to be regulated by vitamin D metabolites in a cell maturation-specific manner. Similarly, Malas *et al*[24] found metalloproteinases, which degrade cartilage proteoglycans could be influenced favorably by the presence of '*sufficient levels*' of vitamin D, whereas '*low vitamin D levels*' were likely to increase their deleterious activity.

In another line of in vitro research, Shen *et al*[25] who examined the role of vitamin D deficiency in the context of temporomandibular osteoarthritis using a mouse model, was able to show significantly reduced levels of bone mineral density and subchondral bone volume in the context of any deficiency of this vitamin in the mandibular condyles, often affected by osteoarthritis. In addition, the joint surfaces were found to have collapsed, and the vitamin D deficient mice displayed an erosive type of osteoarthritis with increased DNA damage, cellular senescence, and associated inflammatory cytokines,

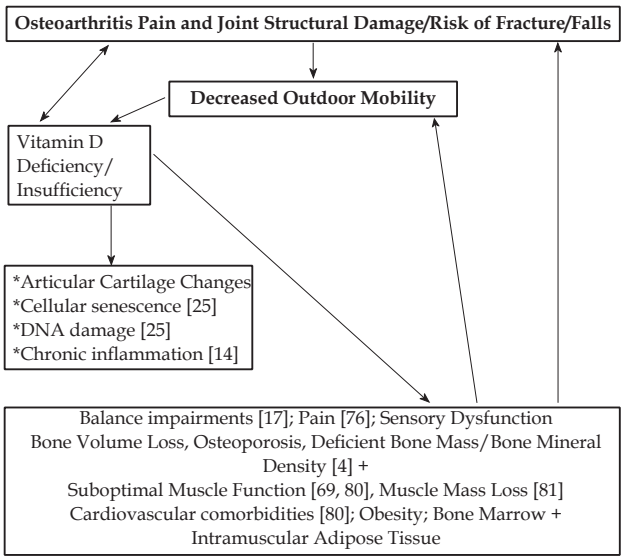

Figure 1 Hypothetical link between the impact of vitamin D deficiency/insufficiency and osteoarthritis showing that there are many pathways involved in vitamin D mediated functions that can directly or indirectly impact articular cartilage and the overall disease process. Accordingly, interventions focusing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

Table 3 Summary of a PUBMED search conducted January, 2018 showing many articles on the topic of vitamin D and osteoarthritis [OA] are older than 5 years and that only the knee joint is being studied with any intensity. Data below stem from animal models, cell culture studies, and various controlled and uncontrolled clinical studies, and surgical studies.

Key words	Number reports since 1980	Past 5 yrs
Knee OA + Vitamin D	138	88
Hip OA + Vitamin D	77	20
Spinal OA + Vitamin D	40	11
Lumbar OA + Vitamin D	36	11
Cervical OA + Vitamin D	27	9
Hand OA + Vitamin D	20	8
TMJ OA + Vitamin D	3	1
Shoulder OA + Vitamin D	2	1
Elbow OA + Vitamin D	0	
Wrist OA + Vitamin D	1	
Thumb OA + Vitamin D	0	
Metacarpal/tarsal OA + Vitamin D		
Total of all publications	394	149

and gradual cartilage thinning. In time, these researchers also found a decrease in cartilage matrix abundance and eventual erosion of the mandibular condyles, implying a vitamin D deficiency can induce the onset of an erosive type of osteoarthritis in the context of the mouse temporomandibular joint.

This result was consistent with that of Li *et al*[26] who used a rat model of osteoarthritis to show that a vitamin D deficient diet could aggravate cartilage erosion, while vitamin D supplementation, in contrast, could yield a protective effect against cartilage erosion. This was a well-designed study with seven comparative groups including a sham group comparison, suggesting the findings were reasonably robust.

Another study employing the rat model[27] similarly concluded 'low vitamin D levels' could produce detrimental changes in the structure of articular cartilage. In partial support of this aforementioned finding,

Castillo *et al*[28] who also employed a rat model of osteoarthritis, found vitamin D supplementation to initially have a protective effect against the disease. Although this effect failed to occur at the later disease stages, the application of intra-articular vitamin D injections yielded less articular cartilage damage and levels of inflammatory mediators for up to 28 days after the articular cartilage damage cycle was initiated.

Vitamin D supplementation also impacted favorably on cartilage loss in the knees of hyperlipidemic microswine, in those microswine deemed vitamin D-sufficient or deficient. The vitamin D deficient sub-group also developed more adipose cells and their rate of proteoglycan expression decreased to a greater degree than the vitamin D sufficient group[29]. In addition, adding vitamin D to other compounds, has been shown to have significant protective properties in the context of joint and bone lesions and related alterations in the ovariectomised rat model of osteoarthritis.

In sum, among the small array of diverse studies examining the association between vitamin D and articular cartilage in various target models or tissue derivatives of osteoarthritis, most imply some dose-response relationship exists between vitamin D and cartilage integrity. The direction or magnitude of this effect is not consistent though, and while vitamin D may be deemed beneficial in some instances, in others it may prove more deleterious than not and facilitate cartilage erosion[28]. With no definitive model, or study approach, the observed outcomes may depend on the substrate employed, the degree of cell dysfunction present, the measurement approaches employed, and durations of exposure among other factors. Animal models of osteoarthritis may also lack validity if they do not emulate the clinical condition, for example, if muscle quality is normal, obesity is not evident, and competing issues such as comorbid conditions are not apparent. However, if we believe medical science works best from the lab to the bedside, the available data are still intriguing (Table 1).

Clinical studies

As with the aforementioned preclinical studies that have examined vitamin D in the context of osteoarthritis, a fair array of quite diverse clinical approaches prevail. However, unlike the prevailing laboratory studies, a cursory examination of those representative clinical studies depicted in Table 2 shows an array of non uniform approaches, as well as inconsistent conclusions and findings.

For example, while some analyses imply supplementary vitamin D is ineffective for treating osteoarthritis[35], and that vitamin D supplementation does not slow the rate of joint space narrowing or reduce pain, stiffness, or functional losses[36], and can increase the risk of hip arthroplasty[37], or heighten pain[38], others imply a high percentage of patients with hip or knee osteoarthritis are likely to be vitamin D deficient[39], even if they live in sunny climates[40]. Others report adverse associations between vitamin D deficiencies and femoral cartilage thickness[24], serum leptin levels-a possible market of osteoarthritis pathology[41], the risk for osteoarthritis progression[42], osteoarthritis disability, and pain[38,43], even though others have failed to support a link between vitamin D and the disease progression[44,45].

However, as per findings of Wang *et al*[46], and consistent with some laboratory findings, vitamin D can significantly allay the progression of joint swelling in cases with knee osteoarthritis if given in the form of monthly exposures of 50,000 IU. In contrast, men with hip osteoarthritis are more likely than not to be vitamin D deficient[47], and those with insufficient vitamin D levels[5], may suffer increased rates of disease progression[48].

As well, Lane *et al*[49] confirmed that low levels of vitamin D may provoke incident changes of radiographic hip osteoarthritis as characterized by joint space narrowing, as did Bergink[50]. Importantly, even though association does not prove causation, McAlindon *et al*[43] found low serum vitamin D levels also predicted the extent of any cartilage loss, as assessed by the magnitude of prevailing joint space narrowing and osteophyte growth.

Ding *et al*[51] likewise found sunlight exposure and baseline serum vitamin D and the extent of knee cartilage loss as assessed by radiograph or magnetic resonance imaging to be associated. In particular, using a broad range of vitamin D levels, rather than any predefined cut-off points, they were able to conclude that achieving vitamin D sufficiency may prevent and/or retard cartilage loss in knee osteoarthritis. However, while this conclusion was recently supported by Chaghanti *et al*[47], Yoshimura *et al*[52] observed no clinically relevant linkage between vitamin D levels and those knee osteoarthritis variables they assessed.

Moreover, adding to the list of competing conclusions are those of Grazio *et al*[53] who compared vitamin D serum levels among differing rheumatic disease patients, and found an apparent association between having higher levels of vitamin D and their measures of disease activity and function. As well, Zheng *et al*[54] found the maintenance of vitamin D sufficiency correlated with improved structural and symptomatic knee osteoarthritis outcomes, even though vitamin D levels when measured did not correlate with radiographic measures[49], nor disease activity, regardless of summer or winter seasons[55].

Manoy *et al*[56] on the other hand found vitamin D supplementation of 40,000 IU per week for six months decreased pain, and improved physical performance and life quality among osteoarthritis cases. In addition, a fairly strong evidence base exists to support a number of different mechanisms whereby osteoarthritis and deficient vitamin D levels are linked[57] such as bone mineralization and cell differentiation, pain sensitization[14], muscle strength[5,58], inflammation[46,59], and outcomes after joint replacement surgery[60]. Vitamin D is also likely to: enhance falls prevention efforts[61], reduce the risk of depression[62] and balance problems that can lead to physical activity declines and an increased risk of joint attrition (Figure 1). In addition, Lazlett *et al*[63] concluded that the presence of a moderate vitamin D deficiency can independently predict incident, or worsening knee pain over a five year period and, possibly, hip pain over a two and a quarter year period, even though Felson *et al*[64] observed no major impact of vitamin D deficiency over time, among osteoarthritis cases.

This finding of Felson *et al*[64] failed to concur with observations of Bassiouni *et al*[65] in a prospective study of cases with knee osteoarthritis, and Alkan and Gokhan[67] who conducted a comparative study of knee osteoarthritis cases with and without vitamin D deficiency, however. In the study by Bassiouni *et al*[65] a vitamin D deficiency was associated with meniscal deterioration, and in the study by Alkan and Gokhan[67], those with vitamin D deficiencies had more pain and dysfunction than those with sufficient levels. This finding by Felson *et al*[64] also failed to concur with that of Abu El Maaty *et al*[6], who concluded vitamin D increases nitric oxide production and inducible nitric oxide synthase expression in osteoarthritic chondrocytes, possibly leading to a protective effect. Indeed, despite possible research shortcomings, Heidari *et al*[5] found that 'correcting' a vitamin D deficiency over a two month period yielded a highly beneficial effect on knee strength and pain in patients with knee osteoarthritis.

In sum, while several researchers imply there is no added value to recommending vitamin D supplementation in the context of

osteoarthritis pathology if vitamin D levels are deficient, 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 number of important clinically relevant findings that do exist tend 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 evidence prevails to support hypothesizing a contributory, moderating or mediating association between vitamin D and osteoarthritis joint damage. 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 is hard to refute based on preclinical studies reported in Table 1, along with the observation of a small number of potentially valuable clinically relevant outcomes shown in Table 2.

However, results may well vary across studies since their durations, age cut-off or inclusion points, sample inclusion criteria, and type and extent of disease entity are often quite disparate. In particular, what constitutes *optimal* versus *insufficient* serum levels of vitamin D is not uniform, nor standardized, with some believing 600 IU of vitamin D per day is too low, while others feel a 'safe' daily vitamin D dose is 4000IU[11]. Similarly, the additional categorical definitions of *deficient* versus *sufficient* serum vitamin D levels are clearly not governed in this present body of research by any universal or agreed upon standard. For example, serum vitamin D '*deficiencies'* have been conceptualized as present if serum levels are found to be ⩽20 ng/ml[5,48], ⩽10 ng/ml[24,65], ⩽40 nmol/l[66], or ⩽15 ng/mL[47]. Adding further confusion to this topic is the fact that '*sufficient*' levels of circulating vitamin D have been categorized as ranging from 20 ng/mL[24,36,65], to 30 ng/mL[40,48], and even 40 nmol/L[66].

In addition to the above factors that may confound the development of a consensus regarding vitamin D and osteoarthritis, the methods of assessing serum vitamin D may vary, with one measure being more sensitive than another, the nomenclature used for describing vitamin D may similarly vary, as may the extent of any dietary or vitamin D supplementation intake along with sunlight exposure. Numbers of applied vitamin D units in supplementation studies, plus the duration and frequency of application, may also vary.

Finally, no presently reviewed report examined whether any osteoarthritis case in any clinical study was possibly exposed to hypervitaminosis, and other potentially confounding clinical correlates of osteoarthritis, such as age, gender, ethnicity, body mass, comorbid health conditions, and inflammation, among other factors were not well documented, categorized, or considered of import in most studies.

Other issues tending to preclude consensus on this present topic of interest are: (1) Discrepant and/or seemingly arbitrary chosen assessment 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) Numbers and types of affected osteoarthritic joints; (5) Extent of and type of any co-interventions; (6) Disparate and/or insensitive outcome assessment measures; (7) Limited attempts to assess biomechanical disease correlates objectively.

In addition, very few studies sought to examine the presence or change in any associated joint inflammation or effusion, the prevailing sleep quality of the individual, the extent of any centralized pain, depression, muscle or balance problems, or obesity, and falls history as possible explanatory correlates of the observed study outcomes.

In sum, and in accord with Sowers and Lachance[57], the aforementioned studies, while not all in concordance, implicate four possible pathways of influence on osteoarthritis pathology, including: (1) modulation of pain and inflammation; (2) favorable cartilage impacts; (3) positive impacts on bone and muscle; (4) and the immune system[68].

Conversely, deficient or insufficient vitamin D levels can be hypothesized to have widespread negative joint and general health implications as per Figure 1.

Other possible linkages may not have been studied or validated because reports on various forms of osteoarthritis and vitamin D as listed below are very limited in number and scope (Table 3).

DISCUSSION

Osteoarthritis, the most prevalent form of arthritis remains a major progressive disabler of older adults. A disease with no known cure, it has been proposed that the properties of vitamin D, in the form of vitamin D_3, a fat-soluble steroid hormone involved in fostering multiple functions related to the musculoskeletal system might be harnessed to ameliorate some of this pathology. Conversely, insufficient levels of vitamin D may raise the risk for perpetuating or causing osteoarthritis due it its well known impact on bone structure and function. However, this hypothesis has been repeatedly disputed[83,84], notwithstanding a reasonably strong set of preclinical evidence as well as clinical evidence that vitamin D may be implicated in some way in the osteoarthritis pain cycle, and the finding that older cases with knee osteoarthritis are more likely to report problems with mobility, self-care, and usual activities if they are vitamin D deficient[85]. But what accounts for this discrepancy? What benefits can be re-examined? What should researchers consider in the future in this sphere?

First, to account for the discordant observations that prevail, careful analysis shows many possible explanatory factors prevail. These include but are not limited to: the study design, the limited samples studied, undocumented comorbid disease-associated features, somewhat arbitrary assessment points and follow-up periods, and the much neglected issue of co-interventions. Other potentially confounding factors when trying to aggregate the prevailing data are the oftentimes differing vitamin D terminologies, measurement approaches, modes and duration of exposure, and assumptions supplementation is optimal and safe in intervention studies. Failure to account for history, maturation, or cross-contamination effects are additional challenges. Moreover, limited attention to age, gender and ethnicity mediating or moderating effects within and across most clinical studies further confounds the acquisition of any robust independent set of conclusions or unity among the current body of prevailing research.

As well, no study to date truly took into account that the lifetime of vitamin D is probably between 2-5 hours, such that if it is used as a therapeutic agent, it may be better to administer this frequently in small doses, rather than mega doses. Whether optimal supplementation was achieved in related studies shown in Table 2 cannot be verified because vitamin D outcomes may depend on many factors such as how and when vitamin D is administered[86], and assessed[88], the extent of muscle atrophy that prevails[89], blood calcium levels[86], plus the activity and health status of the sample studied, especially the presence of any gastro-intestinal or renal disorder, and whether these variables are measured or not.

Small, possibly underpowered studies, supplementation studies with final comparable vitamin D levels across groups[34], semi-quantitative MRI scaling, large sample losses in follow-up study[64], assumptions that 20ng/ml vitamin D are non-deficient levels of the

vitamin[64] are further possible confounders.

Unknown or inaccurate assumptions about vitamin D supplementation adherence rates, unknown dietary and sunlight derived vitamin D exposure rates in supplementation studies, assumptions there is no change in an individual's health regimen or status, along with differing definitions of vitamin D sufficiency versus deficiency, and seasonal fluctuations in vitamin D serum levels[89] must also surely be considered as additional possibly confounding study variables. Moreover, rather than a lack of efficacy, or any seemingly relevant association between vitamin D serum levels and the prevailing degree of osteoarthritis pathology in some studies, findings may reflect suboptimal or harmful supplementation approaches, vitamin D fluctuations due to poor patient adherence, as well as differences in joint and mobility, alterations in health and mental health status[90].

In light of the importance of averting a type II error and discarding a possibly useful clinical idea that might ameliorate some of the osteoarthritis burden, it appears concerted efforts to conduct rigorously controlled studies that employ comparable and agreed upon vitamin D criteria, supplementation and measurement approaches, studies of comparable duration, follow-up schedules, and outcome approaches are highly desirable. Examining the reasons for the disconnect between results of negative studies and those studies that show vitamin D is able to favorably influence bone and muscle health[80], attenuate oxidative stress in paraspinal muscles in low back pain patients[91], improve or impact favorably on articular cartilage status[31,54] and gait parameters post-hip surgery[92], among other benefits, is also surely indicated.

As well, to minimize confusion, research to rule out other explanations for positive and negative findings may help to answer the question of whether vitamin D can be optimally harnessed to positively affect osteoarthritis pain[76] and surgery outcomes[60], while reducing the onset of an erosive form of osteoarthritis[25]. Since more careful study of the association between structures implicated in osteoarthritis, such as muscle and bone, and inflammatory processes, and vitamin D deficiency[29], or effective supplementation[26], may prove especially insightful, planning to pursue these lines of research should also receive due consideration. As outlined by Diao *et al*[43], at the very least, "longer-term clinical trials with rigorous measurement of symptom and radiologic changes are required to further clarify the effect of vitamin D supplementation in patients with symptomatic knee OA and low serum 25(OH)D levels" (p. 1312).

However, the will of researchers to pursue this line of inquiry is very imperative because despite the immense economic and social importance of this topic, resolution of most of the confounding factors discussed in the aforementioned issues, does not seem to be occurring to any concerted degree, other than possibly with respect to knee osteoarthritis. Indeed, if the United States ClinicalTrials.gov data base is carefully examined, it seems that much needed research is not being proposed or funded or both. As of December 2017, this website showed only two active vitamin D related trials, but these are not osteoarthritis specific, and one that has not yet commenced recruitment, is about nutrition, in general, rather than the role of vitamin D in the osteoarthritis pathological cycle. Another to be completed in 2018 does not test vitamin D efficacy, but gives both study arm members 1000 IU units per day vitamin D supply for the two year intervention duration, while another gives both arms calcium/vitamin D supplementation, even though this has been disputed as efficacious.

This limited number of questionable approaches is not consistent with the possible potential of vitamin D as a therapeutic analog or as a disease precursor, and an osteoarthritis disease correlate. In particular, even if diseased cartilage is not always directly responsive to vitamin D supplementation, it is possible that its thoughtful application may yet impact specific osteoarthritis correlates such as inflammation, pain, excess dysfunction and low life quality, regardless of disease stage and site. Alternately, identifying the presence of vitamin D deficiencies and rectifying these across the lifespan earlier rather than later, may yet prove to be a highly efficacious cost-effective form of minimizing excess joint disability in later life. By contrast, a failure to act in a timely way may exacerbate the development of osteoarthritis, along with the patient's pain experience and degree of dysfunction[67], rate and degree of cartilage erosion[35], excess bone loss and muscle weakness, bone fracture risk, and ability to remain independent and socially connected, as may excess delivery of vitamin D supplementation-a little studied topic, albeit a highly important one.

In the meantime, areas of great promise do exist[93], studies on animal models are largely supportive of a vitamin D-osteoarthritis linkage, as are more rather than less observational and prospective clinical studies, hence rather than discounting the importance of past efforts, as proposed by Cianforroti *et al*[94], examining the impact and role of vitamin D in the context of this intractable widespread highly disabling human condition of osteoarthritis appears highly desirable and should continue. In particular, it is especially important to stress this given that despite concerted efforts for several decades to reduce the osteoarthritis burden, no true progress in more than 30 years or more can be detected except for the realm of surgical replacements[95]. Emerging evidence in this realm however, surely shows that patients undergoing joint revision surgery for end-stage osteoarthritis who have low vitamin D levels at that time are more likely to experience 90-day complications as well as periprosthetic joint infections after surgery than those with adequate levels[60,78], and this finding may be more universal, rather than isolated, as it may affect up to 84% of surgical cases[26].

Accordingly, Traven *et al*[78] specifically recommended that preoperative vitamin D levels be considered a modifiable risk factor for complications following revision arthroplasty as have others[60,73,92], suggesting even in later disease phases a role for vitamin D should not be overlooked.

As well, Rai *et al*[29] intimated that either directly, or indirectly through its influence on muscle and bone, other body systems, inflammation and obesity[11] the presence of 'sufficient' vitamin D serum levels may help reduce the chances of excess suffering and joint dysfunction in cases of osteoarthritis, regardless of disease stage[97]. Indeed, early and timely administration of vitamin D supplements in those with deficiencies, along with ensuring vitamin D levels are optimal among young adults during their annual check-ups alone may yet prove extremely valuable in later years, even if this has not truly been examined. Moreover, ensuring vitamin D levels are adequate, but not excessive, may be the key to helping to prevent the spread of osteoarthritis from one joint to the next, even in cases where only a single joint is affected. In addition to muscle related benefits[5,20], vitamin D may help prevent the onset of osteoporosis[98] that can precede, magnify, or accompany articular cartilage degeneration. Even if the rate of disease progression remains static in the face of vitamin D supplementation, conceivably this alone could be deemed to be a positive result in the context of this progressive degenerative disease. In addition to reducing pain sensitivity[5], enhancing life quality[48], and mobility, vitamin D may be key to reducing the risk of obesity, a common determinant or outcome of osteoarthritis[96].

Other benefits may include a lower falls prevalence rate that can lead to secondary osteoarthritis, and bone fractures, along with a lower likelihood of ensuing outdoor activity and sunlight exposure. It is also possible too that further research will reveal that osteoarthritis exacerbates the availability of vitamin D due to its impact on weight gain and subsequent obesity where fat cells are found to attract vitamin D, thus reducing its availability in the serum[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[11]. 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 sedentary and home bound. Low levels of vitamin D are also linked to cardiovascular related syndromes, that can further preclude outdoor activities for protracted periods, and muscle weakness, which may limit mobility, thus reducing the circulation of vitamin D within the body. Those who are advised to use sunscreen, or wear braces, or splints, or use wheelchair devices, or protective clothing might also be subject to lower than desirable vitamin D sunlight exposure[16], and its potential for adverse muscle and bone health consequences.

Consequently, even if vitamin D has no direct role in producing osteoarthritis, and cannot alter the radiographic structure of an osteoarthritic joint readily, 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], and the negative effects of mechanically loading the diseased joint[96]. Conversely, even if vitamin D measures take time, and are not favored by all, 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[99], and possibly even to their reduced consumption of analgesics as proposed by Anthony and Ding[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.

In the meantime, acknowledging the existence of many possible confounding factors in the current body of clinical research, such as the extent of outdoor activity and general nature of a patient's overall daily physical activities, climate and seasonal issues, nutritional practices, overlapping supplementation intake from multivitamins, sunscreen usage, comorbid conditions that affect vitamin D efficacy, or are impacted as a consequence of vitamin D deficiency is paramount in efforts to ascertain the facts pertaining to this current topic in our view.. At the same time, special attention to the extent of any prevailing biomechanical derangement, injurious work related activities and others, along with other factors that may obviate positive responses in prospective supplementation and other related studies, such as intractable pain, should be considered carefully noted. As well, careful efforts to monitor adherence to intervention regimens, and the deployment of high performance liquid chromatography assays as the gold standard, is also arguably of high importance in efforts to solidify this body of knowledge.

CONCLUSION

A hypothesized role for vitamin D, while theoretically plausible and supported by preclinical and other studies in the context of the osteoarthritis process remains non-conclusive at best, despite quite a number of research efforts extending over three decades.

However, due to multiple methodological issues, design and interpretation limitations, attempts to aggregate the available data base have produced conflicting conclusions.

To establish the facts concerning this topic, which shows fair promise as an important correlate in ameliorating and understanding selected aspects of the disease process, carefully controlled longitudinal studies with agreed upon criteria for what constitutes vitamin D sufficiency or insufficiency, plus careful efforts to monitor vitamin D intake or vicarious exposure over time, and adequate samples with varying degrees of pathology and affected joint sites and prevalence of vitamin D deficiencies appear warranted.

As well, the use of validated markers of cartilage pathology, biomechanical measures, as well as functional status applied at regular intervals may help to examine important related-yet often overlooked factors- of muscle strength and structure, balance capacity, functional gait attributes, and whether correcting 'deficient' vitamin D levels yields changes in one or more of these osteoarthritis correlates. 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 desired retesting duration[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 or null outcomes of intervention studies and their causes should be carefully examined as well, 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 may be especially helpful as well.

In the interim, notwithstanding the highly commendable recent attempts to examine vitamin D as a correlate of osteoarthritis, as articulated by Mabey and Honsawek[102] and Cao *et al*[103] conducting further research mindful of the limitations of individual studies and meta-analyses[104] can potentially help to establish if vitamin D status is a clinically relevant correlate or mediating factor of osteoarthritis outcomes or not. 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 eg benefits are overlooked, or harm is caused inadvertently. Crafting more comparable adequately powered research studies across different laboratories and settings, especially the community setting, may greatly help to uncover important clinically relevant intervention and prevention implications. In addition, 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 closing the words of Vaishya *et al*[105] resonate with the findings of this report and are highly relevant in the present context where similarly we believe "it would not be wrong to label vitamin D as one of the most important vitamin involved in the metabolism of the musculoskeletal system and any clinician, especially the orthopaedician, should be well versed with its overall mechanism and roles in the human body [especially in efforts to understand cartilage and joint biology in health and disease]"[105, p.173], and the limitations in the literature should be highlighted rather than unsubstantiated conclusions as discussed very eloquently by George[106] and Hussein *et al*[107].

REFERENCES

1. Colombini A, Cauci S, Lombardi G, Lanteri P, Croiset S, Brayda-Bruno M, Banfi G. Relationship between vitamin D receptor gene (VDR) polymorphisms, vitamin D status, osteoarthritis and intervertebral disc degeneration. *J Steroid Biochem Mol Biol* 2013; **138**: 24-40. [DOI: 10.1016/j.jsbmb.2013.03.001].
2. 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* 2012; **237**: 241-253.
3. St-Arnaud R, Naja RP. Vitamin D metabolism, cartilage and bone fracture repair. *Mol Cell Endocrinol*. 2011; **347**(1-2): 48-54. [DOI: 10.1016/j.mce.2011.05.018].
4. Dhaon P, Das SK, Srivastava R, Asthana A, Agarwal G. Osteoporosis in postmenopausal females with primary knee osteoarthritis in a vitamin D deficient population. *J Assoc Physicians India* 2017; **65**(11): 26-29.
5. 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.
6. Abu El Maaty MA, Hanafi RS, El-Badawy S, Gad MZ. Interplay of vitamin D and nitric oxide in post-menopausal knee osteoarthritis. *Aging Clin Exp Res* 2014; **26**(4): 363-368. [DOI: 10.1007/s40520-013-0192-9].
7. Hussain S, Singh A, Akhtar M, Najmi A. Vitamin D supplementation for the management of knee osteoarthritis: a systematic review of randomized controlled trials. *Rheumatol Int* 2017; **37**(9): 1489-1498.
8. Javadian Y, Adabi M, Heidari B, Babaei M, Firouzjahi A, Ghahhari BY, *et al* Quadriceps muscle strength correlates with serum vitamin D and knee pain in knee osteoarthritis. *Clin J Pain* 2016 Feb 17.
9. Koeckhoven E, van der Leeden M, Roorda LD, van Schoor NM, Lips P, de Zwart A, Dekker J, van der Esch M, Lems WF. 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.
10. Garabedian M, Du Bois MB, Corvol MT, Pezant E, Balsan S. Vitamin D and cartilage. I. In vitro metabolism of 25-hydroxycholecalciferol by cartilage. *Endocrinology* 1978; **102**(4): 1262-1268.
11. Glover TL, Goodin BR, King CD, Sibille KT, Herbert MS, Sotolongo AS, Cruz-Almeida Y, Bartley EJ, Bulls HW, Horgas AL, Redden DT, Riley JL 3rd, StaudR, Fessler BJ, Bradley LA, Fillingim RB. 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]
12. Tetlow LC, Woolley DE. Expression of vitamin D receptors and matrix metalloproteinases in osteoarthritic cartilage and human articular chondrocytes in vitro. *Osteoarthritis Cartilage* 2001; **9**(5): 423-431.
13. Al-Jarallah KF, Shehab D, Al-Awadhi A, Nahar I, Haider MZ, Moussa MA. Are 25(OH)D levels related to the severity of knee osteoarthritis and function? *Med Princ Pract* 2012; **21**(1): 74-78. [DOI: 10.1159/000330025].
14. 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].
15. 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].
16. 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. *Eygptian Rheumatologist* 2017; **39**: 249-254.
17. 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].
18. Chen D, Li Y, Dai X, Zhou X, Tian W, Zhou Y, Zou X, Zhang C. 1,25-Dihydroxyvitamin D3 activates MMP13 gene expression in chondrocytes through p38 MARK pathway. *Int J Biol Sci* 2013; **9**(6): 649-655. [DOI: 10.7150/ijbs.6726].
19. Hansen A, Figenscha Y, Zubiaurre-Martinez I, Figenschau Y. Co-expression of 1α-hydroxylase and vitamin D receptor in human articular chondrocytes. *BMC Musculoskeletal Disorders* 2017; **18**: 1-13.
20. 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].
21. Corvol MT, Dumontier MF, Tsagris L, Lang F, Bourguignon J. Cartilage and vitamin D in vitro. *Ann Endocrinol* 1981; **42**(4-5): 482-487.
22. 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. Dean DD, Boyan BD, Muniz OE, Howell DS, Schwartz Z. Vitamin D metabolites regulate matrix vesicle metalloproteinase content in a cell maturation-dependent manner. *Calcif Tissue Int* 1996; **59**(2): 109-116.
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, Chen L, Yuan X, Goltzman D, Chen N, Miao D. 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-β1 in ovariectomized rats. *Osteoarthritis Cartilage* 2016; **24**(2): 345-353. [DOI: 10.1016/

j.joca.2015.08.013].

27. Pasquel-Garrido C, Angeline ME, Ma R, Chahla J, Voigt C, Deng XH, 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 Journal* 2016; **12**: 150-157.
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 Sep 13;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 ovariectomised rats. *BMC Musculoskelet Disord* 2015; 16: 92. [DOI: 10.1186/s12891-015-0547-9].
31. Boyan B, Hyzy S, Schwartz Z, Scott KM, Coutts RD, Healey R, Schwartz Z. 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. Cantorna MT, Hayes CE, DeLuca HF. 1, 25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. *J Nutr* 1998; **128**(1): 68-72.
33. Hirota Y, Nakagawa K, Mimatsu S, Sawada N, Sakaki T, Kubodera N, Kamao M, Tsugawa N, Suhara Y, Okano T. Nongenomic effects of 1α,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 eldecalcitol 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, Wluka A, Zhu Z, Han W, Antony B, Wang X, Winzenberg T, Blizzard L, Ding C. 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, Hunter DJ, James S, Cooper C, O'Neill TW, Macgregor A, Birrell F, Keen R. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. *Osteoarthritis Cartilage* 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 of 25-hydroxyvitamin D and the risk of hip arthroplasty for osteoarthritis: result from a prospective cohort study. *Osteoarthritis Cartilage* 2015; **23**(12): 2134-2140.
38. 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].
39. Breijawi N, Eckhardt A, Pitton MB, Hoelzl AJ, Giesa M, von Stechow D, Haid F, Drees P. Bone mineral density and vitamin D status in female and male patients with osteoarthritis of the knee or hip. *European Journal Surg Res* 2009; **42**: 1-10.
40. Goula T, Kouskoukis A, Drosos G, Tselepis AS, Ververidis A, Valkanis C, Zisimopoulos A, Kazakos K. 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. 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].
42. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, Rush D, Wilson PW, Jacques P. 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.
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.
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, Knekt P, Arokoski J, Karppinen J. 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, Lu B, Nevitt M, Jackson B, Garganta C, Hochberg MC, Kwoh K, McAlindon TE. 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.
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. [DOI: 10.1016/j.semarthrit.2015.09.010]
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, Naglić ĐB, Anić B, Grubišić F, Bobek D, Bakula M, *et al*Vitamin D serum level, disease activity and functional ability in different rheumatic patients. *Am J Med Sci* 2015; **349**(1): 46-49. [DOI: 10.1097/MAJ.0000000000000340].
54. Zheng S, Jin X, Ding C, *et al* Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in

knee osteoarthritis. *Am J Med* 2017; **130**(10): 1211-1218.
55. Yazmalar L, Ediz L, Alpayci 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; 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.
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* 2015; **94**(42): e1812. [DOI: 10.1097/MD.0000000000001812].
59. Zwerina K, Baum W, Axmann R, Heiland GR, Distler JH, Smolen J, Hayer S, Zwerina J, Schett G. 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.
62. Shaffer JA, Edmonson D, Taggart Wasson L, 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. *Psychsom Med* 2014: **76**: 190-196.
63. Laslett LL, Quinn S, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. 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.
65. 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.
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 Musculoskelet 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.
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 Feb 19;2:466-74. [DOI: 10.1016/j.redox.2014.01.024].
70. Bergink AP, Uitterlinden AG, Van Leeuwen JP, Buurman 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, Lo G, Dawson-Hughes B. 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. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cart* 2011: **19**: 1301-1306.
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): 543-553. [DOI: 10.1089/rej.2015.1671].
80. Kaneko I, Miyamoto KI, Nikawa T. Update on recent progress in vitamin D research. Vitamin D and muscle tissues. *Clin Calcium* 2017; **27**(11): 1571-1578. [DOI: CliCa171115711578].
81. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, Cooper C, Brandi ML, Diez-Perez A, Reginster JY; ESCEO Task Force. The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Maturitas* 2014; **79**(1): 122-32. [DOI: 10.1016/j.maturitas.2014.07.005].
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. Onuora S. Osteoarthritis: Vitamin D not effective for knee OA. *Nat Rev Rheumatol* 2016; **12**(5): 252. [DOI: 10.1038/nrrheum.2016.47].
84. Guthrie RM. Review of: effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis. *Phys Sportsmed* 2013; **41**(3): 115-117. [DOI: 10.3810/psm.2013.09.2030]
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. DeLuca HF. Metabolism and molecular mechanism of action of vitamin D: 1981. *Biochemical Society Transactions Second Morton Lecture* 10: 1982: 147-158.
87. Balogun S, Aitken D, Winzenberg T, Wills K, Scott D, Callisaya M, Jones G. Longitudinal associations of serum 25-hydroxyvitamin-d, physical activity, and knee pain and dysfunction with muscle loss in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2017 Aug 14. [DOI: 10.1093/gerona/glx157].
88. Arya SC, Agarwal N. Apropos 'association of suboptimal 25-hydroxyvitamin D levels with knee osteoarthritis incidence in postmenopausal Egyptian women'. *Rheumatol Int* 2014; **34**(4): 587. [DOI: 10.1007/s00296-013-2721-4].
89. Brayda-Bruno M, Viganò M, Colombini A, *et al* Plasma vitamin D and osteo-cartilaginous markers in Italian males affected by intervertebral disc degeneration: Focus on seasonal and pathological trend of type II collagen degradation *Clinica Chimica Acta* 2017; **471**: 87-93.
90. Musumeci G, Aiello FC, Szychlinska MA, Di Rosa M, Castrogiovanni P, Mobasheri A. Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression. *Int J Mol Sci* 2015; **16**(3): 6093-6112. [DOI: 10.3390/ijms16036093].
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. da Cunha BM, Gava AD, de Oliveira SB, de David AC, Dos Santos-Neto LL. VitaminD is related to gait recovery after total hip arthroplasty: a prospective analysis. *Gait Posture* 2016; **50**: 96-101. [DOI: 10.1016/j.gaitpost.2016.08.014].
93. Gu X, Gu B, Lv X, Yu Z, Wang R, Zhou X, Qiao W, Mao Z, Zuo G, Li Q, Miao D, Jin J. 1, 25-dihydroxy-vitamin D3 with tumor necrosis factor-alpha protects against rheumatoid arthritis by promoting p53 acetylation-mediated apoptosis via Sirt1 in synoviocytes. *Cell Death Dis* 2016; **7**(10):e2423. [DOI:10.1038/cddis.2016.300].
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]
95. Oliviero F, Ramonda R, Punzi L. New horizons in osteoarthritis. *Swiss Med Wkly* 2010 Sep 17;140:w13098. [DOI: 10.4414/smw.2010.13098].
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. Abu el Maaty MA, Hanafi RS, El Badawy S, Gad MZ. Association of suboptimal 25-hydroxyvitamin D levels with knee osteoarthritis incidence in post-menopausal Egyptian women. *Rheumatol Int* 2013; 33(11): 2903-2907. [DOI: 10.1007/s00296-012-2551-9].
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.
99. Pal CP, Kumar H, Kumar D, Mittal V, Deshwar G, Altaf D, Verma S. Prevalence of vitamin D deficiency in orthopaedic patients - A single centre study. *J Clin Orthop Trauma* 2016; 7(Suppl 2): 143-146. [DOI: 10.1016/j.jcot.2016.06.009]
100. Antony B, Ding C. Vitamin D and osteoarthritis: disparity between observational studies and clinical trials. *Int J Rheum Dis* 2017; **20**(6): 671-674. [DOI: 10.1111/1756-185X.13133].
101. Brennan-Speranza TC, Mor D, Mason RS, Bartlett JR, Duque G, Levinger I, Levinger P. Skeletal muscle vitamin D in patients with end stage osteoarthritis of the knee. *J Steroid Biochem Mol Biol* 2017; **173**: 180-184. [DOI: 10.1016/j.jsbmb.2017.01.022]
102. Mabey T, Honsawek S. Role of vitamin D in osteoarthritis: molecular, cellular, and clinical perspectives. *Int J Endocrinol* 2015; 2015: 383918. [DOI: 10.1155/2015/383918].
103. Cao Y, Winzenberg T, Nguo K, Lin J, Jones G, Ding C. Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review. *Rheumatol* 2013; **52**(7): 1323-1334. [DOI: 10.1093/rheumatology/ket132].
104. 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.ijsu.2017.08.010].
105. Vaishya R, Vijay V, Agarwal AK, Jahangir J. Resurgence of vitamin D: old wine in new bottle. *J Clin Orthop Trauma* 2015; **6**(3): 173-183. [DOI: 10.1016/j.jcot.2015.02.002]
106. George J. Vitamin D supplementation and progression of knee osteoarthritis. *JAMA* 2016; **316**(3): 347-348. [DOI: 10.1001/jama.2016.6314].
107. Hussain S, Singh A, Akhtar M, Najmi AK. Letter to the editor on the article "The effect of vitamin D supplementation on knee osteoarthritis: a meta-analysis of randomized controlled trials". *Int J Surg* 2017 Oct 31. pii: S1743-9191(17)31400-0. [DOI: 10.1016/j.ijsu.2017.10.068].