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Review

The role of vitamin D deficiency and supplementation in onset and progression of diabetic nephropathy: A systematic review

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Abstract

Background: Diabetes mellitus (DM) and chronic kidney disease (CKD) are linked to vitamin D deficiency in the realm of diabetic nephropathy. Vitamin D3 and vitamin D analogs are increasingly assessed to hinder the progression of diabetic nephropathy. Hence, vitamin D supplementation in combating the progression of diabetic nephropathy was focused. Pathogenesis of diabetic nephropathy is associated with oxidative stress and inflammation, regulated by nuclear receptors such as vitamin D receptor (VDR). Thus, inhibiting progression underlies the molecular mechanistic mode of receptor-based changes. Comprehensive analysis for mitigation of progression of diabetic nephropathy upon vitamin D enrichment reveals potentiating benefits for retarding progression. **Methodology:** A systematic review was conducted to establish the role of vitamin D and kidney function in diabetic patients. Calcium, HbA_{1c}, effect on 25 (OH) vitamin D was also evaluated in Rev-Man for data analysis. For the role of calcitriol, cholecalciferol, and paricalcitol in patients six studies were used. Two studies were summarily affirmative of the protective roles established by vitamin D in combating the progression of diabetic nephropathy. Results: Effect on kidney function in terms of UACR, AER, and UPCR showed a significant change in UACR of the uncontrolled study (mean: 95% CI), after 2 months, the study with cholecalciferol moved from 12.7 (7.3–22.3) mg/mmol to 9.9 (5.5–17.9) mg/mmol, p=0.0141. Forest plot visualization revealed insignificant heterogeneity remained with Chi^2=0.67, df=1, p=0.41. The effect of kidney function in terms of eGFR did not show any measurable improvement in the eGFR. The test of heterogeneity was insignificant (Chi^2=0.67, df=1, p=0.41), also there was no heterogeneity between these studies i.e., I2=0%. Effect on serum 25(OH) vitamin D indicated a significant change in the baseline serum 25(OH) vitamin D levels after 6 months treatment with cholecalciferol, 17.56 (95% CI, 12.23, 23.83) ng/ml versus 10.52 (95% CI 7.75, 11.42) ng/ml, p=0.0024. The effect on serum calcium also depicts no notable difference. Effect on HbA_{1c} in the uncontrolled study signifies the effects of cholecalciferol on HbA_{1c}, and the results were not significant. The calcitriol-randomized controlled trial observed an insignificant change in HbA_{1c}. However, it should be noted that calcitriol's effect on HbA_{1c} was reported as significant statistically in the uncontrolled study. **Conclusion:** Vitamin D positively indicates the positive clinical outcomes in hindering the progression of diabetic nephropathy. Vitamin D analogs and the evidence-based authentic proof of their protective effects are scarcely reported. Further randomized controlled trials are needed to prove vitamin D/vitamin D analogs supplementation against vitamin deficiency and arresting the progression of diabetic nephropathy. Vitamin deficiency accounts for progressive diabetic nephropathy and vitamin D supplementation helps to cope the progression.

Keywords: diabetic nephropathy, vitamin D deficiency, vitamin D3, vitamin D analogs, prevention of progression.

Introduction

Physiology and vitamin D metabolism

Vitamin D required for the human body is obtained from synthesis on the skin upon exposure to sunlight and dietary supplementation. Solar ultraviolet B radiation results in the synthesis of cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) in the wavelength range between 290 nm and 315 nm. Provitamin D3 is converted to vitamin D3 by UV-B irradiation that aids in the formation of vitamin D3 from provitamin D3 (Holick, 2004). 25[OH] D (25-hydroxyvitamin) is synthesized in skin due to exposure to sunlight (Holick, 2004). Vitamin D3 is formed from the isomerization of provitamin D3 upon UV-B irradiation. Vitamin D receptors in most of the cells in the human body can synthesize 1, 25-dihydroxy vitamin D, which is necessitated for normal functioning of metabolic pathways to curb the majority of metabolic disorders. More exposure to sunlight combats vitamin D deficiency and not all vitamin D can be supplemented through dietary incorporation. Hence, vitamin D sufficiency can be attained holistically through optimal exposure to sunlight, food supplementation of vitamin D and fortified food products to abate vitamin D deficiency. CYP2R1 (cytochrome P 2R1) acts as a key enzyme in the 25-hydroxylation of vitamin D and is attributed to diabetes mellitus due to mutations causing polymorphism. Hence for active metabolism of vitamin D, two hydroxylation steps take place in adipose tissues and liver. So the storage perspectives require food products of plant and animal origin like fish and mushrooms, respectively. However, dietary supplementation alone cannot offer vitamin D sufficiency. To optimize the vitamin D levels, sunlight exposure renders maximal benefits, as the whole process of energy absorption and further metabolism starts with the skin and storage in the liver as 25[OH]D (Holick, 2005). Vitamin D receptor (VDR) regulates gene expression as VDR along with other transcription factor retinoid X receptor result in transcription when bound to cofactors (Silver, 2013). Even other tissues present in the liver have CYP27B1 showing enzymatic activity. It has also been reported that CYP27B1 is also involved in gene expression (Dusso, 2011). CYP27B1 activation can be affected by hypophosphatemia, calcitonin, hypocalcemia, and parathyroid hormone (PTH) that can increase 1,25-(OH) 2D levels. At the same instant, (FGT-23) fibroblast growth factor-23 inhibits the CYP27B1and 1,25-(OH) 2D levels (Silver, 2013). 25(OH)D has a very weak binding capacity for VDR, thereby affecting the paracrine or autocrine system (Dusso, 2011). Vitamin D metabolism is pictorially illustrated in Figure 1. Thus, the physiology and metabolism of vitamin D are discussed based on molecular mechanisms and regulatory perspectives. Vitamin D deficiency results in a plethora of health issues like renal function, diabetes, albuminuria, and hypoalbuminemia and poses as the risk factors contributing to the basis of diabetic nephropathy (Chonchol, 2007).

Diabetes (type 1 and type 2) and vitamin D

Auto-antibodies against pancreas beta' cells and macrophage infiltration depict the complex auto-immune mechanism of DM-Type1. Vitamin D deficiency has been linked to immunomodulation, not only in DM-Type1, but also in diseases like systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (Yang, 2013).

Vitamin D alters the Th1/Th2 cytokine profile, and human 'T' and 'B' lymphocytes produce vitamin D receptors (VDR). Further, vitamin D correlates to immune system regulation through inhibition of lymphocyte production. NOD-mice with vitamin D deficiency displayed heightened severity and incidence of DM-Type1, (Zella, 2013). 1,25$(OH)_2$D reduced DM-Type1 manifestation in such mice by lowering the effect of 'T' cell numbers. 1,25$(OH)_2$D offsets 'Fas'(cytokine-induced) that affect the death of human islet cells. A correlation exists between sunlight exposure and DM-Type1 incidence showed that daytime exposure being shorter in Northern Europe revealed a low risk of DM-Type1 new-onset in infants supplemented with vitamin D (Ataie-Jafari, 2013). Hence, vitamin D deficiency can also be correlated with molecular signaling amelioration and autoimmune mechanisms. Autoimmune

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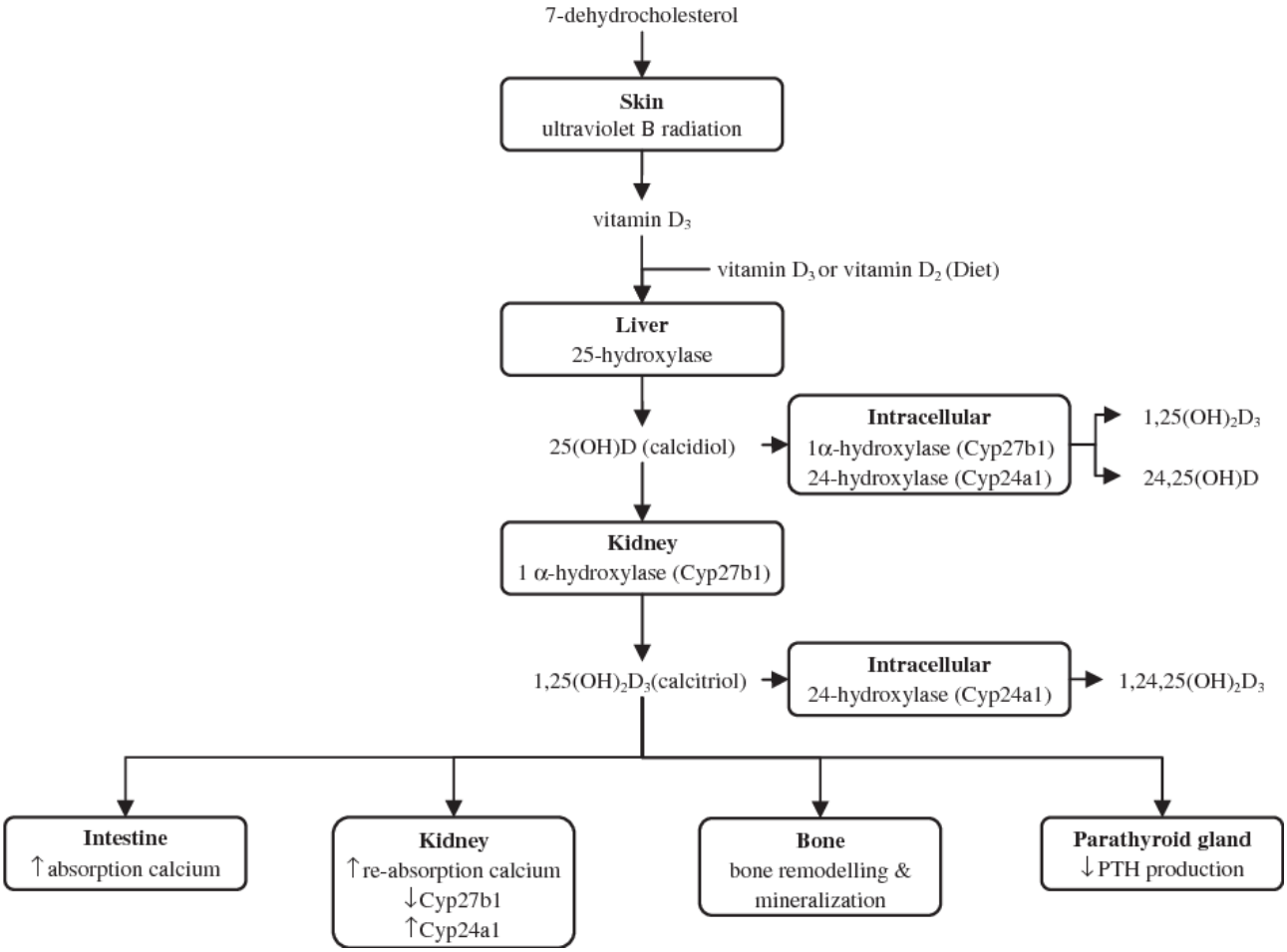

Figure 1: Vitamin D metabolism pathway in humans (Gorter et al., 2014).

diseases like DM-Type 1 and insulin-dependent DM-type 2 have alleviated symptoms due to vitamin D deficiency. Ample research has proved that children with rickets reported an RR of 3.0 (1.0–9.0) for DM-Type1. Children on 2000 IU Vitamin D/day reported an RR of 0.22 (0.05–0.89). Vitamin D's effect on conserving beta-cell functions upon detection of DM-Type1 reveals significant structural and functional conformation variations. Vitamin D effect on conserving beta-cell functions in DM-Type1 also revealed that the new-onset DM-Type1 patients (n=38) were randomly administered oral therapy (daily) comprising 2000 IU $C_{27}H_{44}O$, or placebo, the collective incidence of disease progression to untraceable (≤0.1 ng/ml) fasting and stimulated C-peptide was reduced in the $C_{27}H_{44}O$ group. Whereas, $C_{27}H_{44}O_2$ (0.25 µg/d) helped beta-cell function in children with freshly diagnosed new-onset DM-Type1, (Cheng, 2013). Onset DM-Type1 management with 25(OH)D or $1,25(OH)_2D$ needs further study to establish concrete proof.

Pancreatic beta-cell VDR is critical in DM-Type2 progress. Vitamin D deficiency is linked to insulin sensitivity (I-Se) and insulin resistance (IR), hence dysfunction of pancreatic beta-cells. I-Se is hampered by vitamin D deficiency. This was shown in a diabetic animal model. Beta-cell survival improves upon vitamin D administration. It reinstates glucose-based I-Se. The modulation of cytokines' generation helps the process, thus impacting its effects. Calcium levels and flux from the beta-cells influence I-Se. A systolic protein that binds calcium, is present in pancreatic beta-cells, this is called calbindin. Vitamin D regulates its function and modulates depolarization of stimulated I-Se by intracellular calcium regulation. PTH levels are regulated by vitamin D and influence insulin absorption and discharge within the pancreas. Insulin receptors expression is linked with vitamin D, thus indirectly impacting IS. However, vitamin D stimulates IS by promoting PPAR delta, a nuclear receptor-fatty acid sensor that

influences skeletal muscle and adipose tissue fatty acids (Cheng, 2013).

Peripheral IR is affected by intracellular calcium. This is due to the diminished signal transduction pathway that reduces glucose movement. Diabetes is linked with increased PTH, whereas low vitamin D encourages secondary hyperparathyroidism. Serial-metabolic characterization in women (n=494) showed hypo-vitamin D where high PTH was self-regulating beta-cells' dysfunction predictor, glycemia, and IR. IR is affected by vitamin D through RAAS. In the mice model, vitamin D impacted renin gene expression negatively. Also, lower 1,25 $(OH)_2$ D levels triggered renal renin, activating the RAAS within the model. Angiotensin-II stopped insulin activity in skeletal and vascular muscle tissues, hence compromising glucose uptake. In DM-Type2 patients, systematic inflammation is critical in IR and cardiovascular instances. Affected pancreatic beta-cells (apoptosis, cytokine-induced) can cause high inflammation worsening glycemic status. Vitamin D is instrumental in reducing this inflammatory condition and guarding beta-cell apoptosis through regulating cytokines' production and activity. This was seen in animal models (Riachy, 2009).

A holistic review by Parekh, (2010) indicates DM-Type2 patients display a reduction in inflammatory cytokines (IL-1, IL-6, tumor necrosis factor-alpha) when monocyte-isolates were incubated with 1,25 $(OH)_2$D. Non-diabetic patients (9841) with base-level 25(OH) D were correlated inversely with risks like hyperglycemia and insulin resistance (IR) in a 10-year follow-up. Similarly, it was also observed that lower 25(OH) D levels posed a high risk for DM-Type2. Though, a Mendelian randomization study observed that 25(OH) D at low levels was genetically non-associated with DM-Type2 risks. It can be deduced that 25(OH)D levels and DM-Type2 are not causally related. Sixteen studies' meta-analysis reported 25(OH)D odds ratio for DM-Type2 was 1.5 (1.33–1.7) for bottom versus top quarter. The effects of vitamin D supplementation on glycemic homeostasis were summarized on evidence-based research, (Parekh, 2010).

Since vitamin D improves IR and helps I-Se, clinical trials report IR-homeostasis assessment, fasting-plasma glucose levels, A_{1c}-hemoglobin levels. Supplementation of vitamin D and calcium on glucose homeostasis in diabetics and non-diabetics indicated that vitamin D with sufficient calcium may be necessary for glycemia status improvement. Meta-analysis indicated that the administration of vitamin D to address glycemic issues and IR in diabetics is not advised, even when vitamin D doses were not optimal. All clinical trials had at least 2000 IU/d vitamin D doses. Further, glycemia and IR-based and of short duration (1 year or less) for longer follow-up studies were focused. The defensive effect of vitamin D versus DM-Type2 was studied amongst 2447 people, 77 years mean age. Subjects were administered 800 IU/day Vit.D3 with 1000 mg calcium, or placebo for 2 years to over 5 years. It was observed that while this combination was unable to prevent diabetes development, it did not allow an increase in medication in diabetics either. In 33951 postmenopausal women for 7 years and confronted that daily 400 IU Vit.D3 with 1000 mg elemental calcium did not lower the risk of diabetes in that period (Boer, 2008). 'Women's Health Initiative vitamin D/calcium randomized', placebo-monitored trial elucidated the fact that vitamin D at 400–800 IU/day with/without calcium does not avert new-onset DM-Type2. Clinical trials with sufficient sample size over significant time frames are necessary to confirm no effect on glycemic control or DM-Type2 prevention with optimal vitamin D administration. Hence, future research upon vitamin D against CVD and mortality poses as study termination points. Thus, vitamin D possesses a prominent impact upon delinking the molecular complications involved in diabetes type 1 and type 2.

Chronic kidney disease and vitamin D

$C_{27}H_{44}O_3$ reduced residual albuminuria in diabetic nephropathy patients. Random administration of (1:1:1) placebo, 1 µg/d $C_{27}H_{44}O_3$, 2 µg/d $C_{27}H_{44}O_3$ for 6 months showed potential outcomes. Mean UACR evaluation showed that 2 µg/d $C_{27}H_{44}O_3$ continued lowering in this measure, i.e., –18% to –28% (p=0.014 vs. placebo). Yet, limited trials used VDRA on diabetics, while almost

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none had significant patient numbers or follow-up timeframes. To understand, Vit.D3 and VDRA's effects on CVD, diabetes, and all-cause mortality, trials with larger numbers and longer durations are necessary. Studies have observed that 1,25 $(OH)_2D$ levels drop in CKD patients, (Kendrick, 2009); several philosophies on Vitamin D deficiencies in CKD exist. Megalin in endocytic receptors of proximal tubule cells aides DBP reabsorption from the glomerular ultrafiltrate. Catalysis of 25(OH)D leads to intracellular conversion into the active form. When kidney functions are compromised, megalin also falls, this is due to low molecular weight proteinuria. CYP27B1 activation is linked with reducing kidney function. Lowering FGF-23 directly affects proximal tubules' co-transporters NaPi (IIa and IIc) thus compromising phosphorus absorption. CKD patients witness a drop in 1,25$(OH)_2D$ and 25(OH)D level mechanisms could be accounted to several mechanisms. A complex of 25(OH)D with DBP leaks along with proteinuria. Megalin dip impacts 25(OH)D uptake. A 35% vitamin D deficiency was seen in 4000 CKD patients in the US. Vitamin D deficiencies affect clinical outcomes in CKD patients, (Mehrotra, 2009). 25(OH) D reduction is linked with CVD and all-cause mortality. ESRD risk is enhanced in low vitamin D patients. Those taking dialysis low vitamin D is linked with CVD, though evidence of vitamin D reinstitution exists in CKD and dialysis patients, VRDA is used in kidney failure patients having low 1,25$(OH)_2D$. Future studies are necessary to understand vitamin D effectively in kidney function maintenance (Mehrotra, 2009).

$C_{27}H_{44}O_3$ decreased BNP in CKD patients and $C_{27}H_{44}O_3$ did not help in improving the function of the left ventricular mass. Contradictory evidence of VDRA's role in CVD was revealed, like 1.25$(OH)_2D$ restricts RAAS activity and mortality was lower among VRDA users versus non-users. The DOPP study noted that vitamin D intake did not affect dialysis patients clinically. Pharmacological $C_{27}H_{44}O_2$ doses were linked with gradual aortic stiffness in hemodialysis patients, (Charitaki, 2014). KDIGO guidelines indicate that 25(OH) D levels must be monitored in stage 3-5CKD patients, accordingly, Vitamin D supplementation may be considered. Reduced 25(OH)D levels are linked with CVD in CKD, all-cause mortality, and dialysis patients, yet another report indicated those low on 25(OH)D levels and risen FGF-23 levels had poor outcomes, yet there is not enough proof of vitamin D administration helping CKD and dialysis patients.$C_{27}H_{44}O$ seems to lower albuminuria and helps PTH in CKD patients, However, study reports are lacking for CVD or all-causing mortality. $C_{27}H_{44}O$ reduces BNP and left ventricular hypertrophy in dialysis patients. With the increase in VDRAs, calcium, and phosphorus levels increase and hence continuous monitoring of these parameters is recommended. Vitamin D like $C_{27}H_{44}O$ has no restorative effect on phosphorus or calcium levels, (Armas, 2012). In CKD patients, Vit.D3 use in hemodialysis cases does not have evidence in hard endpoints.

Literature review

Role of vitamin D in inflammatory responses and immune regulation

The possible role of vitamin D, as an active metabolite 1,25$(OH)_2D$, in moderating immune response has been compared to the treatment of leprosy and tuberculosis, both caused by *Mycobacterium* (Kim, 2013). Nevertheless, the underlying mechanisms were clarified only recently through numerous critical findings including three prominent mechanisms:

Activated human inflammatory cells display VDR expression along with CYP27B1 production at the inflamed area revealing the production of 1,25$(OH)_2D$ and response to the hormonally active metabolite.

1,25$(OH)_2D$ participation in multiple immunological pathways of the innate and adaptive immune system.

1,25$(OH)_2D$ influences the different types of cells of the immune system. Under the innate immune response, toll-like receptors are activated within monocytes/macrophages and in numerous cells like epithelial, intestinal, corneal, and lung cells, and placenta trophoblasts, keratinocytes. All these represent a barrier as the first line of defense. In innate immunity, the effect of vitamin D is through its stimulatory action

during the synthesis of cathelicidin antimicrobial peptide (CAMP) and defensin β2 upon the activation of toll-like receptors. Host defense antimicrobial peptides have a low-molecular-weight. Bio-activity against viruses, fungi, and bacteria in the immune cells illustrates the antimicrobial peptides' broad-spectrum activity. The binding of $1,25(OH)_2D$-VDR-retinoid-X-receptor (RXR) complex to the vitamin D – response elements (VDRE) in the gene promoter induces CAMP, a transcriptional target of vitamin D, (Uchida, 2016). Vitamin D modulates the innate immune system by raising phagocyte cells' autophagy, chemotaxis, and phagolysosomal fusion. Consequently, interleukins regulate vitamin D's activity on macrophages. Vitamin D invigorates antimicrobial activity on macrophages upon IL-15 stimulus. IL-10 stimulus does not account for vitamin D activity on phagocytic macrophages directly, despite the high-intensity phagocytic activity (Krutzik, 2008).

On the adaptive immune system, vitamin D shows inhibitory action, producing cytokines and immunoglobulin by 'T' and 'B' lymphocytes, respectively, to fight antigens by dendritic cells (DC) and macrophages. Research studies throw light upon the immunomodulatory effect of calcitriol of T-helper (Th) cells, especially with $1,25(OH)_2D$. Thus, inhibiting the production of pro-inflammatory cytokines as interferon γ (IFN-γ), IL-2 and 6, and tumor necrosis factor- α (TNF- α) (Buondonno, 2007). With the lack of IFN-γ, the additional antigen is not available for 'T' lymphocytes for further proliferation. Lower IL-2 remains a barrier to 'T' lymphocyte production and differentiation. Moreover, it was shown that CD4+/CD25+ regulatory T-cells (Treg) activity increased with calcitriol accumulation and structural conformation mediated by IL-10 expression and high FoxP3 levels (Hau, 2007). Higher levels of IL-10 along with other anti-inflammatory cytokines triggered by calcitriol, act as barriers to differentiation of Th1, leading to shifting cell phenotype to Th2 (White, 2008). Previously vitamin D effects on Th1 cells were understood as a part of the pathogenesis of numerous autoimmune diseases. However, recently these were attributed, at least to some extent, to the inhibitory action of $1,25(OH)_2D$, which leads to the production of IL-17, on account of Th17 cell formation (Seuter, 2009). The cumulative impact on Th cells can be addressed to the suppressing effect of vitamin D on the antigen-presenting cells (APC) in the innate immune system, including the potent dendritic cells (DCs). A 'tolerogenic state', induced by $1,25(OH)_2D$ via auto-reactive 'T' cell apoptosis, Treg cells differentiation, lowered inflammatory cytokines, and high levels of anti-inflammatory cytokines. Through chromatin immunoprecipitation assay it was revealed that VDR binds onto a VDRE via the IL-10 promoter's proximal area. The IL-10 promoter present in the 'B' cells or the antibody-producing cells of the immune system are the sites of action by $1,25(OH)_2D$, thereby acting as a barrier to the proliferation of activated 'B' cells thus stimulating apoptosis. Vitamin D displays its inhibitory action on the secretion of IgG and IgM like activated 'B' cells maturing into memory and plasma cells, (Dąbrowska-Leonik, 2018). Numerous trials have observed an inverse relationship between $1,25(OH)_2D$ levels and serum IgE, while some others illustrate a positive relationship (Susanto, 2017).

Because of vitamin D's ability to suppress the adaptive immune system, its role during deficiency and effects of supplementation in autoimmune and inflammatory diseases gets significant outcomes. The positive attributes were proved using animal models for experimental allergic encephalitis, inflammatory arthritis, and autoimmune diabetes. Disease conditions comprising enterocolitis, calcitriol reduced disease progression as well as initiation was taken into account. Besides, adequate human trials for elucidating the authentic role of vitamin D in the regulation of the adaptive immune system combating autoimmune diseases. Though, some trials do confirm positive effects of vitamin D on the progression of various inflammatory diseases, 'T' cell subsets and inflammatory markers. Affirmative assessment in this regard requires further advanced research protocols for a positive indication (Zhou, 2018: Buondonno, 2007).

Insulin sensitivity and maintaining pancreatic β-cell function by vitamin D

Vitamin D is correlated as a key component in the management of immune homeostasis.

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Molecular mechanisms arbitrated by vitamin D in the inflammation episode comprise pancreatic β-cell dysfunction and the triggering of insulin resistance (IR). Copious research indicates that vitamin D regulates pancreatic β-cells, insulin secretion and Ca^{2}+ levels. Through VDR, vitamin D executes its role as an immunomodulator, thus preventing pancreatic β-cell dysfunction and death. The VDR expressed with CYP27B1 in APCs, islet pancreatic β-cells, activates 'T' cells (Rak, 2014). Validation of vitamin D deficiency on non-obese diabetic mice with $1,25(OH)_2D$ or analogs demonstrate an aggressive form of DM-Type1. A bioactive form of vitamin D shields either against insulitis development within the pancreas or compromises severity through a dual action on pancreatic β-cells and immune cells (Wolden-Kirk, 2011).

In vitro and *in vivo* studies show that, $1,25(OH)_2D$ decreases in pancreatic islets indicating the pro-inflammatory cytokines like IL-6 involved in the pathogenesis of DM-Type1, which makes β-cells less chemically attractive thus less prone to inflammation (Ysmail-Dahlouk, 2016). 'T' cell proliferation and infiltration decreases and allows a delay the in autoimmune process and increases the regulatory cells. Further, $1,25(OH)_2D$ reduces MHC-class-I, dropping the sensitivity of islet β-cells to the cytotoxicity of 'T' lymphocytes, (Wolden-Kirk, 2011; Ysmail-Dahlouk, 2016).

From the immune system standpoint, the $1,25(OH)_2D$ curtails maturation and differentiation of DCs, encouraging their apoptosis, restricting their conversion into APCs. These are initial steps in triggering an immune response. In pancreatic islets, $1,25(OH)_2D$ causes inflammatory responses that are skewed towards benign forms by way of restoring suppressor cells, reducing cytokine formation by Th1 cells that affect β-cell death. It also restricts IL-6 formation, a Th17 cell stimulator involved in the pathogenesis of numerous autoimmune diseases with DM-Type1, (Eerligh, 2004).

$1,25(OH)_2D$ causes an anti-apoptotic effect on apoptosis of pancreatic β-cells that is cytokine-induced. It makes and regulates high levels of protein in the A20 (an anti-inflammatory protein that restricts NF-κB-signaling), which leads to a fall in nitric monoxide levels. Nitric monoxide causes dysfunction of β-cells and death through the expression of Fas, a trans-membrane cell receptor belonging to the TNF receptor superfamily. Cell receptors get activated due to inflammatory cytokines by mononuclear cells infiltrating islet cells. A reduced nitric monoxide level allows for a halt of all the above mechanisms, thus leading to a cytoprotective effect on islet β-cells. The countering effect of $1,25(OH)_2D$ on the cytokine-led expression of Fas in human pancreatic islets has been established, both at protein and mRNA levels, thus modulating cell death and preventing β-cells apoptosis (Riachy, 2006).

Vitamin D deficiency damages insulin secretion due to glucose. Several studies are supporting this observation in rat pancreatic β-cells. This mechanism was restored upon vitamin D supplementation. The bioactive form of vitamin D causes insulin secretion by direct binding between VDRE and the VDR-RXR complex (Maestro, 2003). The above-said phenomenon was experimentally proved using mice lacking VDR function, thus modulating dysfunctional insulin secretion upon glucose stimulation (Zeitz, 2003).

VDRE excites transcription of a variety of genes that enable the organization of the cytoskeleton, differentiation, and cell growth and survival of pancreatic β-cells. Similarly, transcription of the insulin gene, upon the non-genomic action of vitamin D regulating intracellular Ca^{2+} leads to depolarized insulin exocytose. Calcitriol takes effect through a membrane, whereby the VDR-led rise in inositol trisphosphate and phospholipase-C promote the Ca^{2+} release due to diacylglycerol-mediated PKC activation from the endoplasmic reticulum. Phosphorylation by activated PKC results in phosphorylating the ATP-dependent K+ and 'L' voltage-led Ca^{2+} channels. Hence, depolarization of the cytoplasmic membrane and opening of Ca^{2+}, 'L', and 'T' type channels raises intracellular Ca^{2+} levels and eventually insulin secretion, (McCarty, 2006). Calcitriol that activates the PKA pathways also regulates the 'L' type voltage-dependent Ca^{2+} channels. An increase in intracellular Ca^{2+} by vitamin D could enhance CAMP-responsive-element-binding-protein (CREB). This CREB is understood

to be responsible for efficient transcription of the insulin gene and insulin exocytose glucose sensing and the survival of pancreatic β-cells (Dalle, 2011). Insulin secretion is alternatively impacted by heightened expression of proteins giving low resting Ca^{2+} levels, like calcium-binding proteins (calbindin-D28k and D9k, and parvalbumin), Na+/Ca^{2+}- exchanger, and plasma membrane Ca^{2+}-ATPase (Christakos, 2007). Preclinical studies show that vitamin D recovers β-cells' function by lowering excess activity of the RAAS (Renin-Angiotensin-Aldosterone System) (Leung, 2006). An optimal level of Ca^{2+} within cells is necessary for the correct function of pancreatic β-cells as well as for insulin-responsive tissues like adipose tissue, liver, and skeletal muscles. Impairment in the regulation of intra and extracellular Ca^{2+} levels on account of incorrect insulin transduction in these tissues evokes dephosphorylation along with the reduced activity of glucose transporter-4 (GLUT-4) resulting in peripheral insulin resistance. Vitamin D deficiency leads to the onset of IR, while adequate vitamin D concentrations show improvement in IR in DM-Type2, (Greco, 2019). The active metabolite of vitamin D triggers the expression of insulin receptor that strengthens IS, (Corbetta, 2018).

Another mechanism that demonstrates the beneficial effect of calcitriol on insulin sensitivity is PPAR-δ, PPAR-δ in an activated state is a transcription factor that reduces fatty acids led IR in adipose tissue and skeletal muscles. Elevation of parathyroid hormone (PTH) in response to vitamin D deficiency can raise intracellular Ca2+ levels within the insulin-sensitive tissues and aggravate IR by lowering GLUT1 and 4 in adipose tissue, liver, and muscle cell membranes, thus lowering uptake of glucose. The adipose tissue is a vital metabolic and endocrine organ that impacts glucose homeostasis and energy reserves by maintaining a balance. Adipose tissues are a major storehouse of vitamin D in life forms having the ability to seize fat-soluble pro-hormone, significantly reducing its concentration in blood circulation. It was found that vitamin D helps in gene expression that promotes adipogenesis that causes re-modeling of adipose tissue. Early stages of adiposeness see VDR expression that catalyzes calcitriol's inhibitory effects on the adipocyte differentiation through mitogen-activated protein kinase (MAPK) and Wnt/β-catenin pathways, (Lee, 2012). $1,25(OH)_2D$ has a suppressive action on CAAT/enhancer-binding protein-α (C/EBP-α) and PPAR-γ. Alterations in various genes involved in lipogenesis, lipolysis, insulin sensitivity (by GLUT-4 presentation) and secretion of adipokines, and the transfer of fatty acids through the membrane (White, 2009). Elevated release of pro-inflammatory cytokines (IL-6, 8, MCP1, TNF-α, and resistin) by macrophages resident in the adipose and 'T' lymphocytes are a characteristic feature of enlarged hypertrophic adipose tissue. The secretion of adiponectin gets reduced and results in the secretion of sensitive insulin (Migliaccio, 2019). Hence, obese cases show impaired adipokines secretion and inflammation of the system. These results co-exist with IR and favor the development of DM-Type2. Thus, obesity poses a prominent precursor of diabetes and results in devastating consequences.

Vitamin D protects from IR triggered by inflammation through modulating immune cells' function and the secretion of adipokines like adiponectin and leptin. It has been reported that high vitamin D levels depict low inflammatory markers like TNF-α, IL-6, and CV-reactive protein. From a human observational study, it was observed that inflammatory diseases like diabetes, arteriosclerosis and inflammatory polyarthritis can be addressed using vitamin D (Jamka, 2016). A positive correlation is seen between adiponectin and vitamin D, and a reverse correlation between leptin and vitamin D during adipokine secretion (Vaidya, 2012). Hence, vitamin D attenuates oxidative stress and allows beneficial effects in regulating inflammation, out-of-balance energy metabolism, and cell apoptosis. Vitamin D acts by targeting respiratory functions at the mitochondria level. This summarizes the functions of vitamin D associated with β-cells and insulin sensitivity through mitochondrial level interactions.

Protective effects of vitamin D and its analogs in diabetic nephropathy

Current therapeutic guidelines propose 25-hydroxy-vitamin D level augmentation by

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ergocalciferol administration for renal protection (Zisman et al., 2007). The investigations reported observations of 52 patients in stage 3 or stage 4 CKD by raising the levels above 30ng/ml, slightly. The observations showed that patients with stage 3 CKD had a relatively small dip in intact PTH levels, while those in stage 4 did not show any optimal response.

Vitamin D's pleiotropic effects may extend to other areas of CKD progression; these are beyond the parathyroid function management or the metabolism of minerals. Under clinical studies, paricalcitol was orally administered for hyperparathyroidism management in CKD patients, showed reduced proteinuria using angiotensin-converting enzyme inhibitors or receptor blockers (Agarwal, 2005). It was shown that oral paricalcitol in CKD had an antiproteinuric effect, which was demonstrated in lowered proteinuria in 51% cases versus 25% in the placebo group. The placebo group had 61 patients whereas the paricalcitol group had 57 patients. The p-value was 0.004. These observations were age, gender, race, health status like diabetes, and hypertension neutral. The result neutrality remained even for cases that had angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers' therapy. Findings as above throw light on several possibilities that therapy with paricalcitol may have a chance to alter CKD progression. Renin-Angiotensin-System (RAS) is controlled by vitamin D (Li et al., 2004). Vitamin D's favorable effects on CKD progression show glomerulosclerosis could be controlled in study models with 5/6th nephrectomy, (Schwarz, 1998). In CKD progression, the vitamin D receptor's (VDR) role in lowering glomerular growth, RAS suppression, cell differentiation, and fibrosis is critical. In glomerulonephritis models, similar effects have been shown. Vitamin D therapy cause modifications in the various aspects of CKD such as the macrophage type cell attack on remnant kidneys, the monocyte chemo-attractant protein-1 expression, hypertrophy of podocytes, and the TGF-β expression (Kuhlmann, 2004). All the above studies indicate that there is a vast potential for mitigating the progression of CKD (Wang et al., 2003). Zhang et al., (2008) reported glomerulosclerosis and albuminuria of higher severity in diabetic-VDR knockout mice. A higher expression of fibronectin along with lower nephrin was reported when compared with diabetic wild animals. 1-25-dihydroxy-vitamin D inhibited fibronectin production in mesangial cells whereas raised nephrin in podocytes when glucose was supplied under *in vitro* conditions. Hence, indicating that vitamin D can offer favorable effects in the management of diabetic nephropathy. Observations, indications, and findings need to be tested in various patients suffering from one or the other complication associated with CKD. Several studies abridging the limitations are required to design stages for direct evidence and findings. In the myocardium, vitamin D plays a role in myocyte hypertrophy management, (Xiang, 2005). It was shown by Bodyak et al., (2007) that abnormalities of the left ventricular in Dahl salt-sensitive hypertensive rats got attenuated by paricalcitol. Hence it is open to speculation that vitamin D's impact on the RAS or the heart is likely to affect cardiovascular episodes that are a major cause of death in such patient groups. Thus, vitamin D_3 and vitamin D_3 analogs inhibit the progression of diabetic nephropathy.

Methodology

Literature search strategy

Published and unpublished, ongoing observational and experimental studies were referred, to understand and evaluate the role of vitamin D and its analogs in the management of diabetes mellitus.

- Patients with DM with nephropathy that confirmed at least one of the outcome measurement techniques, namely:
- Urinary Protein Creatinine Ratio (UPCR) or,
- Estimated Glomerular Filtration Rate (e-GFR) or,
- Urinary Albumin Creatinine Ratio (UACR) or, the albumin excretion rate
- Serum 25-(OH)-vitamin D, glycosylated hemoglobin (HbA_{1c}), and serum calcium.

- The other measures considered for efficacy were: e-GFR, blood pressure, and transforming growth factor-β (TGF-β).

Exclusions

- Studies on diabetic patients other than those having juvenile diabetes.
- Females who were pregnant and patients with debilitating conditions.

Search methods employed

Electronic searches of databases in their electronic format like MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) together with relevant websites were considered and studied comprehensively. These searches were limited to human studies though without filters like area or language. The medical subject headings/Mesh keywords used to search the various databases were: "diabetes", "nephropathy", and "Vitamin D". Other sources include bibliographies' reviews of relevant studies. To deal with missing data in studies that were included, a back-reference valuation was adopted to coerce the significant contribution of the authors of such missing data for a bibliographic analysis. Zetoc database and the Google search engine were used for referring to and acquiring relevant supporting literature. The study selection, predetermined inclusions and exclusions criteria were standard for all the studies examined. The design of the study, intervention types such as vitamin D and analogs, and the various measures for outcomes comprising UPCR, e-GFR, and UACR were part of the inclusion criteria utilized in the review.

Extraction of data and quality assessment (Risk of Bias)

The Cochrane Handbook for Systematic Review of Interventions, and the Consolidated Standards of Reporting Trials (CONSORT), was the basis for the specific assessment sheets that were prepared to keep a quality check on the data being extracted and the quality of studies being evaluated. These sheets looked into the randomized and non-randomized studies. Chokhandre et al., (2015) assessed concealment allocation, sequence generation, blinding, and incomplete reporting of any data relating to the various outcome measurements employed. These steps were part of the determination of the internal validity of the studies being included. The data extraction was independently done and data on means or degree of change as well as the standard deviation (SD) in studies included were all extracted for all outcome measures. During the data extraction process, study characteristics were analyzed to gain an understanding of the research design, methods employed, participants' characteristics, outcome measurement details, and the type of analysis used to arrive at the various observations, results, findings, etc. for all included studies (Subramaniam, 2001).

Data synthesis and quality assessment

Studies considered in this review are first presented as per the study design, followed by stratification as per the outcomes reported the UPCR, e-GFR, UACR, and albumin excretion rate. To add, the outcomes that were evaluated include serum 25-(OH)-vitamin D, glycosylated hemoglobin (HbA_{1c}), and serum calcium. The Review Manager of the Nordic Cochrane Centre, Copenhagen, Denmark was utilized for analysis of data and review preparation. Mean differences (MD) were used to report the effects measured, percent change (%) was used to communicate the differences in the various means reported, the confidence interval (CI) of 95% was considered or standard deviations (SD) were taken as {MD(CI/SD)}. For visual representation, forest plots were used wherein MD and SD were utilized. The Chi^2 and I^2 tests were taken for heterogeneity in results coming from the stratified data of the included studies (Kruger, 2001). Figure 2 summarizes the PRISMA guidelines undertaken for demarcating the analysis in the present study. A total of five hundred and seventy-two (572) papers came through following the search exercise undertaken. These papers

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mainly came from Medline, Embase, Cochrane library, and some other sources. The quantifications are as under:

Source	Number of papers
Medline	502
Embase	46
Cochrane library	19
Others	5

The separation of duplicates was followed by the examination of reports by titles, abstracts, and keywords. Finally, the papers were screened for inclusions and exclusions. To seek eligible papers fitting the inclusions criteria, a set of 23 papers were considered; these were put through further evaluation. Among these 23 papers, 17 papers were removed from the set during the evaluation process. Studies included: 6 studies were considered for the final analysis; of these 3 were evaluated to understand the effect of cholecalciferol and paricalcitol. The studies comprised of 1 each randomized controlled trial (RCT), non-RCT, and uncontrolled trial.

1. Two of calcitriol: one (1) RCT and one un-controlled trial
2. One of paracalcitol in patients with type-2 diabetes mellitus.

Vitamin D deficient patients with mild to moderate kidney dysfunction were included in these studies. The primary outcome measures considered:

Primary outcome measures
1. Percent (%) change in UACR
2. Change versus: a. Baseline UACR b. Baseline UPCR
3. Albumin excretion rate (AER)

Excluded studies: the number of studies excluded from review for this study's purposes was 17. Of these, 15 studies had chronic kidney disease patients without any specific data reported for diabetic patients among these patients. Nine studies did not include kidney functions in their outcome. One study examined the effect of calcium-based analogs of vitamin D on kidney functions, whereas the other was an RCT that studied calcitriol effect on RAAS activation in diabetes mellitus patients. The latter study was underway and its results, observations, and findings were awaited. Table 1 indicates the study characteristics included in the systematic review. The included studies displayed significant variations in quality, on an overall basis. Randomized studies that were included in the review showed variation in the design of the study, the structure as well as the methodology. The bias risk, on the whole, was low in 2 randomized controlled trials, though the bias risk arising from attrition was significant because the studies did not report follow-up data of the participant patients.

The other form of bias that was expected was that of performance, wherein 1 RCT did not report the randomization method that includes: generation sequence and concealment of allocation, and blinding. Non-RCTs lacked a full report on sample calculation and representativeness, making these trials weaker in terms of external validation. In the non-randomized studies also, there is the risk of bias due to performance, as none of these studies put forth participant patients' blinding towards the treatment. Hence, there was a notable risk of detection bias in each of the 3 non-randomized studies. Though the outcome measures showed validity and reliability, however, a point needs to be noted that not one of these non-randomized studies reported assessors being blind to the outcomes. There was a significant risk of biases due to attrition and selection in one study that had a uniform follow-up pattern for the various patient groups. The participant patients unavailable for follow-ups were not reported. It is also notable, at this junction, that participant patients, in the final analysis, were less than 80% of the original number of participant patients at the start of the study. Also, it is critical to keep in view that none of these non-randomized studies identified confounding factors or displayed any adjustments in the statistical analysis due to these shifts and changes in sample composition.

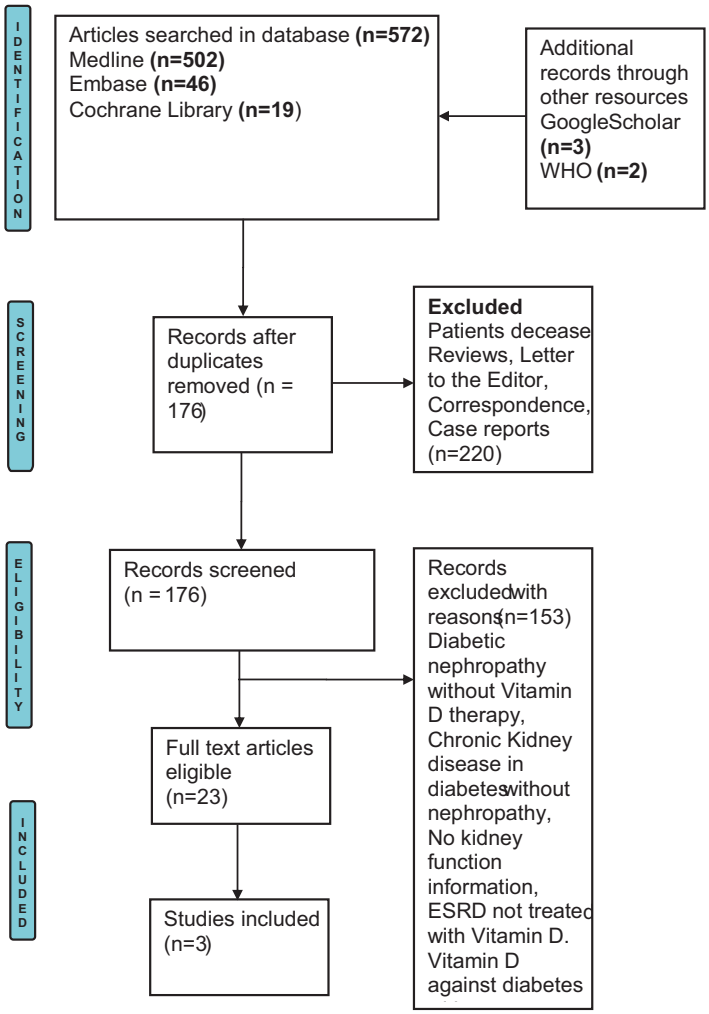

Figure 2: PRISMA Guidelines depicting the study characteristics.

Results

Effect on kidney function assessing proteinuria (UACR, AER, and UPCR)

The UACR was p=0.84 in the case of the RCT with cholecalciferol, wherein the outcome measure did not show any notable change. The mean UACR for the treatment group was (mean±SD) of 120.59; ±145.5 mg/g at baseline, and ±128.99 mg/g when the treatment ended. The UACR baseline (mean ± SD) of the control group was 95.49±57.4 mg/g and at the close of treatment, it was 88.43±65.96 mg/g. A significant change was reported in UACR of the uncontrolled study (mean: 95% CI), after 2 months, the study with cholecalciferol moved from 12.7 (7.3–22.3) mg/mmol to 9.9 (5.5–17.9) mg/mmol, p=0.0141. The RCT study with calcitriol found a significant change in UPCR, –18.7% in the calcitriol group, while the control group showed +9.9%, p=0.004. The uncontrolled study showed beneficial yet insignificant changes in AER with calcitriol administration. The paricalcitol RCT reported an intergroup variation in UACR versus that in placebo, these being –18% (95% CI –32 to 0), p=0.053. A significant intergroup variation was reported in the 24-hour rate of AER, i.e., –28% (95% CI –43––8), p=0.009. Reports on studies with UACR data were taken together for the representation of results to help visualize them. Here, the raw data was unavailable for 1 study for the intended forest plot visualization. Also, it was found that heterogeneity levels between studies were markedly low, I2=0%. Though heterogeneity remained insignificant with Chi^2=0.67, df=1, p=0.41, and due to the small number of studies considered, with different treatments such as paricalcitol

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and cholecalciferol, a meta-analysis was not undertaken. Overall, all three supplementation assessments with paricalcitol, cholecalciferol, and calcitriol showed generalized benefits in the parametric scale, protective efficacy requires further analysis.

Effect of kidney function in terms of eGFR

To understand this aspect, randomized trials were done with calcitriol, cholecalciferol, and paricalcitol. No crude data was reported for a non-randomized trial of cholecalciferol, as well as uncontrolled studies of calcitriol and cholecalciferol. Notably, not one of these studies reported any measurable improvement in the eGFR. eGFR reported in studies was taken together to create a forest plot to aid visual representation. However, it should be noted that the test of heterogeneity was insignificant (Chi^2=0.67, df=1, p=0.41), also there was no heterogeneity between these studies i.e., I2=0%. Again, meta-analysis was considered inappropriate for this small number of studies using different interventions such as cholecalciferol, paricalcitol, and calcitriol. Cumulatively, no significant and notable benefits were recorded in eGFR functionality too.

Effect on serum 25(OH) vitamin D levels

Random-controlled trials with cholecalciferol reported a notable change versus baseline in the serum 25(OH)vitamin D levels, mean±SD from 14.06±7.76 to 71.23±26.51, p=0.001 for the group under treatment vis-à-vis 16.05±6.08 to 17.63±18.52, p=0.10 for the control group of participant patients. Likewise, the difference noted in the between-group in terms of absolute percentage change was significant statistically, p<0.0001. Further, a significant change was reported in the baseline serum 25(OH)vitamin D levels after 6 months of treatment with cholecalciferol, 17.56 (95% CI, 12.23, 23.83) ng/ml versus 10.52 (95% CI 7.75, 11.42) ng/ml, p=0.002. At the end of 4 months of cholecalciferol treatment in the uncontrolled study, a significant change was reported in serum 25(OH)vitamin D levels, mean ± SD from 15.6±7 to 39.7±12.8, p<0.0001. The studies undertaken with analogs of vitamin D such as paricalcitol and calcitriol reported no such findings and observations. Serum levels indicate significant results and depict protective outcomes in affirming the inhibition of progression in diabetic nephropathy.

Effect on serum calcium

In the random controlled trials with cholecalciferol, a significant increase was reported in the serum calcium levels, mean ± SD, 9.75±0.32 mg/dl from 9.22±0.4 mg/dl, p<0.0001 for the treatment group of patients. That for the control group of patients is 9.76±0.42 mg/dl from 9.4±0.34 mg/dl, p<0.002. However, no notable difference was reported in the 2 groups, p=0.14. Non-significance of the results shows neither beneficial nor adverse effects.

Effect on HbA1c

In the case of HbA_{1c}, the random controlled trial studied cholecalciferol's role and observed insignificant percentage change in this metric for both, the treatment and the control group. Similarly, the non-randomized study, as well as the uncontrolled study studied the effects of cholecalciferol on HbA_{1c}, also noted that the results were not significant. The calcitriol-randomized controlled trial observed an insignificant change in HbA_{1c}. However, it should be noted that calcitriol's effect on HbA_{1c} was reported as significant statistically in the uncontrolled study. In this case, the percentage of HbA_{1c}, mean ± SD, altered to 7.6±1.6 from the previous 8.4±1.8, p=0.01. This was for the treatment group of participating patients. The paricalcitol study, however, reported no data on HbA_{1c}.

Summarily, except for serum 25 (OH) vitamin D beneficial effect, no significance was noted using vitamin D sources in progression of diabetic nephropathy. Hence adequate trials and assessment of the strategy through cross-sectional studies will show potent clinical outcomes.

Discussion

The systematic review reconciled the observations on the role of vitamin D and the various analogs of vitamin D in chronic kidney disease management. These analyses indicated a baseline positive modification stressing protective kidney functioning parameters. The adverse effects of the treatment strategies were found to be insignificant. The clinical practice guidelines by the NKF-KDOQI, KDIGO and NICE guidelines advise chronic kidney disease patients with hyperparathyroidism along with mineral and bone disorders to be supplemented with vitamin D or vitamin D analogs for regulating homeostasis. Randomized double-blinded clinical trials are emphasized for authentic affirmation of vitamin D and its analogs in managing diabetic nephropathy. However, it has been correlated to reduce proteinuria and renal inflammation but not effective in glycemic control and renal function (Wang et al., 2019). In this review, the summarization brings forth evidence of vitamin D uses as well as that for its analogs in diabetic nephropathy. Vitamin D analogs have not been proved effective in the abatement of diabetic nephropathy. However, most researchers propose further research need in this perspective. Six studies were found, though with notable variations in research or study design: of these three were randomized controlled, one was non-randomized controlled, and two were uncontrolled studies. The quality assessment of these studies brought forth a low bias risk in two studies that were randomized controlled trials; these have been included in this review. However, a similar quality assessment of the other studies indicated an unclear to relatively high bias risk. The data was put through stratification keeping in view the different interventions and outcomes. However, a meta-analysis on a similar perspective was not considered significant due to the differences in research design and the use of different interventions such as paricalcitol in one study, calcitriol in two, and cholecalciferol in three studies (Wang et al., 2019). The study by Wang et al., (2019) depicted the role of vitamin D and its analogs in the management of diabetic nephropathy. The treatment with cholecalciferol showed a reduction in UACR by 7, thus touching 26.4% levels. However, the notable aspect about this UACR reduction is it does not sustain after the initial 2 months when checked for at the end of 4 or 6 months. The use of vitamin D analogs like calcitriol and paricalcitol notably reduced proteinuria, though this lowered proteinuria showed no correlated change in eGFR. It was noted that the analogs or vitamin D itself had no deteriorating effects on renal function. The effects of vitamin D supplementation in chronic kidney disease patients and the review observations showed no significant damaging effect on the functioning of the kidney. Patients with diabetic nephropathy in these studies were vitamin D deficient; this is common in chronic kidney disease patients.

Notably, this change reported was statistically insignificant by the end of 4 months (Zhu, 2001). Similar results were reported by the non-randomized study, wherein UACR (mean: 95% CI) dropped notably from 97.39 (62.43–476.70) mg/g to 71.65 (40.40–469.98) mg/g, p=0.01 at the end of 2 months. In this case, the change displayed did not remain significant at the end of 6 months (Wang, 2004).

The cholecalciferol therapy was examined by Chandra et al., (2008) by administering 50,000 units per week over 12 weeks to a randomized, controlled trial of stage 3 and 4 CKD patients. Observations showed a raised geometric mean value for 25-hydroxy-vitamin D to nearly 50 ng/ml with a 31% dip in PTH levels in the group that received this therapy versus a 7% decline in the placebo group. However, the PTH values had significant variability in the PTH values. Studies similar in design as Zisman et al., (2008) were conducted by Al-Aly et al., (2007), though the results were somewhat varied and similar to those of the study by Chandra et al. Both investigators showed that approximately 50% of CKD patients displayed satisfactory increment in 25-hydroxy-vitamin D levels when standard treatment was administered. The rest showed no such results post-administration. PTH levels declined in those study patients who showed an increment in 25-hydroxy-vitamin D levels, while PTH levels remained unchanged or changed insignificantly in study patients. Similar findings were reported in stage 4 CKD patients as well. However, more

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studies are required to fathom the unresponsive status of half the patients who showed no increment in 25-hydroxy-vitamin D levels. Findings, investigations, observations, and results become critical when seen from the standpoint of managing dialysis patients' health. Active vitamin D therapy to such patients indicates a survival chance versus those dialysis patients that are not given any vitamin D. Such observations have been confirmed by various researchers like Young et al., (2005) using the DOPP study database and Kalantar-Zadeh et al., (2006) in different study patients. Thus, additional mechanisms in the context of vitamin D therapy for therapeutic management need to be unraveled. Observations and findings in these studies seem to indicate that the effect of vitamin D in the potential survival benefit results irrespective of phosphorus, calcium, or PTH levels. Hence, the effects of vitamin D are independent of its effects on mineral metabolism and bone per se.

Non-randomized trials of cholecalciferol reported no notable changes in calcium levels between and within these 2 groups. Insignificant changes were reported in a similar study (Chokhandre et al., 2015). Vitamin D analogs like paricalcitol display similar behavior. This analog has shown improvement in the survival status when compared with native vitamin D like sterol calcitriol, (Teng, 2007). Likewise, another vitamin D analog 1-α-hydroxy-vitamin D2 displays better survival status over native hormone calcitriol, (Tentori, 2008). Further, these studies have noted that the improved survival status was independent of PTH, calcium, or phosphorus levels. However, it is essential to deep dive into the mechanisms that make it possible for an improved survival status so that observations, findings, and possibly results can be used to improve the same for patients.

Fifty-two hemodialysis patients were examined in a cross-sectional research study for possible correlations among brachial artery distensibility, aortic stiffness, and arterial calcification scores having serum levels of $25(OH)D_3$ and $1,25(OH)_2D_3$. London et al., (2009) observed that these scores correlated positively with brachial artery distensibility and flow-mediated dilation, while correlated negatively with aortic pulse wave velocity. However, further investigations are necessary to assess if vitamin D supplementation could improve endothelial dysfunction and arteriosclerosis in hemodialysis patients.

It is difficult to grasp the difference in the various vitamin D analogs' effectively versus that of the native hormone because essentially there is a single VDR. *In vitro* studies, calcitriol is indicated as a growth factor for vascular smooth muscle cell development, whereas in the vitamin D analog, paricalcitol is not a growth factor (Cardus, 2007). To add *in vivo* studies in experimental animals, the effect of vitamin D sterol was reported as different on vascular calcification. 1-α-hydroxy-vitamin D2 or calcitriol indicated to be associated with higher vascular calcification versus that paricalcitol. PTH suppression in equivalent proportion in animal models in the study was significant (Mizobuchi, 2007). Wu-Wong et al., (2006) and other investigators have reported similar studies putting forth similar observations on calcitriol vis-à-vis 22-oxacalcitriol, (Hirata, 2003). However, more studies are required to fully grasp the various mechanisms making these differentiated effects happen.

The clinical guidelines (KDOQI) recommend a dose of 1,000–2,000 IU/d of cholecalciferol towards the treatment of vitamin D deficiencies in the general population. It is rare to find any cases of hypercalcemia due to such dosages. An elevated level of serum 25(OH) vitamin D is possible with the administration of cholecalciferol in significant dosage; such elevation is considered as dose-dependent elevation. The resulting rise in serum calcium levels was not markedly different from what was observed in placebo groups. The difference was found to be insignificant and indicated the safety of cholecalciferol in high doses for patients with diabetic nephropathy. No effects of vitamin D have been reported basis the post-treatment levels of 25(OH) vitamin D or that for 1, 25(OH) vitamin D. The studies reviewed also did not report any notable rise in the serum calcium levels. The other secondary efficacy end-point, HbA_{1c} reported in the studies considered for this review, was also evaluated this review exercise. Diabetes and the deficiency of vitamin D were observed to have a causal relationship in observational studies. Basis findings

during this review exercise, it can be inferred that while calcitriol reduces HbA_{1c}, paricalcitol and cholecalciferol have no effect on HbA_{1c}. A report generated upon conducting a meta-analysis showed no change in HbA_{1c} in patients with abnormal glucose tolerance upon receiving vitamin D treatment when a marginal improvement was observed in the fasting blood glucose and insulin resistance. However, patients with normal glucose levels at fasting showed no improvement in any of the outcome measures. Also, no significant improvement was reported in the glycemic parameters upon supplementation with vitamin D in diabetic patients. The pathogenesis in diabetic nephropathy shows the presence of a variety of pro-inflammatory molecules that have been identified. Vitamin D modulates such pro-inflammatory compounds by exhibiting anti-inflammatory properties. Data from clinical studies indicate the possibility of calcitriol's anti-inflammatory role in diabetic nephropathy. Upon treatment with calcitriol, it was observed that the low serum levels of 25(OH) vitamin D3 were associated with heightened serum and markers of urinary inflammation like TNF-α, IL-6, and ICAM-1. However, the calcitriol treatment being administered lowered these significantly. Studies of cholecalciferol effects were reviewed wherein supplementation of this analog was done on inflammatory markets like urinary monocyte chemo-attractant protein-1 (MCP-1) and TGF-β1. It was reported that a notable drop in urinary TGF-β1 was achieved, thus indicating a beneficial effect of vitamin D. The possibility of cardiovascular morbidity and mortality in the face of vitamin D deficiency has been commented upon earlier in this review document. It was found that hypovitaminosis D is linked with asymptomatic cardiovascular ailment or disease, abbreviated as CVD in diabetic patients having nephropathy. Further, hemodialysis patients who have vitamin D deficiency face a greater risk of all-cause early mortality. Vitamin D deficiency is prevalent in hemodialysis patients. However, concrete evidence that supports the role of supplementation with vitamin D in such patients is inadequate. Gupta et al. (2019) showed that α-calcidiol reported a survival advantage in chronic hemodialysis patients indicate that the risk of cardiovascular disease or survival in diabetic nephropathy patients were included. The studies that are included in this review were grouped basis the design of the study and further sub-grouped as per various outcomes. Due to these variations in the study design, intervention, and outcomes, the results pooling for meta-analysis was not undertaken as it was deemed inappropriate. The methodology, process implementation, and reporting of this review were as per the guidelines' recommendations. It was observed that there exists an in general criticism of a standardized 'one-size-fits-all' approach for systematic reviews. However, this review is based on an adapted bias risk and quality assessment approach, yet some limitations of this approach have been acknowledged. A comprehensive search strategy was undertaken, though there could have been incidences of some studies being missed out from being considered for this review. Despite attempts to contact these authors, there still exist portions of data that are missing or unpublished, thus not accessible to the authors of the review. A fair extent of personal bias may have seeped into this review despite all reviewers having extended their quality assessment of the various studies that have been included.

The study designs of the six (n=6) studies, examining the vitamin D or analogs' role in diabetic nephropathy, have sizeable variations. The analogs of vitamin D were reported to have a significant positive effect on kidney function. Higher doses of cholecalciferol administered earlier in a treatment regimen showed positive results. However, these positives could not be sustained over a while. These short duration studies' results were ambiguous, hence need to be consumed cautiously. Though vitamin D or its various analogs do not show any adverse effect on kidney functions however it is recommended that the patient's serum calcium concentrations are monitored, keeping safety in view for diabetic nephropathy patients. Before and after studies as well as those with no controls or comparative groups were not considered as a suitable study design for studying the effects of vitamin D. Studies having standardization in dosage and duration of vitamin D or its analogs therapy was taken as having the necessary clarity in gauging

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the effect of such supplementation in these diabetic nephropathy patients. Further randomized double-blinded controlled trials are required to refine these observations, strengthen the effects of vitamin D and the various analogs in diabetic nephropathy cases (Gupta et al., 2019). The present systematic review marginally confirms that serum 25 (OH) vitamin D_3 alone shows a baseline benefit and general protection of kidney function. However, other parameters assessed were not significant. Hence additional studies are required for authoritative studies to establish vitamin D protective effects in diabetic nephropathy. Genetic basis of the regulatory roles in vitamin D effects in the management of progression of diabetic nephropathy. Observational studies and case-control studies with a large sample sizes could yield protective benefits. Further assessment of vitamin D analogs can have a structure-function activity relationship in analyzing metabolic regulation in addressing vitamin D deficiency and diabetic nephropathy. Drug discovery assessment through computer-aided drug design, simulation studies and extensive clinical trials will provide ample resources for effectively managing diabetic nephropathy.

Conclusion

The systematic review reveals the literary summary affirming the positive roles of vitamin D supplementation in retarding the progression of diabetic nephropathy. Except for better outcome in serum (OH) vitamin D levels, proteinuria parameters involving albumin excretion, calcium, HbA_{1c} did not show significant effects depicting the need for a rational study in the realm; the study concluded that vitamin D showed improvement in two randomized studies of kidney function. Vitamin D inhibits the progression of diabetic nephropathy and further clinical trials are envisaged for the utility of vitamin D analogs for effective management of diabetic nephropathy and better clinical outcomes, thereby reducing mortality and morbidity. The clinical trials can include the cross-sectional assessment for diabetic nephropathy comprising both type-1 and type-2 diabetes mellitus. Further randomized controlled placebo trials for accentuating the additional nephritic conditions apart from the parameters used in the present evaluation can have impending benefits. Large-scale observational studies among chronic patients of diabetic nephropathy also could address additive outcomes and management strategies against diabetic nephropathy. The present study affirms the protective efficacy of vitamin D supplementation and kidney function. Nevertheless, a holistic inhibition of the progression of diabetic nephropathy was not recorded.

Glossary

UACR - Urine Albumin-to-Creatinine Ratio
AER - Albuminuria
UPCR - Urine Protein:Creatinine Ratio
*e*GFR - Estimated Glomerular Filtration Rate
25(OH) - 25-*hydroxy* vitamin D
HbA_{1c} - Hemoglobin A_{1c}
DM - Diabetes Mellitus
VDR - Vitamin D Receptor
CYP2R1 - Cytochrome P 2R1
VDR - Vitamin D Receptor
NOD Mice - Non-obese diabetic mice
RR - Rate Ratio
I-Se - Insulin Sensitive
IR -Insulin Resistant
PTH -Parathyroid Hormone
PPARs - Peroxisome Proliferator-Activated Receptors
RAAS - Renin-Angiotensin-Aldosterone System
IL - Interleukin
CVD - Cardiovascular disease
CKD - Chronic Kidney disease
VDRA - Vitamin-D Receptor Activation
ESRD - End stage renal disease
DOPP - Dialysis Outcomes and Practice Patterns
KDIGO - Kidney Disease Improving Global Outcomes
CAMP - Cathelicidin Antimicrobial Peptide
RXR - Retinoid-X-Receptor
VDRE - Vitamin D-Response Elements
TNF- α - Tumor Necrosis Factor- α
DCs - Dendritic cells
APCs - Antigen presenting cells
GLUT-4 - Glucose transporter-4

MCP-1- Monocyte chemoattractant protein 1
CONSORT - Consolidated Standards of Reporting Trails
CENTRAL- Cochrane Central Register of Controlled Trials
RCT - Randomized Controlled Trial
NKF-KDOQI – National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
NICE - National Institute for Health and Clinical Excellence
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Conflict of interest

The authors declare no conflict of interest.

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