

REVIEW ARTICLE

Impact of vitamin D in chronic kidney disease and its effect on the musculoskeletal system

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What is not yet known on the issue addressed in the submitted manuscript

The role of vitamin D metabolism abnormalities in the pathogenesis of bone mineral disorders in chronic kidney disease is known, but it is not known the level of reduction of vitamin D in relation to the stage of nondialysis chronic kidney disease.

The research hypothesis

Chronic kidney disease is a global health problem, and a decrease in glomerular filtration rate increases the risk of bone mineral disorders and secondary hyperparathyroidism, which plays an important role in vitamin D deficiency.

The novelty added by manuscript to the already published scientific literature

Highlighting the decrease in vitamin D levels depending on the stage of chronic kidney disease.

Abstract

Introduction. Vitamin D plays an important role in maintaining musculoskeletal health. As the glomerular filtration rate decreases, vitamin D deficiency also occurs. The aim of this paper is to highlight the level of vitamin D depending on the stage of chronic kidney disease.

Materials and methods. A structured search was performed in the PubMed, Scopus and HINARI databases, where the relevant articles have been taken into account, published in the last 20 years. The search terms used (in English) were: „vitamin D deficiency”, „pathogenesis of vitamin D”, „the impact of vitamin D in chronic kidney disease”, „chronic kidney disease”.

Results. Several studies have shown that the change in vitamin D levels is dependent to the decrease of glomerular filtration rate. The lowest serum vitamin D concentration was observed in stage 5 of chronic kidney disease. Vitamin D deficiency occurs due to a decrease in the number of nephrons and a decrease in the number of proximal tubular cells that absorb vitamin D (25 (OH) D) to be subsequently hydroxylated to its active form by 1 α -hydroxylase.

Conclusions. Patients with vitamin D-deficient due to chronic kidney disease have an increased risk of decreased bone mineral density and multiple fractures.

Keywords: vitamin D, deficiency, pathogenesis, chronic kidney disease

Introduction

Vitamin D plays an important role in maintaining musculoskeletal health. As the glomerular filtration rate decreases, vitamin D deficiency also occurs. This is due to the decrease of functional nephrons and in the number of proximal tubular cells that absorb vitamin D 25 (OH) D, which is then hydroxylated in its active form by 1 α -hydroxylase. It is well known that the abnormalities of vitamin D are important factors in the pathogenesis of bone mineral disorders. At present there is more and more data about the role of vitamin D on muscle health and function [1-3]. It is known that patients with chronic kidney disease have clinical manifestations such as: muscle pain and weakness, sarcopenia, fatigue, low exercise tolerance, fractures and falls that may have an adverse effect on the quality of life [4-9, while vitamin D deficiency is directly related to the severity of muscle manifestations [10]. Multiple data show that the vitamin D receptor (VDR) is expressed in muscles and that the vitamin D receptor regulates gene expression and the absorption of 25 (OH) D in skeletal muscle cells [11, 12]. Vitamin D is part of a group of fat-soluble vitamins. There are two

forms of vitamin D: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant-derived form (ergosterol or provitamin D2). Vitamin D3 comes either from food of animal origin, or is synthesized in the skin from 7-dehydrocholesterol (provitamin D3) under the action of ultraviolet radiation [13]. Vitamin D activation takes place in two stages: the first stage takes place in the liver, and the second stage takes place in the kidneys. In plasma, vitamin D is transported as a complex with a specific alpha1 globulin-vitamin D transporter protein. The first hydroxylation takes place in the liver, where 25-OH vitamin D (calcifediol), a metabolite with limited biological activity, is formed. Then 25-OH vitamin D binds to a specific protein that is transported to the kidneys where the second hydroxylation takes place. Under the action of 1-alpha hydroxylase, the most active metabolite of vitamin D is formed: 1,25-(OH) 2 vitamin D (calcitriol) in the proximal renal tube.

Renal hydroxylation plays an important role in controlling the metabolism of vitamin D, which is regulated by serum calcium, phosphate and parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), which is produced by bone osteocytes and osteoblasts [14].

The decrease in plasma concentration of both metabolites – 25 (OH) D and 1,25 (OH) 2D, is observed with the progression of chronic kidney disease [15]. There are known several factors contributing to vitamin D deficiency: renal dysfunction, dietary restrictions, reduced sun exposure, skin hyperpigmentation, diabetes, obesity, the presence of uremic syndrome, hyperphosphatemia, metabolic acidosis, proteinuria and increased FGF23 [16].

The role of vitamin D in the kidneys is to increase the tubular reabsorption of calcium. Thanks to the maintenance of calcium homeostasis, calcitriol has an important role in the process of bone remodeling. Along with the interaction of specific receptors, it induces the expression of bone matrix proteins (osteopontin, osteocalcin, alkaline phosphatase) and inhibits the synthesis of type I collagen. At the same time, there is an increase in bone resorption together with the action of parathyroid hormone, by stimulating immature osteoclastic precursors, which will later turn into mature osteoclasts. They remove calcium and phosphorus from the bone, maintaining the levels of calcium and phosphorus in the blood.

Normal concentrations of Ca^{2+} and phosphorus in the blood favor the mineralization of the osteoid. Vitamin D deficiency leads to disorders of osteoid mineralization, as a result favors the appearance of osteomalacia.

Materials and methods

A search of scientific papers published since 2001 in the MEDLINE electronic database was performed using the search engine PubMed, Scopus and HINARI (Health Internet Work Access to Research Initiative) - Research4Life program. We have selected English articles provided by these platforms. The search terms used were: „vitamin D deficiency”, „pathogenesis of vitamin D”, „the impact of vitamin D in chronic kidney disease”, „chronic kidney dis-

ease”. Original articles, meta-analyses and systematic reviews were selected.

Results and discussion

After processing the information from the PubMed, Scopus and HINARI databases, according to the search criteria, 220 articles on vitamin D deficiency in chronic kidney disease were selected. The final bibliography contains 38 relevant sources, which were considered representative of the material published on the topic of this synthesis article. Excluded from the list were the content of publications that did not reflect the research topic, as well as articles that were not accessible through the HINARI database.

Vitamin D deficiency in chronic kidney disease

The fibroblastic growth factor 23 (FGF23), which is increased in chronic kidney disease, inhibits the activity of 1α -hydroxylase, which subsequently stimulates 25-hydroxylase, and, at the same time, vitamin D further increases the production of FGF23 [14, 17]. Increased FGF23 stimulates increased renal phosphate excretion [18]. FGF23 inhibits alkaline phosphatase as a result. Moreover, FGF23 leads to extracellular increase in pyrophosphate, decreases the amount of inorganic phosphate, and stimulates the expression of the osteopontin gene.

Vitamin D 1,25 (OH) D binds to the vitamin D receptor (VDR), which is present in almost all tissues. The VDR-1,25 (OH) 2D complex subsequently binds to the retinoic X receptor (RXR) which controls the transcriptional activity of target genes. 1,25 (OH) 2D has an important role in maintaining calcium and phosphate homeostasis, stimulating intestinal absorption and bone resorption [19]. The 1,25 (OH) 2D-VDR-RXR complex increases the expression of the epithelial calcium channel in the cells of the small intestine. This allows more calcium to enter the cell, ensuring the necessary availability of calcium and phosphate for the proper mineralization of the newly formed bone matrix. Vitamin D enhances the expression of LRP5, which, together with sclerostin, Dkk1 and frizzled, forms the Wnt pathway, which is an important process in bone mineralization [20, 21]. In most patients with chronic kidney disease, 25-hydroxyvitamin D levels were observed to be <30 ng/ml, which is lower than normal. In patients who have a high level of proteinuria have an even lower level of vitamin D. Interestingly, there was a positive relationship between 25-hydroxyvitamin D levels and 1,25-dihydroxyvitamin D levels, in contrast to patients without chronic kidney disease.

Muscle damage in vitamin D deficiency

Several studies have shown that in addition to maintaining calcium homeostasis, which is imported for muscle function, vitamin D deficiency can act directly on skeletal muscle. Vitamin D also binds to the vitamin D receptor in muscle cells. This, in turn, leads to the rapid up-regulation of calcium channels [22]. The influence of vitamin D hypovitaminosis on skeletal muscle also refers to muscle structure. Structural muscle changes include disruption of the intermyofibrillar network, increased intramuscular lipids, and rapid atrophy of white fibers (type 2) [23-25]. Subjects

with severe vitamin D deficiency show generalized muscle atrophy, before the appearance of biochemical signs of bone disease [26].

Multiple studies show that the presence of myopathy in chronic kidney disease occurs at a GFR <25 mL/min/1.73m² and increases with worsening of renal function [27, 28]. The diagnosis of uremic myopathy is established based on clinical manifestations: weakness and sarcopenia found mainly in the lower limbs [29]. Meanwhile, muscle enzyme levels and electromyographic studies are usually normal [30]. These characteristics are also found in patients with vitamin D deficiency [23].

Bone damage in vitamin D deficiency

Skeletal disorders associated with bone mineral disorders in chronic kidney disease are associated with bone loss and fractures. Compared to the general population, the incidence rates of fractures are more than four times higher and are associated with higher morbidity and mortality. With the progression of chronic kidney disease, metabolic disorders risk is higher, including abnormal bone remodeling, which leads to osteoporosis and subsequent decrease in bone strength. Chronic kidney disease is a risk factor for osteoporosis. Osteoporosis is a skeletal condition characterized by compromised bone density that increases the risk of fracture [31]. Bone mineral density measurement using osteodensitometry by Dual X-ray Absorption (DXA) is a commonly used method for assessing bone mineral density. In chronic kidney disease, the relation among bone mineral density, bone fragility and the risk of fracture is not always clear. In chronic kidney disease there is a greater loss of cortical bone than trabecular bone, due to the presence of hyperparathyroidism compared to postmenopausal osteoporosis, where there is loss of trabecular bone in the axial skeleton [32]. The preferred sites for measuring bone mineral density in patients with chronic kidney disease are the hip and radio-carpal joints. The use of computed tomography could also be a useful tool for

assessing bone loss and micro-architectural changes [33]. Although there have been doubts about the usefulness of bone mineral density in chronic kidney disease [34], measuring bone mineral density may become useful in these patients. This issue is currently being reviewed and bone mineral density testing is most likely to be recommended in patients with chronic kidney disease and evidence of bone mineral disorders or in patients with CKD who have risk factors for osteoporosis, especially if the results may change the management [35, 36].

Bone biopsy is not commonly performed in uremic patients, although it is the gold standard and the only way to assess the type of renal osteodystrophy in bone mineral disorders in chronic kidney disease [37, 38]. Bone histological changes in chronic kidney disease range from low bone turnover, mineralization disorders, and changes in bone volume. These histological changes may occur alone or together. The prevalence of renal osteodystrophy in bone mineral disorders in chronic kidney disease is high; the presence of osteoporosis is usually a diagnosis of exclusion.

Conclusions

Vitamin D participates in the control of bone metabolism and calcium homeostasis and plays an important role in muscle function in chronic kidney disease. Patients with chronic kidney disease with vitamin D deficiency have a high risk of decreased bone mineral density and multiple fractures due to mineralization defects. The clinical manifestations observed in patients with chronic kidney disease correlate with levels of 25 (OH) D.

Conflict of interests

Nothing to declare.

Authors' contribution

All authors contributed equally to the research, data analysis, and writing of the manuscript. All authors read and approved the final article.

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