BALNEO RESEARCH Balneo and PRM Research Journal English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

Research article

Update in exploring the connection and clinical implications between vitamin D and knee osteoarthritis

Bianca Georgescu [1,2], Doinița Oprea [2,3]*, Bogdan-Alexandru Georgescu [1,4], Cristina-Mădălina Lungu [2, 5], Erdin Borgazi[6], Mădălina-Gabriela Iliescu [1,2,3]

Citation: Georgescu B., Oprea D., Georgescu B.A., Lungu C.M., Borgazi E., Iliescu M.G. - Update in exploring the connection and clinical implications between vitamin D and knee osteoarthritis
Balneo and PRM Research Journal ***2024***, *15(3): 736*

Academic Editor(s):
Constantin Munteanu

Reviewer Officer:
Viorela Bembea

Production Officer:
Camil Filimon

Received: 23.08.2024
Published: 25.09.2024

Reviewers:
Mihai Hoteteu
Elena Amaricai

Publisher's Note: Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

BY-NC-ND
Copyright: © 2024 by the authors. Submitted for open-access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1 "Ovidius" University Faculty of Medicine Doctoral School, Constanta, Romania;
2 Hospital Rehabilitation Unit, Balneal Sanatorium of Techirghiol, Romania;
3 Department of Medical Rehabilitation, Faculty of Medicine, Ovidius University of Constanta, Romania;
4 "Dr. Alexandru Gafencu" Military Emergency Hospital Constanta, Romania;
5 "Carol Davila" University of Medicine and Pharmacy from Bucharest, Master program "Nutrition and Food Safety", Bucharest, Romania;
6 Department of Orthopedics, Faculty of Medicine, Ovidius University of Constanta, Romania

* Correspondence: Oprea Doinita, doi_opr@yahoo.com

Abstract: Background: Knee osteoarthritis is a prevalent joint disorder characterized by cartilage degeneration, pain, and impaired physical function. Vitamin D might be implicated in the management of knee osteoarthritis through its effects on bone health, cartilage preservation, inflammation modulation, and muscle function. **Objectives**: This literature review aims to synthesize the current state of literature to provide information about the correlation between vitamin D and knee osteoarthritis. Methods: We conducted a comprehensive literature search in databases such as PubMed, Web of Science, Scopus, and Google Scholar to identify studies published in the last ten years investigating the association between vitamin D and knee osteoarthritis. **Results**: Vitamin D deficiency has been linked to cartilage degeneration and more severe symptomatology of knee osteoarthritis. **Conclusions**: The evidence supports an association between vitamin D levels and knee osteoarthritis, but with some studies showing mixed results, there is a need for further research.

Keywords: vitamin D, knee osteoarthritis, cartilage degeneration

1. Introduction

Osteoarthritis (OA) is a prevalent chronic joint disorder characterized by articular cartilage degeneration, subchondral bone sclerosis, and joint space narrowing, leading to pain, stiffness, swelling, and functional impairment. The prevalence of OA is rising along with the average lifespan, sedentary behavior and obesity [1]. This complex disease is considered a significant cause of disability that reduces the quality of life among patients and represents a great economic and mental burden. The worldwide prevalence of OA has been roughly estimated at 20% [3]; however, till this moment, there is no specific treatment to slow the progression of OA. Therefore, there is an intense research effort to find effective treatment options for managing the symptoms and progression of OA.

It is well known that the main role of vitamin D is to regulate calcium and phosphate metabolism, which is essential for maintaining optimal bone mineralization [4], but vitamin D has been hypothesized to have a contribution in supporting the health of several joint structures, including articular cartilage, subchondral bone and muscle tissue, all of this being involved in the progression of OA [5,6]. Studies show that globally, vitamin D deficiency is a common health problem that affects more than

over one billion people, regardless of age or ethnicity [7]. According to a meta-analysis on 7.9 million participants, the prevalence of serum levels of 25-hydroxyvitamin D (the main indicator of vitamin D serum level) lower than 30 nmol/L (which means severe vitamin D deficiency) is 15.7%, and the prevalence below 50 nmol/L (vitamin D deficiency) is 47.9% [8]. This pandemic of hypovitaminosis D is influenced by a sedentary lifestyle that reduces sun exposure, as well as environmental factors and a deficient diet in vitamin D [9].

Studies have investigated the potential role of vitamin D in managing and treating OA, exploring if the adequate level or supplementation treatment with vitamin D can reduce the severity of symptoms and the progression of OA or improve the joint function. A meta-analysis by Wang et al. [10] published last year suggest that while vitamin D supplementation may offer some symptomatic relief in knee OA, particularly in patients with low baseline vitamin D levels, its effect on slowing down the degenerative progression remains uncertain. Understanding the complex interplay between vitamin D and the basis mechanisms of the development of knee OA is a very important step for developing effective strategies to prevent the evolution of this degenerative joint disease. There is a lack of research evidence linking vitamin D to cartilage repair or maintenance, bone changes, muscle strength, and how this influences the severity of symptoms in knee OA.

This narrative review aimed to explore the current state of literature to investigate the potential role of vitamin D in OA, specifficaly regarding its impact on articular cartilage, subchondral bone and muscle strength, as well as its effect on the symptomatology of knee OA, providing a complete picture of how vitamin D could influence the disease. The hypotheses that led us to this comprehensive review were that the combined effects of vitamin D on cartilage, bone, and muscle resulted in a synergic reduction of symptomatology of knee OA.

2. Materials and Methods

Regarding this topic, we structured the review in two parts, first by exploring how vitamin D impacts articular cartilage, subchondral bone and muscle strength and after by analyzing the clinical studies in order to determine what is the impact of vitamin D levels in knee OA symptomatology. We searched in different databases such as PubMed, Web of Science, Scopus and Google Scholar by using the next keywords: “vitamin D”, “25 hydroxyvitamin D”, “osteoarthritis”, “articular cartilage”, “subchondral bone”, “muscle strength”, “osteoarthritis severity”, “joint pain”. We selected only articles written in English and published in the last ten years. We included clinical studies, studies carried out on animals, in vitro and in vivo studies, that evaluate the effect of vitamin D on articular cartilage, subchondral bone, muscle strength and knee OA symptomatology. We didn’t take in consideration another reviews, case reports, books or editorial articles. We identified 15 eligible studies conducted in the last ten years that we included in our review (Table 1).

Table 1 – Studies conducted in the last ten years on the effect of vitamin D in osteoarthritis

Authors	Country	Year	No. of patients
Szychlinska et al. [18]	Italy	2019	12
Chen et al. [19]	China	2022	Not mentioned
Malas et al. [20]	Turkey	2014	80
Veronese et al. [21]	Italy	2018	783
Zheng et al. [22]	Australia	2017	413

Conzade et al. [31]	Germany	2019	1079
Anari et al. [32]	Iran	2019	158
Bassiouni et al. [33]	Egypt	2017	35
Naik et al. [34]	India	2021	80
Kadijani et al. [35]	Iran	2021	116
Zhang et al. [36]	USA	2014	418
Javadian et al. [38]	Iran	2017	92
Koeckhoven et al. [39]	Amsterdam	2016	319
Barker et al. [40]	USA	2014	56
Kim et al. [44]	Korea	2015	2165

3. Results and Discussion

3.1 Vitamin D metabolism and mechanism of action

Vitamin D exists in two forms: vitamin D3 or cholecalciferol which is mainly synthesized in the skin following the action of solar ultraviolet B radiation (UVB) on 7-degydrocholesterol (7-DHC) and vitamin D2 or ergocalciferol obtained from food sources. Due to the difficulty of meeting the European Food Safety Authority's recommendations of daily intake of 15 μg of vitamin D through diet [11], the main natural source of vitamin D synthesis is sun exposure, which is influenced by a number of individual and environmental factors such as age, skin pigmentation, obesity, latitude, season, air pollution, use of sunscreen lotions [12].

Regardless of the source, both vitamin D3 and vitamin D2 are biologically inactive metabolites and require two enzymatic hydroxylation to become active. The first hydroxylation occurs in the liver under the action of 25-hydroxylase enzyme also known as cytochrome P450 2R1 (CYP2R1), resulting in 25-hydroxy vitamin D (25-(OH) D) or calcidiol. After this process, 25-(OH)D require an additional hydroxylation in the kidneys by 1α- hydroxylase (CYP27B1) to produce the biologically active form, 1,25-dihydroxy vitamin D (1,25-(OH)2D) or calcitriol. This active form functions like a hormone, binding by vitamin D binding protein (DBP) to the vitamin D receptor (VDR), which is a part of the nuclear receptor family of ligand regulated transcription factors [4]. The fact that vitamin D receptors are found in multiple tissue like bone, skeletal muscle, kidney, intestines and chondrocytes, strengthens the idea of the various roles of vitamin D in the body [13,14]. The complex 1,25-(OH)2D-VDR attached to retinoid X receptor (RXR) [15] and after this, it is transported to the nucleus where 1,25-(OH)2D-VDR-RXR binds to vitamin D response elements (VDRE) in the DNA which results in activation of transcription [16].

3.2 Evidence regarding the impact of vitamin D on articular cartilage, subchondral bone and muscle strength

Studies have explored the complex relationship between vitamin D status and articular cartilage in order to find a potential impact on the progression of OA. Articular cartilage degenerates in OA due to a complex interplay of mechanical stress, genetic factors, biochemical imbalances between degradation and synthesis of the extracellular matrix components mediated by growth factors and cytokines, chondrocytes senescence and oxidative stress [17].

3.2.1 Studies carried out on animals

In our narrative review, we included two studies on animal subjects, specifically on rats.

In 2019, Szychlinska et al. [18] demonstrated that vitamin D supplementation with diet can increase the thickness and structure of articular cartilage in arthritic rat models, compared to those with vitamin D restriction for ten weeks. The study used a young, healthy, sedentary, male rat model. They were divided into a a group that received a vitamin D based experimental diet and a control group. They evaluated the morphology thickness and expression of collagen type II/X, vitamin D receptor and lubricin on rat tibial cartilage samples [18]. The research findings suggested that ten weeks of vitamin D restriction led to lower cartilage thickness, reduced proteoglycans in the extracellular matrix, decreased collagen II and increased collagen X expression compared to normal and supplemented diets [18]. On the other hand, vitamin D supplementation resulted in higher cartilage thickness, increased extracellular matrix proteoglycan deposition, and elevated lubricin expression compared to the restricted and normal diets [18]. These finding suggest a positive effect of vitamin D supplementation on articular cartilage by enhancing thickness, lubrication, and extracellular matrix fiber deposition in young healthy sedentary rats [18].

In a study published in 2023, Chen et al. analyzed the influence of 1,25 (OH)2D deficiency on the progression of aging-related OA in mice [19]. The study specifically examined how this deficiency impacted the expression of Sirt1, a protein involved in cellular regulation and aging [19]. Mice with 1,25 (OH)2D deficiency presented more severe cartilage degeneration than the control group suggesting an acceleration of OA. The results found that the mice with vitamin D deficiency had a significantly reduced expression of Sirt1 which was associated with increased levels of matrix metalloproteinases (MMPs) and inflammatory cytokines. It was also found that VDR knockout mice exhibited knee OA phenotypes indicating the importance of VDR in OA prevention [19].

3.2.2 Clinical studies

An article published by Malas et al. in 2014 focused on the effect of vitamin D level on the distal femoral cartilage thickness in healthy subject measured by musculoskeletal ultrasound. The study found out that severe vitamin D deficiency affect the articular cartilage thickness in patients [20].

Another article by Veronese et al. published in 2018, investigated if a higher intake of vitamin D from diet or from oral supplementation was associated with a better architecture of the cartilage of the knee, assessed by MRI. They concluded that there is an association between a higher intake of vitamin D and a better architectural structure of the cartilage of the knee [21].

In 2017, a post-hoc analysis of a multicenter randomized, double-blind placebo-controlled clinical trial on 340 patients with symptomatic knee OA by Zheng et al. measured knee cartilage volume, bone marrow lesions and effusion-synovitis volume using MRI at baseline and after 24 months since the participants finished the first study. The authors measured 25-(OH)D at baseline, month 3 and 24 and grouped the patients as consistently insufficient (<50 nmol/L at month 3 and 24), fluctuating (>50 nmol/L at one point) and consistently sufficient (>50 nmol/L at month 3 and 24) [22]. Those who maintained a vitamin D sufficient status during the study had beneficial effects on cartilage loss, effusion-synovitis and physical function [22].

Another role of vitamin D is in muscle cell differentiation and function through genomic and no-genomic pathways mediated by vitamin D receptor which is localized both in cytoplasm and in the nucleus of muscle fibers [23-25]. Vitamin D deficiency can lead to myopathy which is characterized by persistent inflammation and infiltration of immune and inflammatory cells into skeletal muscle, degeneration and fibrosis of myofibers and clinically by weakness and decreased effort tolerance [26,27]. Studies revealed that increased expression of VDR after muscle injury positively impacts

mitochondrial health, while vitamin D deficiency adversely affects mitochondrial function by decreasing ATP production and increasing oxidative stress, as demonstrated in VDR knockout myoblasts [28,29].

Low levels of vitamin D had been also associated with sarcopenia [30]. Conzade et al. investigated the relationship between baseline 25-(OH)D levels and changes in muscle parameters [31]. The results revealed that the participants with reduced baseline levels of 25-(OH)D were more likely to have sarcopenia and vitamin D deficiency was associated with lower grip strength, slower gait speed and longer times in the Timed Up and Go test [31]. After three years of follow-up they did a prospective analysis showing that participants with low baseline 25-(OH)D had 0.94% greater annual decrease in muscle mass index and a 3.06% greater annual increase in time to complete their TUG test [31].

3.3 Studies regarding the association between vitamin D levels and OA

In 2019, Anari et al. investigated if there is an association between vitamin D deficiency and a higher risk of knee OA. They recruited 158 patients and divided them in two groups: a case group with clinical and radiographic criteria for knee OA and a control group. They measured 25-(OH)D in the participants and classified them into sufficient, insufficient and deficient. There was a statistically significant association between low serum vitamin D levels and the prevalence and severity of knee OA. Also patients with lower vitamin D levels tend to have a higher radiological grade of knee OA [32].

In 2017, Bassiouni et al. compared serum level of 25-(OH)D between individuals diagnosed with medial femuro-tibial knee OA and controls in order to assess changes in knee OA over time in relation to baseline serum vitamin D levels. They divided the patients according to 25-(OH)D level in two groups and the progression of knee OA was evaluated through MRI at baseline and after 12 months. The results revealed that the patients with knee OA had 25-(OH)D levels significantly decreased and the patients with vitamin D deficiency less than 10 ng/mL had significant deterioration of the medial meniscus, suggesting an increasing risk of exacerbation of the degenerative processes [33].

In a cross-sectional study of 80 subjects published in 2021, Naik et al. measured the serum levels of osteoprotegerin (OPG), receptor activator of nuclear kappa K ligand (RANKL) and vitamin D serum level in patients with different stages of knee OA, in order to assess the correlation of these biomarkers that play an important role in bone metabolism and immune regulation with the severity of OA. The study results pointed out significantly higher levels of vitamin D in group one (early knee OA) compared to group two (advanced knee OA), therefore decreased vitamin D levels accelerated the advance stage of knee OA. Regarding the serum level of OPG, it was found to be increased in the early stage of OA compared to the advanced stage of knee OA. RANK-L level increased with the severity of OA and the RANKL/OPG ratio was significantly correlated with disease severity [34].

In another cross-sectional study published also in 2021, Kadijani et al. investigated the correlation between vitamin D level and serum cytokines level on 116 patients with symptomatic primary knee OA. Even though vitamin D was not associated with OA either radiological or clinical point of view, they showed a negative correlation between vitamin D level and higher release of IL-6, which was significantly higher in advanced degrees of OA [35].

A study by Zhang et al. published in 2014, aimed to explore if there is any association between serum level of 25-(OH)D, PTH and progression of OA, evaluated radiographic by joint space narrowing grade (JSN) (0-3). The findings of the study revealed that individuals with vitamin D levels below 15 μg/L had a higher risk of knee OA progression, highlighting the impact of vitamin D in the advancement of knee OA. Additionally, the study pointed out that participants with both low vitamin D and elevated PTH level have an increased risk of knee OA progression [36].

Vitamin D plays a crucial role in maintaining musculoskeletal health, which is particularly relevant in the context of knee OA, where muscle strength directly influences joint stability and function. A review by Rosu et al. [37] highlighted that vitamin D supplementation should be considered in athletes with vitamin D deficiency. While this research primarily focuses on healthy and physically active populations, the findings may have important implications for individuals with degenerative conditions such as knee OA.

Regarding the symptomatology of OA, there are studies that focus on the functional part of the disease in order to find a method to improve the patient's quality of life. A study by Javadian et al. investigated the relationship between quadriceps muscle strength (QMS), serum vitamin D levels and knee pain in 92 patients with knee OA. The results of the study showed a positive correlation between QMS and 25-(OH)D and a negative correlation between QMS and knee pain. The findings also suggest that there is no correlation between 25-(OH)D and pain. The study wants to point out that vitamin D deficiency influence QMS which is important for the maintenance of the stability of the knee and also for the management of the knee pain, being positive correlated with it [38].

A cross-sectional study by Koeckhoven et al. analyze the relationship between serum 25-(OH)D level and muscle strength of the upper limb in patients with knee osteoarthritis. They found a significant association between low serum 25-(OH)D level and muscle weakness. The researchers adjusted the results with body mass index (BMI) of the patients and the association was no longer significant which means that BMI can influence both vitamin D metabolism and muscle strength [39]. Another study by Barker et al. investigates the impact of vitamin D deficiency on muscle strength in individuals with knee OA. The results suggested that vitamin D levels were negatively correlated with pain and physical function indicating an improvement in knee pain and physical function with an increase in vitamin D concentrations [40].

A cross-sectional study investigated the association between vitamin D status and health related quality of life measured by standardized instrument for general health status in adults diagnosed with knee OA based on radiographic changes defined as Kellgren-Lawrence from grade 2. The study found a significant association between vitamin D deficiency and low health related quality of life. The results of the study highlighted that adequate vitamin D levels may play a role in mitigating the negative impact of knee OA on quality of life [41-45].

While the animal studies suggest promising results for using vitamin D in OA management, further research on human is crucial to establish its efficacy in clinical practice. In the animal studies, vitamin D supplementation was shown to increase the thickness and improve the structure of articular cartilage [18,19]. These findings suggest that vitamin D might have a protective effect in humans as well, but we must take into account the fact that animals are kept in controlled environments, which may not reflect the variability in human lifestyles, diet and sun exposure, all of these influencing vitamin D levels. In clinical studies, vitamin D deficiency was shown to negatively impact the thickness of articular cartilage, as measured by musculoskeletal ultrasound or by MRI [20-22].

Several studies suggested a significant association between low serum of vitamin D levels and the prevalence and severity of knee OA [32-34]. This suggests that vitamin D deficiency could be a risk factor for degenerative processes of the knee joint, possibly by promoting inflammatory pathways [35] and reducing the structural integrity of cartilage.

While many studies show that there is a correlation between vitamin D levels and various aspects of knee joint, there are inconsistencies results that could be due to differences in study design, population characteristics, baseline vitamin D levels, dosage of vitamin D used and the duration of supplementation.

Limitations of the current narrative review

In this review, we have synthesized the current literature on the link between vitamin D and knee OA. However, several limitations should be acknowledged. First, the selection of studies was not based on a systematic search strategy. The included studies varied in their design, populations studied and methods for assessing osteoarthritis outcomes. As this is a narrative review, we did not conduct a quantitative data synthesis. These limitations suggest that while the review provides a broad overview of the current evidence, more research and future systematic reviews are essential to determine the benefits of vitamin D in knee OA.

5. Conclusions

In conclusion, the review highlights an association between vitamin D deficiency and various adverse outcomes in knee OA, including reduced articular cartilage thickness, increased severity and progression of OA, reduced muscle strength, and physical function. Despite the overall positive findings, some studies found no significant relationship between vitamin D levels and OA outcomes, either radiologically or clinically. These inconsistencies could be from various reasons, such as study design, population characteristics, or vitamin D assessment methods. Further research is essential to confirm these findings and to elucidate the underlying mechanisms by which vitamin D influences cartilage health.

Author Contributions: Conceptualization, B.G. and M.G.I.; methodology, B.G. and D.O.; software, B.G.; validation, M.G.I. and E.B.; formal analysis, D.O. and E.B.; investigation, B-A.G. and C.M.L; resources, B.G.; data curation, B-A.G.; writing—original draft preparation, B.G.; writing—review and editing, B.G. and M.G.I..; visualization, D.O.; supervision, M.G.I. and O.D.; project administration, M.G.I. All authors contributed equally in this paper.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All information found in this review is documented by relevant references.

Acknowledgments: The research was conducted with the support of the Research Nucleus of Balneal Sanatorium of Techirghiol, Romania.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Heidari B, Babaei M. Therapeutic and Preventive Potential of Vitamin D Supplementation in Knee Osteoarthritis. ACR Open Rheumatol. 2019 Jul 3;1(5):318-326. doi: 10.1002/acr2.1042. PMID: 31777808; PMCID: PMC6857993.
2. Coaccioli S, Sarzi-Puttini P, Zis P, Rinonapoli G, Varrassi G. Osteoarthritis: New Insight on Its Pathophysiology. J Clin Med. 2022 Oct 12;11(20):6013. doi: 10.3390/jcm11206013. PMID: 36294334; PMCID: PMC9604603.
3. Safiri S., Kolahi A.A., Smith E., Hill C., Bettampadi D., Mansournia M.A., Hoy D., Ashrafi-Asgarabad A., Sepidarkish M., Almasi-Hashiani A., et al. Global, regional and national burden of osteoarthritis 1990–2017: A systematic analysis of the Global Burden of Disease Study 2017. Ann. Rheum. Dis. 2020;79:819–828. doi: 10.1136/annrheumdis-2019-216515.
4. Rebelos, E., Tentolouris, N. & Jude, E. The Role of Vitamin D in Health and Disease: A Narrative Review on the Mechanisms Linking Vitamin D with Disease and the Effects of Supplementation. Drugs 83, 665–685 (2023). https://doi.org/10.1007/s40265-023-01875-8
5. Alabajos-Cea A, Herrero-Manley L, Suso-Martí L, Viosca-Herrero E, Cuenca-Martínez F, Varangot-Reille C, Blanco-Díaz M, Calatayud J, Casaña J. The Role of Vitamin D in Early Knee Osteoarthritis and Its Relationship with Their Physical and Psychological Status. Nutrients. 2021 Nov 12;13(11):4035. doi: 10.3390/nu13114035. PMID: 34836290; PMCID: PMC8622912.

6. McAlindon, T.; LaValley, M.; Schneider, E.; Nuite, M.; Lee, J.Y.; Price, L.L.; 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, 155–162.
7. Holick MF. Vitamin D deficiency. N Engl J Med. 2007 Jul 19;357(3):266-81. doi: 10.1056/NEJMra070553. PMID: 17634462.
8. Cui A, Zhang T, Xiao P, Fan Z, Wang H, Zhuang Y. Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants. Front Nutr. 2023 Mar 17;10:1070808. doi: 10.3389/fnut.2023.1070808. PMID: 37006940; PMCID: PMC10064807.
9. Holick MF. The vitamin D defciency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord Germ. 2017;18:153–65.
10. Wang R, Wang ZM, Xiang SC, Jin ZK, Zhang JJ, Zeng JC, Tong PJ, Lv SJ. Relationship between 25-hydroxy vitamin D and knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Front Med (Lausanne). 2023 Aug 2;10:1200592. doi: 10.3389/fmed.2023.1200592. PMID: 37601800; PMCID: PMC10433223.
11. Benedik E. Sources of vitamin D for humans. Int J Vitam Nutr Res. 2022 Mar;92(2):118-125. doi: 10.1024/0300-9831/a000733. Epub 2021 Oct 18. PMID: 34658250.
12. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. Acta Derm Venereol. 2011 Mar;91(2):115-24. doi: 10.2340/00015555-0980. PMID: 21384086.
13. Haussler MR, Haussler CA, Bartik L, Whitfield GK, Hsieh JC, Slater S, Jurutka PW. Vitamin D receptor: molecular signaling and actions of nutritional ligands in disease prevention. Nutr Rev. 2008 Oct;66(10 Suppl 2):S98-112. doi: 10.1111/j.1753-4887.2008.00093.x. PMID: 18844852.
14. Garfinkel RJ, Dilisio MF, Agrawal DK. Vitamin D and Its Effects on Articular Cartilage and Osteoarthritis. Orthop J Sports Med. 2017 Jun 20;5(6):2325967117711376. doi: 10.1177/2325967117711376. PMID: 28680892; PMCID: PMC5480771.
15. Smith CL, O'Malley BW (2004) Coregulator function: a key to understanding tissue specificity of selective receptor modula-tors. Endocr Rev 25(1):45–71
16. Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Thompson PD, Selznick SH et al (1998) The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. J Bone Miner Res 13(3):325–349
17. Bryam, Esteban, Coello, García., Angel, Patricio, Fajardo, Zhao., Byron, Xavier, Cabrera, Castillo., Holger, Xavier, Rojas, Es-pinoza., Brian, Andrés, Serpa, Ocampo., Karina, Noemí, Contreras, García. (2023). Degenerative articular cartilage disease, os-teoarthrosis. EPRA international journal of multidisciplinary research, 232-240. doi: 10.36713/epra12476
18. Marta, Anna, Szychlinska., Rosa, Imbesi., Paola, Castrogiovanni., Claudia, Guglielmino., Silvia, Ravalli., Michelino, Di, Rosa., Giuseppe, Musumeci. (2019). Assessment of Vitamin D Supplementation on Articular Cartilage Morphology in a Young Healthy Sedentary Rat Model.. Nutrients, 11(6):1260-. doi: 10.3390/NU11061260
19. Jie, Chen., Jiao-Jiao, Zhang., Jie, Liu., Ran, Qin., Na, Lu., David, Goltzman., Dengshun, Miao., Renlei, Yang. (2023). 1,25-Dihydroxyvitamin D Deficiency Accelerates Aging-related Osteoarthritis via Downregulation of Sirt1 in Mice. International Journal of Biological Sciences, 19(2):610-624. doi: 10.7150/ijbs.78785
20. Malas, F.Ü., Kara, M., Aktekin, L. et al. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. Clin Rheumatol 33, 1331–1334 (2014). https://doi.org/10.1007/s10067-013-2432-y
21. Veronese N, La Tegola L, Mattera M, Maggi S, Guglielmi G. Vitamin D Intake and Magnetic Resonance Parameters for Knee Osteoarthritis: Data from the Osteoarthritis Initiative. Calcif Tissue Int. 2018 Nov;103(5):522-528. doi: 10.1007/s00223-018-0448-7. Epub 2018 Jun 25. PMID: 29943188.
22. Zheng S, Jin X, Cicuttini F, Wang X, Zhu Z, Wluka A, Han W, Winzenberg T, Antony B, Aitken D, Blizzard L, Jones G, Ding C. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoar-thritis. Am J Med. 2017 Oct;130(10):1211-1218. doi: 10.1016/j.amjmed.2017.04.038. Epub 2017 May 24. PMID: 28549923.
23. Harshwardhan, Dhananjay, Ghadge., Kalyanee, Vijay, Gavande., Amol, Navnath, Khedakar., Tanvir, Santosh, Rohokale. (2023). Review on Vitamin D Tablet in Health and Disease Overview. International Journal For Multidisciplinary Research, doi: 10.36948/ijfmr.2023.v05i06.8734

24. Haussler, M.R.; Jurutka, P.; Mizwicki, M.; Norman, A.W. Vitamin D receptor (VDR)-mediated actions of 1,25(OH)2vitamin D3: Genomic and non-genomic mechanisms. Best Pract. Res. Clin. Endocrinol. Metab. 2011, 25, 543–559.
25. Zmijewski, M.A.; Carlberg, C. Vitamin D receptor(s): In the nucleus but also at membranes? Exp. Dermatol. 2020, 29, 876–884.
26. Ceglia, L.; Harris, S.S. Vitamin D and Its Role in Skeletal Muscle. Calcif. Tissue Int. 2013, 92, 151–162.
27. Alberto, Caballero-García., Alfredo, Córdova-Martínez., Néstor, Vicente-Salar., Enrique, Roche., Enrique, Roche., Daniel, Pérez-Valdecantos. (2021). Vitamin D, Its Role in Recovery after Muscular Damage Following Exercise. Nutrients, 13(7):2336-. doi: 10.3390/NU13072336
28. Giovanni, Iolascon., Antimo, Moretti., Marco, Paoletta., Sara, Liguori., Ombretta, Di, Munno. (2021). Muscle Regeneration and Function in Sports: A Focus on Vitamin D. Medicina-buenos Aires, 57(10):1015-. doi: 10.3390/MEDICINA57101015
29. Ashcroft, S.P.; Bass, J.J.; Kazi, A.A.; Atherton, P.J.; Philp, A. The vitamin D receptor regulates mitochondrial function in C2C12 myoblasts. Am. J. Physiol. Physiol. 2020, 318, C536–C541.
30. Remelli F, Vitali A, Zurlo A, Volpato S. Vitamin D Deficiency and Sarcopenia in Older Persons. Nutrients. 2019 Nov 21;11(12):2861. doi: 10.3390/nu11122861. PMID: 31766576; PMCID: PMC6950416.
31. Conzade, R.; Grill, E.; Bischoff-Ferrari, H.A.; Ferrari, U.; Horsch, A.; Koenig, W.; Peters, A.; Thorand, B. Vitamin D in Rela-tion to Incident Sarcopenia and Changes in Muscle Parameters Among Older Adults: The KORA-Age Study. Calcif. Tissue Int. 2019, 105, 173–182.
32. Anari H, Enteshari-Moghaddam A, Abdolzadeh Y. Association between serum Vitamin D deficiency and Knee Osteoarthri-tis. Mediterr J Rheumatol. 2020 Mar 31;30(4):216-219. doi: 10.31138/mjr.30.4.216. PMID: 32467872; PMCID: PMC7241660.
33. Bassiouni H, Aly H, Zaky K, Abaza N, Bardin T. Probing The Relation Between Vitamin D Deficiency and Progression of Medial Femoro-tibial Osteoarthitis of the Knee. Curr Rheumatol Rev. 2017;13(1):65-71. doi: 10.2174/1573397112666160404124532. PMID: 27041085.
34. Naik S, Sahu S, Bandyopadhyay D, Tripathy S. Serum levels of osteoprotegerin, RANK-L & vitamin D in different stages of osteoarthritis of the knee. Indian J Med Res. 2021 Mar;154(3):491-496. doi: 10.4103/ijmr.IJMR_873_19. PMID: 35345075; PMCID: PMC9131798.
35. Amini Kadijani A, Bagherifard A, Mohammadi F, Akbari A, Zandrahimi F, Mirzaei A. Association of Serum Vitamin D with Serum Cytokine Profile in Patients with Knee Osteoarthritis. Cartilage. 2021 Dec;13(1_suppl):1610S-1618S. doi: 10.1177/19476035211010309. Epub 2021 Apr 23. PMID: 33890506; PMCID: PMC8808942.
36. 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 Dec;144(12):2002-8. doi: 10.3945/jn.114.193227. Epub 2014 Oct 1. PMID: 25411034; PMCID: PMC4230211.
37. Rosu R, Gusetu G, Comsa H, Caloian B, Irimie D, Fringu F, Ra T, Pop D. Vitamin D Supplementation Improves Physical Performance in Athletes and Healthy Aging in Physically Active Adults. risk (eg homebound, inactive persons or inhabitants of nursing homes). 2023;1:3.
38. Javadian Y, Adabi M, Heidari B, Babaei M, Firouzjahi A, Ghahhari BY, Hajian-Tilaki K. Quadriceps Muscle Strength Corre-lates With Serum Vitamin D and Knee Pain in Knee Osteoarthritis. Clin J Pain. 2017 Jan;33(1):67-70. doi: 10.1097/AJP.0000000000000358. PMID: 26889621.
39. Koeckhoven, Esmee, Marike van der Leeden, Leo D. Roorda, Natasja M. van Schoor, Paul Lips, Arjan de Zwart, Joost Dek-ker, Martin van der Esch, and Willem F. Lems. "The Association Between Serum 25-Hydroxy Vitamin D Level and Upper Leg Strength in Patients with Knee Osteoarthritis: Results of the Amsterdam Osteoarthritis Cohort." The Journal of Rheu-matology 43, no. 7 (July 2016): 1400–1405. https://doi.org/10.3899/jrheum.150751.
40. Barker, T., V.T. Henriksen, V.E. Rogers, D. Aguirre, R.H. Trawick, G. Lynn Rasmussen, and N.G. Momberger. "Vitamin D Deficiency Associates with γ-Tocopherol and Quadriceps Weakness but Not Inflammatory Cytokines in Subjects with Knee Osteoarthritis." Redox Biology 2, no. 1 (2014): 466–74. https://doi.org/10.1016/j.redox.2014.01.024.
41. Iliescu, M.G.; Stanciu, L.-E.; Uzun, A.-B.; Cristea, A.-E.; Motoască, I.; Irsay, L.; Iliescu, D.M.; Vari, T.; Ciubean, A.D.; Caraban, B.M.; et al. Assessment of Integrative Therapeutic Methods for Improving the Quality of Life and Functioning in Cancer Patients—A Systematic Review. J. Clin. Med. 2024, 13, 1190. https:// doi.org/10.3390/jcm13051190.

42. Irsay L, Ungur RA, Borda IM, Tica I, Iliescu MG, Ciubean AD, Popa T, Cinteza D, Popa FL, Bondor CI, Ciortea VM. Safety of Electrotherapy Treatment in Patients with Knee Osteoarthritis and Cardiac Diseases. Life (Basel). 2022 Oct 24;12(11):1690. doi: 10.3390/life12111690. PMID: 36362845; PMCID: PMC9699242.
43. Lupu A.A., Oprea D., Obada B., Iliescu D.M., Botnarciuc M., Ionescu A.M., Mihailov C.I., Iliescu M.G., Caraban B.M. - Variation of serum serotonin values under specific peloido-therapy in patients with degenerative pathology of the lumbar spine Balneo and PRM Research Journal 2023, 14(3): 588.
44. Kim HJ, Lee JY, Kim TJ, Lee JW. Association between serum vitamin D status and health-related quality of life (HRQOL) in an older Korean population with radiographic knee osteoarthritis: data from the Korean national health and nutrition ex-amination survey (2010-2011). Health Qual Life Outcomes. 2015 Apr 18;13:48. doi: 10.1186/s12955-015-0245-1. PMID: 25927585; PMCID: PMC4424888.
45. Diaconu C., Cipăian R.C., Iliescu M.G., Ciortea V.M., Irsay L., Ungur R.A., Diaconu C.G. - Medical management and rehabilitation in a patient with avas-cular necrosis of the femoral head in the context of vitamin D deficiency and secondary hyperparathyroidism – case report. Balneo and PRM Research Journal 2023, 14(2): 547.