

## Review

# Vitamin D in Diabetic Nephropathy: Today, Tomorrow, Always

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### Abstract

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Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin (Type 1 diabetes, T1D). Diabetic nephropathy (DN) is one of the complications of T1D. Diabetic nephropathy is a direct reason for morbidity and mortality in children and adults. Many mechanisms including influence of hyperglycemia (causing hyperfiltration and renal injury), advanced glycation products, and activation of cytokines discussed in development of DN. Nowadays a big attention addressed towards the effects of Vitamin D on DN course. Both animal studies and clinical trials have documented an inverse correlation between low vitamin D levels and DN risk, and supplementation with vitamin D or its active derivatives has been demonstrated to improve DN course. This was as a result of positive effect of vitamin D on endothelial cell injury, reduced proteinuria, attenuated renal fibrosis, direct renoprotective effects of Vitamin D (prevention of the podocytes injury, GBM damage). Additional clinical studies needed to understand deeply the entire network of Vitamin D-dependent changes in diabetic kidneys especially in pediatric patients.

**Keywords:** T1D, diabetic nephropathy, kidney damage, Vitamin D

## INTRODUCTION

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes" (About diabetes, World Health Organization, 2014). Insulin is a hormone that regulates blood sugar. Hyperglycaemia is a key metabolic disorder in diabetes leading to serious irreversible damage to many of the body's systems, especially the nerves and blood vessels (American Diabetes Association, 2014).

In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 - 2.2 million deaths (American Diabetes Association, 2014; Classification and Diagnosis of Diabetes, 2019). Between 2000 and 2016a 5%

increase in premature mortality from diabetes registered. In high-income countries the premature mortality rate due to diabetes decreased from 2000 to 2010 but then increased in 2010-2016. In lower-middle-income countries, including Ukraine, the premature mortality rate due to diabetes increased across both periods (Global report on diabetes. World Health organization, 2016).

According to the latest edition of the Diabetes Atlas, an estimated 490,100 children below the age of 15 years are living with type 1 diabetes. Type 1 diabetes rate is increasing in some central and eastern European countries, where the disease remains less common than in other regions. Above 24% of all children with T1D live in the European region (World Health Organization, 2014).

A decreasing incidence of diabetes complications, particularly nephropathy and proliferative retinopathy, has been reported in the type 1 diabetes population around

the world over the past 15–20 years. Metabolic control including self-monitoring of blood glucose and HbA<sub>1c</sub> (A1C) testing, blood pressure management are main factors in prevention of the diabetic complications development (Chawla et al., 2016). However, there data showing increased rates for diabetic nephropathy and retinopathy after 15 years in a hospital-based cohort (Pambianco et al., 2006).

Diabetic nephropathy is a direct reason for morbidity and mortality. Proteinuria is a predictor of morbidity and mortality in patients with DN. The overall prevalence of microalbuminuria and macroalbuminuria in both types of diabetes is approximately 30-35% (Persson and Rossing, 2018). Patients without proteinuria have low relative mortality rate, whereas patients with proteinuria have a 40-fold higher relative mortality rate. Patients with type 1 DM and proteinuria have the typical bell-shaped relationship between diabetes duration and relative mortality. The highest rate of the relative mortality in the age interval of 34-38 years (as reported in 110 females and 80 males).

End-stage renal disease (ESRD) is the major cause of death in patients with DN. In patients with T1D and DN, ESRD leads to 59-66% of deaths. A study by Rosolowsky et al. reported that despite renoprotective treatment, including transplantation and dialysis, patients with type 1 diabetes and macroalbuminuria remain at high risk for ESRD. Cardiovascular complications are a cause of death (15-25%) in persons with nephropathy and type 1 DM, even young (Rosolowsky et al., 2011).

Thus, understanding of the mechanisms of the development and approaches to prevent the DN still needed to study, especially in pediatric patients.

### **Diabetic nephropathy(DN). General overview**

Diabetic nephropathy is a clinical syndrome characterized by the following:

- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure (Tang et al., 2016).

Firstly, proteinuria recognized in diabetes mellitus in the late 18th century. In the 1930s Kimmelstiel and Wilson described the nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension. In 1950s diabetic kidney disease was recognized as a common complication of diabetes. 50% of patients with diabetes and disease course of more than 20 years having this complication (Sowers and Epstein, 1995).

Nowadays, diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western countries (Imkampe and Gulliford, 2011). Diabetes leads to 30-40% of all end-stage renal disease

cases in the United States (Burrows et al., 2017). Adequate treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease.

There are data showing an atypical course of diabetic nephropathy with dissociation of proteinuria from reduced kidney function. Some authors noted that microalbuminuria is not always predictive of diabetic nephropathy. However, a majority of the cases of diabetic nephropathy accompanied by proteinuria, which is a key player in disease progression.

### **General pathophysiology of the diabetic nephropathy**

The exact cause of diabetic nephropathy is unknown. Many mechanisms including influence of hyperglycemia (causing hyperfiltration and renal injury), advanced glycation products, and activation of cytokines discussed (Vallon and Komers, 2011). Glycemic control reflects the balance between dietary intake, gluconeogenesis and tissue uptake or utilization through storage as glycogen or fat and oxidation. This balance is regulated by insulin production from the  $\beta$ -cells in the pancreas. Insulin regulates serum glucose through its actions on liver, skeletal muscle, and fat tissue (Vallon and Komers, 2011; Amos et al., 1997; Huebschmann et al., 2006).

Several pathways induced by hyperglycemia involved in DN pathogenesis. Hyperglycemia and high levels of saturated fatty acids lead to an inflammatory background formation, resulting in activation of the innate immune system. This results in activation of the nuclear transcription factors-kappa B (NF- $\kappa$ B), and release of inflammatory mediators, including, interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$ , promoting systemic insulin resistance and  $\beta$ -cell damage as a result of autoimmune insulinitis (Galkina and Ley, 2006; Furuta et al., 1993). Hyperglycemia and high serum levels of free fatty acids and IL-1 lead to glucotoxicity, lipotoxicity, and IL-1 toxicity, resulting in apoptotic  $\beta$ -cell death (Galkina and Ley, 2006; Furuta et al., 1993; Wu et al., 2012).

Hyperglycemia also stimulated matrix remodeling via enhanced expression of transforming growth factor- $\beta$  (TGF- $\beta$ ) in the glomeruli. TGF- $\beta$  and vascular endothelial growth factor (VEGF) may contribute to the cellular hypertrophy and enhanced collagen synthesis (Qian et al., 2008).

Three major histologic changes occur in the glomeruli affected by diabetic nephropathy, i.e. mesangial expansion, thickening of the glomerular basement membrane (GBM), glomerular sclerosis. Mesangial expansion is a result of chronic and persistent influence of hyperglycemia, perhaps via increased matrix production or glycation of matrix proteins (Pourghasem et al., 2015).

Glomerular basement membrane (GBM) thickening occurs in all patients with diabetic nephropathy. In DN apoptosis, loss of podocytes has been observed. It could

be mediated by increased Smad7, AGE, angiotensin II and reactive oxygen species. Moreover, hyperglycemia causes detachment of podocytes from GBM.

Hyperglycemia induces oxidative stress via generation of reactive oxygen species (ROS) through the NADPH oxidase. ROS initiate apoptosis of podocytes (Fakhruddin et al., 2017). Under diabetic conditions, all cell types of the kidney including endothelial cells, tubulointerstitial cells, podocytes and mesangial cells can be affected. These processes in turn lead to all kidney cells injury and affects renal function (Maezawa et al., 2015).

Glomerular sclerosis a result of intraglomerular hypertension (Kolset et al., 2012). Glomerulosclerosis in DN is a result of multifactorial mechanisms that lead to excessive accumulation of extracellular matrix proteins such as collagen types I, III, and IV and fibronectin in the mesangial space, which through stages of mesangial expansion and development of Kimmelstiel–Wilson lesions finally result in glomerulosclerosis (Maezawa et al., 2015; Kolset et al., 2012).

### Vitamin D functions overview

The classic function of vitamin D is to regulate calcium absorption and homeostasis. It promotes calcium absorption from the gut, enables mineralisation of newly formed osteoid tissue in bone and plays an important role in muscle function (Khazai et al., 2008). It is well known that chronic vitamin D deficiency results in rickets in children and osteomalacia in adults (Sahay M, Sahay R (2012). Not severe vitamin D deficiency, sometimes called vitamin D insufficiency, may lead to secondary hyperparathyroidism, bone loss, muscle weakness, fractures in older people (Khazai et al., 2008).

Main sources of Vitamin D in the human body are dietary intake and from synthesis in the skin triggered by ultraviolet B (UVB) irradiation. UVB irradiation stimulates synthesis of cholecalciferol in skin, which is stored in adipose tissue or undergoes hydroxylation in the liver to 25(OH)D. Then further hydroxylation in the kidney to the biologically active form, 1,25-dihydroxyvitamin D occurs (Nair and Maseeh, 2012). UVB sunlight exposure is the main source of Vitamin D in human body (Calvo et al., 2005). Environmental factors, such as latitude and prevailing weather conditions affect the Vitamin D synthesis. Synthesis of vitamin D varies during the year. The highest level of Vitamin D in plasma recorded during summer months. In the northern hemisphere sunlight is not strong enough to trigger synthesis of vitamin D in the skin from October to March. European population, including Ukraine, require dietary vitamin D supplementation during the winter season (O'Connor and Benelam, 2011).

Vitamin D mediates its function by binding to the VDR, which is a member of nuclear hormone receptors

superfamily. VDR activated by vitamin D interacts with retinoid X receptor to form a heterodimeric complex, which is recruited to the vitamin D response elements (VDRE) in the target genes to activate or to repress their expression through interaction with additional co-regulators (Pike and Meyer, 2010).

The extra-skeletal effects of vitamin D dealing with its effect on the cellular proliferation, differentiation, and immune modulation. There are data about the protective effects of vitamin D in several diseases like hypertension, diabetes, cardiovascular diseases, autoimmune diseases, and cancers. These indicate a significant input in its role beyond the well-known anti-rachitic factor (Khazai et al., 2008; Bikle, 2016).

### Basic role of Vitamin D in diabetic nephropathy

Vitamin D has been suggested to show multiple biological activities, among them the potential role of vitamin D in the protection of diabetic nephropathy (Khazai et al., 2008; Sanchez-Niño et al., 2012). Both animal studies and clinical trials have documented an inverse correlation between low vitamin D levels and DN risk. Supplementation with vitamin D or its active derivatives demonstrated to improve diabetic nephropathy course. This was as a result of positive effect of vitamin D on endothelial cell injury, reduced proteinuria, attenuated renal fibrosis.

Vitamin D exerts its pharmacological effects via vitamin D receptor. Their activation inhibits the renin-angiotensin system, a key damaging factor for DN under the permanent effect of hyperglycemia. In series of studies shown that consumption of vitamin D-related products negatively regulates inflammatory response at multiple levels, indicated by inhibiting macrophage infiltration, nuclear factor-kappa B (NF- $\kappa$ B) activation, and production of such inflammatory mediators as transforming growth factor- $\beta$  (TGF- $\beta$ ), monocyte chemo-attractant protein 1 (MCP-1), and regulated upon activation normal T cell expressed and secreted protein (RANTES) (Sanchez-Niño et al., 2012; Zhang et al., 2008).

Moreover, there are data about the direct effect of Vitamin D on kidney cells. Renal podocytes form the main filtration barrier (Glomerular Basement Membrane, GBM). This is an absolutely dependent on an appropriate structure and function of proteins including podocalyxin and nephrin, the expression of which suppressed in pathological conditions (Wang et al., 2012).

In studies (Wang et al., 2012; Verouti et al., 2013) it was induced a high glucose-mediated downregulation of podocalyxin and nephrin, loss of which has been linked with loss of the permselective renal barrier and proteinuria. Calcitriol and paricalcitol reversed high

glucose-induced decrease of nephrin and significantly enhanced podocalyxin expression in podocytes cultured in high glucose. It was shown that in the presence of calcitriol and paricalcitol, VDR expression was upregulated. Furthermore, VDR specifically regulates podocalyxin expression by bounding to a site upstream of the podocalyxin promoter. Thus, Vitamin D analogues maintain and re-activate the expression of specialized components of podocytes including podocalyxin. This is a key mechanism of its protective role (Verouti et al., 2013).

Also paricalcitol reduced MCP-1 and IL-6 in podocytes and tubular cells as well as glomerular infiltration by macrophages, glomerular cell NF- $\kappa$ B activation, apoptosis, and extracellular matrix deposition. Also in this study in cultured podocytes, paricalcitol and calcitriol at concentrations in the physiological range prevented the increase in MCP-1, IL-6, renin, and local inflammation in kidney – processes leading to the progression of diabetic nephropathy.

The vitamin D receptor (VDR) activator paricalcitol has an antiproteinuric effect in human diabetic nephropathy at high doses. On In vivo study the effect of calcitriol and paricalcitol on renal function, albuminuria, and renal inflammation was explored in a rat experimental model of diabetes induced by streptozotocin. It was found that at the doses, neither calcitriol nor paricalcitol significantly modified renal function or reduced albuminuria in experimental diabetes. However, both drugs reduced the total kidney mRNA expression of IL-6, monocyte chemoattractant protein (MCP)-1, and IL-18. Immunohistochemistry showed that calcitriol reduces fibronectin mRNA expression and the secretion of MCP-1 to the culture media induced by high glucose (Sanchez-Niño et al., 2012). In conclusion, in experimental diabetic nephropathy VDR activation has local renal anti-inflammatory effects that can be observed even when proteinuria is not decreased. This may be an evidence that vitamin D able to decreased inflammatory responses in renal cells, including podocytes exposed to high glucose.

In another study (Wang et al., 2016) it was found that 1,25(OH)<sub>2</sub>D<sub>3</sub> inhibited the proliferation of mesangial cells induced by hyperglycemia. 1,25(OH)<sub>2</sub>D<sub>3</sub> also significantly reduced albumin excretion, mean glomerular volume, glomerular basement membrane, and total kidney volume in rats with diabetic nephropathy. Vitamin D receptor gene silencing blocked all of the above results. The current study demonstrates that 1,25(OH)<sub>2</sub>D<sub>3</sub> can effectively inhibit mesangial cells proliferation induced by hyperglycemia, thus suppressing the development of diabetic nephropathy. These is a study showing that the nephron-protective effect of 1,25(OH)<sub>2</sub>D<sub>3</sub> occurs partly through the DDIT4/TSC2/mTOR pathway - a serine/threonine kinase and central regulator of important cellular functions, i.e. cell cycle, apoptosis (Khodir et al., 2020).

### **Vitamins D, diabetes and diabetic nephropathy in clinical studies**

The epidemiological studies have demonstrated a worldwide high prevalence of vitamin D deficiency or insufficiency in healthy individuals. The problem of vitamin D deficiency is widely known, especially in patients with T1DM. However, some aspects of vitamin D role in diabetes and its complications remain un-known or controversial.

Swedish study carried out on 459 T1DM patients aged 15–34 demonstrated significantly lower vitamin D blood level at diagnosis of T1D as compared to the control group. Diabetic men had a lower vitamin D level than diabetic women (Wahlberg et al., 2006). Australian children and adolescents with T1DM also had significantly lower serum vitamin D concentration compared to healthy individuals (Greer et al., 2013). Similar results were reported by Federico et al. in Italian children (Federico et al., 2018). A similar conclusion was presented by Rasoul et al. They observed higher frequency of vitamin D deficiency and insufficiency in Kuwaiti children with T1DM than in their healthy individuals (Rasoul et al., 2016). Low vitamin D concentration is also common among Swiss children and adolescents with T1DM. Authors show that 60.5% of 129 examined patients had vitamin D deficiency and 26.4% had vitamin D insufficiency (Janner et al., 2010).

Many interventional studies and randomized controlled trials found positive clinical effects of vitamin D in patients with T1DM. Series of studies show that insulin therapy supplemented with different forms of vitamin D (cholecalciferol, alfacalcidol and calcitriol)improve the preservation of residual pancreatic  $\beta$ -cells function in T1DM patients (Felicio et al., 2018; Bogdanou et al., 2016; Li et al., 2009).

Mishra et al. showed insignificant trend toward a lower decline in residual pancreatic  $\beta$ -cell function in vitamin D supplemented patients (Mishra et al., 2016). Federico et al. demonstrated significant inhibition of auto-aggression and protective effect on pancreatic  $\beta$ -cells function in patients supplemented with vitamin D. Positive effect on immune reactions, i.e. decreased reactivity of peripheral blood mononuclear cells against glutamic acid decarboxylase and pro-insulin observed in this group (Federico et al., 2014).

However, there are too few studies on vitamin D and diabetic complications, i.e. diabetic nephropathy. It is known, that vitamin D is a nutrient of concern for individuals with diabetes and nephropathy, particularly for those living in northern climates with limited sunlight exposure. Dietary restriction of vitamin D-rich food sources is a common issue due to concerns around phosphorus, potassium and carbohydrate content. Avoidance of sunlight is also common due to instructions for concomitant medications. The result of latter are bone

**Table 1.** Experimental and clinical studies on Vitamin D, diabetes and diabetic nephropathy

<b>Vitamin D effect</b>	<b>Type of study</b>	<b>Reference</b>
RAAS inhibition, macrophage infiltration reduction, NF- $\kappa$ B activation, down-regulation of inflammatory molecules	In vitro	Sanchez-Niño et al., 2012 Zhang et al., 2008
VDR activity induced by Vitamin D stimulates the expression of nephrin	In vitro	Wang et al., 2008
Vitamin D analogues rescue podocytes via podocalyxin damage prevention	In vitro	Verouti et al., 2013
Vitamin D administration reduced albuminuria	In vivo	Sanchez-Niño et al., 2012
Vitamin D administration reduced albumin excretion, mean glomerular volume, glomerular basement membrane and total kidney volume.	In vivo	Wang et al., 2016
Vitamin D protects nephrons via DDIT4/TSC2/mTOR signaling pathway activation	In vitro, in vivo	Khodir et al., 2020
Serum Vitamin D level is low in T1D patients	Clinical study	Wahlberg et al., 2006
Serum Vitamin D level is low in children and adolescents with T1D	Clinical study	Greer et al., 2013 Frederiko et al., 2018 Rasoul et al., 2016 Jenner et al., 2010
Insulin therapy supplemented with different forms of vitamin D (cholecalciferol, alfa calcidiol and calcitriol) improves the preservation of residual pancreatic $\beta$ -cells function in T1DM patients	Clinical study	Felicio et al., 2018 Bogdanou et al., 2016 Li et al., 2016
Vitamin D supplementation causes insignificant trend toward a lower decline in residual pancreatic $\beta$ -cell function in patients with T1D	Clinical study	Mishra et al., 2016
Vitamin D shows protective effect on pancreatic $\beta$ -cells function in patients with T1D	Clinical study	Federico et al., 2014
Vitamin D supplementation shows positive effect on bones in patients with T1D and signs of DN	Clinical study	Mager et al., 2014
Vitamin D administration in patients with stage 3–4 CKD optimized bone health	Clinical study	Gal-Moscovici et al., 2010 Weaver et al., 2004
Patients with early DN showed a significant reduction of urinary albumin excretion with Vitamin D treatment. An improvement in the GFR has been observed	Clinical study	Liyanage et al., 2018
Vitamin D deficiency is independently associated with a higher risk complications in patients with Type II diabetic nephropathy	Clinical study	Fernández-Juárez et al., 2013
Vitamin D deficiency has a negative effect on albuminuria in T2D patients	Clinical study	Bonakdaran et al., 2012
Treatment with calcitriol in addition to ACEI or ARB results in a significant reduction in albuminuria in T2D nephropathy	Clinical study	Taheri et al., 2018

disorders. Mager et al. shows positive effect of vitamin D supplementation on bones in patients with T1D and signs and DN. Nevertheless, none of kidney functions evaluated in this trial (Mager et al., 2014).

A recent studies in patients with stage 3–4 CKD caused by diabetes demonstrated that daily oral supplementation of vitamin D optimized bone health (Gal-Moscovici and Sprague, 2010; Weaver and Fleet, 2004). Liyanage et al. conducted randomized double-blind placebo-controlled clinical trial among patients with early DN. A significant reduction of urinary albumin excretion and GFR level increase under Vitamin D treatment shown (Liyanage et al., 2018).

Another study included patients with T2D. Results show that 25(OH)-vitamin D deficiency is independently associated with a higher risk of complications in patients

with type II diabetic nephropathy (Fernández-Juárez et al., 2013).

Bonakdaran et al. suggests that vitamin D deficiency has a negative effect on albuminuria in T2D patients (Bonakdaran et al., 2012). Treatment with calcitriol, ACEI or ARB resulted in a significant albuminuria reduction in patients with diabetic kidney disease (Taheri et al., 2018).

Thus, there are many preclinical studies of vitamin D effect on different aspect of T1D and DN pathogenesis. Moreover, several epidemiological, observational and supplementation clinical studies investigated potential biological interactions between hypovitaminosis D and diabetes. However, too few clinical studies describe the effect of Vitamin D supplementation on T1D disease course and DN development (Table 1).

## CONCLUSIONS

Diabetic nephropathy is one of the T1D complications and has a great impact in Chronic Kidney Disease development. Vitamin D has calcitropic and pleiotropic effects mediated through vitamin D receptor (VDR) expressed in kidneys, including podocytes, intestine, bones, parathyroid glands, pancreatic beta cells, cells of immune system and other cells.

Calcitriol has shown to have antiproteinuric and nephroprotective effects in multiple animal models alone and in combination with angiotensin receptor blockers (ARBs), i.e. mesangial proliferation reduction, renin suppression, renin-angiotensin-aldosterone system negative regulation. These effects are due to its effect on macrophage infiltration, and transcription factor nuclear factor- $\kappa$ B activity, anti-inflammatory and antifibrotic activity. Vitamin D deficiency in diabetic patients, especially in patients with T1D, well studied and shown in numerous studies. The potential of vitamin D as a therapy for T1DM patients is evaluated in different aspects. Its immunomodulatory properties, anti-inflammatory effects etc. resulted in prevention and treatment of T1DM. However, it should be emphasized that many clinical intervention studies used various forms of vitamin D for the prevention of T1DM or in patients already affected with the disease, making results disappointing. However, whether vitamin D may have preventive effect on kidney function impairment in patients with DN remains unclear. Too few clinical studies dedicated to this issue. Additional clinical studies are needed to establish appropriate vitamin D dosage and form (cholecalciferol, alfalcidol or calcitriol) used as an adjuvant therapy with insulin treatment, adjusted for individual needs of diabetic patients (age, degree of vitamin D deficiency or insufficiency, duration of diabetes and current insulin needs, stage of DN), especially in pediatric patients with DN.

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