Review

Vitamin D deficiency, Chronic kidney disease and Periodontitis

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Review

Vitamin D Deficiency, Chronic Kidney Disease and Periodontitis

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Abstract: Vitamin D has important anti-inflammatory, anti-microbial properties and plays a central role in host immune response. Due to the crucial role of the kidneys in the metabolism of vitamin D, patients with chronic kidney disease (CKD), are prone to vitamin D deficiency. The resultant reduction in the production of calcitriol, the activated form of vitamin D in patients with CKD is responsible for exacerbating the existing renal impairment and periodontal inflammation. Recent evidence suggests a bidirectional, causal relationship between periodontitis and renal functional status. Both conditions have shared pathophysiologic mechanisms including oxidative stress, increases in the systemic inflammatory burden and impaired host response. This review explores the association between vitamin D, CKD and periodontitis. The review summarises the current evidence base for the classical and non-classical vitamin D metabolic pathways, the biological mechanisms linking vitamin D deficiency, CKD and periodontitis, as well as the bidirectional relationship between the two chronic inflammatory conditions. Finally, the paper explores the impact of vitamin D deficiency on CKD, periodontitis, and related co-morbidities.

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1. Introduction

Vitamin D deficiency is associated with various noncommunicable diseases, among which are chronic kidney disease (CKD) and periodontal disease. As well as its fundamental roles in calcium and phosphate homeostasis, vitamin D possesses important antibacterial, anti-inflammatory and host modulatory effects [1], which exert "renoprotective" and "perio-protective" effects.

CKD is a global health concern affecting 5-10% of the world population [2]. According to Kidney Disease Improving Global Outcomes, CKD is diagnosed on the basis of an estimated glomerular filtration rate (eGFR) and values less than 60ml/min/1.73m^2 have been identified as the threshold for CKD [3,4], together with abnormalities of renal structure or function, present for more than 3 months with implications for health [4] There are 5 stages in CKD, the higher the staging the lower the eGFR [4].

Periodontitis is a chronic multifactorial inflammatory disease with an overall prevalence of 11.2% and is the 6th most prevalent disease worldwide [5]. It is associated with dysbiosis of the oral flora, characterised by the progressive destruction of the periodontium, with loss of clinical attachment, loss of alveolar bone, presence of periodontal pockets and gingival bleeding [6]. Periodontitis is a serious public health issue, as it can cause not only local symptoms, but it can also have a negative impact on the individual's general health, contributing to the development, and to the worsening, of chronic non-communicable degenerative diseases, such as chronic kidney disease (CKD) [7].

Periodontal disease and CKD have shared pathophysiological mechanisms, namely increased inflammatory state, impaired immune response, and oxidative stress [8]. Therefore, the occurrence

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of both conditions is likely to result in an amplification of adverse outcomes [9]. A recent large cohort study suggested a bidirectional, causal relationship between periodontal inflammation and renal function [10], such that a 10% increase in periodontal inflamed surface area (PISA) led to 3.0% decrease in eGFR and a 10% decrease in eGFR led to a 25.0% increase in PISA [10].

This review will discuss 1) the vitamin D metabolic pathway and how this is altered in CKD patients 2) the bidirectional relationship between periodontal inflammation and renal impairment; 3) the biological mechanisms linking vitamin D deficiency, CKD, and periodontitis, and 4) the impact of Vitamin D deficiency on systemic inflammation and co-morbidities associated with CKD and periodontitis.

2. Vitamin D Metabolic Pathways

Vitamin D is a fat-soluble hormone that can be obtained from two main sources. Firstly, dietary sources such as fatty fish and mushrooms. It is found in the form of Ergocalciferol (D2) from plant sources or Cholecalciferol (D3) from animal sources [11]. Secondly, through the action of sunlight ultraviolet rays on skin in the form of 7-Dehydrocholesterol which is converted into previtamin Cholecalciferol (D3) [12]. Due to the relatively small proportion of vitamin D from the diet, dermal synthesis accounts for 90% of vitamin D provision [13].

2.1. Classical Pathway

The classical pathway for activation of vitamin D involves two stages of hydroxylation. Firstly, the Vitamin D2 and D3 precursors are transported to the liver by Vitamin D binding protein (DBP) 14. Precursors D2 and D3 are then converted into inactive 25-hydroxvitamin D (25(OH)D) by hydroxylation at the C25 position by 25-hydroxylase, coded by cytochrome P2R1 (CYP2R1)15. 25(OH)D acts as the main circulating and storage form of vitamin D in the body. 25(OH)D is then circulated in blood as 25(OH)-DBP complex and undergoes glomerular filtration and uptake into the kidney proximal tubule cell by the receptor megalin. 25(OH)D-DBP then undergoes 1-α-hydroxylation by the Cytochrome P450 Family 27 Subfamily B Member 1 gene (CYP27B1) to its most activated state, 1,25-dihydroxyvitamin D (1,25(OH)2D) also known as calcitriol 15. This is illustrated in (Figure 1).

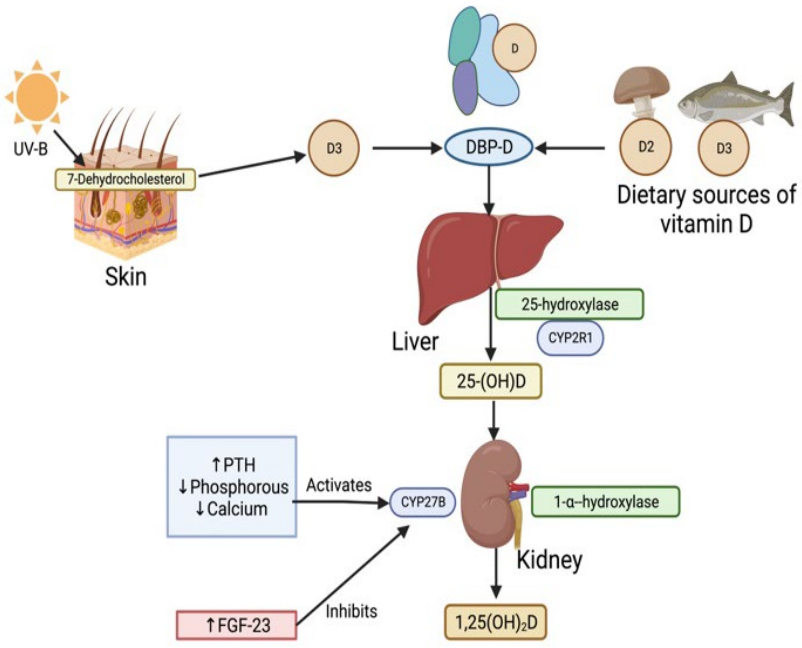

Figure 1. | Vitamin D classical activation pathway in the human body. Sources of Vitamin D such as UV rays and diet, deliver vitamin D in their precursor forms D2 and D3 [11]. These precursors then

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bind to the Vitamin D binding protein (DBP) at site of synthesis and form the DBP-D protein complex. Vitamin D is then carried in DBP-D complex through the blood plasma to the liver. Precursors D2 and D3 are hydroxylated into inactive 25-hydroxvitamin D [25(OH)D] by 25-hydroxylase, coded by cytochrome P2R1 (CYP2R1) gene [14]. 25(OH)D uptake into kidney from blood and activated by 1-α-hydroxylation by CYP27B gene to 1,25-dihydroxyvitamin D (1,25(OH)2D) activated state. Determinants of CYP27B gene activity include increased parathyroid hormone (PTH), decreased phosphorous and calcium activating CYP27B; and increased fibroblast growth factor-23 (FGF-23) inhibiting its activity [15].

Calcitriol has wide ranging physiological and pharmacological effects [1]. Calcitriol is responsible for increasing intestinal calcium and phosphate absorption when serum calcium and phosphate levels are low. It also increases phosphorus resorption from bone and is involved in the production of antimicrobial peptides, epithelial defence mechanisms, host modulatory effects, maintenance of the renin-angiotensin system, inhibition of host tumour cells and suppression of parathyroid hormone (PTH) release1.Calcitriol exerts these affects by binding to intracellular vitamin D receptors (VDRs), which are steroid hormone nuclear receptors and function as transcription factors [16].

In health, the activation of CYP27B gene is regulated by PTH, phosphorus, calcium, and fibroblast growth factor-23 (FGF-23) levels, and subsequently calcitriol levels [17]. Increased PTH levels combined with decreased phosphorus and calcium levels activate CYP27B gene and lead to increased calcitriol levels [13]. Meanwhile, increased FGF-23 levels inhibit CYP27B gene and decrease calcitriol levels [18].

2.2. Non-Classical Pathway

Aside from the classical metabolism of vitamin D and its role in calcium and phosphate homeostasis, a non-classical pathway of calcitriol synthesis appears to be present in various tissues, both including and peripheral to the kidneys. Additionally, 1-α-hydroxylase (which is primarily expressed in the kidneys) may also be expressed in extrarenal cells and tissues [19]. Thus, the extra-renal production of calcitriol primarily functions as an autocrine or paracrine factor at extra-renal sites and thus play a role in non-classical actions of vitamin D [20,21].

Central to the non-classical function is the regulation of the renin-angiotensin- aldosterone system (RAAS). Calcitriol is regarded as a negative endocrine regulator of the renin gene, thereby inhibiting RAAS and preserving renal function. RAAS stimulates the production of renin, which cleaves angiotensin into angiotensin I, which is then processed into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II binds to the type 1 angiotensin II receptor (AT_1R) to produce various delirious effects for renal and cardiovascular tissues, including hypertension [22,23]. This is described in more detail in (**Figure 2**).

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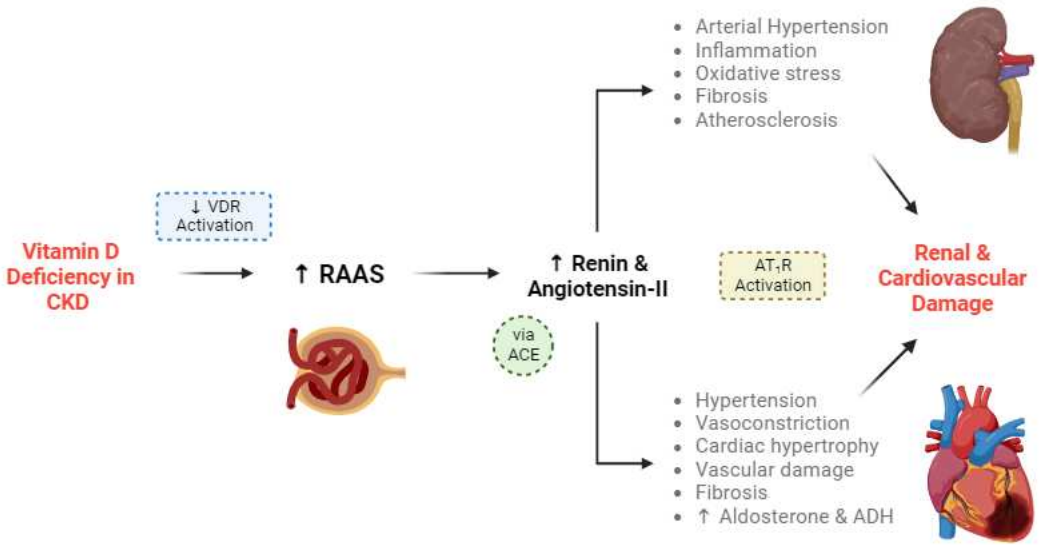

Figure 2. – Vitamin D deficiency leads to the progression of chronic kidney disease (CKD) and cardiovascular disease (CVD). In health, vitamin D binds to vitamin D receptors (VDRs) and increases intracellular calcium in the juxtaglomerular apparatus, suppressing the renin-angiotensin-aldosterone system (RAAS) and the secretion of renin. Renin cleaves angiotensinogen into angiotensin I, which is then converted into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin-II can produce more downstream angiotensin sub-types [23,24]. Angiotensin-II binds to type 1 angiotensin-II receptor (AT_1R) [25], increasing sympathetic tone [26], blood pressure [22,27], inflammation [28], fibrosis [29], aldosterone production [30], anti-diuretic hormone (ADH) production [31] and cardiac hypertrophy [32]. Aside from the vascular damage caused, AT_1R activation increases vascular smooth muscle cell dedifferentiation, leading to atherosclerosis [33]. AT_1R activation also decreases parasympathetic tone [34] and nitric oxide production [35], contributing to hypertension. These effects culminate as renal and cardiovascular damage [22,23,36]. Vitamin D works to protect against this damage by suppressing RAAS, but this su.ppression is reversed during CKD.

There is also evidence that VDR activation by calcitriol may also downregulate other RAS components aside from renin, including the Ang II type one receptor, renin receptor and transforming growth factor-beta [37].This can aid in the reduction of renal blood pressure and fibrogenesis. VDR activation by calcitriol could also have anti-inflammatory effects, via suppression of nuclear factor-kB (NF-kB) activation. It also appears that VDR can form complexes with various transcription factors and engage in crosstalk with a wide range of cellular signals [38], thus illustrating the depth of the relationship between VDR activation and the RAAS components.

The suppression of the NF-kB pathway by calcitriol has extra-renal consequences too. Its suppression of the pathway is twofold: calcitriol suppresses NF-kB nuclear migration and phosphorylation, and it downregulates IkB phosphorylation (a protein involved in NF-kB signalling) by suppressing ROS activity [39]. The NF-kB pathway promotes pro-inflammatory cytokine expression, and thus a reduction in NF-kB activity results in a reduction in inflammatory markers. Thus, the suppression of NF-kB pathway in turn can prevent insulin resistance [40], have neuroprotective effects against ischaemic strokes [39], and protect against other inflammatory disorders. Finally, it is worthy to note that both the inhibitions of the RAAS and NF-kB pathway are responsible for the "reno-protective" effects of vitamin D [41].

3. Serum 25(OH)D Thresholds

Serum 25-(OH)vitamin D level is the ideal indicator of deficiency. However, there is a lack of agreement in the defining serum concentrations associated with deficiency and adequacy [1]. Most

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guidelines currently define vitamin D sufficiency as any value above 50 nmol/L (20ng/ml) [42,43]. However, various studies have indicated that optimal serum levels should be anywhere between 100 to 200 nmol/L (40-80ng/ml) [44,45], and that a concentration below 50nmol/L (20ng/ml) is considered vitamin D deficient [46].

4. Biological Mechanisms Linking Vitamin D Deficiency, CKD and Periodontitis

Vitamin D plays a central role in host immune response and possesses important anti-inflammatory, anti-microbial and host modulatory properties [1]. Due to the wide- ranging physiological and pharmacological role of calcitriol [1], vitamin D deficiency is responsible for the exacerbation of renal impairment and progression of periodontitis. CKD is characterised by altered vitamin metabolism, as well as elevations in PTH and FGF23. Additionally, oxidative stress which promotes inflammation and impaired host response provide the pathophysiological mechanisms for disease progression in both CKD and periodontitis. Finally, vitamin D binding protein (DBP) polymorphisms which are associated with bioavailable 25(OH)D, is linked to severity and progression of CKD and periodontitis.

4.1. Altered vitamin D pathways in CKD

The kidney plays a central role in vitamin D metabolism and regulation of its circulating levels. Vitamin D deficiency has been identified more than 80% of patients with CKD [47]. The trend is that the deficiency worsens with progressive renal impairment, ultimately the onset of hyperparathyroidism. There are several mechanisms responsible for the reduced production of calcitriol: 1) in CKD, there is an overall reduction in renal mass, limiting the 1-α-hydroxylase available for production of calcitriol [38]; 2) reduced eGFR also limits the conversion of 25(OH)D to 1-α-hydroxylase, further reducing the production of the calcitriol [20]; 3) reduced renal megalin receptors in CKD will lead to reduced uptake of 25(OH)D and therefore reduced production of calcitriol; 4) the elevation of FGF23 in CKD, inhibits the CYP27B gene [48] [49], which also reduces 1-α-hydroxylase activity [50,51]; 5) hyperphosphatemia due to impaired renal phosphate excretion in CKD also contributes to reduced 1-α-hydroxylase activity [52]. Thus, the downregulation of 1-α-hydroxylase activity reduces the overall production of calcitriol from the kidneys.

While the inverse relationship between serum 25(OH)D, and renal function has traditionally been explained by alterations in the classical vitamin D metabolism (section 2.1), it is clear that non-classical functions of calcitriol also play a role (section 2.2). A deficiency in vitamin D and thus a reduction in calcitriol promotes RAS activity, and the sequential activation of angiotensin II could raise blood pressure and damage the renal microvasculature. Aside from its direct action on RAS, vitamin D promotes insulin resistance via a wide range of molecular mechanisms involved in glucose homeostasis and immune modulation [53]. Therefore, a deficiency in vitamin D might lead to diabetes, and diabetic nephropathy has been shown to activate RAS [54]. Indeed, intrarenal angiotensin II levels may be up to a hundred times higher in diabetic patients [54],and diabetic nephropathy remains a leading cause of CKD [55]. Locally synthesised angiotensin II is also detrimental to the cardiovascular system, and cardiovascular disease is responsible for much of the mortality of CKD [56]. In these ways, a deficiency in vitamin D can lead to profound consequences for renal, endocrine and cardiovascular function, all of which exacerbate the development and severity of CKD.

4.2. Elevations of PTH and FGF23 levels in CKD

Vitamin D levels are also regulated by PTH and FGF23. Increases in serum levels of FGF23 and PTH are responsible for vitamin D deficiency (**Figure 1**). PTH increases renal calcium reabsorption, excretion of phosphorus, and stimulates calcitriol synthesis [57,58].

FGF23 is a phosphaturic hormone secreted by osteoblasts and osteocytes which is strongly associated with inflammation. The elevation of FGF23, which is to offset phosphorus retention in CKD, inhibits the renal expression of 1-a-hydroxylase [59],and reducing the production of calcitriol.

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Thus, serum FGF23 increase with decline in eGFR and increased phosphate level. This results in downstream reduction of 1,25(OH)D concentrations and onset of secondary hyperparathyroidism, SHPT [59,60] ,due to elevated PTH but low or normal calcium levels. SHPT ultimately progresses to tertiary hyperparathyroidism (THPT), where both PTH and calcium levels are elevated [61]. As a result, vitamin D deficiency (<20 ng/mL) and insufficiency (20–29 ng/mL) are common in individuals with CKD [62].

4.3. Oxidative stress

Oxidative stress promotes inflammation by stimulating the release of pro-inflammatory medicators (NF-kB related cascade) [63]. A recent animal study showed that renal tissue damage is linked to oxidative stress following periodontitis [64]. This concept was reinforced in a recent longitudinal study that pointed to oxidative stress, rather than inflammatory load, as the biological basis for the bidirectional relationship between oxidative stress and periodontitis [65]. Thus, oxidative stress is responsible for progressive renal impairment [66], tissue damage in periodontitis [66]; as well as systemic implications for the development of atherosclerosis [67], and cardiovascular disease [68]**.** Interestingly, oxidative stress is considered a non-traditional risk factor for all-cause mortality [69,70].

4.4. Impaired host response

The mechanisms linking vitamin D status, CKD and periodontitis are related to the biological functions of calcitriol, which possesses various immunomodulatory properties that affect both the innate and adaptive immune system. Calcitriol downregulates the expression of MHC class II (and co-stimulatory molecules) on antigen-presenting dendritic cells (**Figure 3**). It also suppresses pro-cytokine production – whilst stimulating anti-inflammatory cytokine production – and both these mechanisms suppress subsequent T-cell activation and differentiation [71,72].

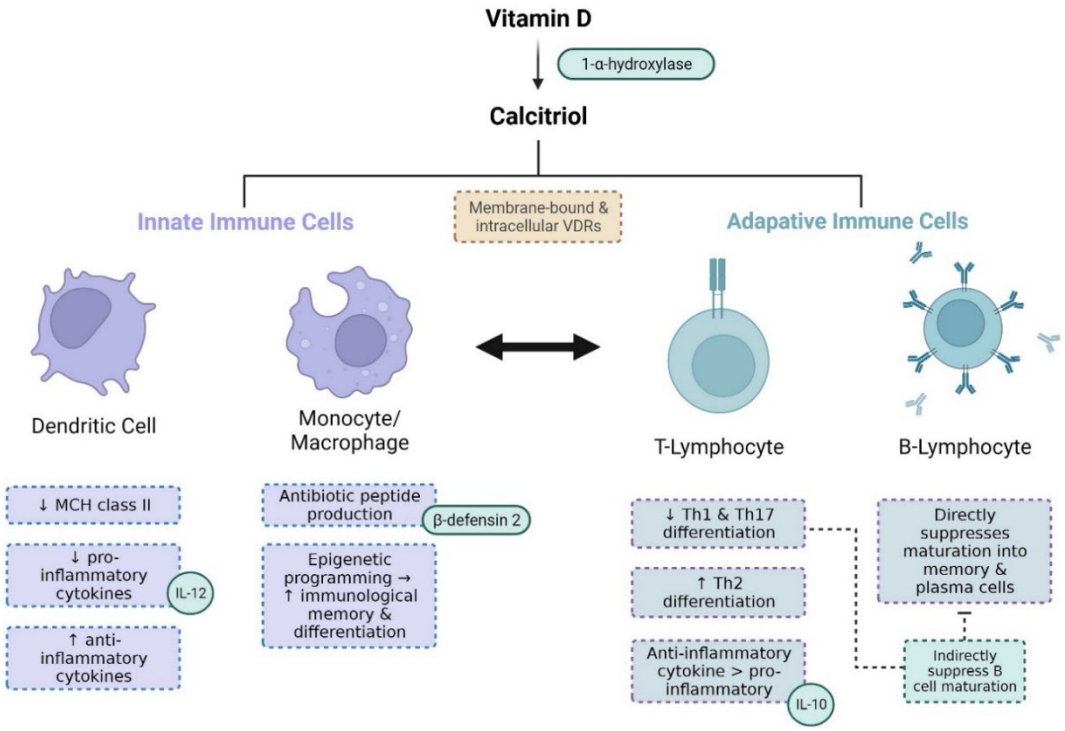

Figure 3. – Vitamin D modulates the functions of various immune cells. 25-hydroxyvitamin D (vitamin D) is metabolised into its active form 1,25-dihydroxyvitamin D (calcitriol) by CYP27BQ (1-***α*** -hydroxylase) [1]. Calcitriol binds to vitamin D receptors (VDRs) both on the cell-surface (membrane-bound VDRs) and in the cytoplasm (intracellular VDRs) of immune cells [73]. Calcitriol downregulates the production of MHC class II in dendritic cells, which is necessary for antigen

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recognition and dendritic cell activation. Activated dendritic cells stimulate T-lymphocyte (T-cell) activity, so the suppression of dendritic cells leads to reduced T-cell function [74,75]. Dendritic cells contribute to innate immunity, whilst T-cells contribute to adaptive immunity, so in this way, innate and adaptive immunity are linked. Calcitriol also suppresses the production of pro-inflammatory cytokines like interleukin-2 (IL-12) in dendritic cells, whilst stimulating the production of anti-inflammatory cytokines. Calcitriol binds to intracellular VDRs in macrophages and their monocyte precursors, forming heterodimers with retinoid-X receptor [33]. This stimulates the production of cell membrane-destroying antibiotic peptides, including β-defensins [70,76]. Calcitriol also epigenetically regulates the immunological memory and differentiation of macrophages and monocytes [77]. Calcitriol reduces the differentiation of T-helper cells into types Th1 and Th17 and their production of pro-inflammatory cytokines [78,79], whilst stimulating differentiation into the Th2-type and favouring their production of anti-inflammatory cytokines like interleukin 10 (IL-10). T-cell-derived pro-inflammatory cytokines are important for B-lymphocyte (B-cell) differentiation, and so the suppression of T-cell pro-inflammatory activity also suppresses B-cell activity. Calcitriol also directly suppresses naïve B-cell differentiation and maturation into memory and plasma cells [80].

Vitamin D exercises various effects on macrophages and their monocyte precursors, which are involved in phagocytosis and cytokine production (**Figure 3**). Upon pathogen recognition and antigen presentation, monocytes and macrophages upregulate VDR expression and metabolise vitamin D into calcitriol. Calcitriol activates intracellular VDRs to promote the production of antibiotic peptides including β-defensins and cathelicidins [76,81,82]. Calcitriol also epigenetically regulates the immunological memory and differentiation of monocytes and macrophages (**Figure 3**) [83].

Calcitriol also suppresses the activity of T and B-lymphocytes. It reduces differentiation of T-helper cells into the Th1-type and pro-inflammatory cytokine generation, in favour of Th2-type differentiation and the production of anti-inflammatory cytokines [78]. It also suppresses Th17-type differentiation and its inflammatory cytokines [79]. Calcitriol also suppresses naïve B-cell differentiation and maturation into memory and plasma cells [80].

Overall, a lack of calcitriol promotes chronic inflammation through the inhibition of the aforementioned mechanistic pathways. Therefore, a vitamin D deficiency enhances the risk of both CKD and periodontitis through impaired host response.

4.5. DBP Genetic Polymorphisms and Bioavailable 25(OH)D

DBP serves to transport vitamin D and its metabolites such as 25(OH)D in the blood to specific target tissues where vitamin D will exert its biological effects. Only the bioavailable 25(OH)D, rather than the total serum 25(OH)D that is associated with serum calcium, and plasma PTH concentrations in patients on haemodialysis [84]. Bioavailable forms of vitamin D include the free fraction (<1% of total 25(OH)D) and the fractions bound to albumin or lipoprotein 10-15% of total 25(OH)D.

DBP genetic polymorphism rs7041 and rs4588 result in different phenotypes of the DBP that have varying binding affinities to 25(OH)D [82]. These polymorphisms have been associated with differences in bioavailable levels of vitamin D and have been implicated in elevated risk of CKD [85] as well as periodontitis [86].

Additionally, DBP polymorphisms potentially explain racial predilection for a particular DBP phenotype [87,88], as well as differential responses to vitamin D supplementation in patients with low serum total 25(OH)D concentrations [89]. Thus, DBP polymorphisms can impact the relationship between with serum total 25(OH)D concentrations and clinical outcomes and the effect of vitamin D supplementation [90].

Therefore, it may be inappropriate to assess the vitamin D status of individual patients by serum total 25(OH)D concentrations alone. Rather, the DBP phenotype (affinity) should be taken into account, due to the likely implications in the clinical prognosis of CKD and periodontitis, as well as responses to vitamin D supplementation.

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5. Impact of CKD on Periodontal Inflammation

Longitudinal studies have demonstrated an association between CKD and progression of periodontal disease [91]. CKD is associated with a two-fold increase in the prevalence of periodontitis [9]. A recent meta-analysis also suggested that individuals with CKD presents with higher mean PPD, and CAL, compared to healthy subjects without CKD. The difference in PPD and CAL between CKD and healthy subjects was 0.25mm and 0.041mm respectively [92].

5.1. CKD- Mineral and Bone Disorder and Impact on Periodontitis

Homeostatic imbalances associated with CKD leads to changes in the regulation of calcium, phosphorous, PTH, and fibroblast growth factor 23 (FGF23) levels, resulting in increased bone demineralisation, often referred to as CKD-mineral and bone disorder (CKD-MBD) [93]. In failing kidneys, there is a significant reduction in the hydroxylation of inactive vitamin D (25-hydroxvitamin D) [25(OH)D] into active calcitriol (1,25(OH)2D) by 1-α-hydroxylase enzyme [1] . Hence, reduced calcitriol levels combined with reduced renal phosphate excretion, leads to systemic hypocalcaemia and hyperphosphataemia, and secondary hyperparathyroidism. Eventually, secondary hyperparathyroidism progresses to tertiary hyperparathyroidism and the development of hyperparathyroid bone disease, that is characterised by high bone turnover, thinned cortical bone, and increased abnormal trabecular bone [93].

CKD-MBD can exacerbate periodontitis by accelerating alveolar bone loss [94]. This concept was reinforced in an animal study where mice with chronic uraemia and hyperparathyroidism showed significantly reduced cortical alveolar bone compared to healthy controls, and that a further decrease in bone levels was seen after a high phosphate diet was given to increase PTH hormone serum levels [95].

6. Impact of Periodontal Inflammation on Renal Function

Large epidemiologic surveys such NHANES III [96] have demonstrated that periodontitis was predictive for the occurrence of CKD [64,73,97]. In particular, periodontitis has been identified as a non-traditional risk factor for eGFR decline [98], and a contributor of oxidative stress [65]. Furthermore, *P. gingivalis* lipopolysaccharide (LPS) exposure resulted in the elevation of FGF23 in the kidneys [99]. FGF23 has been identified as a risk factor for cardiovascular mortality in CKD patients [67,100,101].

Recently, it was shown that presence of periopathogenic bacteria, resulted in an elevation of tumour necrosis factor- alpha (TNFα), that was predictive of the severity of renal impairment reflected by eGFR, and periodontal clinical parameters such as plaque index (PI), gingival index (GI), probing pocket depths (PPD) and clinical attachment loss (CAL) [102]. A meta-analysis suggested that periodontitis significantly increased the risk of all-cause mortality in CKD [103]. However, this result was refuted by a large database study from Taiwan – where it was concluded that periodontitis was not a predictor for long-term mortality or morbidity in patients with advanced CKD [104]. Therefore, future well-designed prospective studies are needed to verify these findings.

Further evidence supporting the impact of periodontal inflammation on renal function comes from improved renal outcomes following non-surgical periodontal treatment. Recent systematic reviews and meta-analyses which have only included a limited number of studies suggested that periodontal treatment improved renal function in CKD patients [105,106]. This is also demonstrated by two case series studies, which showed improved eGFR and creatinine, as well as periodontal clinical outcomes at 3-6 months after non-surgical periodontal therapy [107]. The biological plausibility underlying the favourable outcomes relates to the shared pathophysiologic mechanisms between CKD and periodontitis including oxidative stress, and impaired host response (**section 4**). Therefore, these findings reinforce the impact of periodontal inflammation on progression of renal failure.

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7. Impact of Vitamin D Deficiency on CKD

Vitamin D deficiency is associated with a higher risk of mortality, secondary and tertiary hyperparathyroidism [108]. Due to impaired renal function, the eGFR is reduced, and therefore a decline in the conversion of 25(OH)D to calcitriol, the active form of vitamin D. The latter reduces intestinal calcium absorption and, together with phosphate retention, contributes to the onset of secondary and tertiary hyperparathyroidism.

CKD Patients who are vitamin D deficient have high mortality rates [109] and increased cardiovascular risk [110]. In addition, the elevation of FGF23, which is linked with vitamin D deficiency, is associated with progression of CKD towards end stage renal disease (ESRD), occurrence of cardiovascular (CVS) events and increased mortality rates in patients with CKD [100,101].

Serum total 25(OH)D concentrations was predictive of renal outcomes such as doubling of serum creatinine in ESRD, and associated with disease progression and morality [55,111]. A meta-analysis of prospective studies demonstrated an increase relationship between all- cause mortality in patients with CKD and serum total 25(OH)D concentrations [112]. Conversely, A recent systematic review and meta-analysis concluded that Higher levels of serum 25(OH)D were associated with lower risk of all-cause mortality [113].

Therefore, to ensure that patients with CKD avoid vitamin D deficiency and prevent complications such as secondary and tertiary hyperparathyroidism and other co-morbidities [62,114,115], the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) group have suggested the use of vitamin D supplementation. Therefore, to ensure that patients with CKD avoid vitamin D deficiency and prevent complications such as secondary and tertiary hyperparathyroidism and other co-morbidities [59,114,115], the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) group have suggested the use of vitamin D supplementation.

7.1. Vitamin D Supplementation in CKD Patients

Vitamin D supplementation is associated with reduced risk of all-cause mortality [116] and cardiovascular mortality in patients in CKD, including those with ESRD [78,115]. In particular, therapies with calcitriol and analogues are associated with reduced mortality in CKD patients, particularly those suffering from SHPT [117].

CKD patients are deficient in vitamin D, even in the early stages of disease [118]. Vitamin D plays a vital role not only in mineral homeostasis, but also in systemic health. As such, it is advised that vitamin D supplementation in CKD patients begins as soon as possible, to ensure a pool of vitamin D can be turned into calcitriol.

During the early stages of CKD, where there is still evidence of residual renal function, supplementation can be achieved CKD patients with oral forms of inactive vitamin D_3 or D_2. Vitamin D_3 (cholecalciferol) is the natural form synthesised in the dermis, whilst vitamin D_2 (ergocalciferol) is a synthetic product made using fungi [119]. Another reason is that vitamin D2 is associated with higher catabolic processes and therefore the overall improvement in serum vitamin D levels is not as sustainable as that seen with D_3. Therefore, vitamin D_3 is superior to vitamin D2 in raising total 25(OH)D and thus ideally used for supplementation [120].

It is important to appreciate that renal production of calcitriol becomes suppressed during Stage 3 of CKD, with the significant loss of renal 1-α-hydroxylase. Therefore, calcitriol replacement should begin during Stage 3 to avoid the development of secondary hyperparathyroidism and other associated co-morbidities [44]. This is particularly necessary since vitamin D is rarely present in foods, and sun exposure is commonly insufficient in the general population [45]. Therefore, the generally accepted strategies involve starting vitamin D supplementation (ideally with D_3) immediately after diagnosis and beginning calcitriol therapy only once the CKD has reached Stage 3.

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8. Impact of Vitamin D Deficiency on Periodontitis

The relationship between vitamin D and periodontitis was recently reviewed [1]. In general, an inverse association exists between serum 25(OH)D and periodontal disease inflammation. Most of the studies supporting this association were cross-sectional or case-control studies. One of these was the NHANES III study which showed that low serum vitamin D was associated with periodontal inflammation [121]. Furthermore, it was demonstrated in an RCT that administration of vitamin D (700IU/day) and calcium (500mg/day) significantly reduced tooth loss in older patients during 3 years of observation [122]. A more recent RCT showed that vitamin D supplementation resulted in significant but modest improvement in periodontal outcomes [123].

Interestingly, it was shown in a case-control study that patients with CKD and periodontitis showed lower serum levels of vitamin D compared to control patients without periodontitis [124]. In other words, vitamin D deficiency was more severe in patients with CKD and periodontitis than patients with CKD only [124]. This is plausible, given the shared pathophysiologic mechanisms between CKD and periodontitis, including the elevation of pro-inflammatory cytokines, impaired host response cytokines, and an increase in oxidative stress.

9. Impact of Vitamin D Deficiency on Co-Morbidities Associated to CKD and Periodontitis

Vitamin D has wide-ranging roles in promoting inflammation and reducing the risk of various co-morbidities. Therefore, aside from exacerbating CKD and periodontitis, a deficiency in vitamin D can also negatively and independently affect systemic health. The impact of vitamin D deficiency on systemic health will be specifically discussed here for cardiovascular disease, diabetes mellitus, autoimmune disease. However, as both CKD and periodontitis are directly and independently associated with a myriad of co-morbidities [86,125–127], it can be challenging to establish whether it is the contribution from vitamin D deficiency or the cause and effect of CKD and periodontitis in driving the systemic inflammatory burden.

9.1. Cardiovascular Disease

A severe deficiency in vitamin D is positively correlated with a higher risk of cardiovascular disease (CVD) [128]. This is partly due to the reduction of cardiovascular risk factors by vitamin D, but also due to the direct effects of vitamin D on vascular tissues and cardiomyocytes, which express VDRs that respond to calcitriol [129]. Calcitriol has various positive effects on the vascular wall, namely reduced thrombogenicity and vasoconstriction, the inhibition of atherogenesis and the promotion of endothelial repair [130]. These effects protect against atherosclerosis and hypertensive damage.

In cardiomyocytes, calcitriol regulates intracellular calcium metabolism [131]. Calcitriol binds to VDRs on the cell-surface and in the cytoplasm. Membrane-bound receptors activate adenylate cyclase, which increases cytoplasmic calcium via downstream pathways. Cytosolic receptors complex with retinoid-X receptors, migrate to the nucleus and upregulate synthesis of the calcium-binding protein cholecalcin.

Interestingly, cardiovascular synthesis of calcitriol from its vitamin D precursor can be regulated by PTH, as is known to be the case in renal tissues [132]. Calcitriol is a known inhibitor of PTH action [133]. In this way, a deficiency in serum vitamin D (and therefore calcitriol) can lead to secondary and tertiary hyperparathyroidism, which has its own consequences for cardiovascular health. These include an increase in oxidative stress, RAAS, thrombogenicity and foam cell formation, which can all lead to cardiovascular disease [129]. Given the fact that nutritional rickets, hypocalcaemia and SHPT have all been associated with heart failure [134], this PTH-mediated pathway could explain the negative cardiovascular effects of vitamin D deficiency, aside from VDR activation.

Finally, **CVD and associated mortality are significant concerns for patients with CKD [135]**. Studies have also shown that periodontitis is a major contributor to the development of atherosclerosis by potentiating endothelial dysfunction, inflammation, and the advancement of

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atherosclerotic plaque [126]. As such periodontitis is considered to be independently linked to cardiovascular morbidity in patients with CKD [127].

9.2. Diabetes Mellitus

Diabetes mellitus is largely characterised by insulin resistance, where systemic inflammation plays a key role [136]. **Diabetic nephropathy is responsible for almost 50% of ESRD cases [137]**. Serum 25(OH)D levels of patients with type II diabetic nephropathy has been linked to renal disease progression [138]. In patients with diabetes, periodontitis is also independently associated with the progression of renal disease [139], while individuals suffering with diabetic nephropathy have a higher risk of periodontitis resulting in missing teeth compared to those patients without CKD [140].

Calcitriol protects tissues against inflammatory damage, by suppressing the systemic production of pro-inflammatory cytokines whilst encouraging the release of anti-inflammatory cytokines [141], as well as playing a protective role against insulin resistance by modulating pancreatic β cell activity [142]. Therefore, vitamin D deficiency could lead to insulin resistance and potentiate the development of diabetes mellitus.

Calcitriol also maintains insulin secretion by β-cells, which, when reduced can lead to the development of DM. It modulates calcium-mediated exocytosis, which is necessary for the secretion of insulin vesicles [143]. During the progression of insulin resistance, the β-cells secrete more insulin in response and this hyperactivity results in β cell dysfunction and eventually apoptosis [144]. Calcitriol also controls intracellular reactive oxygen species (ROS) levels, by promoting the expression of cellular antioxidants, maintaining mitochondrial function [145], maintaining redox homeostasis [146] and decreasing nitrogen oxide production [147]. Vitamin D also regulates target cell response to insulin, by promoting insulin receptor expression [148]. Vitamin D deficiency can lead to secondary and tertiary hyperparathyroidism, which are also linked to glucose intolerance and insulin resistance [149]. In these ways, calcitriol protects the tissues against insulin resistance.

Vitamin D also influences DM epigenetically. It suppresses hypermethylation of diabetes-related genes by increasing the expression of demethylases, ensuring that those genes remain inactivated [150,151].

9.3. Autoimmune Disease

Vitamin D deficiency is correlated with the development of various autoimmune diseases [152]. Rheumatoid arthritis (RA) is an autoimmune disease of the joints, characterised by chronic synovial inflammation. Various studies found a negative correlation between serum vitamin D levels and disease severity [152,153], though this could be blamed – at least in part – on the associated lack of mobility and sunlight exposure in RA patients [154]. Even so, a decrease in vitamin D is associated with increased TNF-α and interleukin-6 (IL-6) secretion by inflammatory cells, and suppression of endothelial function [155]. The pharmacological use of calcitriol in RA patients has been shown to inhibit pro-inflammatory cytokines and matrix metallopeptidase production in synoviocytes [156], reducing the recruitment of inflammatory cells to the site and consequent joint destruction. In these ways, vitamin D deficiency could contribute to the onset or progression of rheumatoid arthritis.

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by systemic inflammation and the presence of immune complexes. SLE patients tend to have lower serum vitamin D levels, and there is some evidence of a relationship between vitamin D levels and disease severity [156–158]. The main reason for this association is due to the role of calcitriol, which suppresses T lymphocytes and antinuclear antibody production by B lymphocytes and thus dampens the formation of immune complexes [159]. However, the depth of the relationship between SLE and vitamin D is still poorly understood.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system and is more common in high-latitude regions where sunlight exposure and consequent vitamin D synthesis is limited [160]. It is known that reduced serum vitamin D levels are negatively correlated with disease severity in MS [161]. Calcitriol inhibits the differentiation and proliferation of type 1 T helper (Th1) cells by promoting the production of pro-inflammatory cytokines, such as IL-10 and transforming

growth factor-beta (TGF-β) over anti-inflammatory cytokines (such as IL-12 and TNF-α) in dendritic cells [72,162,163]. The anti-inflammatory effects of calcitriol on dendritic cells in the CNS can suppress the onset or exacerbation of MS, thus increasing the risk of MS without vitamin D and calcitriol.

Vitamin D deficiency can also be implicated with various autoimmune disorders of the endocrine system, including diabetes mellitus, Hashimoto's thyroiditis, and Addison's disease. One possible mechanism is the production of autoantibodies associated with VDR polymorphisms [164–166].

10. Conclusion

A wealth of evidence supports the association between Vitamin D deficiency and chronic inflammatory conditions such as chronic kidney disease and periodontitis. Both conditions share common pathophysiologic mechanisms including insufficient inflammation, impaired host response and oxidative stress. The kidneys play a crucial role in the metabolism of vitamin D. Thus, altered vitamin D metabolic pathways and elevations of PTH and FGF23 are key biochemical observations in CKD. Emerging evidence also support to the bidirectional relationship between renal impairment and periodontal inflammation. Vitamin D plays a significant role in host immune response and possesses important anti-inflammatory, anti-microbial and host modulatory properties. Vitamin D status is also associated with renal outcomes and clinical outcomes related to periodontitis. However, as many of studies were based on large observational studies, further prospective randomised controlled trials are needed to provide deeper insights into this relationship.

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