





REVIEW PAPER

## Vitamin D – a key player in diabetes management – a review

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### ABSTRACT

**Introduction and aim.** Diabetes mellitus is a major health concern around the world and requires new management strategies. Several investigations have shown the connection between a lack of vitamin D and diabetes and its complexities. The objective of this review was to investigate the impact of vitamin D on maintaining glucose levels.

**Material and methods.** The material and methods section of this review involved conducting a literature review. This process included searching databases such as PubMed Crossref, Google Scholar, Scopus, Web of Science, Embase, and the Cochrane Library for studies examining the relationship between vitamin D levels and complications of diabetes. These databases were selected to ensure a comprehensive exploration of the existing literature to provide a comprehensive analysis of the relationship between vitamin D status and diabetic complications.

**Analysis of the literature.** Vitamin D plays an important role in preventing macrovascular and microvascular complications such as diabetic retinopathy, diabetic neuropathy, diabetic kidney disease, and diabetic foot ulcer in people with diabetes mellitus. Correcting vitamin D deficiency through optimal dosages of vitamin D supplements is an effective way to address the management and prevention of macrovascular and microvascular complications in diabetic individuals. This review emphasizes the critical importance of vitamin D supplementation for individuals with diabetes mellitus as it significantly maintains optimal blood glucose levels and reduces diabetes-associated risks.

**Conclusion.** Vitamin D is vital for managing and preventing diabetes complications. It stabilizes blood glucose levels and reduces risks of complications like retinopathy, neuropathy, kidney disease, and foot ulcers. Including it in diabetes management is crucial for better health outcomes.

**Keywords.** diabetes mellitus, diabetic complications, vitamin D deficiency

### Introduction

Diabetes mellitus is a chronic metabolic condition in which blood glucose levels increase due to an absolute or relative impaired ability to produce insulin and may be associated with peripheral resistance to the action of insulin.<sup>1</sup> Due to the increasing incidence of diabetes mellitus, it is a major health concern worldwide.<sup>2</sup> Vitamin D is vital in bone health, immune function, and calcium regulation.<sup>3</sup> In addition to this function, most related studies have shown promising results for

the correlation between Vitamin D and diabetes mellitus.<sup>4</sup> For example, a cross-sectional study by Vijay et al. found that individuals with diabetes mellitus had significantly lower levels of vitamin D compared to those without the condition.<sup>5</sup> Another study conducted by Wu et al. explores factors such as age, ethnicity, lifestyle habits, genetics, and seasonal variation i.e. vitamin D deficiency mostly occurs during winter which is also linked to the progression of type 2 diabetes mellitus (T2DM).<sup>6</sup> A meta-analysis conducted by Hu et al.

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demonstrated that vitamin D supplementation was associated with improved glycemic control.<sup>7</sup> Therefore, due to the increasing prevalence of diabetic complications, it is important to determine the role of vitamin D in the prevention and management of diabetic complications in diabetic individuals.<sup>8</sup> However, the association between vitamin D levels and diabetes mellitus complications in diabetic individuals is still under investigation.

### Aim

This review aimed to investigate the impact of vitamin D on maintaining glucose levels and preventing complications in individuals with diabetes mellitus.

### Material and methods

The material and methods section of this review involved conducting a literature review. This process included searching databases such as PubMed Crossref, Google Scholar, Scopus, Web of Science, Embase, and the Cochrane Library for studies examining the relationship between vitamin D levels and complications of diabetes. These databases were selected to ensure a comprehensive exploration of the existing literature to provide a comprehensive analysis of the relationship between vitamin D status and diabetic complications.

### Analysis of the literature

#### *Vitamin D and its importance*

Vitamin D is a fat-soluble vitamin that is also called calciferol and has two primary forms that are D2 and D3.<sup>8–10</sup> Both vitamin D2 and D3 are biologically inactive forms that are activated by two enzymatic reactions in the liver and kidney.<sup>9,10</sup> Vitamin D2 (ergocalciferol) cannot be produced within the human body so it can be generated from either plants or supplements. Vitamin D2 and D3 both help in calcium and phosphorus absorption.<sup>8,10</sup> Vitamin D3 (cholecalciferol) synthesis occurs in the skin through the action of ultraviolet B (UVB) radiation.<sup>9–12</sup> Vitamin D3 can be obtained from dietary sources such as fatty fish, eggs, and dairy. Calcidiol, also known as 25(OH)D, is a form of vitamin D used to assess vitamin D levels.<sup>12</sup> It acts as an intermediary before being converted to calcitriol.<sup>8,9,11</sup> Calcitriol (1,25(OH)<sub>2</sub>) is the active form of vitamin D.<sup>9–11</sup>

A deficiency in vitamin D is a serious concern that can be worsened by factors such as limited sunlight exposure, lower dietary intake, malabsorption, and chronic disease related to the liver or kidney.<sup>10–12</sup> It is necessary to recognize the consequences of low vitamin D levels for public health to increase awareness and implement strategies, especially in areas with limited sunlight and different lifestyles.<sup>13</sup>

This study aims to provide novel insights into the association between vitamin D deficiency and diabetes

mellitus and explore potential mechanisms and therapeutic implications.

#### *The relationship between vitamin D and diabetes*

Pancreatic beta cells are responsible for insulin production and also express vitamin D receptors.<sup>14</sup> Therefore, various studies have been conducted to investigate the relationship between vitamin D deficiency and diabetes which is a favorable area of research. Low levels of vitamin D are associated with insulin-related issues such as insulin resistance and impaired insulin secretion which are important factors in diabetes.<sup>14</sup> Additionally, vitamin D protects against autoimmune mechanisms that lead to diabetes.<sup>3,15</sup> In contrast, some studies conducted by Szymczak-Pajor et al., Xiao et al., and Zhao et al. suggest that vitamin D supplementation could be beneficial for preventing and managing diabetes and diabetes-associated complications.<sup>14,16</sup>

Vitamin D insufficiency is linked to diabetes complications such as diabetic foot ulcers, diabetic retinopathy, diabetic neuropathy, and diabetic kidney disease.<sup>16,17</sup> However, well-designed clinical trials with detailed studies are needed to determine the underlying mechanism involved.

#### *HbA1c and vitamin D*

Hemoglobin A1c (HbA1c) is used for diagnostic purposes to determine whether a patient has diabetes mellitus if the blood sugar levels are abnormally elevated over the previous 2 to 3 months.<sup>18</sup> Monitoring HbA1c levels is essential in reducing the risk of complications associated with diabetes for guiding the treatment and management of the condition.<sup>18</sup> Recent studies have shown that high-dose vitamin D supplements can help reduce HbA1c levels and improve blood glucose levels by enhancing beta cell function and insulin sensitivity and reducing inflammation.<sup>14,19</sup> Obesity is linked to vitamin D deficiency and insulin resistance.<sup>20</sup> In addition to insulin sensitivity and anti-inflammatory properties, it's worth noting that there is substantial evidence to the contrary regarding the assertion that vitamin D helps in muscular function, as suggested by studies such as Bislev et al.<sup>21</sup> Specifically, vitamin D strengthens skeletal muscles that enhance glucose utilization by promoting insulin sensitivity and facilitating glucose transport into muscle cells. That leads to efficient glucose utilization and stable HbA1c results.<sup>21–23</sup> However, further research is needed to determine the optimal dosage and duration of vitamin D for effectively managing HbA1c levels in diabetic individuals.

#### *Diabetic peripheral neuropathy and vitamin D*

Diabetic peripheral neuropathy (DPN) is a condition that causes nerve damage and affects both sensory and motor functions. DPN presents with symptoms such as tingling, numbness, and weakness in the extremities.<sup>24</sup>

Numerous studies have demonstrated a correlation between inadequate levels of vitamin D and neuropathic symptoms in patients with diabetes mellitus. These findings suggest that vitamin D deficiency may worsen DPN by increasing oxidative stress and inflammation, which can exacerbate nerve damage.<sup>25</sup> Vitamin D protects nerves by reducing oxidative stress, facilitating nerve tissue repair, and maintaining calcium balance.<sup>25,26</sup> Additionally, it promotes the immune system by reducing inflammation through the reduction of oxidative stress and helps in managing DPN.<sup>26</sup> Nerve growth factor (NGF) is necessary for nerve tissue regeneration and deficiency in vitamin D is associated with decreased NGF levels.<sup>27</sup> Studies conducted by Putz et al., Habib et al. and Ou et al. have conducted studies exploring the relationship between vitamin D and diabetic neuropathy, highlighting its potential therapeutic implications.<sup>25,28</sup> Therefore, several studies suggest that restoring vitamin D levels or promoting NGF expression may improve nerve impairment and can be used for the therapeutic management of DPN.<sup>26,28</sup>

Thus, vitamin D can play a protective role in DPN by reducing oxidative stress, facilitating nerve tissue repair, and maintaining calcium balance which will be a useful resource for managing and preventing DPN.

#### ***Diabetic nephropathy or diabetic kidney disease and vitamin D***

Diabetic nephropathy is also known as diabetic kidney, and this is a condition in which deterioration of kidney function results from an increased excretion of urine albumin or a decreased glomerular filtration rate (GFR).<sup>29</sup> Several studies suggest that a low level of vitamin D can cause the overexpression of renin.<sup>30</sup> This overexpression can ultimately lead to the activation of the renin-angiotensin-aldosterone system (RAAS), which contributes to kidney damage.<sup>30</sup> Another possible way that a low level of vitamin D can cause diabetic kidney disease (DKD) is by progressing to kidney damage via renal fibrosis and impairing podocyte function, which leads to glomerular damage and proteinuria.<sup>31,32</sup> Studies conducted by Zhang ZH et al. (2020) on animals have shown that vitamin D deficiency increases the levels of fibrogenic factors and collagen deposition, which promotes renal fibrosis.<sup>32</sup> Therefore, managing vitamin D deficiency is essential in treating diabetic kidney disease.

#### ***Diabetic foot ulcer and vitamin D***

The practical guidelines formulated by the International Working Group on the Diabetic Foot (IWGDF) defined diabetic foot ulcer (DFU) as symptoms secondary to current or previous diabetes, including skin chapping, ulceration, infection, or destruction of foot tissue.<sup>33</sup>

Vitamin D helps in wound healing through its anti-inflammatory effects.<sup>16,34,35</sup> Vitamin D receptor (VDR)

expression in wound margin tissues (T-VDR) is directly proportional to the level of vitamin D.<sup>36</sup> Decreased expression of T-VDR due to low levels of vitamin D in diabetic individuals is also a risk factor for the onset of DFU.<sup>36</sup> Vitamin D plays a crucial role in tissue restoration as well as the stimulation of antimicrobial peptides (AMPs) like cathelicidin and  $\beta$  defensin 2. This has been supported by the study conducted by Lowry MB et al. on a mouse model that demonstrated the effect of vitamin D on the expression of the human cathelicidin antimicrobial peptide gene expression.<sup>37</sup> Cathelicidin and  $\beta$  defensin 2 also participate in the wound healing process.<sup>37</sup> Thus, supplementation with vitamin D can increase the secretion of antimicrobial peptides making the affected foot healing process faster.<sup>37,38</sup>

Furthermore, insufficient vitamin D levels hinder the angiogenesis process resulting in a lack of nutrients and oxygen supplied to the injury site. This leads to increased inflammation and oxidative stress, which hinder the tissue repair process and worsen the condition.<sup>38</sup> Therefore, addressing low vitamin D levels is necessary for the effective management of DFU in promoting wound healing and tissue repair which offers innovative approaches for managing DFU.

#### ***Diabetic retinopathy and vitamin D***

Diabetic retinopathy (DR) is one of the common causes of vision loss among diabetic individuals.<sup>39</sup> Vitamin D plays a crucial role in regulating angiogenesis, which is the process of forming new blood vessels. In DR, abnormal neovascularization in the retinal tissue impairs vision.<sup>40</sup> In an animal model study done by Li et al., where vitamin D has been shown to reduce vascular endothelial growth factor (anti-VEGF) which decreases retinal vascular permeability and retinal capillary cell apoptosis.<sup>40,41</sup> Additionally, in vitro model studies conducted by Lazzara et al., have also shown that the thioredoxin-interacting protein/ Nod-like receptor protein 3 (TXNIP/ NLRP3) pathway was activated due to increased reactive oxygen species (ROS) production induced by high glucose.<sup>40,42</sup> Studies conducted by Li et al., Lazzara et al., and Tecilazich et al. have shown vitamin D can cause inhibition of the TXNIP/NLRP3 pathway and act as an anti-VEGF agent, which may serve as an effective marker of the progression, prevention, and treatment of DR.<sup>40-42</sup> Additionally, low vitamin D levels intensify inflammation and oxidative stress, leading to further retinal damage.<sup>42,43</sup> Lower vitamin D levels correlate with higher DR incidence and severity among type 2 diabetes patients.<sup>44,45</sup> Furthermore, the exact optimal vitamin D dosage for preventing DR by which vitamin D regulates angiogenesis and inhibits retinal damage in diabetic retinopathy, provides valuable insights for preventive and therapeutic interventions.<sup>41,45</sup>

## Conclusion

This literature review explores the associations between vitamin D and diabetes mellitus, emphasizing the potential of taking vitamin D supplementation to maintain optimal blood glucose levels, which can prevent and manage microvascular diabetic complications. However, further research is needed to determine the optimal dosage of vitamin D supplementation for effective prevention and management of diabetes-associated risks in individuals with diabetes mellitus. This study has the potential to highlight the crucial role of vitamin D in managing diabetes, which could significantly improve the quality of life for the millions of people affected by this condition.

## Declarations

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### Author contributions

Conceptualization, N.P. and M.H.; Validation, N.P. and M.H.; Resources, N.P. and M.H.; Writing – Original Draft Preparation, N.P.; Writing – Review & Editing, N.P.; Supervision, M.H.; Project Administration, N.P.

### Conflicts of interest

All authors declare that they have no conflicts of interest.

### Data availability

Data sharing not applicable – no new data generated.

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