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Review

Anti-Inflammatory Benefits of Vitamin D and Its Analogues against Glomerulosclerosis and Kidney Diseases

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Abstract: Apart from the significant progress the scientific community has made during the last few decades, inflammation-mediated kidney-related diseases like chronic and diabetic kidney diseases (CKD and DKD) and glomerulosclerosis still continue to raise mortality rates. Recently, conventional therapeutic interventions have been put aside, since natural vitamin D-derived treatment has gained attention and offered several promising outcomes. Within this article, the utilization of vitamin D and its analogues as potential treatment toward kidney-related diseases, due to their anti-inflammatory, antioxidant and anti-fibrotic activity, is outlined. Vitamin D analogues including calcitriol, paricalcitol and 22-oxacalcitriol have been previously explored for such applications, but their hidden potential has yet to be further elucidated. Several clinical trials have demonstrated that vitamin D analogues' supplementation is correlated with inflammatory signaling and oxidative stress regulation, immunity/metabolism augmentation and subsequently, kidney diseases and healthcare-related infections' prevention, and the results of these trials are thoroughly evaluated. The highlighted research outcomes urge further study on a plethora of vitamin D analogues with a view to fully clarify their potential as substantial anti-inflammatory constituents of renal diseases-related treatment and their health-promoting properties in many kidney-associated healthcare complications and infections.

Keywords: vitamin D; analogues; anti-inflammatory; glomerulosclerosis; renal diseases; diabetic kidney disease; chronic kidney disease; fibrosis; metals; calcium; immune modulation

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1. Introduction

Nowadays, as a result of a sedentary lifestyle, poor eating habits and abstention from social activities, people are more susceptible to numerous chronic diseases [1,2]. Reportedly, one out of ten people worldwide as of 2022 suffered from chronic kidney disease (CKD), which based on recent population data translates to 800 million people worldwide [1–3]. In 2015, 1.2 million people died from CKD that was induced by either hypertension, type II diabetes mellitus, or glomerulonephritis, increasing the corresponding mortality rates by 32% compared to those recorded in 2005 [4].

Kidneys are an organ of utmost importance to every living organism, since their main function lies upon converting metabolic by-products into urea, which is excreted into the urine and then dismissed from the body through the process of nitrogen metabolism urea cycle [5,6]. Normally, urine is free of compounds that the kidneys come into contact with like carbohydrates, protein, glucose and ketones. Other equally important functions kidneys are involved in include their contribution to regulating the balance of electrolytes in the blood and the adjustment of blood pressure [7,8]. In addition, through the secretion of hydrogen cations, kidneys balance the pH value of the blood and are also responsible for the production of hormones such as prostaglandins or renin [9]. The hydroxylation of vitamin D, which concludes to its activation, is also one of the most vital functions of our kidneys [10–12]. In general, the kidneys consist of the renal cortex and the renal

medulla, while the organelles that carry out all the important processes inside the kidneys are known as nephrons and are located in the renal medulla's pyramids [6,7]. At this point, it is worth mentioning the kidney's important role in the production of an important glycoprotein hormone by the peritubular cells that stimulates efficiently red blood cells' generation as a regulator of erythropoiesis [13,14]. Furthermore, kidneys play a major role in drugs and selected cytokines' metabolization, as they partake in the intricate interplay between immune and metabolic pathways in kidney diseases and hence promote the efficacy of modern pharmacotherapy [15,16]. Other significant hormones, are secreted and degraded as well by our kidneys, which are in fact crucial for regulating blood pressure and renal flow, including hormones like renin, urodilatin and medullipin, as kidneys normally maintain arterial pressure within a narrow range by employing the mechanism of pressure natriuresis [17–19].

Kidneys in general perform complex processes that are crucial for homeostasis, ensuring that our internal environment remains stable and free of toxins [8,20]. The length of the adult kidney ranges from 10 to 20 cm based on the correlation of body height and age, while the right kidney is most of the times slightly longer than the left one [21,22]. Kidneys are divided into renal parenchyma and renal sinus. The renal sinus is hyperechoic and comprises catalyces, the renal pelvis, accumulated fat and major intrarenal vessels. In a normal-functioning kidney, the urinary-collecting system located in the renal sinus, although it is invisible, initiates a heteroechoic appearance with both the intervening fat and vessels [21,22]. On the other hand, the renal parenchyma is more homogenous and hypoechoic and is in fact separated into the innermost and outermost cortex as well as some marginally less echogenic medullary pyramids that consisted of cortical infoldings, namely columns of Bertin [21–24]. More specifically, the renal parenchyma of kidneys consists of nephrons, collecting tubules, lymphatic vessels, neurons and arteries. A nephron consists of a renal corpuscle, which is attached to a coiled "tubule". This tubule leads first to the Bowman's capsule and secondly to the proximal tubule, where the secretion of water and sodium chloride from the pre-urine takes place. The coiled tubule then meets the Henle's loop, in which the secretion of water molecules and the reabsorption of sodium chloride is initiated. Right after the distal tube, an exchange of sodium ions with potassium ones (excretion) as well as hydrogen ions (absorption) occurs: a situation wrapped up in a collection tube. The renal corpuscle continuously filters blood plasma through the glomerulus, providing filtrate to the renal tubules [25]. As a consequence, several collection tubes merge to form the Bellini ducts, which in turn exit the renal pyramid carrying along body fluids destined to end up in the bladder and then excreted from our body [6]. It is useful to note that the collection tubes play a crucial role in the permittance or the forbidding of the excretion of water and electrolytes in the blood as well as in the desired activation of vitamin D [6,22,26].

Vitamin D, a fat-soluble vitamin traditionally known for its role in calcium homeostasis and bone health, has gathered attention in the recent years for its broader implication in the human health and particularly for its anti-inflammatory properties [27,28]. This vitamin is predominantly produced when the surface of the skin is exposed to sunlight [29,30]. Vitamin D has two equal forms: D_3 ("cholecalciferol") and D_2 ("ergocalciferol"), that differ in the one extra double bond of vitamin D_2 [30]. Vitamin D's metabolism is at first initiated by a cholesterol precursor molecule known as 7-dehydrocholesterol, found in the sunlight-exposed skin, and subsequently a series of chained reactions lead to vitamin D_3's generation in the epidermis [12,27,31,32]. As vitamin D_3 reaches the liver, it is enzymatically converted into 25-hydroxy vitamin D_3, which is then transformed in the kidneys to 1α,25-dihydroxy-vitamin D_3, a complex with a crucial role, as a regulator, in several biochemical pathways, that will be further analyzed in the main body of our research [13].

The activated form of vitamin D_3, namely calcitriol, participates in multiple functions, interrelated or not inside the human body; thus, it is essential for its proper functioning. First of all, calcitriol aids in the balance of calcium ratio in the blood. Calcium in turn is a trace element present in human bones and teeth in the form of hydroxyapatite, providing

them with strength and stability [27,33–35]. Regarding its metabolism, three areas of the human body are associated with a regulatory role in maintaining calcium ions in normal levels in the blood serum: the intestine (small and large), kidneys and bones. The hormones that assist in this regulation are calcitriol and parathyroid hormone (PTH). At low recorded levels of calcium ions in the blood, PTH is secreted, which acts on the proximal tubules of kidneys and bone osteoclasts, leading to the reabsorption of calcium ions, the increase in the renal enzyme 1-a-hydroxylase (catalyst of the reaction of vitamin D_3's activation) and finally osteoclasts' activation so as to initiate the intended release of calcium ions [33,34].

Newly emerging research highlights the potential of vitamin D and its analogues in mitigating inflammatory processes, which are central to the pathogenesis of various chronic diseases, including glomerulosclerosis and kidney-related diseases. Vitamin D analogues like calcitriol halted cell proliferation, glomerular growth, glomerulosclerosis and albuminuria [36,37], while treatment with 22-oxacalcitriol notably suppressed and/or prevented urinary albumin expression, serum creatinine and serum urea nitrogen increase as well as inhibited glomerular cell number/growth/volume and glomerulosclerosis [38,39]. Concurrently, paricalcitol was able to restrain procedures such as macrophage infiltration, mRNA expression of proteins and growth factors including the transforming growth factor-β-1 (TGF-β1) and the phosphorylation of others like the mothers against decapentaplegic homolog-2 (Smad2) [40,41].

Glomerulosclerosis is highly characterized by the scarring of the glomeruli within the kidneys that leads to compromised kidney function and is a common endpoint of many kidney diseases [42–44]. The inflammatory milieu in glomerulosclerosis is responsible for the exacerbation of tissue damage and the acceleration of the disease's progression. Vitamin D, through its active form namely calcitriol, exerts immunomodulatory effects that may help attenuate these inflammatory pathways [42–44]. Notably, patients that suffered from CKD exhibited reduced serum calcitriol values in their blood, because the fibroblast growth factor 23 (FGF-23) suppressed the enzyme of 1-a-hydroxylase [45]. As a result, no active transport of calcium ions occurred. Hence, it has been established that the recommended daily dose of calcium for patients with chronic kidney disease is 800 to 1000 mg/d [46], as amounts greater than 1000 mg/d put patients at risk due to the suppression of the process of excretion of calcium ions from the urine [47]. Concurrently, considering glomerulosclerosis treatment, the recommended dose of calcitriol (1α,25-dihydroxy-vitamin D_3) that did not cause hypercalcemia in sham-operated and subtotally nephrectomized (SNX) rats was 3 ng/100 g body weight/day [48], while 1–2 μg of paricalcitol and 0.25–0.50 μg of calcitriol were the recommended doses for CKD patients suffering from glomerulosclerosis; however, more clinical trials must be conducted in order to discover the best possible dose [49]. On the contrary, an excess of calcium cations in the blood leads to the calcification of soft tissues and arteries. Some calcium deposits are declared harmless; however, others may be a sign of serious and possibly asymptomatic health conditions that can even be potentially fatal [50,51].

Understanding the anti-inflammatory benefits of vitamin D could open new therapeutic avenues for managing glomerulosclerosis and promoting better outcomes in kidney disease patients. This review aims to elucidate the mechanisms by which vitamin D and its analogues influence inflammatory responses in the kidneys against the progression of glomerulosclerosis by analyzing in vitro research and in vivo studies, including clinical trials, with respect to several inflammation-related renal disorders. Emphasis is given to vitamin D's potential as a therapeutic agent in the context of glomerulosclerosis, as well as mainly chronic (CKD) and diabetic (DKD) kidney diseases. Vitamin D's benefits against glomerulosclerosis and kidney diseases are depicted in Figure 1.

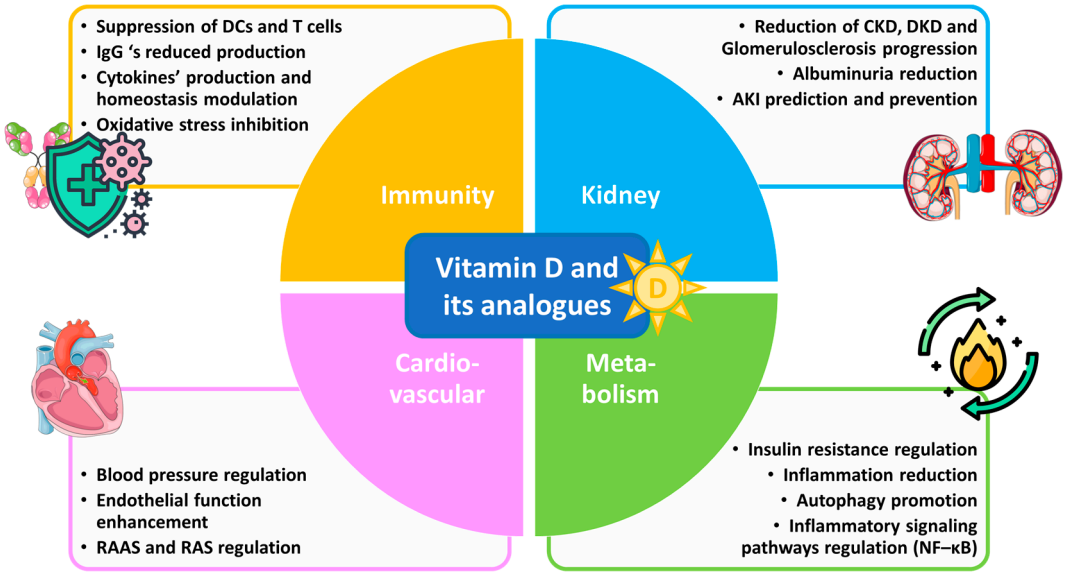

Figure 1. Vitamin D and its analogues in glomerulosclerosis and kidney disease therapy.

2. Materials and Methods

In order to carry out the necessary literature review, various databases were explored including MDPI, PubMed, Scholar Google, Science Direct, Scopus and the NIST library. The combinations of keywords used were each one word from the first parenthesis AND one of the words of the second parenthesis: ("Vitamin D" OR Vitamin D analogues OR Renal Diseases OR Glomerulosclerosis OR Focal and Segmental Glomerulosclerosis OR Chronic Kidney Disease OR Diabetic Kidney Disease OR Fibrosis OR Acute Kidney Disease OR Diabetic Neuropathy OR Glomerulonephritis OR Kidney Disease Induced by Metals OR Nephrotic Syndrome OR Polycystic Kidney Disease OR Hyperparathyroidism OR End-Stage Renal Disease OR Amyloidosis OR 22-Oxacalcitriol OR Paricalcitol OR Calcipotriol OR Calcitriol OR Doxercalciferol OR Falecalcitriol OR Alfacalcidol OR Calcium OR Lead OR Cadmium) AND (Antioxidant OR Anti-inflammatory OR Inflammation OR Inflammation-Related Signaling Pathways OR Inflammation Biomarkers OR Cytokines OR NF-κB Signaling Pathway OR Oxidative stress OR Platelet-Activating Factor OR Thrombin OR Anti-Diabetic OR Renin–Angiotensin System OR Immune Modulation OR Malnutrition OR Atherosclerosis OR Heart Failure OR Mineral and Bone Disorders OR "In vitro" OR "In vivo").

Initially, the search was focused on the dates 2014–2024, however, the results were not sufficient, especially for the other renal diseases except for CKD and DKD, and thus the search time frame was expanded mainly to 2004–2024. In some cases, some older reported studies were also included, which were not previously thoroughly reviewed.

Articles in other language than English, duplicates and the majority of review articles were excluded, apart from some important recent review articles on general information considering renal diseases.

3. The Multifaceted Role of Vitamin D toward Inflammation, Immune Modulation and Kidney Diseases

3.1. Inflammation and Kidney Diseases

3.1.1. Kidney Function in the Pathophysiology and Symptomatology of Glomerulosclerosis and Kidney-Related Diseases

The kidneys play a vital role in maintaining the body's overall health by predominantly filtering waste, balancing electrolytes, and regulating blood pressure while participating in the maintenance of homeostasis and the provision of a toxins-free internal environment [8,20]. Glomerulosclerosis is a progressive kidney disease characterized by scarring of the glomeruli, which are the tiny filtering units within the kidney. This scarring

disrupts the normal filtration process, leading to a decline in kidney function and ultimately contributing to CKD's and other kidney-related diseases' progression [40].

Focal and segmental glomerulosclerosis (FSGS) is a disease with primary damage to podocytes (podocytopathies), which is clinically evident by high proteinuria and the nephrotic syndrome (NS) [52]. FSGS is marked by the presence of sclerosis in parts (segmental) of at least one glomerulus (focal), as apparent by a kidney biopsy specimen, which is examined by ultrasound techniques involving the superb microvascular imaging (SMI) [53] and other microscopic techniques like the light, immunofluorescence and electron microscopy [52]. Severe FSGS, the most frequent idiopathic NS, is defined by high proteinuria, renal impairment during the initial stages, and an adverse outlook on the advancement of renal dysfunction, which may even conclude to an end-stage renal disease (ESRD) [52,54,55]. The onset of FSGS is evident where 25–50% of patients face a decrease in the kidney function, 50% hematuria and 20% arterial hypertension [52].

Several circulating permeability factors (CPFs) are able to damage the glomeruli and cause podocyte injury, leading to proteinuria, loss of podocytes, permeabilization of the glomerular filtration barrier and the induction of FSGS's recurrence. As a result, proteins affiliated with CPFs' mechanism of action and/or potential biomarkers for CPF's presence have been suggested to possibly inhibit their menacing role in FSGS's progression [56,57]. Recent study results have demonstrated that CPF-containing plasmas from FSGS patients enhance both podocyte lipid droplet accumulation and the expression of perilipin-2, which is consequently considered as a potential FSGS biomarker [56,57]. Additionally, the inhibition of reactive oxygen species' (ROS) formation or facilitating the rapid ROS scavenging may exert some beneficial effects toward FSGS's progression and subsequently a framework for regulating CPF activity, which may contribute to the better future monitoring and prognosis of NS-related diseases [57]. Furthermore, differentiating proteins, including apolipoprotein A4 (APOA4), hemopexin, gelsolin, vitronectin, complement C4B protein gene (C4B), retinol and vitamin D-binding proteins, could also be potent FSGS biomarkers against the evolvement of kidney-related diseases [52].

The use of vitamin D_3 and its derivatives toward kidney-related diseases' prevention has been justified in several clinical trials by mainly its vast antioxidant and anti-inflammatory ability to modulate key elements of the inflammatory process, including the reduction of pro-inflammatory cytokines (like interleukin 1 (IL-1β)) that contribute to inflammation, fibrosis, blood pressure elevation and kidney damage progression as well as the abatement of oxidative stress and the renin–angiotensin–aldosterone system's (RAAS) overactivation [58,59]. Moreover, vitamin D's anti-fibrotic properties that enhance the reduction of fibrogenic factors and thus fibrosis, along with the immune system modulation (T cells' activity promotion) and proteinuria decrease, place this hormone between the most promising candidates in the battle against kidney diseases [45].

3.1.2. The Role of Inflammation in the Progression of Kidney Diseases

Although our kidneys have protective mechanisms toward systemic inflammation, CKD's occurrence or other renal diseases make it vulnerable to damage deriving from pro-inflammatory cytokines and oxidative stress. Unlike other highly vascularized organs (e.g., the liver) that own antioxidants and detoxifying agents, kidneys receive almost 25% of the body's blood volume without any similar anti-inflammatory defenses [59–61]. Thus, despite the fact that regulatory hormones and vasoactive molecules normally prevent damage from the physiologic hypoxic medulla environment, these constituents are disrupted by inflammation-related processes, with CKD causing several intrarenal alterations in the microvasculature, which eventually leads to renal damage [60]. Furthermore, the renal tubules house many regulated inflammatory cytokines, chemokines, and fibrosis mediators that play key roles in renal injuries' progression, since pre-existing conditions, such as diabetes, incomplete recovery from acute kidney disease (AKI), genetic and epigenetic factors, age, hypertension, chronic and recurrent infections, altered adipose tissue metabolism, acidosis, glomerulonephritis, and uncontrolled inflammatory responses, may

enhance kidney dysregulation [58–60]. Regarding the proximal tubules, their high energy demands set them prone to inflammation-mediated ischemia, while oxidative damage induced by increased reactive oxygen species (ROS) and decreased nitric oxide (NO) levels due to elevated homocysteine exacerbate CKD. Additionally, when antioxidant systems like the glutathione redox cycle reach their maximum capacity, a higher oxidized-to-reduced glutathione ratio occurs and hence, the ability to combat oxidation in CKD patients is restrained [59,60,62].

Inflammasomes and inflammasome components in general are highly implicated in infectious and non-infectious tissue injury [63]. The inflammasome structurally comprises a sensory component, a mediator of caspase-associated recruitment domains (CARD), apoptosis-associated speck-like protein that contains a CARD (ASC) and procaspase-1. Inflammasome sensors are categorized as nucleotide-binding domain-like receptors (NLRs) that enclose inflammasome-forming NLRs (NLRP1, NLRP3, NLRC4, etc.) and potent inflammasome sensors (NLRP6 and NLRP12) as well as missing in melanoma 2-like receptors (ALRs) and pyrin [58,60,63,64]. The ASC protein may bind with the NLRP3's amino-terminal pyrin domain; thus, it stimulates procaspase-1 with all three constituents forming a multiprotein inflammasome complex able to activate caspase-1. Activated caspase-1 mediates the conversion of pro-IL-1β and pro-IL-18 to their mature forms, namely IL-1β and interleukin 18 (IL-18), via the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signaling (signal 1) and their cleavage by caspase-1 (signal 2) [63,65,66]. Signal 1 is responsible for the regulation of the expression of several inflammasome components and pro-cytokines' synthesis. In particular, pathogen-associated and danger-associated molecular patterns (PAMPs and DAMPs, respectively), provide signal 1 through the activation of the toll-like receptor (TLR-mediated) NF-κB signaling. Signal 2 is concurrently provided by various formed crystal particles via environmental or metabolic pathways and adenosine triphosphate (ATP), and thus, the inflammasome complex is activated and marks cells' reaction to cellular stress [59,63–66]. The NLRP3 activation displayed interesting clinical results. NLRP3 expression affects tissue remodeling following chronic trauma and death signaling in epithelial cells, enhances angiogenesis as observed in a rat model and augments the TGF-β1/Smad signaling pathway, leading to tubular–interstitial fibrosis during CKD and kidney fibrosis [63,65,67,68]. The diverse activation of the NLRP3 inflammasome implied its potential detective role of cellular stress or injury. Three activation mechanisms are reported to successfully enhance NLRP3's activation: cathepsin B after lysosomal injury, potassium efflux and phagocytosis, while caspase-1 and other caspases' related signaling as well as post-transitional protein modifications (PTMs) still need to be further evaluated in order to fully comprehend their activity in kidney diseases [59,63–68].

During CKD specifically, an increase in adipokines and adhesion proteins (e.g., intercellular and vascular cell adhesion protein 1 (ICAM-1 and VCAM-1, respectively) is observed, which triggers uremic toxins' activity. Uremic toxins subsequently play a vital role in the both the onset and the evolvement of inflammation signaling pathways by activating and increasing c-reactive protein (CPR), NO and NF-κB. More specifically, growing evidence further supports the degenerating impact of uremic toxins including indoxyl sulfate, *p*-cresyl sulfate, hippuric acid, homocysteine, etc. on the progression of CKD-related health complications [69,70]. As a result, increased levels of pro-inflammatory cytokines such as interleukins 1β and 6 (IL-1β and IL-6) that suppress PTH secretion, tumor necrosis factor α (TNF-α) and other pro-inflammatory enzymes and molecules are exhibited. Consequently, the inflammatory state is amplified and complications like malnutrition, atherosclerosis, heart failure, mineral and bone disorders, coronary artery calcification, anemia, etc., are aggravated (Figure 2) [47,58,60].

A plethora of inflammatory markers produced by the adipose tissue, like IL-1β, fibrinogen and TNF-α, independently predict CKD progression. IL-1β is responsible for activating the adhesion molecule expression in the endothelium and for inducing chemokine expression so as to recruit white blood cells (WBCs), while interleukin 6 (IL-6) may be involved in atherosclerosis and/or acute phases protein response, and IL-18 triggers the upregula-

tion of other inflammatory cytokines and participates in inflammasome formation [60,64]. Moreover, TGF-β1 increases the extracellular matrix (ECM) and induces kidney fibrosis, while TNF-α upregulates other inflammatory biomarkers; thus, it enhances renal fibrosis via decreasing pro-apoptotic signals [71,72]. At this point, it must be noted that IL-1β and IL-6 have been claimed to enhance renal scarring, while TGF-β1 in synergy with IL-6 have been implicated in renal fibrosis [23,58–60,62,63]. In addition, other pro-inflammatory cytokines such as adiponectin receptor 1, cluster of differentiation 68 (CD68), monocyte chemoattractant protein-1 (MCP-1), pentraxin-3, CPR, etc., are validated biomarkers of inflammation and predictors of kidney-related diseases and mainly CKD progression, as depicted in Figure 2 [58,60].

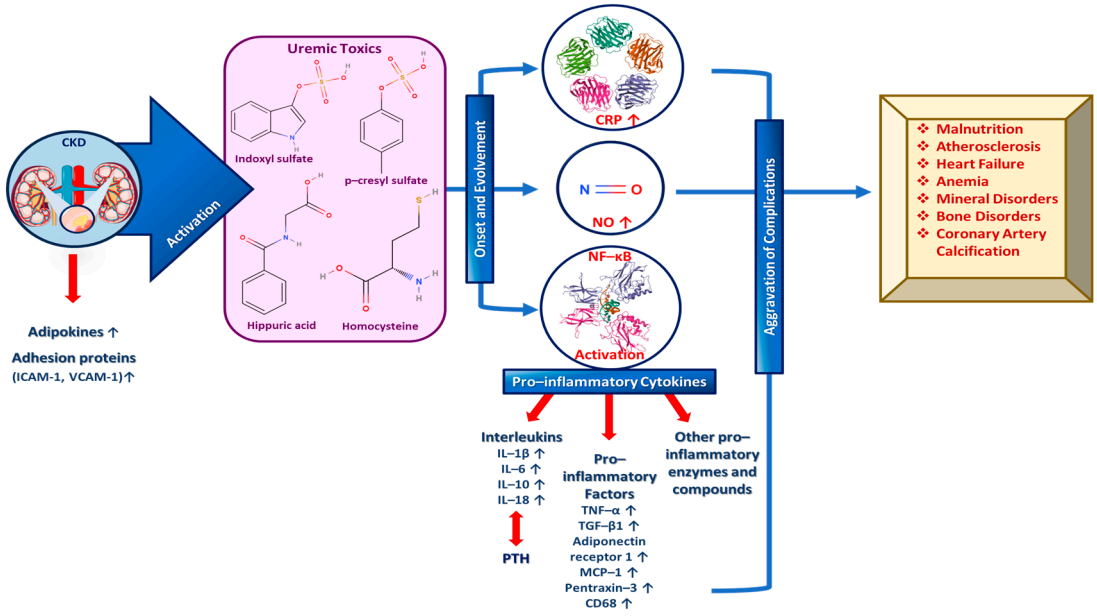

Figure 2. The role of important inflammation biomarkers in CKD and other kidney-related diseases progression as well as several complications' enhancement.

Inflammation-induced, progressive oxidative stress is also worth mentioning, since it is implicated in the manifestation of numerous complications such as for example malnutrition, atherosclerosis, heart failure, or mineral and bone disorders [58]. Growing evidence has currently supported that vitamin D and its analogues exhibit beneficial effects in these disturbances, as this anti-oxidant facilitates balanced mitochondrial activities and immune modulation; thus, it prevents oxidative stress-related protein oxidation, lipid peroxidation, autoimmune diseases or diabetes onset and DNA damage [58,73]. Vitamin D, surprisingly, reduces systemic inflammatory cardiovascular diseases (CVDs) oxidative mediators [74], downregulates RAAS activity [58], and counteracts hydrogen peroxide (H_2O_2)-induced oxidative stress [75], as a potent ROS-targeting treatment [76].

3.2. Vitamin D: Structure, Function and Its Potential Role on the Immune Modulation

3.2.1. Vitamin D's Structure, Metabolism, Renal Production and Analogues

Since the 17th century and the mass movement from rural to urban, smoke-filled cities, many efforts to combat the public burden of rickets, a childhood disease responsible for softening and weakening children's bones, had been made. It was only in the 20th century that Mellanby and McCollum claimed that cod liver oil could be a potential cure to rickets. Specifically, McCollum heated this cod liver-derived oil in an attempt to destroy all the vitamin A content; however, some antirachitic properties still remained with the antirachitic factor corresponding to vitamin D [77–79]. Shortly thereafter, scientists Steenbock and Black proved that exposing food, especially its non-saponifiable lipids to UV radiation could be a potential cure to rickets, which led to the realization that rickets may be prevented or

cured in children exposed to sunlight and/or artificial UV radiation [80,81]. As a result, vitamin D was believed and demonstrated to be produced by irradiation of precursors in vivo [77]. Eventually, Askew et al. [80,82] isolated and established vitamin D_2's structure from irradiated plant sterols (ergosterol), while Windaus et al. [79,83], ascertained both the structures and the specific pathway where 7-dehydrocholesterol (7-DHC), found in the skin, is converted to vitamin D_3 [79].

Generally, vitamin D is predominantly produced when the surface of the skin is exposed to plain sunlight. However, it is also obtained from food sources and dietary supplements, while its production is suppressed by the use of sunscreen emulsions and clothing [29,30]. Vitamin D has two equal forms: D_3 ("cholecalciferol") and D_2 ("ergocalciferol"). The difference between these two derivatives lies in their side chain [30,77]. Essentially, vitamin D_2 has one more double bond in its molecule ($C_{22–23}$) than its counterpart vitamin D_3 [77]. Moreover, vitamin D_3 is synthesized de novo in our skin after UV-B radiation exposure or it is obtained from animal source foods, and at the same time, vitamin D_2 is acquired from plants like mushrooms and yeast [79,84]. The 2D form of these two vitamin D derivatives is depicted in Figure 3.

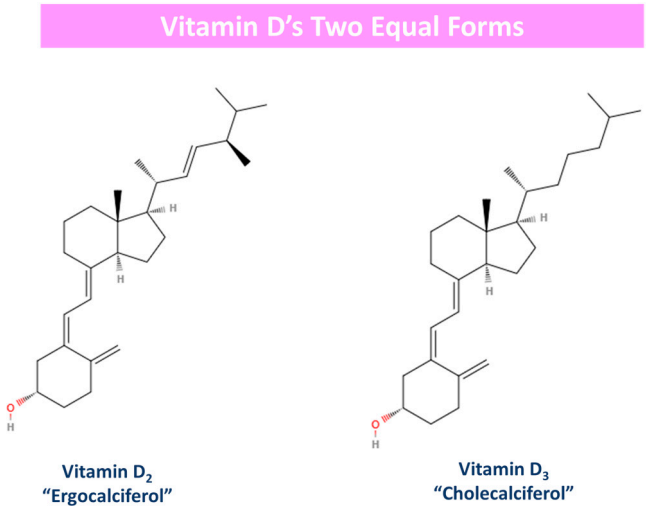

Figure 3. Vitamin D's two equal forms: derivatives. Vitamin D_2 has one more double bond ($c_{22–23}$) in its molecule in opposition to vitamin D_3.

Vitamin D's metabolism is at first initiated by a cholesterol precursor molecule known as 7-DHC, which is located in the skin. As aforementioned, Windaus et al. proposed and determined the pathway of 7-DHC's conversion to vitamin D_3. As long as our skin is exposed to sunlight, the precursor molecule is converted into pre-vitamin D_3, which is then converted by heat into vitamin D_3. This specific reaction is induced in the epidermis (skin), where sunlight (UV-B form, *hv*) successfully breaks the B ring of 7-DHC with a view to form pre-vitamin D_3, which is in turn converted to vitamin D_3 after undergoing a thermal-induced rearrangement. Furthermore, the prolonged irradiation of pre-vitamin D_3 concludes to the reversible formation of two more vitamin D_3 derivatives, namely tachysterol and lumisterol, that are able to be reverted back to pre-vitamin D_3 in dark conditions [31,77,79]. Vitamin D_3 later on enters the bloodstream and is transported to the liver after binding to vitamin D's specific binding protein (Figure 4).

Vitamin D_3's metabolism is conducted first in the liver and secondly in the kidneys so as to obtain its active form with both vitamins D_2 and D_3 being widely acquired from food, plant and animal food sources. Vitamins deriving from food especially bind likewise to a vitamin D carrier protein, and this newly formed binding complex reaches the liver, where it is enzymatically converted to 25-hydroxyvitamin D_3 [85].

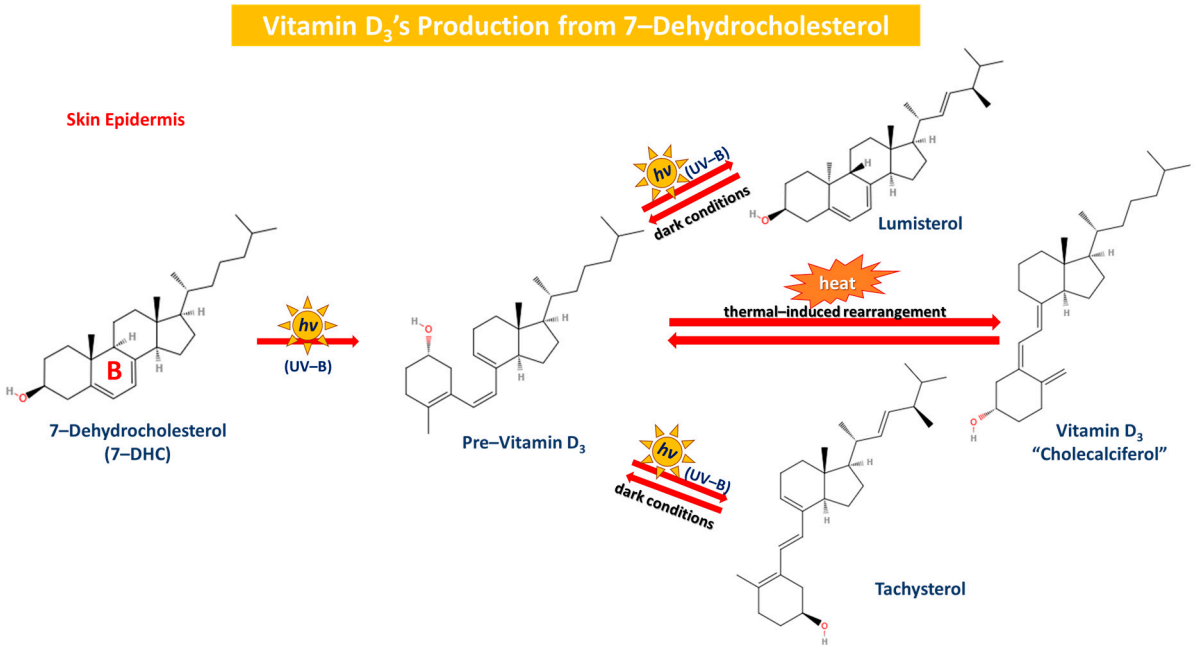

Figure 4. The production of vitamin D_3 from 7-DHC in the skin epidermis. 7-DHC is converted to pre-vitamin D_3 via the exposure to UV (UV-B) and then pre-vitamin D_3 is thermally rearranged to form D_3 reversibly. Lumisterol and tachysterol are formed through continuous exposure to UV-B irradiation, and they are reverted back to pre-vitamin D_3 in dark conditions.

The first step of this process is 25-hydroxylation, which primarily occurs in the liver, even though other tissues exhibit enzymatic activity as well [77]. The liver converts vitamin D_3 to its major circulating form 25-hydroxyvitamin D_3 ($25OHD_3$), which is then converted by the kidney (undergoes filtration by the proximal glomerular tubules and absorption by surface receptors of proximal glomerular cells). This enzymatic procedure is induced by the cytochrome CYP27B1, where via the hydroxylation in the 1α (A ring) position, $25OHD_3$ is converted to 1α,25-dihydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$) and via the hydroxylation in the 24th position, $25OHD_3$ is converted to 24,25-dihydroxyvitamin D_3 otherwise ($24,25(OH)_2D_3$). The conversion of $25OHD_3$ to $24,25(OH)_2D_3$ increases phosphorus and calcium concentrations, while $1\alpha,25(OH)_2D_3$ on the contrary decreases them, as PTH and FGF-23 production is plus promoted. More specifically, vitamin D's metabolites of $25OHD_3$ and $1\alpha,25(OH)_2D_3$ may be hydroxylated at the 24th position, with $1\alpha,25 (OH)_2D_3$ and $1,24(OH)_2D_3$ showing similar behavior. However, the 24–hydroxylation of metabolites with a pre-existing $25OHD_3$ group leads to further, mostly unfavorable catabolism, since vitamin D_3 is preferentially 24-hydroxylated and vitamin D_2 is mostly 25-hydroxylated (Figure 5) [31,45,77,86–88]. The $1\alpha,25(OH)_2D_3$ complex binds as well to its specific receptor and owns a regulative role in several biochemical pathways [85].

Vitamin D is mainly utilized in kidney-related therapeutic interventions in the form of one its several analogues. Calcitriol ($1\alpha,25(OH)_2D_3$) is the main utilized vitamin D analogue in kidney diseases' treatment and has been widely supplemented in many CKD patients globally. Vitamin D in the form of calcitriol has been demonstrated to lessen the severity of proteinuria in CKD patients with low serum $25(OH)D_3$ levels [89], while recently, research findings claimed that CKD patients could benefit from calcitriol supplementation toward COVID–19's potent infection [90]. As calcitriol's deficiency enhances hyperparathyroidism evolvement, a calcitriol treatment strategy could activate the VDR and replenish vitamin stores while avoiding hypercalcemia and hyperphosphatemia in patients suffering from renal diseases [91]. Oral calcitriol treatment has also been pointed out in the past as a potent attributor to lower death and dialysis risk, decreased renal failure incidence, reduced proteinuria and albuminuria, regulated mesangial cell proliferation, increased

inflammatory cytokines and oxidative stress modulation and murine lupus attenuation in CKD or renal diseases patients [36,43,92].

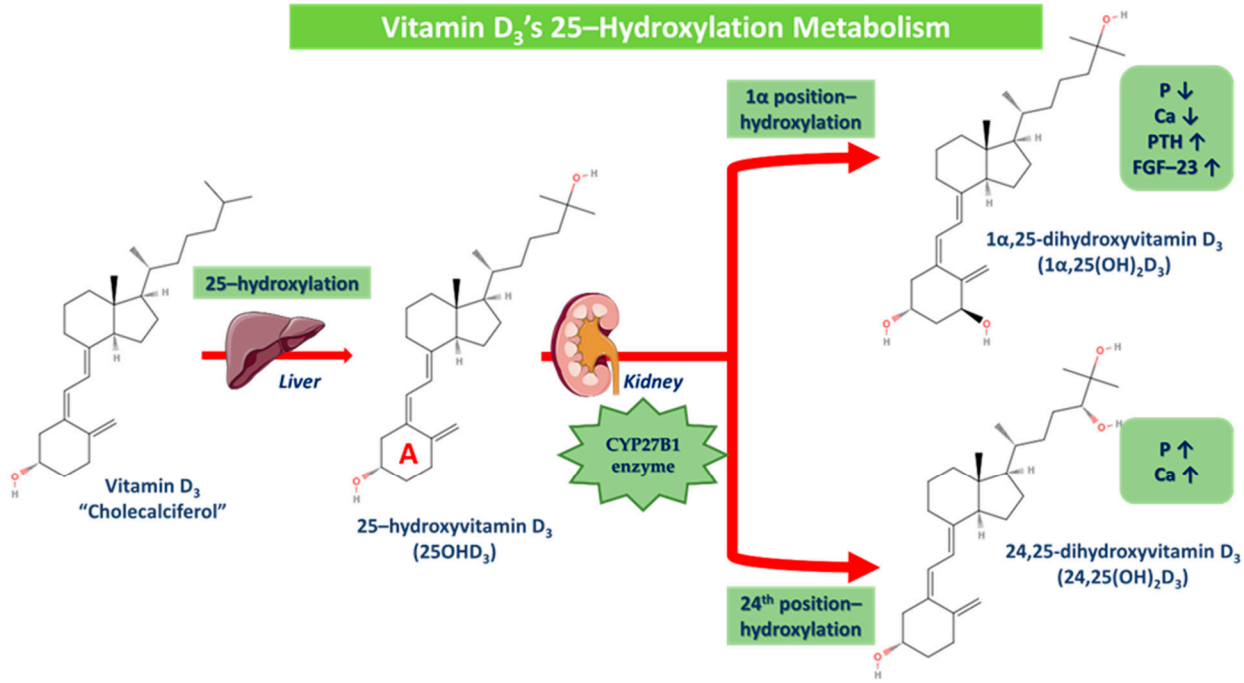

Figure 5. Vitamin D_3's 25-hydroxylation metabolism. 25-hydroxylation occurs in the liver, where vitamin D_3 is converted to 25-hydroxyvitamin D_3 ($25OHD_3$), which is then converted in the kidney via the cytochrome CYP27B1 enzyme in two different derivatives. Via the hydroxylation in the 1α (A ring) position, $25OHD_3$ is converted to 1α,25-dihydroxyvitamin D_3 (P and Ca are decreased while PTH and FGF-23 are increased) and via the hydroxylation in the 24th position, $25OHD_3$ is converted to 24,25-dihydroxyvitamin D_3 (P and Ca are increased).

One of the most explored vitamin D analogues yet to be discussed is maxacalcitol, which is also known as 22-oxacalcitriol (22-oxa-1α,25$(OH)_2D_3$). Maxacalcitol has been revealed to possess protective effects toward the renal structure and function in mesangial cell proliferative and ECM productive nephrosis models. Specifically, the daily administration of either calcitriol or this analogue is able to ameliorate the nephrotic state while protecting podocytes, thus leading to the prevention and/or treatment of podocyte injury [36,93]. Furthermore, maxacalcitol treatment attenuated functional deterioration and histological damage in induced AKI, significantly decreased cell fibrosis and apoptosis and hence further confirmed the renoprotective value of this analogue [38,39]. On the other hand, paricalcitol (19-Nor-1α,25$(OH)_2D_2$) is also an important vitamin D analogue with a remedial impact against kidney diseases. Paricalcitol is able to suppress macrophage infiltration, proteinuria, PTH activity, MCP-1 production, renal interstitial fibrosis, TGF-β1 mRNA protein expression and Smad2 phosphorylation [36]. In addition, albuminuria attenuation as well as mesangial matrix expansion and DKD podocyte injury alleviation by the enhancement of podocyte autophagy activity has also been recorded after paricalcitol treatment [94]. Moreover, paricalcitol has been pointed out to provide beneficial effects to hemodialysis patients, as it strongly affects PAF/thrombin activity and metabolism, while it also regulates IL-8, IL-1β and TNF-α circulating levels [61,95]. Paricalcitol improves the inflammatory status of hemodialysis patients, since the produced inflammatory hemodialysis mediator—namely, the platelet-activating factor (PAF), that is implicated in CKD's progression, is affected by this analogue. Specifically, paricalcitol inhibited in vitro and in vivo the PAF/thrombin-induced platelet aggregation comparably to PAF and thrombin antagonists while strongly affecting PAF/thrombin activities, PAF metabolism, and IL-8, IL-1β, and TNF-α circulating levels [95].

Vitamin D analogues like calcipotriol (1α,24(OH)$_2$-22-ene-24-C_3H_5-D_3) have been recently claimed to manage more effectively uremic pruritus and have been used as adjunctive CKD-associated pruritus (CKD-ap) and ESRD treatment [96,97]. Clinical studies have firmly established alfacalcidol's (1α(OH)D_3) beneficial effects on CKD, bone disease and secondary hyperparathyroidism [98,99]. Doxercalciferol (1α(OH)D_2) is a highly effective vitamin D analogue as well, as it suppresses secondary hyperparathyroidism in CKD patients at stage 4 [100], and PTH levels in patients suffering from CKD stages 3 and 4 [101]. Falecalcitriol has also been suggested to be a potent inhibitor of PTH, and in fact, it has been proved to be more effective than alfacalcidol in reducing PTH with similar rates of hypercalcemia, almost as calcitriol's corresponding impact [102]. As apparent, there are several beneficial effects of vitamin D analogues toward kidney-related diseases, but in order for a more sustained utilization of the related treatment to be promoted, further and newer clinical trials must be conducted worldwide. Vitamin D and its most widely used analogues in kidney-associated diseases treatment are depicted in Figure 6.

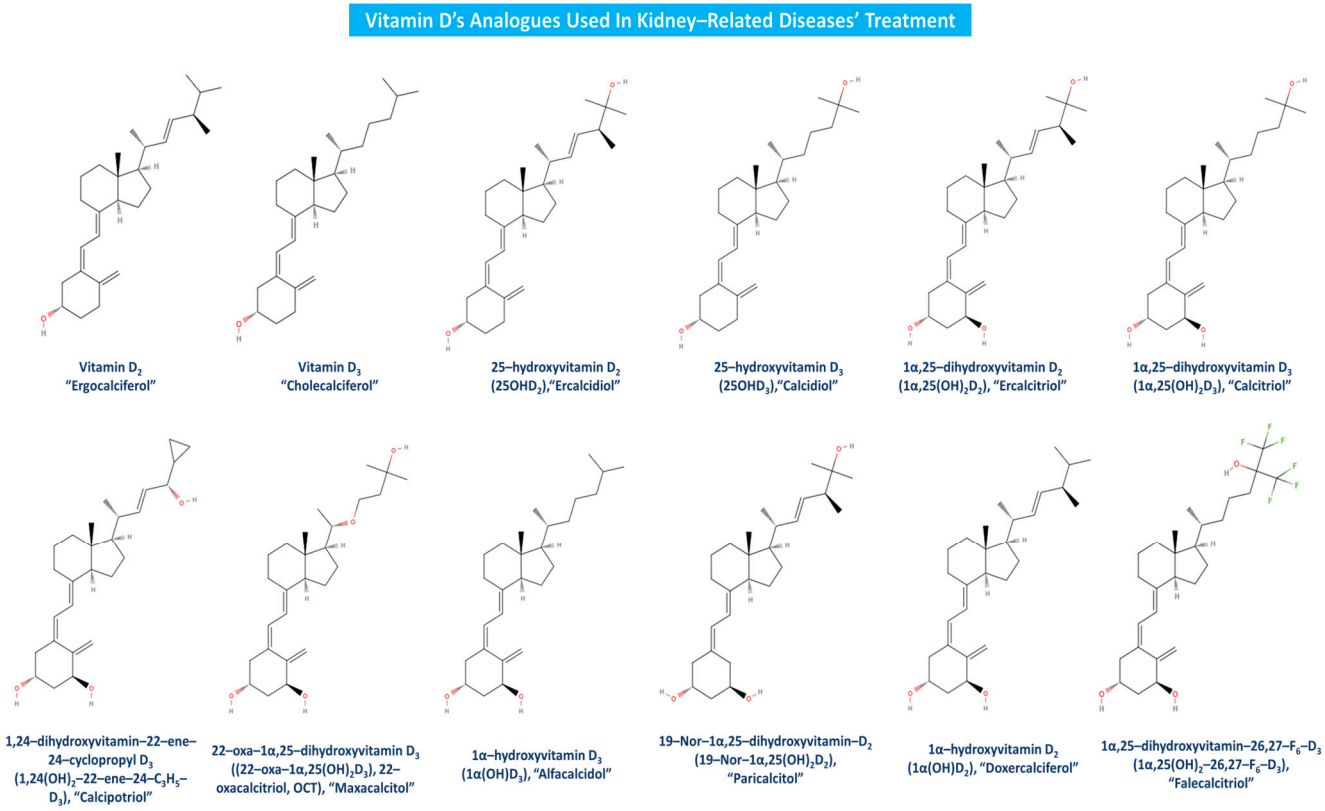

Figure 6. Vitamin D analogues utilized in kidney-related diseases treatment.

3.2.2. Vitamin D's Function and Anti-Inflammatory Effects

As apparent, globally, there is a growing interest in vitamin D's broader health implications and especially, in terms of its regulative role against the observed inflammation in a plethora of different pestering disorders and in our context, against kidney-related diseases' progression and development [44,59,92].

Vitamin D holds great anti-inflammatory potential since it aids at first in the regulation of mainly pro-inflammatory cytokine production including TNF-α and IL-6 and plus promotes the expression of many anti-inflammatory cytokines like IL-10, thus reducing the overall inflammation [103,104]. Moreover, this vitamin in the form of calcitriol participates in the inhibition of NF-κB by directly interacting with the inhibitory κB kinase β (IKKβ kinase) [105,106]. Vitamin D also participates in the downregulation of the renin–angiotensin system (RAS) and the transformation of renal cells into myofibroblasts, which are often induced by kidney diseases, leading to the reduction of inflammation, scarring in glomeru-

losclerosis and fibrosis, respectively [107–111]. In terms of fighting both inflammation and kidney diseases, vitamin D plays several roles as it enhances the regulation of T cells [112], protects by enhancing antioxidant defenses against the oxidative stress [73], modulates the immune cell activity of several macrophages and dendritic cells [113], improves the endothelial function [114,115], inhibits the mesangial cell proliferation in the glomeruli, which is connected with glomerulosclerosis and kidney disease progression [87], and promotes autophagy and cell survival in kidneys [86,116].

Vitamin D deficiency has been commonly observed in CKD and ESRD and thus has been implicated in deteriorating renal and podocyte function, proteinuria and neuropathy, as well as in increasing morbidity, acute failure and mortality rates in CKD patients. Vitamin D has attenuated effectively kidney injury by suppressing inflammation, fibrosis and apoptosis via the inhibition of multiple kidney injury pathways such as the RAAS, NF-κB, TGF-β/Smad and Wnt/β–catenin signaling pathways [9,44,58,105,106,117]. Vitamin D deficiency was also linked to the exacerbation of renal impairment, hyperparathyroidism and the evolvement of periodontitis, since vitamin D-binding protein (VDBP) polymorphisms that are associated with bioavailable 25(OH)D_3 induced CKD and periodontitis severity and progression [43]. More specifically, vitamin D deficiency and especially calcitriol-reduced production were affiliated with a reduction in the renal mass of CKD patients that limited the free and available 1-α-hydroxylase responsible for the production of calcitriol. Furthermore, the decreased estimated glomerular filtration rate (eGFR) levels reduced renal megalin receptors, and the elevated FGF-23 activity and oxidative stress restrained the conversion of 25(OH)D_3 to 1-α-hydroxylase, which further attenuated calcitriol's production [43,73,118,119]. Vitamin D supplementation in overweight and obese populations has also been correlated with a plethora of beneficial effects, since vitamin D intake exerts its anti-inflammatory effect predominantly through decreasing the protective stabile values of IL-10 rather than severely impacting pro-inflammatory cytokines like IL-7 and leukocytes [120]. Additionally, vitamin D has been demonstrated to reduce the expression of TLR-4, IL-6, TNF-α, IL-10, cathelicidin and MCP-1 in monocytes incubated with uremic serum. This uremic pool environment activated an inflammatory response in monocytes, which was successfully reversed by 25(OH)D_3 supplementation [121]. Vitamin D deficiency is not only highly affiliated with CKD and CVDs, but it may also accelerate their incontrollable progression; thus, treatment with vitamin D analogues could be therapeutic options for renal and cardiovascular problems due to their role in regulating blood pressure, improving the endothelial function and monitoring RAAS' activity [122,123].

Vitamin D supplementation has reduced blood inflammatory cytokines' expression and has improved graft function in kidney transplant recipients by enhancing the regulation of excessive immune inflammation and restoration of immune homeostasis [124]. At the same time, a vitamin D_3-related pretreatment has been correlated to renal inflammatory responses' regulation during lipopolysaccharide-induced AKI [125], while vitamin D_3 administration has counteracted diabetes-induced kidney damage primarily via a mediated inhibition of the NF-κB activation [126]. Vitamin D deficiency is also linked to the prevalence of albuminuria in the presence of diabetes due to increased microalbuminuria when the serum 25(OH)D_3 level was less than 20 ng/mL. Vitamin D seemed to have anti-inflammatory and anti-fibrotic effects in diabetic patients suffering from glomerular hyperfiltration, mesangial expansion, inflammation and finally glomerulosclerosis and tubulointerstitial fibrosis (Table 1) [127]. However, further insight is required in order to fully comprehend vitamin D's anti-inflammatory potential toward kidney-associated diseases including CKD, DKD and glomerulosclerosis [61,128].

3.2.3. Overview of the Immune System Modulation by Vitamin D

Vitamin D, apart from its aforementioned anti-inflammatory potential impact, is also implicated in immunity (immune cells) and oxidative stress regulation. Pointedly, the mechanisms linking vitamin D and CKD, as well as periodontitis which is a potent risk factor for kidney disease [129], are related to mainly calcitriol's biofunction and its immunomodula-

tory properties that impact both the innate and the adaptive immune system [43]. Vitamin D_3 via its 25-hydroxylation in the liver is converted into 25(OH)D_3, which in turn through 1α-hydroxylation turns into the active form of calcitriol (1α,25 (OH)D_3) [87,121,130]. At first, calcitriol binds to VDRs located both on the cell surface (membrane bound) and inside the cytoplasm of immune cells (intracellular) and hence, it activates both innate and adaptive immune cells [43,77,131,132].

Considering its activity toward the dendritic cells, calcitriol downregulates the expression of the major histocompatibility complex (MHC) class II, which induces antigen recognition and dendritic cell activation [43,133]. At this point, it must be noted that activated dendritic cells stimulate the activity of T-lymphocytes (T-cells), and consequently, the suppression of dendritic cells leads to T-cells' reduced function, which implies the communicative exchange between innate and adaptive immunity [131,134,135]. Calcitriol also represses pro-inflammatory cytokines including IL-2's production while encouraging anti-inflammatory cytokines development [135,136]. Concerning macrophages/monocytes on the contrary, calcitriol binds to and activates VDRs in macrophages and their monocyte precursors by forming heterodimers with the RXR in order to produce antibiotic peptides like β-defensin 2 and cathelicidins [43,137,138]. Moreover, in macrophages' activation, calcitriol enhances epigenetically the immunological memory and differentiation of macrophages and monocytes [139,140]. During the crosstalk of innate and adaptive immunity, T-lymphocytes and B-lymphocytes namely T-cells and B-cells are also heavily affected and suppressed [131,134]. Calcitriol is responsible for reducing T-helper cells' differentiation into types T helper 1 and T helper 17 (Th1 and Th17) as well as their anti-inflammatory cytokines' generation. Concurrently, calcitriol stimulates Th2 types' differentiation and favors their mass production of anti-inflammatory cytokines such as IL-10 [43,77,134]. T cell-derived pro-inflammatory cytokines finally induce B cells' differentiation, so T cells' suppression initiates indirect B cells' action suppression as well [134], and direct naïve B cells differentiation and maturation into memory and plasma cells is thus supported (Figure 7) [43,77,134,138–140].

Vitamin D deficiency is also affiliated with oxidative stress' aggravation and CKD's progression [43,58,73]. Hypovitaminosis D is one of the key controllers of systemic inflammation, the excessive intracellular oxidative stress and mitochondrial respiratory function, and hence, the aging process in humans, while in turn cellular actions that form calcitriol, the active form of vitamin D antioxidant, hinder oxidative stress conditions, cell and tissue damage and subsequently the aging process [73]. Generally, oxidative stress has been linked to the generation of highly reactive inflammatory intermediates, while ROS are able to further boost the inflammatory response by triggering pro-inflammatory mediators (NF-κB signaling cascade) [58,73]. Vitamin D supplementation downregulates various intracellular oxidative stress-associated pathways such as the erythroid–2-related factor (Nrf2) and Klotho family proteins that are mainly expressed in the kidney. Especially, α-Klotho protein has been proved to reduce oxidative stress by modulating NF-κB signaling cascade's expression and CKD complications [43,58,73,141].

The progression of CKD is closely linked to oxidative stress and inflammation, while vitamin D and its analogues have been proposed in the outcomes of a plethora of clinical trials to promote the reduction of systemic implications following vitamin D's deficiency including atherosclerosis and CVDs [43,58,73]. Calcitriol is able to alleviate oxidative stress and fibrosis due to regulating the CXCL12/ERK1/2 pathway, so as to inhibit every inflammatory response and renal cell apoptosis and to induce renal autophagy via the AMPK/mTOR cascade [142]. Moreover, this active vitamin D form is able to decrease inflammation, endothelial damage and oxidative stress as well as increase vascular regeneration markers and antioxidant enzymes' expression in AKI induced by cisplatin [143]. In addition, Vero cells pre-exposed to iohexol, a low osmolar comprising iodine contrast media, were submitted to iron-enhanced renotoxicity, which was ameliorated by calcitriol's utility and its prevention of AKI [144].

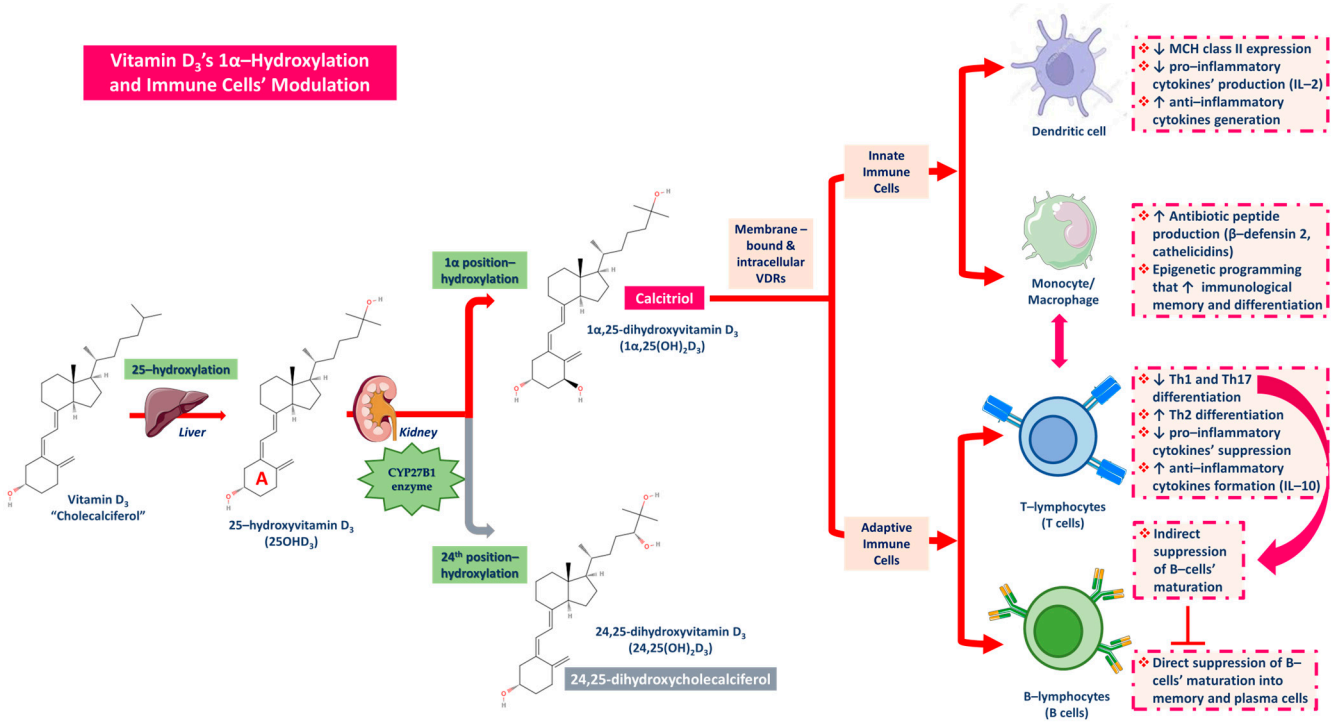

Figure 7. The roles of Vitamin D_3 and its active forms produced in the kidney, calcitriol, on immune cells' modulation towards activation of anti-inflammatory cell responses and suppression of pro-inflammatory signaling.

Vitamin D, as analyzed previously, contributes greatly to pro-inflammatory and anti-inflammatory cytokine regulation as well as in the NF-κB pathway's modulation and inhibition [103,105,106,145]. RAS suppression is also further encouraged by vitamin D or its analogues' supplementation, since recent study outcomes have supported its role in lowering blood pressure in vitamin D-deficient patients [108]. Calcitriol especially has been proved to restrain renin genes' expression, inhibiting the RAS system and ameliorating hypertension [109]. Hence, the vitamin D hormone has a major impact on the homeostasis of the renal and cardiovascular system through RAS' suppression [107].

Inflammation-related cytokine regulation, NF-κB cascade's inhibition, RAS suppression and fibrosis hindering, as well as immunity perseverance and oxidative stress reduction, are only a few of vitamin D's pleotropic roles in maintaining homeostasis and enhancing our immune system toward various kidney related diseases.

4. Anti-Inflammatory Health-Promoting Effects of Vitamin D and Its Analogues in Glomerulosclerosis and Kidney Diseases

4.1. Vitamin D's Role in Kidney-Related Diseases

The spotted molecular differences between standard anti-inflammatory treatments for glomerulosclerosis and the anti-inflammatory activities of vitamin D are rooted in their distinct mechanisms of action, molecular targets, and effects on the immune system and inflammatory pathways. Glomerulosclerosis represents the final stage of glomerular injury during kidney-related diseases and may represent a primary disturbance in disorders like FSGS or a secondary response to tubulointerstitial disease, which accounts for 10–20% of patients of all ages who progress to ESRD. Current immunosuppressive therapy and conservative management including RAAS inhibitors and sodium–glucose cotransporter are in fact insufficient and no FDA-approved therapeutic options effectively prevent or delay kidney failure onset. More specifically, existing glomerulosclerosis treatment and FSGS focus on non-specific treatment blood pressure and proteinuria-reductive agents, and they involve corticosteroids (e.g., prednisone), calcineurin inhibitors or immunosuppres-

sants (e.g., cyclosporine), that mainly target the NF-κB pathway, cytokine suppression and leukocyte activity [146,147]. Vitamin D and derivatives on the contrary exert their effects by binding to the VDR, and they induce VDR-mediated gene regulation, NF-κB and MAPK inhibition, immune cells and RAS modulation, as well as the reduction of oxidative stress without any unfavorable side effects, great selectivity, crucial specificity and a long–term impact [19,52,58].

Vitamin D has anti-inflammatory and anti-fibrotic effects, and it may block the intrarenal RAS system. Adequate vitamin D levels in conjunction with the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) may restrain CKD's progression. Moreover, vitamin D_3 supplementation presented a significant eGFR decrease in CKD patients and attenuated a compensatory increase in the RAS associated with the use of ACEI/ARB by suppressing renin transcription, reducing interstitial fibrosis, decreasing glomerular and tubulointerstitial injury, improving endothelial function and reducing blood pressure, risk of hypercalcemia, hyperkalemia and proteinuria [148,149]. Additionally, targeting the unbalanced RAS and angiotensin-converting enzyme 2 (ACE2) downregulation with vitamin D in SARS-CoV-2 infection may be a potential therapeutic approach to combat the expansion of COVID-19 and the acute respiratory distress syndrome (ARDS), as it potentially decreases the risk of severe pneumonia, renin and angiotensin plasmatic levels [150–152].

At this point, it must be highlighted that there are many factors affecting the response to vitamin D supplementation, ranging from genetic, environmental, and physiological factors. In particular, patient-specific factors could further affect the amount of vitamin D required in order to attain a sufficient concentration and should be extensively evaluated. At first, there is mounting evidence that genetic variations of proteins involved in the vitamin D metabolic pathway may affect tissue response to vitamin D and thus may influence the risks and severity of multiple chronic diseases. Genetic variations in the VDR, enzymes like CYP2R1 and the GC gene (VDR-related gene produced in the liver), namely polymorphisms, may affect the binding affinity of vitamin D to its receptor, the conversion of vitamin D to its active form, vitamin D's degradation and the availability of this free, bioactive hormone, while appropriate adjustment of this dose may reverse all these outcomes [153,154].

Environmental factors, such as sunlight exposure, also affect vitamin D supplementation as its significantly influences endogenous vitamin D synthesis, and higher treatment doses are recommended [155]. Concurrently, many biological, pathological and demographic characteristics could be determinants of vitamin D-related treatment, including BMI, obesity, smoking, physical activity, aging, ethnicity and calcium intake–dietary status. Body weight has an influence on the blood volume, the amount of muscle and adipose tissue, as higher body fat percentage or body mass index (BMI) have been associated with a smaller increase in 25(OH)D_3 concentration in response to vitamin D supplementation in both younger and older adults [156]. In particular, obesity is linked to lower vitamin D bioavailability due to sequestration in adipose tissue and as a result, obese patients require higher vitamin D doses during treatment [157]. Smoking and more specifically tobacco smoke exposure is known to lower serum 25(OH)D_3 concentrations [158], while vitamin D status above 75 nmol/L was positively correlated with physical activity [159]. Furthermore, aging, ethnicity and dietary calcium intake are associated with lower levels of 25(OH)D_3 in circulation with aging being affiliated with decreased skin synthesis of vitamin D and renal conversion to its active form as well as potential changes in VDR expression. Older patients, therefore, display less response to standard vitamin D doses, and hence, higher ones are required, while increased calcium intake exhibited a slight increase in serum calcium levels and a decrease in PTH ones [155].

Comorbid conditions including hypo- and hyperparathyroidism [160,161], musculoskeletal disorders (e.g., osteoporosis, osteopenia), autoimmune and systemic connective tissue diseases (e.g., rheumatoid arthritis, fibromyalgia, chronic musculoskeletal pain), glucocorticoid-induced osteoporosis, endocrine and metabolic conditions like diabetes

mellitus (I or II), the metabolic syndrome, malabsorption–gastrointestinal syndromes, like inflammatory bowel disease [162,163], Crohn's disease [164], cystic fibrosis [165], ulcerative colitis [166], celiac disease [167], CKD [43,44,47], cancer [168–170], immunocompromization caused by HIV infection [171,172], as well as central nervous system diseases, such as multiple sclerosis, epilepsy, dementia, Alzheimer's and Parkinson's disease [173–176], are plus associated with lower levels of 25(OH)D_3 in circulation and require higher vitamin D doses most of the time [155,177]. Lastly, certain medications like anticonvulsants, antiepileptic drugs, bile acid sequestrants, lipase inhibitors, glucocorticoids, and antifungals may induce enzymes responsible for the increase in vitamin D's metabolism, reducing its effectiveness. Higher doses may be consequently required in order to achieve efficient vitamin D-related treatment [155,178,179].

4.1.1. Vitamin D's Role in Glomerulosclerosis and Chronic Kidney Disease

Without overlooking its function in regulating calcium homeostasis in the blood, vitamin D has recently been reported via cellular, animal and human studies to interact through complex pathways with the kidneys in the context of glomerulosclerosis. Diseases such as diabetes, lupus nephritis, proteinuria and CKD cause injury to the glomerulus and/or podocytes. As a result, such conditions lead to glomerulosclerosis through a plethora of different pathways. The activation of vitamin D in the kidneys occurs mainly in the proximal renal tubules, while the binding of the active form of vitamin D requires a specific vitamin D receptor (VDR) as well. Wang et al. [180] used a very specific antibody (D-6) to detect vitamin D receptors in different types of renal cells. Finally, VDRs were found in both distal and proximal tubules and were also detected in macula densa cells, suggesting a possible role of vitamin D in the regulation of renin's production. Continuing on this path, Mihajlovic et al. [181] observed that by exposing ciPTEC–OAT1 cells—human renal cell lines that mimic the proximal tubule cells of the kidney to uremic conditions—vitamin D was predominantly catabolized. In the cells where vitamin D was administered, the enzymes responsible for its metabolism were traced and plus observed to remain unaffected by uremic toxins [181]. In this recent research case study, ROS were reduced when vitamin D was administered to patients, suggesting that this hormone offers a protective role against inflammatory responses and oxidative stress induced by uremic toxins [181].

Vitamin D supplementation offers a plethora of benefits, many of which are crucial to our well-being. Prior to the previously mentioned research outcomes, a scientific team consisting of Finch et al. [182] showed that the combination of two drugs, enalapril and paricalcitol, improved renal dysfunction and mitigated oxidative stress in uremic rats. Paricalcitol as a vitamin D derivative upregulated the RAAS system, while this type of treatment mitigated oxidative stress by inhibiting the expression of NADPH oxidase, promoting the expression of endothelial nitric oxide synthase (eNOS) and maintaining glutathione (GSH) cycle's activity [182]. Needless to say, many other drugs have been and could be used to treat glomerulosclerosis as well. For example, Gonçalves et al. [183] treated losartan and erlotinib to rats that suffered from vitamin D deficiency and CKD. Such treatment was responsible for the suppression of renal fibrosis formation (RFF)-related elements' expression, including TGF-β1, trans-arterial chemoembolization (TACE), TGF-α, epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR). In addition, attenuated inflammatory cell infiltration was observed, suggesting that such treatment, most likely, targeted the TGF-β and EGFR pathways [23]. Adding to our previous statements, it is acclaimed that under proteinuria conditions, the transient receptor potential cation channel (TRPC6) receptor is increased, where overexpression of the TRPC6 receptor injures renal podocytes. Sonneveld et al. [184] demonstrated both in vivo and in vitro findings that suggested that calcitriol administration reduces glomerular TRPC6 expression in injured podocytes. In particular, calcitriol inhibits TRPC6 promoter's activity through binding to its specific region [184]. In addition, another enzyme, namely heparinase, is involved in the development of proteinuria in various glomerular diseases. In a study conducted by Garsen et al. (2015), calcitriol reduced heparinase's expression in podocytes

both in vitro and in vivo findings. More specifically, vitamin D treatment inhibited the heparinase promoter's activity through binding to the promoter, thus protecting podocytes from injury [185]. This protective mechanism of vitamin D resembles to a great extent the pre-mentioned mechanism described by Sonneveld et al. [184].

Foot cell injury generally leads to autophagy and apoptosis, where deregulated autophagy and apoptosis of specifically podocytes is a pathogenic process taking part in glomerulosclerosis. These processes are activated when podocytes are exposed to various damaging stimuli. Vitamin D is claimed to be responsible for the regulation of the process of autophagy and apoptosis. Yu et al. [186] discovered that vitamin D supplementation in patients suffering from Lupus Nephritis (LN) reduces autophagy. During the LN disease, patients' autoantibodies stimulate in fact podocyte autophagy. Podocytes also expressed VDRs and retinoid X receptors, while Hamano et al. (2009) previously noticed that calcitriol and 22-oxacalcitriol analogues (OCTs) owned a protective effect against podocyte damage as well [86,186].

Several research studies over the years have proved that by administrating vitamin D analogues, nephrin and podocin expression is restored and thus, proteinuria is reduced. Nephrin and podocin are generally recognized markers of renal podocyte protection [187,188]. Wang et al. [93] investigated the effect of high-dose vitamin D_3 in rats with renal fibrosis that was induced by CKD. The supplementation of vitamin D effectively normalized serum calcitriol levels while reducing at the same time serum creatinine, urea and proteinuria levels. Moreover, vitamin D decreased the expression of α-smooth muscle actin (α-SMA) proteins, collagen I, vimentin and E-canterine. As a consequence, the signaling biochemical pathway TGF-β1/Smad3, a key factor of fibrosis, was inhibited [93]. In full agreement with the results of Wang et al. [93], Sari et al. [189] found that vitamin D's administration to mice with CKD inhibited the activation of the NF-κB and TGF β–Smad3 biochemical pathways, leading to reduced expression of pro-inflammatory mediators and profibrotic pathways [189]. Chebotareva et al. [52], by comparing the urinary proteomic profiles of patients with focal segmental glomerulosclerosis (FSGS), proved that patients with severe FSGS displayed elevated levels of specific proteins associated with podocyte damage, such as apolipoprotein A-1 (ApoA-1), hemopexin, vitronectin and gelsolin. ApoA1, in fact, was functional as a marker able to distinguish stereo-sensitive FSGS from stereo-sensitive-resistant FSGS. It was further established that regarding the severe FSGS the extracellular wall matrix's (ECM) deposition in the glomeruli increased, and as a result, the ECM could partake both in the progression and further development of the disease and patient's unresponsiveness to treatment [52].

At this point, it is worth mentioning the possible negative effects of vitamin D's deficiency in the mother of the newborn. Nascimento et al. [190] pointed out that maternal vitamin D deficiency causes harmful alterations in proteins such as podocin or renin and the angiotensin II type 1 (AT1) receptor. These proteins play critical roles in renal function, including podocin's role toward the structural organization of the renal filtration system, renin's action in the regulation of blood pressure and AT1 receptors' participation in the renin–angiotensin system. These proteins' possible deregulation may initiate important changes in kidney structure and function [190]. As a part of their research, Denburg et al. [191] evaluated bioavailable $25(OH)D_3$ and $24,25(OH)_2D_3$ concentrations in children that faced CKD. Regardless of proteinuria, lower concentrations of bioavailable $25(OH)D_3$ were found in children with CKD compared to healthy ones, suggesting impaired vitamin D's metabolism. As the severity of CKD increased, the concentrations of $24,25(OH)D_3$ in patients lowered [191]. Furthermore, Zaniew and Jarmoliński [192] showed that the supplementation of 1300 ± 772 IU/d of vitamin D and calcium in bone health in children suffering from glomerulopathy increased the levels of vitamin D in patients' blood but unfortunately did not optimize their condition. Hence, it is suggested to reconsider the dose of cholecalciferol due to the high frequency of bone deficiencies [192]. All of the aforementioned clinical trials on vitamin D's role against glomerulosclerosis and CKD are depicted in Table 1.

4.1.2. Vitamin D's Role in Diabetic Kidney Disease Compared to Chronic Kidney Disease

Diabetes is a disease that is inextricably linked to modern lifestyle. In particular, type II diabetes, which is common in Western developed societies, initiates the alleged DKD due to constantly elevated blood glucose levels. Wang et al. [193] had originally discovered that in type II diabetes conditions, the amount of 1-a-hydroxylase and calcitriol increased, indicating elevated 1-a-hydroxylation of vitamin D, while it was observed in vivo that fibronectin and collagen IV's production was inhibited. Furthermore, the vitamin D receptor activator (VDRA) is upregulated under high glucose conditions. Early studies have demonstrated that vitamin D might have an indirect protective effect against DKD [193]. Subsequently, in 2009, Petchey et al. [130] conducted a controlled trial on CKD patients, in which the association of vitamin D with insulin resistance and markers of adverse cardiac risk was studied. Notably, it was the first controlled trial to correlate these two variables. All outcomes pointed that vitamin D could partake in a safer drug pathway, as it offered a plethora of different benefits beyond these related to bone and mineral homeostasis [130].

The autophagic capacity of podocytes plays a critical role in the progression of DKD as well, as podocytes act as a barrier to the passage of proteins during the filtration process. Song et al. [194] demonstrated that DKD affects the autophagic function of podocytes by reducing autophagosomes. Proteins like nephrin and podocin are also reduced in diabetic nephropathy. Markedly, the treatment of diabetic rats with calcitriol was found to restore autophagy activity in podocytes as well as to maintain the expression of nephrin and podocin proteins, thus to mitigate podocyte damage [194]. Ristov et al. [195] used the "ShGlom Assay", a semi-automated and high-throughput version of the "Glom Assay", so as to analyze vitamin D's effect on podocyte differentiation considering glomerulopathies. In accordance with the findings of the above-mentioned study, it was indicated that calcipotriol upregulated the expression of specific podocyte genes and proteins, especially the essential for sustaining podocyte morphology and function at the glomerular filtration barrier (GFB) of nephrin [195].

The epithelial–mesenchymal transition (EMT) is a process where epithelial cells undergo a series of molecular changes resulting in mesenchymal cells. During this process, cells become more flexible, resist apoptosis and as a result, many pathological conditions are induced via the TGF-β1 pathway. In particular, Souza [118] exhibited in vivo that the EMT process was accelerated by vitamin D's deficiency in diabetic mice. Diabetes combined with vitamin D's deficiency may lead to an increased expression of mesenchymal markers like the ZEB1 and ZEB2 transcription factors, which regulate the EMT process. Their increase along with the decreased expression of microRNA, miR-200b, and increased levels of TGF-β1 as well inflamed glomerulosclerosis [118].

Furthermore, the dysregulation of autophagy in podocytes is another key factor in the progression of DKD. Zhang et al. [94] revealed recently the protective effect of vitamin D in DKD. In these research outcomes, it was observed in agreement with previous results that the autophagic activity of podocytes was restored both in vitro and in vivo through the regulation of its associated proteins. However, it is worth noting that the exact mechanism underlying this process is not yet fully elucidated [94]. OCTs as other vitamin D analogues were deemed by Hamzawy et al. [196] to reduce blood glucose, while also enhancing autophagy, suppressing podocyte apoptosis and disrupting the G1 cell cycle. Specifically, OCTs activate the VDR receptors, leading to the direct expression of genes such as beclin-1 and the microtubule-associated protein 1A/1B-light chain 3 (LC3). Also, OCTs could affect calcium's metabolism, the activation of cyclin-dependent kinase (CDK) and the activation of calcium/calmodulin-dependent protein kinase 2, which are involved in the regulation of autophagy. In this way, autophagosomes accumulate and autophagy is effectively regulated [196].

Oxidative stress may also induce DKD, as demonstrated in Yang et al.'s study [117]. ROS were identified as key contributors to diabetic nephropathy's onset. In the examined cells, ROS were reduced after vitamin D's administration, while a link between the JAK/STAT signaling pathway and specific microRNAs in mesovascular cells was also

revealed. Essentially, it was claimed that vitamin D inhibited the JAK/STAT pathway and thus, it could be used as a treatment for diabetic nephropathy [117]. On the contrary, many research groups claimed that vitamin D supplementation in adults with type II diabetes does not enhance kidney function. A clinical trial conducted by de Boer et al. [197] showed that the administration of vitamin D and omega-3 fatty acids did not significantly slow the decrease in estimated glomerular filtration rate. Moreover, no significant differences in urinary albumin excretion were found between patients who ingested vitamin D and those who did not. Although previous studies have pointed out many benefits, the long-term findings of this study came into disagreement with the previous results claiming vitamin D's protective role [197]. Recently, da Silva et al. [122] asserted that vitamin D supplementation in patients with CKD reduced the risk of healthcare-associated infections by 59%. The conservative treatment patients undergo needs to ensure the necessary prevention from infections, which is a case where vitamin D may act as an effective preventive agent [122]. Thus, it is understood that the potential of vitamin D is multidimensional and needs further investigation. All of the aforementioned clinical trials on vitamin D's role against DKD are summarized in Table 1.

4.1.3. Vitamin D's Role in Kidney Disease Induced by Metals

In addition to diseases that may enhance pathogenicity in the kidneys, various elements such as cadmium (Cd) and lead (Pb) traced in water may also induce it. Obaid [198] examined the impact of vitamin D supplementation in Cd^{2+}-induced CKD rats. Cd^{2+} at elevated levels impaired calcium's homeostasis and vitamin D's regulation in the serum, kidney tissue and urine due to its high toxicity and, thus, exacerbated oxidative stress and inflammation. Treatment with vitamin D and Ca^{2+}, either separately or combined, reduced the built-up oxidative stress and inflammation, modulated Ca^{2+} regulatory molecules and re-regulated vitamin D's metabolism [198]. Similar findings were presented by Refaat et al. [199], who investigated the connection between chronic lead exposure and vitamin D supplementation, highlighting the antioxidant and anti-inflammatory mechanisms involved. Lead in a similar way to cadmium leads to tissue damage, oxidative stress and inflammation. Studies declared that calcitriol treatment increased the expression of many antioxidant enzymes such as glutathione peroxidase-1 (Gpx1) and peroxiredoxin-1 (Prdx1), boosted the expression of the anti-inflammatory cytokine IL-10 and decreased the levels of IL-4 and TNF-α [199].

Heavy metal exposure, along with other potential environmental hazards, are reportedly a potent CKD cause. Toxic elements including Cd, aluminum (Al), silica (Al_2O_3) and strontium (Sr) have been proved to be nephrotoxic factors of kidney-related diseases and dysfunction as well as several complications, CVDs and elevated blood pressure following CKD patients [200]. Recent study trial findings pointed out improved alleviations against CKD and aging by supplementing vitamin D or its analogues, possibly by a regulation of Ca-dependent, antioxidative and anti-inflammatory actions [201]. Furthermore, vitamin D has been demonstrated to mitigate Cd-induced liver and kidney damage; thus, its protective role against Cd toxicity and its potential assistance in the preservation of organ function under toxin-induced stress has been highlighted [202].

Consequently, it is well understood that vitamin D has protective properties against the toxicity of heavy metals like Pb and Cd. The details of the aforementioned clinical trials on vitamin D's role against kidney disease induced by metals are thoroughly analyzed and further examined in Table 1.

4.1.4. Vitamin D's Role in the Neuphrotic Syndrome (NS) and Other Kidney Diseases

FSGS and MCD are widely known diseases with primary podocyte damage clinically manifested by the NS; however, the pathogenesis of such podocytopathies and their biomarkers are yet to be discovered [52,57]. Previous studies have claimed that the daily administration of calcitriol or 22-oxacalcitriol ameliorated the nephrotic state by protecting podocytes (Table 1) [93]. In addition, Ca homeostasis derangement is common during

NS' occurrence, as possibly, low total Ca and vitamin D levels are attributed to the loss of protein-bound Ca and vitamin D. Recent study outcomes revealed that vitamin D and Ca bone derangement observed during NS had trended toward normalization and thus, Ca and vitamin D replacement was not indicated regarding early-phase NS, but it may be a great treatment solution in the prolonged form of this renal disease [203].

Children with prevalent NS have reportedly displayed medium to high 25(OH)D_3 deficiency rates, a state that was reversed by vitamin D supplementation, which supported a role for supplementation in incident NS [204]. Maji et al. [205] also suggested the immunomodulatory property of vitamin D and the urgent need to introduce this supplementation routinely in all NS cases [205]. Moreover, total 25(OH)D_3 levels are low during the nephrotic state condition and are related to a degree of proteinuria increase. In proteinuric renal diseases, free rather than total 25(OH)D_3 levels should be used so as to diagnose the vitamin D's deficiency and to guide efficiently NS's therapy, while vitamin D administration from steroid-sensitive NS patients is further supported by the study's outcomes [206].

Except for its regulative role in skeletal homeostasis, RAAS endocrine activity, CKD, DKD, NS, ESRD, AKI, glomerulosclerosis, etc., vitamin D has also a crucial impact on glomerulonephritis (GN). Considering GN, vitamin D supplementation notably reduced proteinuria, impeded kidney disease development, inhibited the onset of kidney inflammation and protected podocytes from injury. More specifically, treatment with calcitriol via the VDR action regulated heparanase promoter activity and monitored podocyte distribution by modulating mRNA synthesis and subsequently the protein expression of nephrin and podocin, thus promoting podocyte protection. Maxacalcitol during the same trial showed more promising results, since it overcame hypercalcemia, hyperphosphatemia and calcification enhancement risk, while paricalcitol and doxercalciferol also exhibited lower hypercalcemia and hypercalciuria and partook in RAAS genes' expression, proteinuria and renal damage prevention [42,207,208].

Vitamin D deficiency is common; however, no data were obtained concerning vitamin D levels in light chain (AL) amyloidosis (rare B cell-secreting clonal disorder) until recently. A clinical trial conducted by Muchtar et al. [209] demonstrated that hypovitaminosis is frequent in AL amyloidosis, mainly among patients suffering from heavy proteinuria and confirmed that severe 25(OH)D_3 deficiency during the diagnosis period could predict ESRD progression [209]. Furthermore, regarding polycystic kidney disease (PKD), chronic vitamin deficiency had a negative long-term impact on proteinuria, interstitial inflammation, renal function, and CVDs in PKD, which invalidated its mild inhibitory effect on kidney enlargement [210]. Similarly, low 25(OH)D_3 and VDR levels are linked with a higher kidney volume, supporting that vitamin D's daily administration in the right doses is not only recommended but also needed toward autosomal dominant PKD (ADPKD) and other kidney diseases [211]. Lastly, in kidney stone disease, many different monogenic polymorphisms have been suggested to play a crucial role for calcium nephrolithiasis during hypercalciuria, like the VDR gene. A balanced Ca consumption via an individual's nutritional choices has been thus projected as a protective mean toward kidney stone risk prevention due to the fact that intestinal oxalate availability, its urinate expression and subsequently the risk for stone formation are reduced; however, further research is once again required [34].

Although many clinical trials have been conducted with the aim to fully elucidate vitamin D's specific role in kidney-related diseases, the scientific community is still far from reaching its overall hidden potential. CKD as well as DKD have been extensively studied, but still inadequate data have been collected, while glomerulosclerosis, NS, GN, ESRD, AKI, hyperparathyroidism, PKD, etc. have been less studied, and the little gathered information is insufficient in supporting vitamin D's exact protective, regulative, modulatory, anti-inflammatory, anti-fibrotic, antioxidant and preventive role.

Table 1. Experimental data from corresponding clinical trials concerning vitamin D supplementation/administration of drugs containing vitamin D and its analogues and their renal/kidney health-promoting effects against glomerulosclerosis and kidney diseases.

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
This study was conducted to measure the alleviating effects of vitamin D and/or Ca as single and as dual therapies against pre-established nephrotoxicity enhanced by chronic cadmium (Cd) toxicity prior to treatment initiation	• 40 male, adult Wistar rats (200–250 g/rat) were housed at 22–24 °C, for 12 h, in dark/light cycles (4 rats/cage), while receiving standard laboratory chow with 2000 IU/Kg vitamin D and 0.70% Ca^{2+} carbonate • The rats were divided randomly and equally into five different groups: the negative control (NC), positive control group (PC), single treatments with Ca^{2+} (Ca) or vitamin D (VD) group, and the co-therapy group that concurrently received VD and Ca^{2+} (VC) • $CdCl_2$ was dissolved in drinking water (44 mg/L) for all groups, except the NC, and all rats had free access to water during the total study duration (8 weeks) • The average daily amounts of consumed water/kg body weight was examined by dividing the consumed volumes of the total rats' body weight in each cage • The tested rats received $CdCl_2$ throughout the first 4 weeks, which was followed by treatment including intramuscular vitamin D injections (350 IU/kg for 5 times/week) and/or oral elemental Ca^{2+} (100 mg/kg for 5 times/week) that initiated in the fifth week, and continued by $CdCl_2$ supplementation for another 4 weeks	• The total delivered amounts in the tested rats of therapeutic and dietary vitamin D (360 IU/kg/d) and Ca^{2+} (211.4 mg/kg/d) were equivalent to the daily human doses of 58.1 IU/kg for vitamin D and 34.1 mg/kg for Ca^{2+}; hence, they were almost twice the daily required human doses of vitamin D (29.1 IU/kg) and Ca^{2+} (16.7 mg/kg) • The water consumption per cage was found at 100.4 ± 2.3 mL/kg, while the amounts of ingested Cd at 4.7 ± 2.3 mL/kg, which equates to 1/20 of the oral median lethal dose (LD_{50}) of 88 mg/kg) • The PC group had several disorders including hypovitaminosis, hypercalciuria, proteinuria, reduced creatinine clearance and increased renal apoptosis/necrosis with higher caspase-3 expression as well as abnormal expression of Cyp27b1, Cyp24a1, VDR and VDBP, Ca membranous (CaV1.1/CaV3.1), store-operated channels (RyR1 /ITPR1) and cytosolic Ca-binding proteins (calmodulin (CAM), calcium calmodulin-dependent protein kinase 1 (CAMKIIA), S100A1, S100B) • Markers of renal tissue damage (TGF-β1, iNOS, urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1)), oxidative stress (malondialdehyde (MDA)/H_2O_2) and inflammation (TNF-α, IL-1B, IL-6) increased, whilst the antioxidants (CSH, GPx, catalase (CAT)) and IL-10 decreased in the PC group	• Even though vitamin D was claimed superior to the Ca^{2+} monotherapy, a combination of these two therapies had revealed the best mitigation effects by attenuating both serum and renal tissue Cd concentrations, as well as monitoring inflammation, oxidative stress and vitamin D and Ca's expression	2023	[198]
"ShGlomAssay" was applied to a semi-automatic, high-throughput process combined with analysis techniques. Screening of potential drugs and identification of specific pathways, including the calcitriol and vitamin D pathway by using a minimum number of animals, was demonstrated	• Transgenic Nphs1: cyan fluorescent protein (CFP) mice were analyzed at the age of 6 • 96-well plates were coated with collagen IV and glomeruli, grown with phenol red free RPM1-1640 medium and fed with 10% fasting blood sugar (FBS)/5% CO_2 (37 °C) • The isolated glomeruli was then treated with DMSO (0.1% dissolved in the RPM1-1640 medium with 10% FBS), vitamin D (100 nM dissolved in 0.1% DMSO) and calcipotriol (1 nM in 0.1% DMSO) • All treatments were conducted on the glomeruli of the same mouse	• The "ShGlomAssay" revealed that the podocyte-specific CFP fluorescence, which was induced by the Nphs1 promoter, was notably increased after the vitamin D/calcipotriol treatment in comparison to the control samples • Vitamin D and calcipotriol treatment strongly upregulate the in situ expression of Nphs1 in podocytes, since mRNA and CFP and Nphs1 protein levels increased simultaneously (calcipotriol showed minor upregulation) • Western blot analysis also displayed significantly increased protein levels • In a diabetic rat model, the glucose-mediated downregulation of Nphs1 could be ameliorated by treatment with a vitamin D analogue like calcipotriol	• The "ShGlomAssay" can be utilized so as to evaluate the impact of compounds in the interaction between podocytes, endothelial and mesangial cells, resembling the in vivo situation better than plain permanent podocyte cell lines • The screening of the ShGlomAssay revealed the protective effect of vitamin D on podocytes	2022	[195]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The aim of the present study was to shed a light on the potential impact of a vitamin D analogue, namely 22-oxacalcitriol (OCT), on different cell responses during diabetic neuropathy (DN), as well as the positive interplay between glucose, the immune system and vitamin D in the determination of the cell's fate	• 30 male Wister albino rats were randomly divided into three groups: control, vehicle-treated DN and 22-OCT-treated DN group where 8 weeks after the induction of diabetes, they were killed • Fasting blood glucose levels, renal functions, serum 25(OH)D_3, cytokines, gene expression, cell cycle arrest markers and histological determination of the renal architecture were assessed and conducted • The induction of diabetes to rats was initiated by a single intraperitoneal (i.p.) injection of 55 mg/kg streptozotocin (STZ dissolved in ice-cold sodium nitrate buffer (0.01 M, pH = 44) after 48 h • Rats with a higher fasting blood glucose level than 200 mg/dL were diabetic • All rats were then assigned different treatment into the three groups (10 rats/group): group I (control) which received a single i.p. injection of an equivalent volume to the vehicles ×3/week for 8 weeks, group II (vehicle–treated DN) that administrated an i.p. of an equivalent volume to the vehicles ×3/week for 8 weeks and group III (22-OCT-treated DN) that administrated 0.4 ug/kg OCT dissolved in phosphate buffer saline (PBS) i.p. ×3/week for 8 weeks • All rats were weighted, subjected to arterial blood pressure assessment and housed individually in metabolic cages in order to conduct 24 h urinary collections • Urine was collected in graded tubes, their volume was measured and then were centrifuged to separate the debris • Blood samples were withdrawn via a retro-orbital route by heparinized capillary tubes • Right kidneys were dissected and kept frozen (−80 °C) in liquid nitrogen until being used to estimate gene expressions, while the left kidneys were dissected and weighed by a digital weighing machine • The kidney weight index (KWI, kidney weight to body weight) was calculated so as to measure kidney hypertrophy, and then all examined kidneys were placed in 10% neutralized formalin solution for histopathological examinations	• As long as the 8th week ended, all DN group rats exhibited a major increase ($p < 0.05$) in the mean arterial blood pressure (MABP), KWI, serum creatinine, blood urea nitrogen (BUN), the value of urinary albumin excretion and creatinine clearance compared to the control group • The 22-OCT group had a significant decrease in the previous parameters • A significant decrease in serum levels of 25(OH)D_3 in DN rats compared to control ones was observed, while correspondingly an increase in these levels was revealed in the 22-OCT group compared to the DN group • The DN group displayed increased fasting blood glucose levels as compared to the control group, while the 22-OCT one had a notable decrease in these levels as opposed to the DN group • Serum levels of IL-6 and the renal expressions of INF-γ and TLR-4 increased in DN compared to control rats, and a decrease in these levels was revealed after 22-OCT treatment • Pearson's correlation coefficient (r) was used to evaluate serum 25(OH)D_3, autophagy, apoptotic and G1 phase inducers' gene expressions, where significant positive correlations were found between 25(OH)D_3 levels and both autophagy genes (Beclin-1 and LC3II/LC3I) and notable negative correlations were revealed between 25(OH)D_3 levels, both apoptotic (Bax/Bcl-2 cytochrome c and caspase-3) and G1 phase inducers (IGFBP 7 and TIMP-2) gene expression • Negative correlations were also found among a number of apoptotic cells, degree of glomeruli thickening, ECM expansion and 25(OH)D_3 levels	• 22-OCT was suggested to reduce the blood glucose and urine albumin excretion. • It was also found to enhance autophagy and suppress both apoptosis and the G1 cell cycle arrest, namely the initiating renal pathological changes, like the ECM accumulation, tubular and glomerular cell loss, thus to prevent DN's progression	2017	[196]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The present study was designed to measure the effects of vitamin D_3 supplementation on renal and testicular damage during chronic lead intoxication in rats along with the expression profiles of vitamin D-related molecules, oxidative stress markers and a panel of pro- and anti-inflammatory cytokines in tissues of interest	• 32 male Wister rats of 12 weeks of age and 220–250 g of body weight were housed in clean, sterile polyvinyl cages (4 rats/cage), maintained on a standard laboratory pellet diet and water ad libitum, and kept in a temperature-controlled, air-conditioned place (22–24 °C) in a 12 h dark/light cycle • Rats were divided randomly into four groups (8 rats/group): negative control group (NC), the positive control group (PC) that included animals that only received lead acetate, normal rats treated with only vitamin D_3 group (N-VD) and the group treated simultaneously with lead acetate and vitamin D_3 (P-VD) • Lead acetate was dissolved in drinking water (1000 mg/L) and administered to rats for 4 weeks so as to induce chronic toxicity • Vitamin D_3 was diluted in sterile saline and administered for 4 weeks (1000 IU/kg, ×3/week), intramuscularly so as to prevent any potent effect on the absorption rate of lead and/or vitamin D_3 if both were administered orally	• Inverse correlations between blood lead levels and serum concentrations of both vitamin D_3 and Ca^{2+} • Excess lead deposition in the tissues was suggested to result in abnormal cellular metabolism of vitamin D_3 by upregulating at the same time CYP24a1 enzymes and inhibiting CYP27b1 enzymes, mainly in major organs responsible for vitamin D_3's production, hence concluded in lower blood levels • Chronic ingestion of lead induced its deposition on the kidney and testis, resulting in many injuries in both • An increase was also reported in the lipid peroxidation marker MDA and in antioxidant markers GSH, GPx and CAT • The PC group had notably higher levels of pro-inflammatory cytokines TNF-α and IL-4 and lower levels of the anti-inflammatory IL-10 in serum and tissues	• Excess accumulation of lead in renal/testicular tissues induces damage by increasing cellular ROS, oxidative stress and pro-inflammatory response • Vitamin D_3 restored and preserved the expression of cellular endogenous molecules as opposed to PC group's results • It also diminished lead-induced tissue damage on the kidneys and testis, while it increased anti-oxidative markers' expression	2018	[199]
The podocyte-protective effects of active vitamin D or its analogue 22-oxacalcitriol, in puromycin amino-nucleoside (PAN) nephrotic rats were examined. Plus, the preventative effects of vitamin D treatment on podocyte injury were further analyzed	• 6-week-old male Sprague–Dawley rats were analyzed where PAN nephrosis was induced with a single intravenous PAN injection, dissolved in saline at a dose of 10 mg/100 g body weight • 1α,25$(OH)_2D_3$ or 22-oxacalcitriol dissolved in PBS containing 0.01% Tween 20 and 0.2% ethanol was administered intraperitoneally at 0.08 μg/kg/d or 2.0 μg/kg/d for 22-OCT groups and 0.016 μg/kg/d or 0.4 μg/kg/d for 1α,25$(OH)_2$ D_3 groups once/d from the day of PAN injection (d0) until d6. At d7 all rats were anesthetized by intraperitoneal administration of pentobarbital • RNA was extracted from each tissue via the TRIZOL reagent and the expression of mRNA and renal time were monitored through the SYBR-Green assay • Serum and urinary protein were evaluated via the corresponding samples' subjection to sodium dodecyl sulfate-polyacrylamide gels (SDS-PAGE) analysis using 10–20% super-sep polyacrylamide gel and visualization with Coomassie Brilliant Blue dye	• Prior to proteinuria onset, both renal 1α-hydroxylase and 24-hydroxylase markedly downregulated and upregulated, respectively, leading to impaired vitamin D activation • Serum 25$(OH)D_3$ decreased alongside the increased excretion of vitamin D-binding protein in urine • Podocytes expressed VDR and all RXRs except RXRα • Daily administration of 22-OCT ameliorated the nephrotic state by protecting podocytes, as shown by the reduced staining of desmin and enhanced the upregulation of nephrin and podocin	• All data suggested that vitamin D systems' impairment played a role in proteinuria increase in podocyte injury and hence, vitamin D has a protective role toward the NS	2009	[93]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
	• For the immunoblot analysis of vitamin D binding protein (DBP), serum samples were diluted in Laemmli buffer (1:200), comprising of 50 mM dithiothreitol (DTT) and 2% β−mercaptoethanol and then applied to the polyacrylamide gel at a dose of 10 μL/lane • All urinary samples' concentrations were corrected by creatinine level and also diluted in the Laemmli buffer where each urinary sample had 2 μg of creatinine per lane • In order to examine nephrin expression by immunoblot analysis, isolated glomeruli were lysed in a cell lysis buffer via a glass/Teflon homogenizer and diluted in Laemmli buffer • The glomerular samples were then subjected to SDS-PAGE at a dose of 20 μg of protein/lane • The dilution rates of the antibody were 1:100 for VDR, podocin and desmin and 1:50 for retinoid X receptors (RXRα, β and γ) and Wilm's tumor 1 (WT-1)				
This study aimed to characterize a model of DN progression in vitamin D as well as the EMT role in these procedures	• Wistar Hannover rats received a with or without vitamin D diet before type I diabetes induction • The rats were accompanied for 12 and 24 weeks after this induction and the renal function, structure, cell transdifferentiating markers and zinc finger e–box ½ (ZEB1/ZEB2) contribution to the kidney damage were evaluated during DKD evolvement	• An increase in glomerular tuft, mesangial and interstitial relative areas and renal function exacerbation was shown in vitamin D-deficient rats compared to diabetic ones that received a vitamin D diet • All alterations were associated with increased expression of EMT markers, ZEB1 and ZEB2 protein expression and TGF-β1 urinary excretion • A decrease in the post-transcriptional regulator of ZEB1 and ZEB2, miR-200b was also observed	• Vitamin D has a protective role toward DN progression and renal function impairment	2023	[118]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
In this study, SELDI–TOF and LC-MS were applicated so as to explore potential serum biomarkers for mesangial proliferation and kidney injury in anti-Thy1 nephritis with a view to monitoring better the progress of mesangial cell proliferation (MesPGN)	• Wistar rats (200 g each) were injected with PBS and sacrificed on day 0 (6 rats), while anti-Thy1 model rats were sacrificed on days 5, 7 and 14 (6 rats/group) • Venous blood samples were centrifuged for serum collection and then immediately frozen (−80 °C) until their analysis • Serum creatinine (Scr), BUN and total protein levels were measured and urine samples were collected to detect 24 h urine protein (Upro) and creatinine (Ucr) • Renal tissues were fixed in 10% buffered formalin and embedded in paraffin • Sections of 4 μM were stained with periodic acid-Schiff reagent and counterstained with hematoxylin • SELDI-TOF MS was used to analyze serum samples, where peptides were purified by a weak cation exchange on a ProteinChip WCX-2 array software. The laser shot was set with high mass to 50,000 Daltons (optimized from 2000 to 15,000) • Mass information (m/z and molecular weight (MW)) was used for the identification of peptides. Protein concentration was determined via the Bradford method • Serum of 500 μL was diluted with 500 μL PBS and 50 μL, 1 M DTT was added. The mixture was then denatured for 30 min at 56 °C, centrifuged and lastly the supernatant was collected • Proteins (100 μg) were separated by electrophoresis in 10% SDS-PAGE and then stained with R250 Coomassie Brilliant Blue and cut into 7 fragments for trypsin digestion. After the digestion, peptides were analyzed by Nano UHPLC–LC–MS • Each sample group had three replicates; their results were combined for expression profiling analysis by PLGS 2.4	• Considering the anti-Thy1 nephritis, mesangial proliferation and ECM accumulation were marked during the proliferative phase (days 5 and 7), and there was a recorded decrease in the number of mesangial cells during the recovery phase on day 14 • 24 h Upro, Upro/Ucr, Scr and BUN levels were elevated on days 5 and 7, while the total protein in serum decreased on day 5, possibly due to the loss of albumin from urine; these results pointed out both pathological and renal function damage on these days • 28 differentially expressed peptides were tracked in the serum of the model rats, which were classified into 5 groups according to their recorded alterations after using hierarchical clustering. • Cluster 1 peptides were upregulated at day 5 and remained high on days 7 and 14, cluster 2 ones were upregulated on days 5 and 7 but were recovered by day 14, and cluster 3 peptides downregulated on days 7 and 14. Furthermore, cluster 4 peptides downregulated on days 5 and 7 and were recovered at day 14 and cluster 5; peptides downregulated on day 15 • Results had identified cytochrome c oxidase subunit 7C (COX7C) in cluster 1, thioredoxin (TXN), BET1, and prolactin-realizing peptide (PrRP) in cluster 2, ferredoxin 2 (FDX1) in cluster 3 and nerve growth factor (VGF) and neuropeptide S (NPS) in cluster 4 • The peptides found in clusters 2 and 4 were altered during the mesangial proliferation phase and were potent MesPGN biomarkers • A total of 20 differentially expressed proteins (DEPs) were traced in the serum of rats with anti-Thy1 nephritis, which could be classified into three groups. Group 1 included α-2-macroglobulin (A2M), complement component 3 (C3), inter-α-trypsin inhibitor heavy chain family members 4 and 3 (ITIH4 and ITIH3, respectively), VDBP, afamin (AFM), and serpin peptidase inhibitor F2 (SERPINF2), that were upregulated on days 5 and 7 • Similarly, group 2 of DEPS, included ES1 protein, hemopexin (HPX), SEPRINC1, SEPRINA1F, SEPRINA4, SEPRINA3K, SEPRINF1, serine protease inhibitor (SPI), transferrin (TF), vascular non-inflammatory molecule 3 precursor (VNN3) and paraoxonase 1 (PON1), which were downregulated on days 5 and 7, while group 3 DEPs, consisted of C-reactive protein (CRP) and haptoglobin (HP), that were upregulated from day 5 up to day 14	• Amongst the three groups of DEPs, groups 1 and 2 altered mainly on days 5 and 7, implying that their constituents may be potent biomarkers of occurring mesangial proliferation • On a functional level, these DEPs were primarily involved in acute inflammatory responses to stimuli and serine-related endopeptidase inhibitor activities, proving that proteins associated with differential expression patterns could be potent regulators of inflammation, oxidative stress and enzymic activities during anti-Thy1 nephritis	2016	[212]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The aim of this study was to use a large group of db/db and db/+ mice to investigate genes potentially relevant in the pathophysiology of DN, by the use of high-density and oligonucleotide microarrays, to examine glomerular transcription. The observed upregulation in the number of genes in the glomeruli of db/db mice involved in vitamin D and Ca^{+2} metabolism follow-up studies on these genes, their protein-related products and potent downstream effects was also conducted	• Db/db and db/+ mice up to 60 weeks of age were analyzed • Due to the great severity of the renal disease in the db/db mice on the C57BLKs/J strain background, this was the used background strain for the study • During the creation of breeding pairs heterozygous for both Leprdp and the misty trait (m), db/+ mice were interbred to generate db/+ and db/db mice • Db/db mice were identified by onset obesity and hyperglycemia and db/+ mice were distinguished from mice homozygous for wild-type Lepr by the gray coat color granted by the misty trait (m+/m+) • After weaning, all mice types were able to access to water and Teklad Global 18% Protein Diet 2918 that contained 1.01% Ca and 38.4 ng/g (1.54 IU/g) vitamin D_3 • Beginning at 20 weeks of age and extending in 4-week intervals until a final group reached 60 weeks of age, 3 mice/ group had their blood and urine collected followed by euthanasia in order to examine renal tissue harvest • Experiments were performed with a murine glomerular visceral epithelial cell (podocyte) line • Because of the altered gene expression relevant to normal vitamin D metabolism, additional measurements were made in all mice so as to determine whether these resulted in physiological alterations • To further confirm the presence of 1α hydroxylase in podocytes, RT-PCR was performed so as to amplify full-length 1α hydroxylase mRNA • The ability of cultured podocytes to 1α hydroxylate $25(OH)D_3$ and whether high-glucose conditions (induction of 1α hydroxylase mRNA) would alter this were evaluated in corresponding experiments • The relevance of enhanced exposure to $1\alpha,25(OH)_2D_3$, occurred in vivo in db/db mice, was explored by examining podocyte production of the key matrix proteins, fibronectin and collagen IV	• Even though serum Ca^{+2} was slightly elevated in db/db mice, this had no significant statistical difference from db/+ • $1\alpha,25(OH)_2D_3$ serum levels and urinary Ca^{+2} were both notably elevated in db/db mice by greater than threefold, in comparison to age-matched db/+ mice • In order to evaluate db/db mice at earlier ages, separate mice groups (n = 7–8) were examined: a case that proved that $1\alpha,25(OH)_2D_3$ levels were upregulated in db/db mice by 38.5% at 6 weeks and 64.4% at 12 weeks • Although there was a recorded increase in VDBR mRNA in diabetic glomeruli, the baseline mRNA levels were low • Given all above results, and being consistent with the predominant hepatic origin of the protein, there was no difference in serum VDBR quantities between the two mice groups • The renal cortex, glomeruli and cultured podocytes had a full-length 1α hydroxylase mRNA • After 48 h exposure to 50 nM $25(OH)D_3$, supernatant $1\alpha,25(OH)_2D_3$ levels were 8.6 and 19.5 pmol/L in cultured podocytes exposed to 5 and 25 mM glucose, respectively, implying that 1α hydroxylase was functional in these cells and was upregulated under high glucose • Cultured podocytes exposed to 5 mM glucose were able to produce fibronectin and collagen IV, which increased when they were exposed to high glucose 25 mM conditions • Under these conditions, concomitant exposure to 5 nM $1\alpha,25(OH)_2D_3$ led to a reduction in fibronectin and collagen IV production	• The obtained results suggested that vitamin D metabolism was altered in db/db mice, leading to metabolic and transcriptional alterations • The podocyte was affected by paracrine and potent autocrine effects of vitamin D that may explain the reason why db/db mice were resistant to progressive DN	2006	[193]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
This study aimed to explore the effects of maternal vitamin D deficiency on glomerular development in early postnatal life and its effects on the renal structure while in the maternity phase, focusing predominantly on the F1 and F2 generations after F0 maternal vitamin D restriction	• The analyzed mice were housed at a controlled 21 ± 1 °C temperature and 60 ± 10%, with a 12 h light/dark cycle and free access to food and water • 6-week-old female virgin Swiss Webster mice (n = 20) were divided into one of two groups for 6 weeks: either SC (standard chow, fed a diet made according to the AIN93G protocol, including 1000 IU/kg (recommended minimum of vitamin D_3) or VitD- (vitamin D restricted, fed the same AIN93G diet without vitamin D_3) • Vitamin D was added only to SC diet and the vitamin mixture that did not include vitamin D was added to both diets • The SC diet contained 400,000 IU of vitamin D_3/kg of the feed mix, which supplied the recommended vitamin D levels, and these mice were the F0 generation • Male mice of the same age (n = 20) were divided and fed only the SC diet, and after a 6-week period were mated overnight • After mating, the presence of a vaginal plug was used to diagnose pregnancy • The dams on the contrary were separated from the males and fed their respective experimental diets until the 10th day of sucking (lactation), when the VitD- diet was switched to SC • Pups were sexed by measuring the anogenital distance, asexually dimorphic trace in mice (male's anogenital distance is almost twice as long as the female's) • F1 thus females were divided at 21 days from SC and VitD- groups so as to produce the F2 generation (n = 10/group) and as of 21 days old, F1 females were fed SC • At 3 months, they were mated with males in order to birth the F2 generation, where the offsprings were separated and analyzed the same as the F1 offsprings • Minimum sample size: 5 animals/group	• The first two generations of the VitD- group demonstrated higher blood pressure at 6 months of age than the SC one, as well as an increase in renin and AT1r expression was observed • However, at all included ages, both F1 and F2 VitD- mice displayed shorter glomerular diameters, and their diet played a vital role in total variation • Both F1 and F2 VitD- generations had a more immature glomeruli than the SC group offspring • Immature glomeruli began to disappear at 10 days, but at this age, F1 VitD- mice had more immature and mature glomeruli than F1 SC mice • At 6 months of age, F1 VitD- mice had more glomeruli, while F2 VitD- mice displayed the same number of glomeruli with F2 SC mice, but fewer when compared to F1 VitD- mice • Both diet and generation accounted for the total variation in glomeruli number • A decrease in urine output and podocin expression and an increase in urea and creatinine in the urine were observed in the F1 offspring	• All collected findings demonstrated that maternal vitamin D deficiency accompanies alterations in the renal expression of important factors which may retard the maturation of the glomeruli by extending the nephrogenesis period	2012	[190]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The aim of this study was to confirm the several locations of VDR in our body except for the confirmed one proximal renal tubule. The biological effects of $1\alpha,25\ (OH)_2D_3$ were mediated via the VDR, which was present in distal renal convoluted tubule cells; however, whether it is present in other kidney cell types was uncertain, case examined by immunohistochemistry	• C57BL/6 mice and Demay VDR knockout mice were analyzed at the age of 6–7-week-old wild–type, knockout females were selected and their kidneys were collected and chemically fixed • Paraffin-embedded human samples were given by a 38-year-old female, and the tissues were chemically fixed with formalin and embedded with paraffin • An immunohistochemical assay with an anti-VDR antibody D-6 was employed • Slides co-stained with VDR and CaBR-D29k following the application of the VDR primary antibody were treated with 2nd primary antibodies CaBP-D28k of 20 μg/mL overnight at 4 °C • For slides co-stained with E-cadherin and CaBR-D29k, the sections were treated with rabbit anti-E-cadherin antibody (1:50) for 1 h at 37 °C and then with goat anti-CaBR-D29k overnight • For slides co-stained with E-cadherin and VDR, the sections were treated with E-cadherin and VDR antibodies for 1 h, 37 °C • For slides co-stained with WT-1 and VDR, the sections were treated with WT-1 and VDR antibodies (4 μg/mL) for 1 h, 37 °C • For slides co-stained with anti-αSMA (anti-smooth muscle antibody) (1:200) and VDR, the sections were treated with mouse anti-αSMA and rabbit WT-1 antibodies for 1 h, 37 °C • Immunosignals were visualized by secondary antibodies conjugated with an Alex flour fluorescent dye, and images were captured by a fluorescence microscope or confocal fluorescence microscope • Immunoreactivity was estimated semi–quantitatively by nuclear staining intensity of renal tubular epithelial cells • Sample images were captured with either short-time exposures (400 ms) which were used to measure high immunostaining intensities in segments like the distal tubules or long-time (800 ms) exposures for weaker ones (proximal tubules) • Images with low exposures, quantified positive VDR staining in distal tubules and images with high exposure quantified VDR staining in the proximal tubules • The comparison of these values was made by average values of 400 ms distal immunosignals (Vdt/400), which were proportionally converted to those at 800 ms (Vdt/800) • 30 cells of intermediate intensity were utilized for determining ratios calculated by: Ratio800/400 = V800/V400 • Final distal tubule VDR values were obtained by Vdt/800 = Vdt400 × Ratio800/400	• VDR and CaBP-D29k co-staining proved that VDR was expressed in distal tubules, renal cortex and medulla and was very low in medulla collecting ducts • Analysis of VDR and CaBP-D28k staining intensities indicated that their expression levels were highly correlated, while VDR and E-cadherin were highly expressed/colocalized in distal tubules • The cortical collecting ducts that displayed strong E-cadherin positive staining in the cortex and medullary collecting ducts, highly expressed E-cadherin, but VDR at lower levels • On the contrary, the proximal tubules were found negative/extremely weak for E-cadherin staining but were positive for low VDR levels • The VDR immunosignal strength in the distal tubules was strong but much weaker that in the proximal tubules • Double staining could change VDR antibody staining results, including losing proximal tubules' and collecting ducts' immunosignals • VDR was present in cortex renal tubules and medulla of the wild-type mouse kidney, while distal tubules expressed high VDR levels (kidney cortex) • Most cortex renal tubules were weakly stained and were likely the proximal tubules and cortical collecting ducts • In contrast to renal tubular epithelial cells, VDR was not found in renal interstitial fibroblasts between renal tubules • No notable signals were detected in Demay VDR knockout kidneys and wild-type mice stained with only the secondary antibody mouse isotype IgG • VDR immunosignal in wild-type mouse kidney sections were highly specific, and calculated values represented the average of more than 50 cells from either the distal or proximal renal tubules	• VDR immunosignals were present within wild-type mice' glomerulus but not in Demay VDR knockout mice samples • VDR's expression was lower in podocytes than in proximal tubule cells, while it was very low or not found at other cell types, like intraglomerular mesangial and/or endothelial cells • VDR expression was highly expressed in macula densa, while in contrast, juxtaglomerular cells were not stained by the VDR antibody • VDR was clearly found in the glomerular parietal epithelial cells, podocytes and the JGA macula densa, and on the other hand, it was not detected in the interstitial fibroblasts, intraglomerular mesangial and juxtaglomerular cells	2012	[180]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
This study aimed to investigate the impact of molecular mechanisms in high-dose vitamin D_3 treatment on renal fibrosis	• An experimental model of CKD was established by 5/6 nephrectomy in rats distinguished by high levels of Scr, BUN and urinary protein • Serum 25(OH)D_3, Ca and parathormone levels were measured to evaluate vitamin D levels • Hematoxylin and eosin, periodic acid Schiff and Mallory's Trichrome staining were utilized to evaluate histopathological changes in rats • Moreover, the expression of vimentin, collagen I, α-smooth muscle actin and E-cadherin were analyzed at both molecular and histopathological levels	• High dose of vitamin D_3 may partially improve kidney function and ameliorate renal fibrosis in this rat model • One of the key mechanisms that implied vitamin D's therapeutic effect in renal fibrosis was primarily associated with its receptor (VDR) • VDR's upregulation markedly inhibited the TGF-β1/Smad3 signaling pathway	• Vitamin D_3 is a potent antifibrotic drug in CKD via the VDR and inhibiting the TGF-β1/Smad3 signaling pathway	2021	[213]
This study aimed to investigate the effects of a double treatment with losartan potassium (L), AT1R antagonist, and the tyrosine kinase inhibitor erlotinib € on the alternative pathway of RFF related to TACE–dependent activation of eGFR in 5/6 SN rats that suffered from vitamin D deficiency (D)	• During the 90 d protocol, male Wistar rats under D were submitted to 5/6 nephrectomy (N) on day 30 and divided into 4 groups: N+D with no treatment, N+D+L that received losartan (50 mg/kg/d), N+D+ E that were given erlotinib (6 mg/kg/d), and N+D+L+E (received both treatments)	• N+D+L+E rats had not only their TACE-dependent eGFR activation blocked, but also the expression of TGF-β prevented against RFF in 5/6 N rats under vitamin D deficiency • The renoprotection by losartan and erlotinib altogether was corroborated by a lower ECM proteins' expression and markers of phenotypic alteration as well as by a lesser inflammatory cell infiltrate observed in kidneys from N+D+L+E rats	• Although erlotinib alone has been emerging as a renoprotective drug, its prescription along with losartan was a potential therapeutic strategy on the modulation of RFF	2021	[183]
The aim of this study was to investigate the way ACE inhibitors ameliorate renal disease progression	• Uremic rats (U) were analyzed in this study and treated as follows: U + vehicle (UC), U + enalapril (UE of 25 mg/L in drinking water), U + paricalcitol (UP) of 0.8 μg/kg i.p., ×3/week, or U + enalapril + paricalcitol (UEP)	• Despite hypertension in UP rats, proteinuria decreased by 32% vs. UC rats • Enalapril alone or combined with paricalcitol further decreased proteinuria (~70%), while glomerulosclerosis and interstitial infiltration increased in UC rats, which was inhibited by paricalcitol and enalapril • The increase in cardiac atrial natriuretic peptide (ANP) seen in UC rats was notably decreased by paricalcitol, while enalapril produced a vaster ANP reduction • The marked increase in p22phox, a subunit of NADPH oxidase, and decrease in endothelial NO synthase were inhibited and in all treated groups • In UEP rats, uremia-induced increase in iNOS and GPx activity were inhibited better that either compound alone • Glutathione reductase also increased in UE and UP rats rather that UC ones • Kidney 4-hydroxynonenal notably increased in UC group rats, compared to normal ones, which was blunted by the combined compounds' treatment, that alone had no significant effect • In addition, Mn-superoxide dismutase (SOD) increased and Cu-Zn-SOD decreased by uremia, case ameliorated by the above co-treatment that increased Cu-Zn-SOD's expression	• Similarly to enalapril, paricalcitol improved proteinuria, glomerulosclerosis and interstitial infiltration and reduced renal oxidative stress • Paricalcitol effects were amplified when and ACE inhibitor was added since co-treatment with both compounds had an additive effect on ameliorating uremia-induced alterations in iNOS and Cu-Zn-SOD's expression, peroxidase activity and renal histomorphometry	2012	[182]

Table 1. *Cont.*

Hypothesis–Intervention	Study Design	Main Findings	Specific Benefits—Mechanisms of Action—Conclusions	Year of Study *	Ref.
In Vivo (Animal Studies)					
The renal protective effects of vitamin D in a CKD rat model was examined. Also, this study aimed to prove that calcitriol ameliorates kidney injury via reducing podocytopathy, tubular injury, inflammation and fibrosis through 5/6 subtotal neuropathy assay examination	• CKD was induced in male Sprague–Dawley rats (3-month-old, 200–300 g, *n* = 6, SN group) and then all rats were sacrificed on day 14 after the operation, while Sham operation was used as the control group (SO group, *n* = 6) • Calcitriol was administered in two doses: 0.01 μg/mL 100 g/body weight (BW)/d (SND1 group, *n* = 6) and 0.05 μg/mL 100 g/BW/d (SND2 group, *n* = 6), intraperitoneally for 14 days • Glomerulosclerosis and tubular injury score were valued with PAS staining, while interstitial fibrosis area fraction was assessed with Sirus red staining • RT-PCR was used for assessing nephrin, podocin, IL-6, CD68, collagen I and TGF-β1 mRNA expressions • Immunostaining (IHC) was conducted to observe CD68 and α-SMA activity	• Calcitriol-treated group and mainly SND2 had significantly lower tubular injury, glomerulosclerosis and interstitial fibrosis compared to SN • SND2 displayed not only notably lower CD68, IL-6, collagen I and TGF-β1 mRNA expressions, but also higher expressions of nephrin and podocin • SND2 also demonstrated a reduction in macrophages infiltration and myofibroblasts expansion based on histopathological appearance • Vitamin D may have a renoprotective effect on 5/6 SN model by attenuating podocytopathy, tubular injury, inflammation and interstitial fibrosis • SN group had a CKD condition with higher tubular injury, glomerulosclerosis, interstitial fibrosis and inflammation when compared to SO group	• The findings of this research may be associated with vitamin D's effects in renal fibrosis which are the following: (1) Vitamin D prevents signal transduction of TGF-β-Smad by inhibiting pSmad3(50), (2) it induces the hepatocyte growth factor (HGF) that inhibited myofibroblast activity and epithelial to mesenchymal transition, which lowered ECM production, like collagen I, III and fibronectin in the renal interstitial space • Vitamin D also inhibits the RAS system, via lowering renin gene transcription	2020	[92]
In vivo (Human studies)					
This study was conducted so as to evaluate the effectiveness of the supplementation of vitamin D as a protective agent against the infection of patients with CKD on conservative treatment	• A retrospective cohort study was carried out in the Conservative Treatment Outpatient Clinics of the Hypertension and Kidney Hospital (HRim) • The infection was a dependent variable as well as the use or no-use of vitamin D, sociodemographic data (sex, age, race, profession) and associated comorbidity (diabetes mellitus, high blood pressure, CVDs and others) • Patients were divided into two groups: group A where they received vitamin D supplementation for at least 6 months and group B with patients that did not use vitamin D supplementation in order to analyze the presence/absence of infection • 263 medical records were examined, with 52.85% being male patients, 60.46% white and 56.65% being 66 years old or older	• Most patients of both sexes displayed high blood pressure (88.21%), 45.25% had diabetes mellitus, 69.58% other diseases, 29.66% exhibited hypovitaminosis D and underwent replacement therapy • Among the 43 patients who used vitamin D supplementation, only 7 displayed an infection (16.27%), while among the 185 who used no vitamin D supplementation, 71 had an infection (32.27%) • Urinary tract infection (UTI) was the most frequent infection among patients of both groups (87.17%), while the most tracked microorganisms (91.55%) were the Gram-negative ones • Escherichia coli was the most commonly found bacteria type (50.70%), followed by Klebsiella pneumoniae (16.90%) • Group A patients had a 59% lower chance of developing an infection in opposition to those of group B • The main risk factors were found among patients in the 34–49 age group and those older than 66 years old	• The use of vitamin D as a protective agent for infection, without being adjusted by the presence of other variables (age, sex etc.) in this multivariate analysis, was proved • Statistical significance, however, did not remain since some of the covariates modified the total effect	2018	[122]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The main study hypothesis is that oral vitamin D supplementation could possibly ameliorate insulin resistance to patients with CKD at the 3rd stage compared to placebo. The secondary examined hypothesis will test whether this is affiliated with decreased inflammation and bone/adipocyte–endocrine dysregulation in this single-centered, double-blinded, randomized, placebo-controlled trial	• Inclusion criteria that were taken into consideration were estimated glomerular filtration rate of 30–59 mL/min/1.73 m^2, ages of 18 and above, and 25(OH)D_3 levels <75 nmol/mL to randomized (1:1) patients receiving either oral cholecalciferol of 2000 IU/d or placebo for 6 months • The primary expected outcome was an improvement in the insulin sensitivity, measured by hyperinsulinemic euglycemic clamp, while the second outcome measures, included PTH, cytokines (like IL-1B, IL-6, TNF-α), adiponectin (total and high molecular weighted), osteocalcin (carboxylated and under–carboxylated, peripheral blood mononuclear cell nuclear factor kappa-B p65 binding activity, brachial artery reactivity, aortic pulse wave velocity, waveform analysis and indirect calorimetry • All measured outcomes were be adjusted to baseline at the end of the study	• This randomized controlled trial performed in pre-dialysis CKD patients correlated vitamin D supplementation to insulin resistance decrease and markers of CVDs risk • Cholecalciferol was a safer intervention and had many health benefits toward non-mineral homeostasis	• The supplementation of vitamin D ameliorated insulin resistance to patients with CKD at the 3rd stage compared to placebo. • Additionally, this supplementation was affiliated with decreased inflammation and bone/adipocyte–endocrine dysregulation	2009	[130]
This study aimed to evaluated whether vitamin D_3 or omega–3 fatty acids (FAs) prevent the development or progression of CKD in type II diabetes mellitus	• A randomized clinical trial (2 × 2) was conducted among 1312 adults with type II diabetes mellitus as an ancillary study to Vitamin D_3 or Omega-3 Trial (VITAL), with a follow-up being conducted 3 years later • Participants randomly received vitamin D_3 (2000 IU/d) and omega-3 FAs (eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA) 1 g/d) (n = 370 patients), vitamin D_3 and placebo (n = 333), placebo and omega-3 FAs (n = 289), or 2 placebos (n = 320) for 5 years in this study • Patients had a mean age of 67.6 years, while 46% were women, 31% racial/ethnic minority and 934 (71%) completed the study	• A change in the eGFR was observed from serum creatinine and cystatin C from the baseline up to year 5 • The baseline mean eGFR was 85.5 (SD, 22.1) mL/min/1.73 m^2, the mean change in eGFR was −12.3 (95% CI, −13.4 to −11.2) mL/min/1.73 m^2, vitamin D3 vs. −13.1 (95% CI, −14.2 to −11.9) mL/min/1.73 m^2 with placebo (difference, 0.9 [95% CI, −0.7 to 2.5] mL/min/1.73 m^2) • Moreover, mean eGFR was −12.2 [95% CI, −13.3 to −11.1] mL/min/1.73 m^2, with omega-3 FAs vs −13.1 [95% CI, −14.2 to −12.0] mL/min/1.73 m^2 with placebo (difference, 0.9 [95% CI, −0.7 to 2.6] mL/min/1.73 m^2) • No significant interaction between the two interventions was observed • Kidney stones occurred among 58 patients (32 received vitamin D_3 and 26 received placebo) and gastrointestinal bleeding among 45 participants (28 received omega—3 FAs and 17 received placebo) • Similar results were shown when analysis was restricted to participants who gave serum samples at baseline and year 5 or to patients who reported consistent high adherence to study medications • No notable subgroup heterogeneity was observed for the effect of either vitamin D3 or omega-3 fatty acids (FAs) impact on eGFR change • Neither change in serum 25(OH)D_3 levels nor a change in the omega-3 index from baseline to year 2 was significantly correlated to a change in the eGFR from baseline to year 5	• Vitamin D_3 and omega-3 fatty acids (FAs) prevented the development or progression of CKD in type II diabetes mellitus • The composite outcomes of at least 40% eGFR decline or kidney failure as well as an eGFR decline of at least 30% were not prespecified and did not differ notably • No statistically significant violations of the proportional hazards' assumption were found	2019	[197]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
This study's objective was to expand the assessment of vitamin D's metabolism in this cohort to include measures of serum DBP, FGF-23 and 24,25$(OH)_2D_3$ so as to identify bioavailable 25$(OH)D_3$ concentrations and vitamin D's catabolism in children's CKD	• Children and adolescents (5–21 years) with CKD and with the following underline diseases: congenital abnormalities of the kidney/urinary tract (CAKUT), including aplastic/hypoplastic/dysplastic/ cystic kidneys and obstructive neuropathy, glomerulonephritis (GN), like membranoproliferative GN, IgA neuropathy, Alport's syndrome, systemic lupus erythematosus and Wegener's granulomatosis, focal segmental glomerulosclerosis (FSGS), participated • Serum DBP was measured in duplicate using an enzyme-linked immunosorbent assay and measured intact PTH (iPTH) and bioactive PTH (1-84PTH) concentrations were also examined	• Serum concentrations of total and bioavailable 25$(OH)D_3$, 24,25$(OH)_2D_3$, and 1α,25$(OH)_2D_3$ were each lower with more advanced CKD stages and differed by underlying renal disease etiology • Serum albumin differed crucially by CKD stage, in contrast to DBP, while DBP and albumin were not markedly correlated (Spearman's rho = 0.15, $p = 0.08$) • The prevalence of 25$(OH)D_3$ deficiency (<20 ng/mL) among FSGS and GN participants was 85% and 71%, respectively, compared to 33% CAKUT patients • No statistical difference was found between correlation coefficients for vitamin D metabolites with calcium • iPTH was inversely linked to bioavailable 25$(OH)D_3$, 24,25$(OH)_2D_3$, and 1α,25 $(OH)_2D_3$, and there was no vital difference between correlation coefficients for bioavailable 24,25$(OH)_2D_3$, versus 1α,25 $(OH)_2D_3$ with iPTH, but there was no statistical difference as well • PTH1-84 for iPTH constitution did not impact the corresponding findings	• Among children and adolescents with CKD, glomerular disease and mostly FSGS, it was observed that they were independently associated with lower 25$(OH)D_3$ concentration, while pre-dialysis FSGS patients also had lower 1α,25$(OH)_2D_3$ concentration for a specific 25$(OH)D_3$ substrate • These findings supported that vitamin D disturbances in vitamin D's metabolism extended beyond increased glomerular filtration and urinary loss of its binding proteins to include aberrant tubular handling of 25$(OH)D_3$'s downstream from the glomerulus	2013	[191]
The aim of this study was to assess vitamin D status and bone density in steroid-treated children with glomerulopathies and to evaluate the effect of prophylactic vitamin D and Ca supplementation	• Retrospective analysis was conducted on 55 children (4–18 years old) with glomerulopathies and anthropometrical parameters, bone densitometries, parathormone, bioavailable 25$(OH)D_3$, and urinary Ca excretion were measures, while medication received for low bone mass prevention was prescribed	• 38% of these children had decreased spiral bone mineral density (BMD z-score < −2.0) and their majority (89%) had hypovitaminosis D (25$(OH)D_3$ < 30 ng/mL), 75% vitamin D insufficient D (25$(OH)D_3$ < 20 ng/mL), and 16% vitamin D deficient D (25$(OH)D_3$ < 10 ng/mL) • The mean serum D 25$(OH)D_3$, was comparable to that of controls (19.32 ± 12.87 vs. 15.05 ± 8.52 ng/mL) • 82% of patients received preparations of Ca and/or vitamin D to improve bone health and notably, patients on cholecalciferol had a higher mean concentration of 25$(OH)D_3$ in comparison to those not receiving it and the controls • In 23 children with vitamin D and Ca supplementation for an average 6-month time period, an increase in the mean BMD values was observed; however, mean BMD score and 25$(OH)D_3$ concentrations did not alter markedly	• Vitamin D and bone density deficits are mostly frequent in children with glomerulopathies despite vitamin D and Ca repletion • So as to enhance vitamin D's effectiveness for bone density health improvement, a regular assessment of serum 25$(OH)D_3$ concentration that can guide subsequent dose adjustment of vitamin D was suggested	2012	[192]

Table 1. *Cont.*

Hypothesis–Intervention	Study Design	Main Findings	Specific Benefits—Mechanisms of Action—Conclusions	Year of Study *	Ref.
In Vivo (Animal Studies)					
The proteomic profile of urine from patients with FSGS along with minimal change disease (MCD) was evaluated	• Patients with FSGS (n = 30) and MCD (n = 9), participated in this study • For FSGS's assessment, a special index was introduced which was calculated as follows: first score: eGFR level, second score: proteinuria level and third score: steroid therapy resistance • Patients with the sum of this score <3 were included in group 1 and those with 3 or >3 were allocated in group 2 • Urinary proteome was analyzed with liquid chromatography/mass spectrometry (LC-MS), and the patients' profiles with severe progressive FSGS (group 2), mild FSGS (group 1) and MCD were compared • All results were validated with targeted LC-MS, based on multiple reaction monitoring (MRM), with stable isotope labeled peptide standards (SIS) available for 47 out of 76 identified proteins as differentiating between at least one pair of groups	• FSGS patients had high variability inside the group and clustered into two subgroups, which could be divided based on the proteomic profile • Quantitative MRM/SIS validation measurements for these 47 proteins revealed 22 out of them with vital differences between at least one of the two group pairs and 14 were validated for both comparisons • All 22 proteins showed the same change direction as at the discovery stage with label-free LC-MS analysis, i.e., up- or downregulation in MCD and FSCS1 against FSGS2. • In patients with severe FSGS2, the urine proteomic panel reflected podocyte damage (vitronectin, HP, gelsolin, C4b, C9, APOA1) and accumulation of the ECM damage (cystatin C, VDBP, retinol-binding protein 4 (RBP4), α-2-HS-glycoprotein, plasma protease C1 inhibitor, lumican, clusterin) • Patients with FSGS1 and MCD had lower cystatin C levels, gelsolin and complement factor I	• FSGS and MCD are indeed diseases with primary podocyte damage and clinically manifested by the NS that can be ameliorated by vitamin D's impact	2022	[52]
In vivo + In vitro (Animal studies)					
The protective effect and potential mechanism of vitamin D on the podocyte injury of DKD was thoroughly investigated	• Type II diabetic db/db mice received i.p. injections of paricalcitol 400 ng/kg/d for 16 weeks • Immortalized mouse podocytes were cultured in high-glucose (HG) medium with active vitamin D_3 calcitriol or autophagy inhibitor 3-methyladenine • Renal function and urine albumin creatinine ration were assessed at week 24 • Hematoxylin and eosin staining (HE), PAS staining and electron microscopy were used to evaluate renal histopathology and morphological changes • Immunohistochemistry, immunofluorescence and Western blot were used to evaluate protein expression of nephrin and podocin in kidney tissue and podocytes • The expression of autophagy-related proteins (LCE, Beclin-1, Vps34) and apoptosis-related (caspase-3, Bac) were determined by Western blotting, and podocyte apoptosis was further evaluated by a flow cytometer • Podocytes were cultured at 33 °C with 100% relative humidity and 5% CO_2 in RPMI 1640m medium containing 10% fetal bovine serum, recombinant INF-γ and 100 U/mL penicillin/streptomycin • So, as to induce differentiation, podocytes were transferred in cell culture dishes coated with collagen I, cultured in INF-γ—free RPMI 1640 medium with 5% fetal bovine serum at 37 °C for 14 days	• Albuminuria in a db/db mouse model was notably attenuated after treatment with paricalcitol, which was accompanied by alleviation of the mesangial matrix expansion and podocyte injury • The impaired autophagy in podocytes under diabetic conditions was also markedly enhanced after paricalcitol or calcitriol treatment, combined with restored decreased podocyte slit diaphragm proteins podocin and nephrin • The protective effect of calcitriol against HG-induced podocyte apoptosis could be abated by autophagy inhibitor, namely 3-methyladenine	• Vitamin D ameliorated podocyte DKD injury by enhancing podocyte autophagy activity that may become a potent candidate autophagy activator for DKD therapeutic interventions	2023	[94]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
	• Differentiated and mature podocytes were maintained in serum-free medium overnight, and cultured podocytes were divided into 6 groups according to various treatments: normal glucose (NG of 5.6 mm glucose), mannitol control group (MA of 5.6 mm glucose plus 24.4 mm D-mannitol), high glucose (HG of 30 mm glucose), high glucose plus 1 nm 1α,25 $(OH)_2D_3$ (HG + 1VD), high glucose plus 10 nm 1α,25 $(OH)_2D_3$ (HG + 10VD), and high glucose plus 100 nm 1α,25 $(OH)_2D_3$ (HG + 100VD), where cells were treated with the above intervention for 48 h				
This study aimed to evaluate the effect of vitamin D and VDR signaling on podocyte autophagy in DN	• Specific pathogen-free Sprague–Dawley (SD) male rats (180–200 g, 6-week-old) were utilized and analyzed • After 1 week of adaptation to the ambient environment, all rats were randomly divided into 3 groups: vehicle control group (NC group, n = 20), diabetic neuropathy group (DN group, n = 20) and DN rat treated with calcitriol group (DN + VD group, n = 20) • STZ was dissolved in 0.1 M citrate buffer of pH = 4.4 at a concentration of 4 mg/mL and a single rapid injection into the i.p. at a dose of 60 mg/kg, while the control group was injected with an equal buffer dose • 3 days later, rats whose tail vein blood glucose was measured $\geq$16.7 mmol/L were considered diabetic rats, which were then monitored every 2 weeks via a blood glucose monitoring system • Calcitriol was dissolved in edible peanut oil at 0.04 μg/mL and delivered by oral gavage at a daily dose of 0.1 μg/kg after starting at 3 days after STZ injection until the sacrifice of rats • The DN and control group received equal amounts of edible peanut oil • MPC-5 conditionally immortalized mouse podocyte clonal cells were cultured and induced to differentiate and grown to DMEM-F12 medium containing 10% FBS and mouse recombinant IFN-γ of 10 U/mL at 33 °C, 5% CO_2 and the medium was changed every other day • So as to induce differentiation, the podocytes were cultured in medium without IFN-γ at 37 °C, 5% CO_2 within 10–14 days • The fully differentiated cells with 80% confluence were utilized for subsequent experiments, while for euglycemic or hyperglycemic conditions, the cells were cultured in medium containing 5.5 mM or 30 mM glucose for 24 h	• VDR and autophagosomes in podocytes were notably decreased in renal biopsy from patients with DN compared to healthy kidney tissue • Rats with STZ treatment developed typical DKD with low VDR expression • Calcitriol could activate the VDR and attenuate DN including proteinuria and glomerulosclerosis • Calcitriol treatment also alleviated the podocyte foot process fusion, reduced podocyte injury marker desmin and preserved slit diaphragm proteins in DN • Reduced LC3II/I, Beclin-1 and elevated p62 in renal homogenate and reduced autophagosomes and LC3II in podocytes indicated podocytes autophagy impairment in DN, whereas calcitriol treatment restored podocyte autophagy • In cultured podocytes, the protective effect of calcitriol against high glucose-induced podocyte injury could be abated by autophagy inhibitor chloroquine	• This study delivered evidence that calcitriol/VDR signaling attenuated DN and podocytes' injury by restoring podocyte autophagy, which implied the potential protective mechanisms of calcitriol/VDR in DN conditions	2021	[194]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
In the present study, the effects of vitamin D on glomerular heparanase and heparan sulfate (HS) in animal models of FSGS or 1α,25$(OH)_2D_3$ deficiency and in addition, whether vitamin D was able to directly effectively regulate heparanase expression in selected cultured mouse glomerular endothelial cells and podocytes	• Animals were housed in a temperature-controlled room with a 12 h light/dark cycle with full access to food and water • Adriamycin neuropathy (AN) was induced in 8-week-old Wistar rats by an intravenous injection of 5 mg/kg BW AN • Rats were treated with daily i.p. injections of 2.5 μg/kg BW of 1α,25$(OH)_2D_3$ or vehicle 1α,25$(OH)_2D_3$-deficient 25-hydroxy–1α–hydroxylase knockout (KO) mice were generated and genotyped • 5-week-old KO mice and their wild-type (WT) littermates received daily i.p. injections of 500 pg/g BW of 1α,25$(OH)_2D_3$ or vehicle and after 6 weeks, rats or mice were housed in metabolic cages for 24 h in order to collect urine • All animals were euthanized and kidneys and blood collected • Conditionally immortalized mouse glomerular endothelial cells (mGEnC-1) and mouse podocytes (MPC-5) were cultured • Silencing of heparanase in MPC-5 was achieved after transfecting a heparanase shRNA construct and subsequent selection with G418 • Differentiated mGEnC-1 and MPC-5 were stimulated with vehicle or 0.25 μg/mL adriamycin and treated with different 1α,25$(OH)_2D_3$ concentrations (10, 100 nmol/L, 1 μmol/L) • Differentiated mGEnC-1 cells seeded on polyester membranes (0.4 μm pore size) in tissue culture inserts were treated with adriamycin and/or 100 nmol/L 1α,25$(OH)_2D_3$ • Additionally, mGEnC-1 cells were treated with a 1:1 mix of medium supplemented with adriamycin and/or 100 nmol/L 1α,25$(OH)_2D_3$ and conditioned culture supernatant of podocytes treated with adriamycin and/or 100 nmol/L 1α,25$(OH)_2D_3$ • After 16 h, medium in the insert was replaced by serum-free medium (SFM) containing 0.5 mL FITC-labeled bovine serum albumin (BSA) and medium in the well was replaced by SFM • After 1, 2, and 3 h, aliquots were removed from the well and replaced with SFM • Fluorescence was measured in a fluorometer with excitation at 495 nm and emission at 520 nm and the amount of albumin passing the endothelial cell monolayer was settled by a set of standard dilutions • Whether 1α,25$(OH)_2D_3$ treatment directly regulated heparanase transcription, a luciferase reporter assay was performed using the luciferase HPR1-3.5 • KO cells were transfected with the HPR1-3.5 construct or the empty vector without the heparanase promoter and treated with vehicle, 100 nm or 1 μm 1α,25$(OH)_2D_3$ for 24 h • Culture supernatant lastly, of mouse podocytes was added with either vehicle or adriamycin, in the presence or absence of 1α,25$(OH)_2D_3$	• The in vivo effects of 1α,25$(OH)_2D_3$ treatment on heparanase and HS expression, AN (an animal model for FSGS), was induced in rats, that were subsequently treated with either 1α,25$(OH)_2D_3$ or vehicle for 6 weeks • AN rat model developed proteinuria that could be ameliorated by 1α,25$(OH)_2D_3$ treatment, where the induction of adriamycin resulted in increased cortical heparanase mRNA, glomerular heparanase protein and cortical heparanase • Heparanase levels were reduced by 1α, 25$(OH)_2D_3$ treatment in control rats, suggesting that endogenous heparanase expression is regulated by 1α,25$(OH)_2D_3$ • In addition, glomerular HS was reduced in AN rat model but significantly increased by 1α,25$(OH)_2D_3$ treatment • Stimulation of mouse podocytes with adriamycin increased heparanase mRNA expression, while treatment with 1α,25 $(OH)_2D_3$ dose-dependently reduced heparanase expression in both Adriamycin-injured and uninjured podocytes • Stimulation of mGEnC-1 with adriamycin initially increased heparanase mRNA but these stabilized after 16 h, while adriamycin increased HS on these cells • 1α,25$(OH)_2D_3$ treatment did not affect heparanase mRNA and HS on mGEnC-1, while this study's data revealed that 1α,25$(OH)_2D_3$ did in fact reduce heparanase mRNA expression • 1α,25$(OH)_2D_3$ treatment decreased heparanase promoter activity, whereas luciferase activity in cells with the empty vector was very low and not affected by treatment (ChIP assay) • Real-time PCR showed an 8-fold enrichment of the heparanase promoter when precipitated with the anti-VDR antibody compared with rabbit IgG isotype control • Trans endothelial albumin passage was increased by stimulation with adriamycin, but 1α,25$(OH)_2D_3$ treatment did not have a direct effect on heparanase and HS in mGEnC-1. However, this treatment reduced heparanase mRNA in mouse podocytes • In the presence of podocyte culture supernatant, transendothelial albumin passage was increased after adriamycin stimulation and normalized by 1α,25 $(OH)_2D_3$ treatment of cultured podocytes	• The present study was the first one to prove that heparanase promoter activity and expression are monitored and regulated by the steroid hormone vitamin D • By binding vitamin D, VDR reacts with the RXR to form a heterodimer that binds to vitamin D-responsive elements in the promoter regions of the responsive genes • VDR binds to the heparanase promoter and most genes are positively regulated by vitamin D • Heparanase is one of the few genes regulated negatively by vitamin D, which also includes genes encoding PTH, renin and the transient receptor potential cation channel C6 (TRPC6)	2015	[185]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
In this study, it was hypothesized that vitamin D reduced proteinuria by affecting TRPC6 expression in podocytes	• The AN model for human FSGS was induced in 8-week-old Wistar rats by a single tail vein injection with 5 mg/kg BW of adriamycin and kept in a standard room at 21 °C, controlled humidity, where they were exposed to 12 h light/dark cycle and unlimited access to food and water • Rats were treated with daily i.p. injections of 2.5 μg/kg BW of $1\alpha,25(OH)_2D_3$ or vehicle for 6 weeks, and at the end of the experiment, they were housed in metabolic cages to collect 24 h urine samples, where subsequently they were sacrificed and kidneys and blood samples were collected • MPC-5 were cultured at 33 °C with 5% CO_2 and differentiated at 37 °C in RPMI medium, supplemented with 10% v/v fetal calf serum, 1% glutamine, 10 U/mL of INF-γ and 1% penicillin/streptomycin • Depending on the exact experimental setup, differentiated podocytes were treated with 0.25 μg/mL adriamycin and different $1\alpha,25(OH)_2D_3$ concentrations or vehicle for 24 h, where 4 or 5 separate podocyte cultures were used per experimental condition, and all were repeated at least twice for confirmation • $1\alpha,25(OH)_2D_3$-deficient 25-hydroxy-1 α-hydroxylase KO mice were previously generated by targeted ablation of exon 8 encoding the heme binding domain of the enzyme, and then all mice were genotyped by PCR and Southern blot analysis • 5-week-old WT mice and KO mice were given daily i.p. injections with 500 pg of $1\alpha,25(OH)_2D_3$ or vehicle for 6 weeks and at the end were housed in metabolic cages to collect 24 h urine samples • To evaluate whether $1\alpha,25(OH)_2D_3$ directly regulated TRPC6 transcription, interestingly via vitamin D-responsive elements (VDREs) in TRPC6 promoter, the 1500 bp upstream of the TRPC6 transcription start site, was cloned upstream of the luciferase reporter gene	• Vehicle-treated AN rats had an increased albumin/creatinine ratio in comparison with vehicle-control rats, which was significantly ameliorated by $1\alpha,25(OH)_2D_3$ • $1\alpha,25(OH)_2D_3$ treatment did not alter the urinary albumin/creatinine ration in control rats and AN rats showed increased TRPC6 mRNA and glomerular TRPC6 protein expression • This treatment also notably reduced adriamycin-induced TRPC6 mRNA and protein expression • In the adriamycin-induced podocyte injury model, TRPC6 expression was significantly increased compared to that in vehicle-treated control cells • Injured podocytes were treated for 24 h with 100 nmol/L $1\alpha,25(OH)_2D_3$, TRPC6 expression was reduced, while a dose-dependent reduction in adriamycin-induced TRPC6 expression was observed when adriamycin-injured podocytes were treated with increasing concentrations of $1\alpha,25(OH)_2D_3$, in contrast to the absence of a similar effect in uninjured control podocytes • Treatment with $1\alpha,25(OH)_2D_3$ markedly reduced the activity of TRPC6 promoter by approximately 25% compared to the vehicle-treated cells • Luciferase activity was not altered by $1\alpha,25(OH)_2D_3$ in cells expressing the empty vector • Lastly, when treated with $1\alpha,25(OH)_2D_3$ the podocyte foot process effacement in 25-hydroxy-1 α-hydroxylase KO rats completely recovered to a means $\pm$ SEM of 2.2% $\pm$ 0.7% and the glomerular structure was not distinguishable from that of WT mice	• These results demonstrated that vitamin D downregulated the enhanced TRPC6 expression in vitro and in vivo podocyte injury, possibly via a direct effect on TRPC6 promoter activity • By co-staining for TRPC6 and podocin, the enhanced TRPC6 expression occurred in podocytes	2013	[184]
In vivo + In vitro (Human studies)					

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The aim of this study was to investigate whether vitamin D plays a protective role in podocyte injury induced by autoantibodies purified from the serum of lupus nephritis (LN) patients through reducing aberrant autophagy	• Autophagic activities of renal tissues of patients with LN were estimated under transmission electronic microscope (TEM) • Immunoglobulin G (IgG) from patients with LN was purified to induce human podocyte injury, and the role of vitamin D in this injury was observed • Podocytes were observed under TEM, autophagic activity was evaluated by Western blot analysis and q-RT-PCR and mRFP-GFP-LC3B adenovirus was infected into human podocytes in vitro • Altogether, 25 patients with LN (class III, $n = 5$; class IV, $n = 5$; class V, $n = 5$; class III + V, $n = 5$; class IV + V, $n = 5$) and healthy patients $n = 7$ were enrolled • Healthy volunteers with renal carcinoma had no clinical features of kidney dysfunction and their glomeruli were pathologically normal, while the age of patients ranged from 9 to 50 years (average 25.3), and all participants were female • To avoid possible circadian variation, blood samples were collected after an overnight fasting between 8 and 9 a.m. • Serum 25(OH)D_3 levels of all patients were measured by electrochemiluminescence immune-assay on an automized analyzer (EL-ECSYS-2010) • Immortalized human podocytes (HPCs) were cultured in RPMI 1640 medium, supplemented with 10% FBS, 100 U/mL penicillin and 100 μg/mL streptomycin at 37 °C with 5% CO_2 • Cell treatments were as follows: (1) purified IgG from only-LN patients (1.5 mg/ mL), (2) 1α,25 $(OH)_2D_3$ (100 nM) and purified IgG from LN ones (1.5 mg/mL) plus 1α,25 $(OH)_2D_3$ (100 nM) for 48 h	• Compared to healthy volunteers, the numbers of autophagosome in a copper mesh area (~7065 mm^2) in the glomerulus of podocyte, mesangial and endothelial cells in LN patients were different from those in a proximal renal tubule in an area of a copper mesh of renal tubular epithelial cells, and the differences were in fact significant • LN patients had an increased autophagic activity level compared to that in the healthy volunteers, mostly in podocytes • Serum 25(OH)D_3 levels were found to be less than 30, and less than 20 ng/mL were defined as vitamin D deficiency • Higher numbers of autophagosomes in patients with vitamin D deficiency were observed compared to patients with vitamin D insufficiency • The correlation between the number of autophagosome in podocytes was evaluated via the Pearson correlation where clinical data showed that 24 h total protein was affiliated with the number of autophagosome in podocytes and the correlation coefficient was 0.505	• Vitamin D altogether reduced aberrant autophagy after IgG treatment, concluding in protection against podocyte autophagy • This vitamin D benefit was related with downregulated expression of autophagy-associated proteins including LC38, Beclin-1, p62 and podocyte marker protein nephrin	2019	[186]
In vitro					

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The present study's design was to examine the ciPTEC–OAT1 for the expression of genes responsible for vitamin D's metabolism and function as well as its activation to the vital form 1α,25$(OH)_2D_3$. Additionally, the effect of a specific mixture of eight anionic uremic toxins, mimicking uremic conditions of CKD and ESRD, on vitamin D activation and function. Moreover, the beneficial impact of vitamin D on oxidative stress, inflammation, cell viability and the epithelial monolayer barrier function of ciPTEC–OAT1 cultured on biofunctionalized polyethersulfone hollow fiber membranes (HFMs)	• In ciPTEC-OAT1, the expression of genes involved in vitamin D metabolism, activation and degradation, as well as 1α hydroxylase, CYP24A1 and VDR was examined via real-time PCR • The specificity of primers as the size of PCR products that corresponded to the expected amplicon length was confirmed via agarose gel electrophoresis • The gene used for normalization was the hypoxanthine phosphoribosyl-transferase 1 (HPRT1), whose expression levels were not severely affected by other parameters • Vitamin D's effect on this expression was examined after 24 h exposure to either 100 nM or 1 μM 1α,25$(OH)_2D_3$ • In order to assess whether ciPTEC–OAT1 could produce 1α,25$(OH)_2D_3$, these cells were exposed to 100 nM of 25$(OH)D_3$ for 24 h in the presence of absence of 1α hydroxylase inhibitor ketoconazole (10 μM) • To assess the impact of 1α,25$(OH)_2D_3$ on ciPTEC–OAT1 viability in normal and uremic conditions, cells were exposed to several 1α,25$(OH)_2D_3$ concentrations in the absence or presence of increasing uremic toxins (UT mix) concentrations • ciPTEC-OAT1 cells' susceptibility to oxidative stress in uremic conditions and the antioxidant effect as well of 1α,25$(OH)_2D_3$ were evaluated through intracellular ROS formation. Cells were exposed for 2 h to 5× UT mix, 1α,25$(OH)_2D_3$ (500 nM or 1 μM) or a combination of UT mix and 1α,25$(OH)_2D_3$ simultaneously • IL-6 levels in the cell culture supernatant were measured to assess the effect of UT mix and vitamin D on the inflammatory response of ciPTEC-OAT1 cells • Lipopolysaccharide (LPS) of 10 μg/mL, that was utilized as positive control, induced a 3-fold increase in IL-6 levels after he 24–h exposure, pro-inflammatory process which was successfully reversed by vitamin D's impact on reducing IL-6 • The stability of ciPTEC-OAT1 cells' monolayer in uremic condition and vitamin D's effect on its tightness was assessed by cultured cells on 1-3,4-dihydroxyphenylalanine (1-DOPA) and collagen IV-coated HFM • The tight monolayer was confirmed by the zonula occludens 1 (ZO-1) tight junction protein and the actin staining	• No significant impact on the VDR's expression was found in contrast to the gene expression of the two enzymes • Almost 50% reduction in the 1α hydroxylase expression was induced after 1α,25$(OH)_2D_3$ treatment (1 μM) and a more that 1000-fold increase in CYP24A1 expression regardless of vitamin D concentration • Significant changes in gene expression were observed in gene expression, in the presence of UT mix at 1× or 2.5× concentration • 1α,25$(OH)_2D_3$ levels confirmed that the cells did produce this active vitamin D form and the conversion was sensitive to ketoconazole inhibition, where the 1× UT mix did not influence this activation • 1α,25$(OH)_2D_3$ did not compromise cell viability, but the UT mix did reduce cell viability after 24 h incubation by approximately 10, 25, and 62% for 2.5×, 5×, and 10× concentration mixtures, respectively • Co-incubation of 1α,25$(OH)_2D_3$ and the UT mix mitigated the decrease in cell viability especially in induced toxicity by higher concentration of the UT mix (5×, 10×) • The UT mix induced a 1.5-fold increase in ROS production, which was then attenuated markedly by adding vitamin D regardless the concentration • Plus, the positive control H_2O_2 (200 μM) enhanced ROS generation • A 1.6-fold reduction was observed for 100 and 500 nM, and a 1.8-fold reduction was also found for 1 μM 1α,25$(OH)_2D_3$. Moreover, a 2.0- and 2.8-fold increase in IL-6 levels was also observed following the exposure to 1× and 2.5× UT mix, correspondingly • LPS and IL-6 were reduced after co–treatment with 1α,25$(OH)_2D_3$ • TNF-α levels were measured below the limit of detection in all cases • The UT mix increased inulin–FITC leakage to 813 ± 136 nmol·min^{-1}·cm^{-2} in comparison to untreated fibers (400 ± 78 nmol·min^{-1}·cm^{-2}) • Additionally, a simultaneous exposure to 1α,25$(OH)_2D_3$ could partially prevent the increase in inulin–FITC leakage which is induced by the UT mix 2.5× (655 ± 85 nmol·min^{-1}·cm^{-2})	• The mixture of the eight anionic uremic toxins, mimicked uremic conditions of CKD and ESRD, and shed a light on vitamin D's activation and function • Moreover, vitamin D had a beneficial impact on oxidative stress, inflammation, cell viability and the epithelial monolayer barrier function of ciPTEC–OAT1 cells was confirmed and demonstrated	2017	[181]

Table 1. *Cont.*

In Vivo (Animal Studies)					
Hypothesis–Intervention	**Study Design**	**Main Findings**	**Specific Benefits—Mechanisms of Action—Conclusions**	**Year of Study ***	**Ref.**
The function of vitamin D on the JAK/STAT signaling, TGF-β production and fibronectin expression in glomerular mesangial cells was examined	• Rat glomerular mesangial cells were cultured in high-glucose medium with or without the VDR siRNAs treatment • TGF-β and fibronectin levels were detected by qRT-PCR, immunoblotting and enzyme-linked immunosorbent assay (ELISA), while phosphorylated Janus kinase 2 gene (JAK2), signal transducer and activator of transcription 1 and 3 (STAT1 and STAT3), and JAK/STAT signaling downstream genes' levels were examined by immunoblotting and qRT-PCR	• Vitamin D treatment could repress tyrosine phosphorylation of JAK2, STAT1 and STAT3 • It also inhibited TGF-β and fibronectin expression, which resulted from the VDR siRNA and STATs inhibitor • The JAK/STAT signaling downstream protein coding genes including the suppressor of cytokine signaling 1 and 3 (SOCS1 and SOCS3) and type IV collagen were repressed by vitamin D • The expression of non-coding RNAs like the miR-181a and miR-181b were also suppressed by vitamin D, while miR-34a and Let-7b's expression was on the contrary upregulated by vitamin D	• Vitamin D treatment inhibited the function of high-glucose levels to fibronectin production via regulating the JAK/STAT pathway • Vitamin D thus was demonstrated as a protective agent to glomerular mesangial cells against high-glucose induced injury through repressing effectively the JAK/STAT signaling, which showed its potential for clinical more frequent DN treatment	2021	[117]

* Data obtained from clinical trials conducted over the past two decades.

5. Conclusions

The present study examined the several benefits of vitamin D including its anti-inflammatory promise against glomerulosclerosis and kidney diseases. Vitamin D has a variety of protective effects on kidney diseases, including glomerulosclerosis, CKD, DKD, kidney disease induced by metals like cadmium (Cd) and lead (Pb), NS and other kidney-related diseases. Vitamin D and its analogues are believed to hold great anti-inflammatory, anti-fibrotic and antioxidant potential toward kidney-associated diseases, since their supplementation is linked to kidney diseases prevention, inflammatory signaling pathways' modulation, immunity system/metabolism's enhancement and other related diseases, like CVDs proliferation reduction.

Toward glomerulosclerosis, vitamin D and its analogues regulate many pathways involved in podocyte damage, inflammation and oxidative stress, and they reduce the expression of TRPC6, inhibit heparinase activity and regulate autophagy and apoptosis in podocytes; thus, renal well-being is preserved. Moreover, considering DKD, vitamin D restores autophagy activity, maintains podocyte gene expression and mitigates EMT while combating oxidative stress and inflammation. Despite some conflicting evidence, vitamin D supplementation holds promise for improving outcomes in CKD and other kidney diseases potentially by reducing healthcare-associated infections. As for kidney disease caused by heavy metals such as Cd and Pb, vitamin D supplementation also successfully alleviates inflammation and oxidative stress; hence, its protective role against environmental nephrotoxicity is projected. Overall, the multifaceted effects of vitamin D highlight its therapeutic potential in renal diseases, paving the way to further research in order to elucidate its mechanisms and to develop more effective future treatment strategies toward kidney-related diseases.

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