

VITAMIN D AND VITAMIN D RECEPTOR GENE IN OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis is a degenerative, painful and irreversible disease that affects millions of people worldwide. The causes and mechanisms of osteoarthritis have not been fully understood. Vitamin D is an essential factor in bone metabolism. Its actions are mediated by the vitamin D receptor, a transcription factor that controls gene expression, thus maintaining calcium and phosphate homeostasis. Vitamin D has been hypothesized to play essential role in a number of musculoskeletal diseases including osteoarthritis, and its deficiency is prevalent among osteoarthritis patients. A large number of studies have been done regarding the effects of vitamin D in pathogenesis and progression of osteoarthritis, as well as its use as a therapeutic agent. Up to date, studies have provided controversial results, and no consensus concerning this matter was achieved. With this review, we aim to explore current data on the possible role of vitamin D and its receptor in pathogenesis of osteoarthritis and assess the efficiency of vitamin D supplementation as a therapeutic strategy.

Keywords: Osteoarthritis, vitamin D, vitamin D receptor, inflammation.

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INTRODUCTION

Osteoarthritis (OA) is progressive and degenerative joint disease that affects and causes disability in about 3.3% of global population (1). It starts as an inflammation of the synovium, followed by degradation and loss of articular cartilage, and abnormal subchondral bone growth. The most commonly involved joints are on the fingers, at the base of the thumb, neck, lower back, knee, and hips. The symptoms include joint pain, stiffness and swelling, that primarily appear sporadically in the morning, progress over the years, causing loss of mobility. The etiology, and pathogenesis of OA are not completely understood. However, there are known factors that, when combined, cause damage to the cartilage and subsequent bone remodeling. Based on the risk factors OA is classified as primary and secondary, both of which have the same clinical appearance. Primary OA is caused by, genetic predisposition, age (incidence increases among people over 60), gender (more prevalent in postmenopausal women), obesity (affecting large, weight bearing joints such as knee and hip), physically demanding work, joint immobility or joint injury. Secondary OA is not age related, and represents 20% of the cases. It is associated with congenital diseases such as Ehlers-Danlos syndrome, Marfan syndrome, alkaptonuria, Wilson's disease, with joint infections, injuries and inflammatory diseases (2). Diagnosis is made based on history and clinical examination. On radiography, the severity of joint damage can be graded by evaluating typical radiological changes: subchondral bone sclerosis, joint space narrowing, osteophyte formation, subchondral cyst formation and loss of bone contours (3).

Vitamin D is a steroidal hormone primarily involved in calcium homeostasis and bone metabolism. Through binding to the vitamin D receptor (VDR), vitamin D regulates absorption of calcium and phosphate from kidney and the gastrointestinal system, thus maintaining blood calcium levels. Along with parathyroid hormone (PTH) and calcitonin, vitamin D plays the fundamental role in bone mineralization and resorption (4). However, vitamin D has a wide range of effects on various cell types and has a potential key role in a number of common diseases, including OA, various cancer types, and autoimmune diseases (3). As a consequence of crucial role of vitamin D on bone metabolism and inflammation, number of studies have been conducted to investigate potential role of this vitamin in various degenerative conditions of the bones and joints. Since no treatment or specific diet has been proven for effectively treating or preventing OA, various studies explore the vitamin D supplementation as potential treatment.

Vitamin D Biology

Vitamin D in humans has two forms, dietary form vitamin D₂ or ergocalciferol, and endogenous form vitamin D₃ or cholecalciferol. Major dietary sources of vitamin D₂ are fatty fish, such as salmon and tuna, egg yolks, cheese, as well as food fortified with vitamin D. Cholecalciferol is endogenously synthesized by the skin upon to sunlight exposure.

Biosynthesis begins with the photoisomerisation of 7-dehydrocholesterol by UVB radiation to form previtamin D in the skin. Subsequently, previtamin D undergoes thermal-dependent isomerization to form vitamin D₃ (5). After two hydroxylations biologically inactive lipophilic cholecalciferol reach its active form. First hydroxylation occurs in the liver, creating calcidiol (25-hydroxyvitamin D₃, 25(OH)D₃), which can be measured in the serum. An additional hydroxylation occurs in tubules of the kidney, osteoblasts and osteoclasts, generating the most active form dihydroxyvitamin D₃ calcitriol (1,25(OH)₂D₃) (3,6).

Vitamin D Receptor

Vitamin D receptor (VDR) is a transcription factor located in the nuclei of target cells in various organs, including bones, brain, heart, skin, gonads, prostate, and breast. The binding of vitamin D to the VDR allows the VDR's rapid binding to regulatory regions of target genes, including the transport proteins involved in calcium absorption in the intestine (3). VDR also regulates gene networks involved in bile acid metabolism in the colon, the differentiation of keratinocytes in the skin, the development and cycling of dermal hair follicles, and the functions of key cell types involved in both innate and adaptive immunity (7). Chondrocytes, osteoblasts and osteocytes express VDR, indicating that these cells could be potential targets for vitamin D signalling and supplementation in OA.

Activation of VDR in osteoblasts, leads to synthesis of non-collagen proteins, osteocalcin and osteopontin, that are components of the bone organic matrix. Binding of active form 1,25(OH)₂D₃ stimulates osteoblasts and osteocytes to produce Fibroblast growth factor 23 (FGF23) (7) FGF23 together with PTH from the thyroid glands, and vitamin D, regulate the intestinal absorption and renal excretion of calcium and phosphate, as well as the storage and removal of these key minerals from the skeleton. (8) FGF23 produced in osteocytes has systemic as well as local effects that influence mineralization. Osteocytes directly affect bone remodeling by inhibiting or stimulating osteoblast and osteoclast activity in order to maintain bone homeostasis, therefore all of these functions are partly affected by 1,25(OH)₂D₃ (3). FGF23 lowers phosphate levels by downregulating phosphate co-transporters in the kidney, thus reducing the phosphate reabsorption. It also downregulates the hydroxylase, an enzyme in the kidney which converts the precursor of 25-hydroxyvitamin D₃ into its active form 1,25(OH)₂D₃. FGF23 also induces the expression of 24-hydroxylase, an enzyme that catabolizes 1,25(OH)₂D₃ and reduces its action. 1,25(OH)₂D₃ is the primary factor for increasing FGF23 production and FGF23 self-regulates its production with this negative feedback. Other factors, such as PTH and serum phosphate may stimulate FGF23, but vitamin D₃ is its most significant regulator (7,9).

The physiological function of VDR in osteocytes is questionable under the normal dietary calcium intake. In one study, VDR-ablated mice were fed diet enriched with calcium and phosphorus, and did not show alterations in bone mineral density or bone histology until the old age (10). In another study, genetic ablation of the VDR in osteocytes showed no effect on bone and mineral homeostasis. However, 1,25(OH)₂D₃-induced inhibition of bone mineralization in osteoblasts/osteocytes was shown to be important for maintaining calcium homeostasis when vitamin D levels are upregulated due to increased calcium demand (11).

Due to its crucial role in vitamin D signalling, the VDR gene and its corresponding protein have been investigated in many diseases including OA. Genetic polymorphisms in the VDR gene have been investigated using restriction fragment length polymorphism, which employs restriction enzymes to cut DNA at specific sequence sites, and polymorphisms are named by the restriction enzymes used to identify them. Among others, three single nucleotide polymorphisms (SNPs) located near the 3' un-translated region (3'UTR) TaqI, BsmI, and ApaI have been investigated for possible involvement in the OA (3,12). Although not functional, these SNPs are associated with a poly (A) repeat in the 3'UTR that could influence the stability of the VDR mRNA. Another SNP, FokI is a functional polymorphism of the VDR gene which results in different translation initiation sites on VDR. Finnish study discovered that genetic polymorphisms may be associated with an increased susceptibility to bilateral hand OA in females (13). In 2009, Lee et al. Conducted a meta-analysis of 10 studies into the association of the TaqI, BsmI, and ApaI polymorphisms with OA (14). The analysed studies had investigated various OA sites: knee, lumbar spine, hand and hip. No evidence was found to support an association between any of the polymorphisms and susceptibility to OA. This conflicts with a more recent meta-analysis in which a statistically significant association was found between the ApaI polymorphism and OA in Asian populations, but the association was not observed in Europeans (15). Investigations into relationships between VDR polymorphisms and different aspects of OA, like joint space narrowing, osteophyte formation or inflammation will be valuable in the future.

Role of Vitamin D in OA

Tissue changes in OA like aberrant bone remodeling, sclerosis, and osteophyte formation are caused by three main cell types: osteoblasts, osteoclasts and chondrocytes. Vitamin D has a range of effects on these cells in osteoarthritis affected joints.

Vitamin D, specifically 1,25(OH)₂D₃ stimulates osteoblastic bone mineralization by activating the VDR. Study with cell culture of OA osteoblasts showed increased cell proliferation after vitamin D treatment compared to healthy osteoblasts. After vitamin D treatment, production of osteocalcin and alkaline phosphatase, two proteins crucial for bone mineralization was also significantly higher in OA

osteoblasts compared to healthy and osteoporotic ones (16). Another study found that 1,25(OH)₂D₃ induced a significantly higher production of osteocalcin in OA osteoblast-like cells compared to controls (17). These findings propose that OA osteoblasts, when induced by vitamin D, increase bone formation. That could lead to an explanation of subchondral sclerosis and osteophyte formation in advanced OA.

During the pathogenesis of OA, an extensive vascular network develops in synovium, menisci, pannus, osteophytes, and osteochondral junction within affected joints. Vascular growth is associated with the loss of structural integrity of the cartilage, and progression of pain through the extension of sensory nerves (18). The level of vascular endothelial growth factor (VEGF), main angiogenic cytokine, is associated with the severity of OA. The expression of VEGF is partially regulated by 1,25(OH)₂D₃, thus linking vitamin D to the progression of the disease (19).

Osteoclasts are specialized macrophages, involved in bone resorption. However, they do not express VDR, and vitamin D is thought to affect them indirectly through osteoblastic activity (20).

Chondrocytes are responsible for the production and maintenance of the extracellular matrix in cartilage. In OA there is an imbalance between anabolic and catabolic processes that leads to the destruction and loss of articular cartilage. Osteoarthritic chondrocytes have a higher VDR expression than healthy cells. The VDR expression is associated with the expression of matrix metalloproteinases, specifically MMP-1, MMP-3, and MMP-9, enzymes that degrade bone and cartilage, which worsens OA (21). 1,25(OH)₂D₃ and inorganic phosphate are involved in the hypertrophy and defective mineralization in osteoarthritic chondrocytes through FGF-23 signalling (22) suggesting that vitamin D has a negative effect on cartilage in OA.

Deficiency of Vitamin D in OA

Hypovitaminosis is defined as 25(OH)D₃ levels under 20ng/mL. It is prevalent among older population since, the capacity of skin to produce vitamin D decreases with old age. It frequently coexists with OA, and a large percent of rheumatology patients are vitamin D deficient (23, 24). However, the effect of hypovitaminosis D on the development and progression of OA is still unclear. Up to date, there are many studies with conflicting results.

Felson et al. used 2 different longitudinal studies of knee OA, to reevaluate 25(OH)D₃ levels and their association with knee OA worsening (consisting of disease incidence and progression). In one study the association of 25(OH)D levels with joint space loss over time was examined in cohort selected without regard to the presence of knee OA. In the second study, they examined the cohort of patients who had symptomatic knee OA. They evaluated the association of 25(OH)D levels with loss of joint space seen on radiographs and with cartilage loss as seen on magnetic resonance imaging (MRI). Examining knee OA, no association was found

between vitamin D levels and structural disease worsening, defined as joint space loss on radiography or cartilage loss on MRI (25). These findings were supported by large cohort study of 5,274 OA-free participants in Finland. The study found no association between low serum 25 (OH)D₃ levels and increased risk of developing hip or knee OA over a 10-year period (26). Neither of these studies support the hypothesis that high levels of 25(OH)D protect against knee and hip OA (27). Contrary to these studies, there are those that demonstrate an association between low 25 (OH)D₃ levels and OA. A prospective cohort study of 5,995 men in the US found a high prevalence of vitamin D insufficiency or deficiency in hip OA patients and found that these patients were twice as likely to have radiographic hip OA than the men with normal 25(OH)D₃ levels (28). Bergink et al. conducted prospective cohort study of 1248 cases of knee OA. They concluded that 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 (29). In Egypt, research into postmenopausal women found lower serum 25(OH)D₃ was associated with knee OA, when compared to healthy males (30). A systematic review performed by Cao et al. analyzed 15 studies. They found strong evidence for an association between 25(OH)D₃ and cartilage loss in knee joints. The authors also observed moderate evidence to support a positive connection between low levels of vitamin D and radiographic knee OA (31).

The differences in study results may be related to differing effects of serum vitamin D in bone and cartilage metabolism. Vitamin D influences the mineralization of bone matrix, and low serum levels of vitamin D may result in poorly mineralized bone that might alter forces across the joint and reduce joint deterioration (28). However, low levels of vitamin D may also alter chondrocyte metabolism and augment degeneration (32). Additional studies are warranted to determine what role vitamin D might have on the development and progression of OA.

The most recent overview of research published over the last 50 years in English language found no consensus on this topic (33). Clinical studies, as well as laboratory based studies were reviewed. In sum, among the various laboratory studies examining the association between vitamin D and articular cartilage in diverse models of OA most imply some relationship between vitamin D and cartilage integrity. While vitamin D may be considered beneficial in some instances, in others it may prove to facilitate cartilage erosion (34). With no definitive model, or study approach, the observed outcomes may depend on the substrate employed, the measurement approaches employed, and durations of exposure. Animal models of osteoarthritis may also lack validity if they do not replicate the clinical conditions: if muscle quality is normal, obesity is not evident, comorbid conditions are not apparent. Reviewing clinical studies, Marks found that there is no consensus regarding vitamin D and OA due to many factors. Studies have different results since they also have different durations, age cut-off or inclusion points, sample

inclusion criteria, type and extent of disease, numbers and types of affected joints, presence, number, and type of other chronic conditions and interventions, and unknown medication usage rates. Optimal versus insufficient serum levels of vitamin D are not uniform, nor standardized as well (33).

Therapeutic possibility of Vitamin D in OA

Since there is no consistent data on the role of vitamin D as a precursor of OA, there is no consensus on its use as a therapeutic agent. In a double-blind, randomized placebo-controlled trial, Arden et al. showed that there was no significant difference in the rate of joint space narrowing in the medial compartment of knees due to vitamin D supplementation (35). While vitamin D may have little effect on cartilage loss, it is possible that vitamin D deficiency could importantly affect other elements of disease, including pain and weakness, which are critical to a patient's experience with OA. Low vitamin D levels have been shown to be associated with muscle weakness and with an increased risk of pain (36,37). In a double-blind study with 103 knee OA patients, patients receiving vitamin D oral supplements had slightly less pain compared with those receiving placebos after a 1-year follow-up. These patients, however, were not as physically capable as their placebo counterparts (38). Additionally, 787 members of the Hertfordshire Cohort Study in the United Kingdom took part in a cross-sectional study that found no association between vitamin D levels and radiographic knee OA, but did suggest a significant association between vitamin D and knee pain (39). On the other hand, in a 2-year study in which symptomatic knee OA patients were given oral doses of cholecalciferol, to raise serum levels of vitamin D, there was no reduction in knee pain scores (40).

Despite efforts for several decades to reduce the osteoarthritis burden, no true progress in more than 30 years can be detected except in the realm of surgical replacements (41). Evidence shows that patients undergoing joint revision surgery for end-stage OA, who 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, and this finding may affect up to 84% of surgical cases (42,43). Because of that, Traven et al. (42) suggest considering preoperative vitamin D levels as a risk factor for complications, and to treat it accordingly. Various authors concluded that, either directly or indirectly through its influence on muscle and bone, inflammation and obesity (44,45), the presence of 'sufficient' vitamin D serum levels may help reduce the pain and joint dysfunction in cases of osteoarthritis, regardless of disease stage (30,36,37). Even if the disease progression remains static in the presence of vitamin D supplementation, this alone could be regarded as a positive result in the context of this progressive degenerative disease.

CONCLUSION

Vitamin D through its receptor, is one of the most important factors involved in the function, development as well as the pathology of the musculoskeletal system. Further

studies are required to settle the debate over the role of Vitamin D in the development and progression of OA. Randomized-controlled trial is considered to be the most rigorous way of determining the effects of vitamin D supplementation on the development of osteoarthritis. Even if it has not been truly examined, vitamin D supplementation in OA patients, as well as in OA “risk groups” may prove to be of value. Thoughtful application of vitamin D may impact OA correlates such as inflammation, pain, joint dysfunction and low quality of life. Identifying the presence of vitamin D deficiencies and correcting them across the lifespan earlier rather than later, may prove to be an efficacious cost-effective form of minimizing joint disability in later life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1545-1602.
2. Atanacković M., Bacetić D. (2009). Kosti, zglobovi i tumori mekih tkiva. In *Katedra za patologiju* (Eds.), *Patologija* (747-795). Beograd: Medicinski Fakultet Univ. U Beogradu.
3. Mabey T, Honsawek S. Role of Vitamin D in Osteoarthritis: Molecular, Cellular, and Clinical Perspectives. *Int J Endocrinol* 2015; vol.2015: 383918.
4. Anderson PH, Turner AG, Morris HA, Vitamin D actions to regulate calcium and skeletal homeostasis. *Clin Biochem* 2012; 45(12): 880–886.
5. Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G, Maixent JM. Vitamin D metabolism, functions and needs: from science to health claims. *European Journal of Nutrition* 2013; 52(2): 429–441.
6. Kogawa M, Anderson PH, Findlay DM, Morris HA, Atkins GJ. The metabolism of 25-(OH)vitamin D3 by osteoclasts and their precursors regulates the differentiation of osteoclasts. *J Steroid Biochem Mol Biol* 2010; 121 (1-2):277–280.
7. Lanske B, Densmore MJ, Reinhold G, Erben RG. Vitamin D endocrine system and osteocytes *Bonekey Rep* 2014; 3: 494.
8. Quarles LD. Skeletal secretion of FGF-23 regulates phosphate and vitamin D metabolism. *Nat Rev Endocrinol*. 2012; 8(5):276-86.
9. Jurutka PW, Bartik L, Whitfield GK et al. Vitamin D Receptor: Key Roles in Bone Mineral Pathophysiology, Molecular Mechanism of Action, and Novel Nutritional Ligands. *J Bone Miner Res* 2007; 22(2):2-10.
10. Weber K, Bergow C, Hirmer S, Schuler C, Erben RG. Vitamin D-independent therapeutic effects of extracellular calcium in a mouse model of adult-onset secondary hyperparathyroidism. *J Bone Miner Res* 2009;24:22–32.
11. Lieben L, Masuyama R, Torrekens S, Van Looveren R, Schrooten J, Baatsen P et al. Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. *J Clin Invest* 2012;122:1803–1815.
12. Uitterlinden AG, Fang Y, Van Meurs JBJ, Pols HAP, Van Leeuwen JPTM. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004;338(2):143–156.
13. Solovieva S, Hirvonen A, Siivola P et al. Vitamin D receptor gene polymorphisms and susceptibility of hand osteoarthritis in Finnish women. *Arthritis Res Ther* 2006;8(1): R20.
14. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Vitamin d receptor taqi, BsmI and ApaI polymorphisms and osteoarthritis susceptibility: a meta-analysis. *Joint Bone Spine* 2009;76(2): 156–161.
15. Zhu ZH, Jin XZ, Zhang W et al. Associations between vitamin D receptor gene polymorphisms and osteoarthritis: an updated meta-analysis. *Rheumatology* 2014;53(6): 998–1008.
16. Corrado A, Neve A, Macchiarola A, Gaudio A, Marucci A, Cantatore FP. RANKL/OPG ratio and DKK-1 expression in primary osteoblastic cultures from osteoarthritic and osteoporotic subjects. *J Rheumatol* 2013;40(5):684–694.
17. Hilal G, Martel-Pelletier J, Pelletier JP, Ranger P, Lajeunesse D. Osteoblast-like cells from human subchondral osteoarthritic bone demonstrate an altered phenotype in vitro: possible role in subchondral bone sclerosis. *Arthritis and Rheumatism* 1998;41(5):891–899.
18. Walsh DA, McWilliams DF, Turley MJ et al. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology* 2010;49(10):1852–1861.
19. Saetan N, Honsawek S, Tanavalee A et al. Relationship of plasma and synovial fluid vascular endothelial growth factor with radiographic severity in primary knee osteoarthritis. *Intl Orthop* 2014;38(5):1099–1104.
20. Rossini, S, Adami, O, Viapiana et al. Dose-dependent short-term effects of single high doses of oral vitamin D3 on bone turnover markers. *Calcif Tissue Int* 2012;91(6):365–369.
21. Masuyama R, Stockmans I, Torrekens S et al. Vitamin D receptor in chondrocytes promotes osteoclastogenesis and regulates FGF23 production in osteoblasts. *J Clin Invest* 2006; 116(12): 3150–3159.
22. Orfanidou T, Malizos KN, Varitimidis S, Tsezou A. 1,25-Dihydroxyvitamin D3 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(3):241–253.
23. 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.
24. Haroon M, Bond U, Quillinan N, Phelan MJ, Regan MJ. The prevalence of vitamin D deficiency in consecutive new patients seen over a 6-month period in general rheumatology clinics. *Clin Rheumatol* 2011; 30(6): 789–794.
 25. Felson DT, Niu J, Clancy M, et al. Low Levels of Vitamin D and Worsening of Knee Osteoarthritis. Results of Two Longitudinal Studies. *Arthritis Rheum* 2007;56(1):129–136.
 26. Konstari S, Kaila-Kangas L, Jaaskelainen T et al. “Serum 25- hydroxyvitamin D and the risk of knee and hip osteoarthritis leading to hospitalization: a cohort study of 5274 Finns. *Rheumatology* 2014;53(10):1778–1782.
 27. Kwan Tat S, Lajeunesse D, Pelletier JP, Martel-Pelletier J. Targeting subchondral bone for treating osteoarthritis: what is the evidence? *Best Pract Res*. 2010;24: 51-70.
 28. 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.
 29. 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.
 30. Abu El Maaty MA, Hanaf RS, Badawy SE, 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.
 31. 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. *Rheumatology* 2013; 52(7):1323–1334.
 32. 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):1381-9.
 33. Marks R. Vitamin D and Osteoarthritis: What is the Consensus? *Int J Orthop* 2018;5(1) 849-862.
 34. Castillo EC, Hernandez-Cueto MA, Vega-Lopez MA, Lavallo 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.
 35. 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; 24(11):1858-1866.
 36. Laslett LL, Quinn S, Burgess JR 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.
 37. 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.
 38. Sanghi D, Mishra A, Sharma AC, Singh A, Natsu SM, Agarwal S, Srivastava RN. Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. *Clin Orthop Relat Res*. 2013 Nov; 471(11):3556-62.
 39. Muraki S, Dennison E, Jameson K et al. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis and Cartilage* 2011; 19(11):1301–1306.
 40. 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):155-62.
 41. Oliviero F, Ramonda R, Punzi L. New horizons in osteoarthritis. *Swiss Med Wkly* 2010;17:140.
 42. 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.
 43. 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.
 44. 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, Staud R, 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.
 45. Rai V, Dietz NE, Dilisio MF, Radwan MM, Agrawal DK. Vitamin D attenuates inflammation, fatty infiltration, and cartilage loss in the knee of hyperlipidemic mice. *Arthritis Res Ther* 2016;18(1):203.