імплантатів, які не викликають розвиток патологічних реакцій в організмі пацієнта, тим самим знижуючи частоту післяопераційних ускладнень і покращуючи якість життя пацієнтів, яким проводять хірургічні втручання.

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Vitamin D in kidney: a two-edged sword?

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Abstract. A wide variety of both calcium-dependent and calcium-non-dependent actions are attributed to the vitamin and hormone vitamin D. One of the most vital components of the human body, vitamin D is essential to both health and illness. It is a member of the fat-soluble secosteroid family, which is obtained from diets or direct sun exposure, which is what turns 7-hydroxycholesterol into the precursor of vitamin D. Bio-activation is an alternate phase that provides an active version of vitamin D that contributes to several notable processes like detoxification, fertility, glucose regulation, bone remodelling, and calcium regulation. Numerous research investigations examine the discernible function of vitamin D in kidney illness. The basic physiological and pathological roles of vitamin D in the kidneys of both diabetics and non-diabetics were examined in this study. In this study we analyzed a basic physiological and pathological roles of Vitamin D in kidney in terms of diabetic and non-diabetic proteinuric kidney diseases. Further research in this field is of high importance.

Keywords: Vitamin D, kidney, effects, physiology, diseases, deficiency.

Introduction. The only vitamin that humans can make is Vitamin D, which is lipid-soluble. Throughout their evolutionary history, land vertebrates have produced vitamin D through a photochemical mechanism in order to meet the need for a calcified skeleton for over 300 million years. A class of liposoluble, steroidal chemicals known as «vitamin D» is essential for intestinal absorption as well as the regulation of calcium and phosphate metabolism. The two most significant isoforms in human physiology are cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2). These are also referred to as calciols; the latter is produced endogenously by photolysis of 7-dehydrocholesterol in the skin by UVB radiation, while the former is only synthesised in plants and fungi through diet [1].

Calciols are converted into calcitriol, the physiologically active form, by a two-step hydroxylation process. The first step in the process of converting D2/D3 into 25(OH)D (calcidiol), a measurable form that is primarily employed to measure vitamin D levels in serum, is the liver's 25-hydroxylase enzyme. The next stage involves the formation of calcitriol, also known as 1,25-dihydroxyvitamin D [1,25(OH)2D], via hydroxylation on carbon 1 in the kidney's proximal tubule. Little information about vitamin D status may be found in serum 1,25(OH)2D, which is often normal or even high when Vitamin D deficiency and hyperparathyroidism develop in paralel [2].

Through the systemic circulation, 1,25(OH)2D travels to the target organs where it connects to the local vitamin D receptor (VDR) through a vitamin D-binding protein (VDBP). The VDR is a member of a large family of nuclear transcription factors that are activated by ligands, and it has been shown to express itself in nucleated cells in a tissue-dependent and nearly universal manner [3]. In addition to inducing calcium and phosphorus absorption, output, and mobilisation, vitamin D also performs a number of non-osteogenic and non-calcemic tasks, making it an essential component of extraskeletal health [4].

Deficiency is spreading like wildfire and affects people of all ages. Many countries do not recognise vitamin D insufficiency and do not provide adequate treatment for it. Over a billion individuals worldwide suffer from a vitamin D deficiency. Worldwide, there is a high frequency of vitamin D insufficiency in many nations. The general population's prevalence is 17% in Italy, 33.9 % in Spain, 50 % in Germany, and 87.1 % in the UK. Vitamin D deficiency is an urgent problem in Ukraine as well. An increased risk of cardiovascular, cancerous, metabolic – diabetes, immunological, psychiatric, and other chronic disorders is linked to vitamin D insufficiency [5, 6]. This review aimed to discuss main physiological and pathological functions and effects of the Vimamin D in kindey.

Vitamin D under the physiological conditions in kidney. The skin can produce vitamin D3 when exposed to sunshine, and the liver is where the first hydroxylation (23-hydroxylation) takes place for both products. This important vitamin D metabolite travels to the kidneys and other organs for the last activation stage, hydroxylation, where it changes into the active form of vitamin D, calcitriol, which then uses its unique receptor to carry out crucial biological functions (VDR) [7]. The proximal tubule's VDR-mediated phosphate reabsorption is directly impacted by 1,25D. Additionally, 1,25D has a discernible impact on the metabolism and absorption of calcium. Almost very cell in the body is impacted by 1,25D activity in the kidneys through its receptor, VDR [7–8]. Vitamin D receptor structure given on Figure 1.

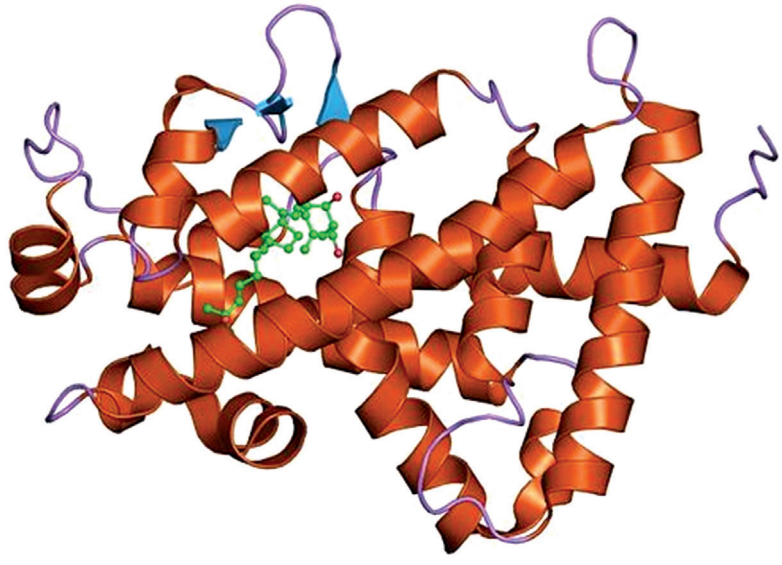

Figure 1. Structure of the Vitamin D receptor

Kidney mechanisms of the Vitamin D deficiency development. The lowered levels of 1,25-dihydroxyvitamin D that arise during kidney illness appear to be caused by multiple mechanisms. As a result, a reduction in renal mass will undoubtedly reduce the amount of 1-α-hydroxylase that may be used to produce the active vitamin D metabolite [9].

A decrease in GFR associated with many kidney diseases could restrict the amount of substrate that is delivered to 1-α-hydroxylase, which could consequently affect the kidney's capacity to synthesise 1,25-dihydroxyvitamin D. The significance of a decreasing GFR in restricting the kidney's capacity to generate 1 to 25-dihydroxyvitamin D is very high. It also showed that the rate-limiting step in delivering 25-hydroxyvitamin D to the 1-α-hydroxylase enzyme was the glomerular filtration of the vitamin D-bound vitamin D-binding protein, which then goes through glomerular filtration and is taken up by the receptor megalin into the proximal tubule cell. Therefore, there is a limit on substrate delivery when GFR drops, which may affect the failing kidney's capacity to generate 1,25-dihydroxyvitamin D [10].

The ability of the failing kidney to maintain levels of 1,25-dihydroxyvitamin D as kidney disease progresses may be limited by the recent discovery that fibroblast growth factor-23 (FGF-23), which increases in the course of kidney disease, can directly suppress 1-α-hydroxylase. According to recent data, there appears to be a high incidence of vitamin D insufficiency or inadequacy linked to kidney illness [11]. Research has shown that most individuals with chronic kidney disease have 25-hydroxyvitamin D levels below 30 ng/ml, which is thought to be the lower limit of normal [12].

Vitamin D in kidney diseases. The primary kidney problems related with vitamin D insufficiency include those caused by proteinuria, inflammation, and autoimmune diseases, such as diabetic nephropathy (DN), chronic kidney disease (CKD), etc. The lowest results are seen in patients who are extremely proteinuric. These researchers have demonstrated that levels of 25-hydroxyvitamin D < 30 ng/ml are linked to almost all cases of secondary hyperparathyroidism that develop during chronic kidney disease (CKD). Interestingly, the link between 1, 25-dihydroxyvitamin D levels and 25-hydroxyvitamin D levels is positively correlated in this sick group, which is not the case in normal individuals [14].

A chronic microvascular complication of diabetes mellitus (DM), DN presents as a clinical syndrome with progressive reduction in glomerular filtration rate (GFR), hypertension, persistent albuminuria (urine albumin-to-creatinine ratio [UACR] > 300 mg/g), and an increased risk of cardiovascular events, including cardiovascular fatal events. The term «diabetic kidney disease» established in 1995 to refer to kidney disease that was clinically diagnosed as being caused by diabetes mellitus (DM). The Japanese Society of Pathology and the Japanese Society of Nephrology share this view, stating that the term «DN» should only be used to refer to kidney damage that was pathohistologically confirmed by diabetes mellitus. In the literature, both words are still in use. We differentiate between two types of diabetic nephropathy based on earlier studies: proteinuric diabetic nephropathy (P-DN) additionally and non-proteinuric diabetic nephropathy (NP-DN) [15].

There are several different and intricate ways that hyperglycemia can lead to diabetic kidney disease (DN), but the most significant ones are renal hemodynamic disorder, impaired glucose metabolism, ischaemia, increased oxidative stress, inflammation, and increased activity of the renin-angiotensin-aldosterone system (RAAS) at the kidney level [16].

The most common and serious long-term diabetes consequence is DN. The final stage of the DN's increasing lesions that might result in end-stage renal disease (ESRD) is renal fibrosis [2]. One important mechanism for the development of fibrosis in the diabetic kidney is the epithelial-mesenchymal transition (EMT). A mesenchymal phenotype is acquired and cell epithelial markers are lost during epithelial-mesenchymal transition (EMT) [14, 15].

One new risk factor for the onset of type 1 diabetes (T1D) and DDN is vitamin D insufficiency. One of the primary organs where vitamin D undergoes modifications to its active metabolite, 1α,25-dihydroxy vitamin D3, is the kidney. Maintaining the extracellular levels of calcium (Ca^{2+}) and phosphorus

(P+) ions in the body is the primary physiological function of 1α,25(H)2D3. Moreover, Vitamin D plays a crucial role in preserving the integrity of podocytes, averting EMT, and lowering albuminuria. Many clinical and experimental investigations of chronic kidney diseases linked or unlinked to diabetic mellitus have documented its deficit [14, 17]. Even with vitamin D replacement and other ESRD-delaying medications mostly focused on blood pressure and glycemic control, the incidence of DN remains is still increasing.

Numerous investigations have demonstrated that, in comparison to the healthy population, patients with T1DM and T2DM have a much greater prevalence of 25(OH)D3 insufficiency. In addition, there is a noteworthy inverse relationship between the concentration of 25(OH)D3 and HBA1c. Serum concentrations of 25(OH)D3 are considerably lower in patients with macroalbuminuria and microalbuminuria than in those with normoalbuminuria [18]. Studies suggested that vitamin D may influence the later onset and slower progression of DN in addition to its potential anti-inflammatory, immunomodulatory, and hypoglycemic effects. It is believed that these renoprotective actions of vitamin D can postpone the onset and slow down the progression of DN.

Fixing vitamin D deficiency in diabetes mellitus has been shown by several writers to have anti-proteinuric effects [19, 20]. This effect should be emphasised because proteinuria is the primary aim of treatment in terms of reducing the course of DN. By binding to the transcription factor cyclic adenosine monophosphate-response element (CRE)-binding protein and inhibiting renal transcription, vitamin D has an anti-proteinuric effect by inhibiting RAAS in the juxtaglomerular kidney apparatus through downstream regulation of gene transcription. Vitamin D not only inhibits renal RAAS but also reduces heart-level renin expression, which decreases blood pressure. It was verified the anti-proteinuric action of vitamin D [21].

Apart from the impact on renin, the direct influence on vascular cells and calcium metabolism also contributes to the hypotensive effect. Vitamin D improves blood pressure and intraglomerular pressure regulation through these mechanisms [38]. The literature indicates that there is a negative relationship between blood pressure and serum vitamin D content. Enhancing glyco-regulation and the anti-fibrotic effect – reducing TGF-β1 activity in the urine, upregulating nephrin expression at the kidney level, and decreasing levels of other growth factors that impede SD and podocyte function, like VEGF-A and MCP-1 – also contribute to the antiproteinuric effect [22, 23]. Furthermore, delaying fibrosis protects and delays the development of cardiac weakening and left ventricular hypertrophy, as well as lowers the expression of genes involved in atherosclerosis as well as vascular growth factors. Summarized scheme of the physiological and pathological effects of Vitamin D in kidneys given by us on Figure 2.

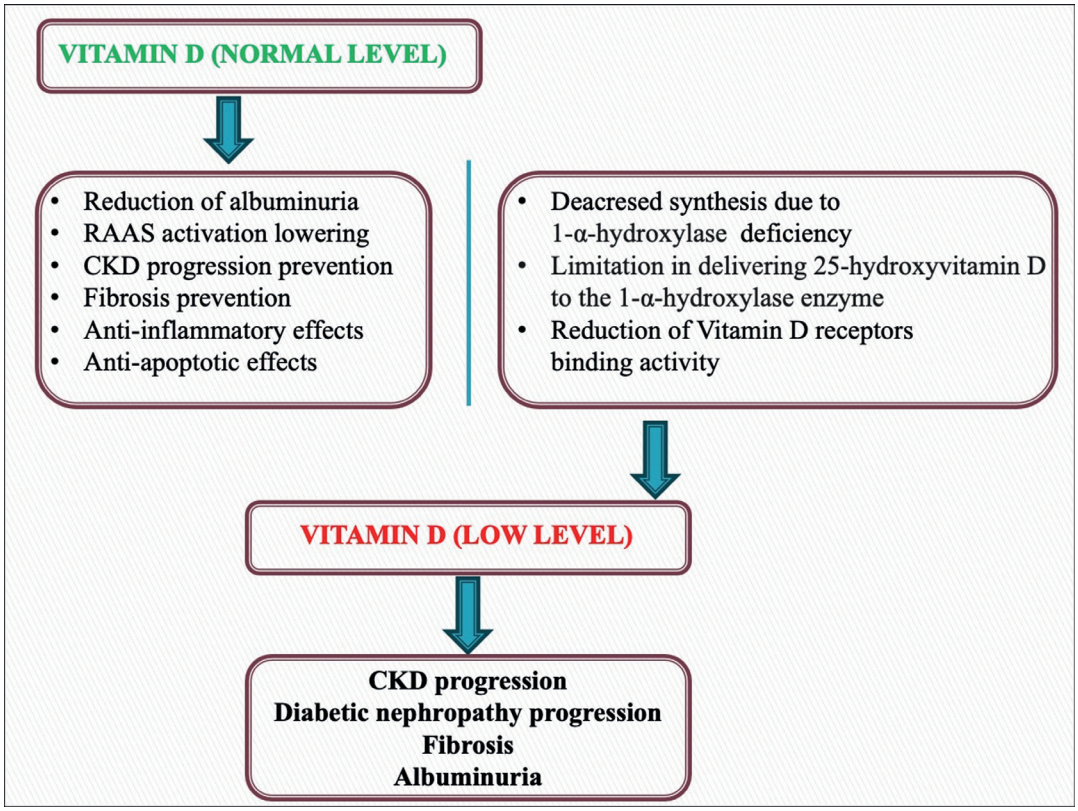

Figure 2. Summarized scheme of the physiological and pathological effects of Vitamin D in kidneys

Conclusions. Numerous advantages of vitamin D exist for bone, blood, homeostasis, and various organs, including the kidneys. As previously noted, vitamin D is a crucial for the kidneys and illnesses associated to them. Numerous studies have been conducted to ascertain the precise function of Vitamin D in the kidneys and how it relates to other organs. Our most recent research of our research group has demonstrated the beneficial effects of Vitamin D on the regulation of apoptosis in diabetic nephropathy patients. As such, the use of vitamin D in the prevention and treatment of disease is still far from realised completely. To do this, more research is necessary. As for the reference values for vitamin D, there is still no clear agreement on what those amounts should be.

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