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ASSOCIATION OF SERUM VITAMIN D AND MICROALBUMINURIA IN DIABETIC NEPHROPATHY

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Abstract

Background: A number of health problems, particularly in those with Type-2 Diabetes Mellitus (T2DM) and its consequences, have been highly associated with vitamin D insufficiency. Therefore, the role of vitamin D in kidney disease among these patients is essential. The Urine Albumin to Creatinine Ratio (UACR) serves as an important marker for early kidney damage in T2DM patients. Emerging research indicates that vitamin D may be involved in controlling kidney function and preventing diabetic nephropathy. In exploring the link between serum vitamin D levels and UACR in individuals with type 2 diabetes, this review highlights the possible advantages of keeping vitamin D levels appropriate for kidney health. **Conclusion:** The available evidence reveals a possible link between low vitamin D levels and an increased risk of microalbuminuria in patients with type 2 diabetes. This link highlights the possible role of vitamin D in preserving renal health and managing diabetic nephropathy. While these findings are intriguing, more research is needed to validate them and evaluate whether vitamin D supplementation may effectively prevent or treat microalbuminuria in this population.

Keywords: Type 2 Diabetes Mellitus, Vitamin D, Urine Albumin to Creatinine Ratio, Diabetic Nephropathy.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic condition that has caused a significant number of premature deaths and morbidities in recent years. The surge in type 2 diabetes cases has emerged as a significant global health issue, with around 6.28% of the world's population, or approximately 462 million people, affected by the condition. In India, the situation is particularly alarming.

Recent studies from 2023 reveal that about 74.2 million adults in India have diabetes, positioning the country among those with the highest diabetes rates globally. This figure represents roughly 10.5% of the adult population, highlighting the substantial public health challenge that type 2 diabetes mellitus (T2DM) presents in India.[1,2] Type-2 Diabetes Mellitus (T2DM) is an increasingly prevalent condition worldwide, characterized by persistent high blood sugar levels due to insulin resistance and insufficient insulin production.[3]

This chronic disease not only burden healthcare systems but also significantly impacts patients' quality of life, largely due to its complications. One of the most serious complications is diabetic nephropathy, which is a leading cause of end-stage renal disease (ESRD). Early detection and management of kidney damage in T2DM patients are crucial, and the urine albumin to creatinine ratio (UACR) is a key marker used to identify early signs of kidney impairment.[4]

Vitamin D deficiency is common in individuals with T2DM and has been linked to a range of negative health outcomes, such as reduced insulin secretion, higher insulin resistance, and increased inflammation.[5] Vitamin D plays an essential role in maintaining kidney health by regulating calcium and phosphate balance, supporting immune function, and modulating the renin-angiotensin system.[6] Recent research suggests that sufficient levels of vitamin D may help to protect against diabetic nephropathy.[7,8]

Several studies have investigated the relationship between serum vitamin D levels and kidney disease in T2DM patients. A study by Obaid A, et.al., (2024)found a strong association between vitamin D deficiency and an increased risk of kidney disease among T2DM patients.[1]Another study by Liang Q, et.al., (2021)concluded that higher levels of vitamin D are correlated with a lower risk of microalbuminuria, an early indicator of kidney damage, in T2DM patients.[9]Additionally, a study by Al Ghadeer HA, et.al., (2022)indicates that vitamin D supplementation may improve kidney function and slow the progression of kidney disease in these patients.[10]

In this review, the current literature on the relationship between vitamin D levels and microalbuminuria in individuals with type 2 diabetes is examined. By compiling and analysing recent research, we hope to clarify how maintaining adequate vitamin D levels can help prevent early kidney damage and support overall kidney health in individuals with T2DM.

Vitamin D: Biochemical Overview and Activation

Understanding the pathophysiology of Type 2 Diabetes Mellitus (T2DM) is essential for assessing its complications. T2DM is characterized primarily by two defects: insulin resistance and beta-cell dysfunction. Insulin resistance affects tissues such as the liver, muscle and adipose tissue impairing their ability to effectively use insulin and leading to elevated blood glucose levels. This persistent hyperglycaemia contributes to a range of complications, including microvascular complications, such as diabetic nephropathy and macro-vascular complications that impact large blood vessels.[3]

Vitamin D, a fat-soluble vitamin, exists mainly in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 found predominantly in animal products like fish, meat, eggs, and dairy, undergoes a series of metabolic transformations to become biologically active.[11] In the skin, the provitamin 7-dehydrocholesterol is converted to previtamin D3 upon exposure to ultraviolet light. Vitamin D must undergo two hydroxylation processes to become fully active. 25-hydroxylase, mostly cytochrome P450 2R1, is the enzyme that initially transforms vitamin D into 25-hydroxyvitamin D [25(OH)D] in the liver.[5]After binding to Vitamin D Binding Protein (VDBP), this form of vitamin D is subsequently carried through the circulation.[6]

The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], or calcitriol, is produced in the kidneys during the second hydroxylation process. The synthesis of calcitriol is regulated by serum levels of calcium and phosphorus, as well as by parathyroid hormone (PTH).[12] Since 1,25$(OH)_2$D has a short half-life (about 15 hours), it is not considered to be a reliable indication of vitamin D levels. 25(OH)D concentrations in the blood are 500–1000 times greater than 1,25$(OH)_2$D concentrations because 25(OH)D is more stable in the blood than 1,25$(OH)_2$D. Consequently, serum 25(OH)D is considered to be the best biomarker of vitamin D status for assessing vitamin D insufficiency and deficiency.[13]

Role of Vitamin D in Diabetes Mellitus

Vitamin D is known for its antiproliferative, immunomodulatory, anti-inflammation, and stimulating cell differentiation functions. It is a hormonal molecule that participates in the homeostasis of calcium and phosphate. Additionally, it is also involved in the genomic (expression of genes) and non-genomic functions (glucose metabolism, enhancing insulin resistance, insulin secretion and stimulation of receptors associated with insulin). Its influence extends to metabolic processes, including those related to Type 2 Diabetes Mellitus (T2DM).[11] Vitamin D significantly impacts glucose homeostasis and insulin sensitivity. Calcitriol [1,25$(OH)_2$D] in its active state affects the production and activity of insulin which are essential for regulating blood glucose levels. Vitamin D Receptors (VDRs) in pancreatic β-cells play an important role in the progression of T2DM. A study by Argano C, et.al., (2023) found that vitamin D deficiency are linked to increased insulin resistance, insulin secretion and β-cell dysfunction in the pancreas and contribute to the development and progression of T2DM.[11,14]A study by Kumar S, et.al., (2020) highlight the connection between vitamin D deficiency and an increased risk of development of complications in T2DM. Deficiency of vitamin D is common among individuals with T2DM and is associated with poorer glycaemic control and a greater incidence of complications.[1,8]

Vitamin D is also linked to insulin sensitivity and control by promoting the expression of insulin receptors. Furthermore, vitamin D improves insulin sensitivity by stimulating the expression of peroxisome proliferator-activated receptor (PPAR) delta, a nuclear receptor fatty acid sensor that is broadly distributed and controls fatty acid levels in adipose tissue and skeletal muscle. Peripheral insulin resistance is largely caused by intracellular calcium, which results in a compromised signal transduction pathway and lower function of the glucose transporter.Through the regulation of cytokine production and effects, vitamin D administration restores glucose-stimulated insulin secretion and supports β-cell survival.By controlling intracellular calcium, vitamin D modulates depolarization-stimulated insulin release and controls the activity of calbindin-D28, a systolic calcium-binding protein present in pancreatic β-cell.The expression of calbindin-D28Khas been shown to protect beta-cells from cytokine-mediated cell death, thereby reducing the risk of type 2 diabetes.Research on the effects of vitamin D on insulin sensitivity and glucose metabolism is still ongoing.[15]

A lack of vitamin D is common and has been associated to a number of illnesses, such as diabetes, heart disease, and osteoporosis. Additionally, Diabetic Nephropathy and other problems linked to the disease can be prevented and managed with vitamin D. Obesity, which is frequently linked to hypovitaminosis D, raises the risk of type 2 diabetes. A considerable fraction of obese people are likely chronically vitamin D deficient because vitamin D is effectively stored in body fat storage, where it is no longer accessible. Increased PTH levels and other functional abnormalities are linked to vitamin D insufficiency in obese individuals. This secondary hyperparathyroidism may be linked to the development of cardiovascular disorders and glucose intolerance, both of which are linked to obesity.Vitamin D production is increased by PTH and insulin and thus acute insulin insufficiency in diabetes mellitus may result in a reduction in vitamin D synthesis. This is corroborated by the well-established fact that individuals with hyperparathyroidism are more likely to develop diabetes and insulin resistance.[16]

Individuals with limited sun exposure or dietary intake, the supplements can be an effective way to maintain adequate vitamin D levels. Maintaining adequate vitamin D

level is vital not only for bone health but also for glucose metabolism and insulin function. The recommended daily allowance (RDA) for vitamin D ranges from 600 to 800 IU for most adults. However, individuals with T2DM or those at risk of deficiency may require higher doses, which should be determined based on individual needs and in consultation with healthcare providers.[17] Supplementation with vitamin D has been shown to improve insulin sensitivity and lower HbA1c levels, making it a potential therapeutic approach for managing T2DM.[10]

Diabetic Nephropathy

Diabetic Nephropathy (DN), sometimes called Diabetic Kidney Disease (DKD), is the most frequent microvascular complication in patients with Type 2 Diabetes Mellitus. It is the primary cause of End-Stage Renal Disease (ESRD), which is linked to a high rate of morbidity and mortality. DKD is defined by the American Diabetes Association (ADA) as Chronic Kidney Disease caused by diabetes. Typically, this condition is indicated by a urine albumin to creatinine ratio (UACR) more than*/* equal to30 mg/g the sustained reduction in eGFR below 60 mL/min per 1.73 m^2. It can be staged into mild, moderate, and severe by utilizing quantitative measurements such as albumin excretion rate (AER), albumin- creatinine ratio (ACR), protein excretion rate (PER), and protein/creatinine ratio (PCR). Because urinary ACR is more standardized than PCR and has a stronger connection with 24-hour urinary albumin measurements, it was chosen to test urinary ACR.

Reduced glomerular filtration rate (GFR), increased urine albumin excretion, or both are indicators of diabetic kidney disease. Type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are both associated with diabetic kidney disease (DKA), a microvascular consequence.[18] Diabetic nephropathy affects 30 to 40% of individuals with diabetes mellitus. Insulin resistance, genetic factors, hyperglycemia, and an autoimmune mechanism are among the possible causes of diabetic nephropathy, while the actual reason is yet unclear. Diabetic nephropathy is characterized by continuous albuminuria (or an excretion rate of albuminuria exceeding 300 mg/d or 200 µg/min) assessed at least twice in a period of 3-6 months, a progressive decline in glomerular filtration rate (GFR) that frequently coexists with elevated blood pressure, and ultimately culminates in end-stage renal disease.[4]

Vitamin D signaling pathway in Diabetic Nephropathy

Vitamin D travels throughout the human body via the bloodstream, where it binds to Vitamin D Binding Protein (VDBP). The molecular weight of VDBP is 58 kDa which allows it to predict the blood levels of 25(OH)D3 bioavailability. Individuals with damaged kidneys have greater VDBP levels in their urine. Lower 25(OH)D concentrations are associated with an increase in albuminuria in the general population, as per the Third National Health and Nutrition Examination Survey (NHANES III). Patients with renal illness sometimes suffer from vitamin D insufficiency.Reduced CYP27b1 activity in human renalproximal tubule epithelial cells(PTECs) reduces the synthesis of $1,25(OH)_2D3$ while affecting 25(OH)D reabsorption.[8,10]

Biochemical role of Vitamin D in Diabetic Nephropathy

The development and progression of Diabetic Nephropathy (DN) is complicated and multifaceted, involving several routes and mediators. The development of Diabetic Nephropathy caused by aberrant homeostasis, which includes hemodynamic

abnormalities, metabolic issues, and hormone production such as Angiotensin-II.[4]Vitamin D contributes significantly to the pathophysiology of diabetic nephropathy (DN), principally through its effects on inflammation, oxidative stress, insulin resistance, and the renin-angiotensin system (RAS). [10]

i. **Insulin Resistance:** Reduced insulin synthesis and higher insulin resistance have been linked to vitamin D insufficiency. By influencing pancreatic β-cells and controlling calcium influx, which is required for insulin release, vitamin D supplementation can improve insulin sensitivity and glucose metabolism.Pancreatic β-cells express both VDR and CYP27B1. Vitamin D directly affects the β-cells of the pancreas through its binding to VDR. The VDR response element in the insulin gene promoter was found in pancreatic β-cells, indicating that calcitriol directly increases the release of insulin.

ii. **Podocyte Injury:** Podocytes are responsible for maintaining the kidney's glomerular filtration barrier. The proteins that make up the slit diaphragm are nephrin, podocin, and podocalyxin. The kidney filtration structure will sustain additional damage when proteins and other big molecules start to show up in urine due to a lack of slit diaphragm integrity. In line with proteinuria, DKD causes nephrin, podocin, and podocalyxin expression to decrease in podocytes while nephrin, podocin, and podocalyxin secretion is raised in the urine. Consequently, glomerulosclerosis and proteinuria have podocyte damage as one of their main causes. Vitamin D protects podocytes by decreasing inflammation and oxidative damage. It also contributes to the structural and functional integrity of the slit diaphragm proteins, which are required for podocyte function

iii. **Inflammation and Oxidative Stress:** Vitamin D is anti-inflammatory and antioxidant. It reduces the levels of pro-inflammatory cytokines and Reactive Oxygen Species (ROS), which are high in diabetic nephropathy patients. Because oxidative stress inhibition improves a characteristic of streptozotocin-induced DN, it has been observed that oxidative stress plays a role in DN. An important aspect of the pathophysiology of DN is increased ROS brought on by hyperglycemia. The polyol chain, AGE, and NADPH oxidase (Nox) are the primary contributors of ROS in diabetes. The primary enzyme involved in the generation of reactive oxygen species (ROS) in the kidneys is isoform Nox 4. The onset and progression of Diabetic Nephropathy (DN) have been linked to higher levels of inflammatory markers in the blood, including IL-6, TNF-α, TGF-β1, and IL-18.

iv. **Renin-Angiotensin-AldosteroneSystem (RAAS):** Reduced proteinuria and well-maintained renal function are hallmarks of chronic kidney disease (CKD), which is characterized by the Renin-Angiotensin-Aldosterone System (RAAS) and its suppression has been demonstrated to slow its progression. Numerous studies have examined the function of RAAS in diabetes in connection to alterations in intraglomerular hemodynamics and structural modifications to the glomerulus and tubulointerstitium. Numerous RAAS constituents, including prorenin, mineralocorticoids, and Ang-II receptors (AIIR), have been demonstrated to be expressed by podocyte cells. Ang-II type 1 receptors (AT1R) have been demonstrated to regulate this crucial podocyte function.[4,8]

Microalbuminuria

Microalbuminuria (MA) is one of the earliest markers of diabetic nephropathy, indicating early kidney damage.Microalbuminuria is defined as a persistent elevation

of albumin in the urine of >30 to <300 mg/d (>20 to <200 µg/min), which can progress to more severe forms of kidney disease if not managed appropriately. The development of microalbuminuria in T2DM patients is influenced by various factors, including glycemic control, hypertension, and vitamin D levels.[19] The relationship between microalbuminuria and vitamin D insufficiency has been explained by a number of different processes. Urine ACR is more standardized than PCR and has a stronger connection with 24-hour urinary albumin measurements, it was chosen to test urinary ACR.

- Mildly increased albuminuria (<30mg/g or mg/day)
- Moderately increased albuminuria (30-300 mg/g or mg/day)

Urine albumin excretion measured or predicted to be between 30 and 300 mg/g or mg/day is considered moderately elevated albuminuria (formerly known as microalbuminuria). The phrase was changed to emphasize that albumin is harmful in any level, even below the threshold for moderately elevated albuminuria, as a rise in albumin predicts a greater risk of renal and cardiovascular disease in the future. Assuming an average creatinine excretion rate of 10 mmol/day or 1g/day, the relationship between PER and PCR as well as that between AER and ACR are reliant upon this.[20]

DISCUSSION

Vitamin D, which is crucial for overall health, has a major impact on kidney function and glucose metabolism.[21] Many studies have focused on its effects on microalbuminuria, a precursor to diabetic nephropathy in Type 2 Diabetes Mellitus (T2DM). The present study delves into the correlation between microalbuminuria and vitamin D levels, as well as the potential impact of vitamin D status management on kidney function in individuals with diabetes. According to Seyed Alireza Zomorodian, et al.'s study in 2022 in patients with type 2 diabetes mellitus, 25(OH)D serum levels were inversely correlated with albuminuria as a sign of diabetic nephropathy. A 25(OH)D serum level of less than 21 ng/ml may be predictive of macroalbuminuria. One of the ways that vitamin D protects the kidneys is by lowering inflammatory cytokines like TGF-β and pro-fibrotic growth factors. Furthermore, the primary renal damage factor in diabetic nephropathy, the renin-angiotensin-aldosterone system (RAAS), may be suppressed by it. Studies have shown that individuals with significant albuminuria are more likely to be vitamin D deficient.[21]

Additionally, a study by Muhammad Khudayar, et al. (2022) concluded that serum vitamin D and Type 2 Diabetes Mellitus (T2DM) had an inverse relationship. According to this study, 83.2% of T2DM patients had vitamin D insufficiency, which is a very high frequency. In summary, vitamin D insufficiency may play a role in the pathophysiology of type 2 diabetes and vitamin D supplements may help to treat the complications of type 2 diabetes. Restoring serum vitamin D levels may help cure glycemia and enhance insulin secretion in T2DM patients who also have concurrent vitamin D insufficiency.[22] According to a study by David Galuška, et.al.,(2021), low serum vitamin D levels are linked to increased microalbuminuria in diabetic patients. This implies that the early phases of kidney damage associated with diabetic nephropathy may be influenced by a vitamin D deficit.[23] Ho-Yin Huang, et.al.,(2023) in their study also found a correlation between vitamin D supplementation and lower levels of microalbuminuria in type 2 diabetics. According to this, increasing vitamin D levels may help prevent

early diabetic kidney damage by enhancing glucose metabolism and lowering inflammatory responses.[8]

Additional research by Yangyang Wang et al. (2019) confirms these results, observing that those with reduced microalbuminuria also had greater vitamin D levels. This implies that vitamin D has a preventive role against kidney injury.[23] However, a research by Liangbin Zhao, et al., (2023) found a complicated, nonlinear association between microalbuminuria and vitamin D levels, suggesting that while low levels are associated with increased microalbuminuria, overtly high levels may not always provide extra advantage.[24] A study by Sevgican Demir, et al., (2021) found that vitamin D insufficiency was prevalent in T2DM patients who had renal problems. This indicates that supplements could be a useful additional therapy for diabetic nephropathy.[25] Moreover, a research by Sharma et al. (2021) showed that individuals with sufficient vitamin D levels saw a decreased incidence of microalbuminuria, supporting vitamin D's possible preventive effect in preserving kidney health.[26]

According to a study by Qian Liang et.al., (2021) the relationship between 25(OH)D and UACR is negative when 25(OH)D is less than 67 nmol/L. Consequently, the 25(OH)D threshold was found to be 67nmol/L. UACR dropped by 8.7 mg/g for every 1 nmol/L rise in 25(OH)D. For the purpose of sensitivity analysis, they also found that there was an inconsistent trend in the impact sizes between the two sides of the Generalized Additive Model (GAM), indicating a non-linear connection between 25 (OH)D and UACR. This criterion states that owing to aging, nutrition, lack of sun exposure, decreased outdoor activity, and other factors, 50–80% of the world's population is thought to be vitamin D deficient or inadequate.[10]

In the elaborate study, the prevalence of diabetic nephropathy among patients with type 2 diabetes was 30.1%; of these individuals, 25.6% had microalbuminuria and 4.5% had macroalbuminuria.[10] These percentages were reported in some studies: According to Tauseef Ahmad, et al., (2017), 31.56% of diabetic patients had microalbuminuria.[27] Muhammad Ahsan Sana, et al. (2020) found that 32.9% of diabetic patients had microalbuminuria.[28]A study by Young Bin Kim, et.al, (2021) demonstrate the negative effects of vitamin D deficiency on albuminuria and diabetic nephropathy because in vitro study showed that vitamin D has a protective effect in the kidneys by reducing levels of transforming growth factor and Suppressorof Mothers against Decapentaplegic homolog 3 (SMAD3) proteins, which are involved in renal fibrosis and oxidative stress.[29]

While reviewing the findings, most of the researchers highlight the functioning and reducing the risk of microalbuminuria in T2DM. Ensuring adequate vitamin D intake through diet, sunlight exposure or vitamin D supplements which may prove to be a valuable strategy for managing and preventing Diabetic Nephropathy.[23,24]

CONCLUSION

The potential link between vitamin D deficiency and microalbuminuria suggested that screening and managing vitamin D levels in T2DM patients may be beneficial for prevention of diabetic nephropathy. Supplementation with vitamin D could be a promising strategy to improve kidney outcomes in these patients. However, further research is needed to establish the efficacy and safety of vitamin D supplementation in the prevention and management of diabetic nephropathy.[12]

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