

## ROLE OF VITAMIN D ON IL-6 IN TYPE 2 DIABETES MELLITUS: LITERATURE REVIEW

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### ABSTRACT

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*Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels, insufficient insulin secretion by pancreatic cells, insulin resistance, and inadequate insulin secretory compensatory response. Various reports have shown that low-grade chronic inflammation is associated with the risk of developing T2DM. In recent years, studies have suggested that increased concentrations of circulating inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and high-sensitivity C-reactive protein (hs-CRP) have been reported may increase the incidence of T2DM. Recently it has been found that vitamin D plays a role not only in bone remodeling, but as an immunomodulator. Administration of vitamin D therapy suppresses the proliferation of T cells and monocytes and downregulates proinflammatory cytokines including CRP, TNF- $\alpha$ , Interleukin-1, 6, 8, and increases the production of the anti-inflammatory cytokine IL-10. A literature review was carried out to collect the latest results from several studies regarding the role of vitamin D on IL-6 in type 2 diabetes mellitus. The literature sources were taken from journal articles published online in the period 2017-2021. The databases used are MDPI, PubMed, ScienceDirect, Wiley, and Hindawi. The results of the literature review*

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*show various findings. Several studies showed a significant difference and no significant difference in IL-6 after vitamin D administration clinically or statistically. Additional studies are needed to specifically examine the optimal dose of vitamin D to reduce IL-6-mediated inflammation in T2DM, determine the best dose between calcemic and immunomodulating effects, and the role of vitamin D in inflammation so that it can be an effective adjunct therapy in the treatment of T2DM.*

**KEYWORDS**

Vitamin D, Interleukin-6, Type 2 Diabetes Mellitus



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## INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels and can cause microvascular and macrovascular complications in the heart, blood vessels, eyes, kidneys, and nerves. More than 90% of diabetes mellitus cases are type 2 diabetes mellitus (DMT2), a condition characterized by insufficient insulin secretion by pancreatic cells, insulin resistance, and inadequate compensatory insulin secretory response. The development of this disease leads to the inability of insulin secretion to maintain glucose homeostasis leading to hyperglycemic conditions (AyuNuari, Andriswana, Ramadhan, & Listyoweni, 2022).

According to the International Diabetes Federation (IDF), in 2021 there will be 537 million adults aged 20-79 years worldwide (10.5% of all adults in this age group) who have diabetes (Anjastika, Haryati, & Kholifah, 2022). In 2030 it is estimated that 643 million people and by 2045, 783 million adults aged 20-79 years are projected to be living with diabetes. According to the IDF, Indonesia is ranked 5th in 10 countries with the highest prevalence of diabetes in adults in the world in 2021, with 19.5 million people. It is estimated that in 2045, Indonesia will experience an increase in the number of DMT2 patients to 28.6 million people (Pandanwangi, Ali, & Meriska, 2022).

There is a strong relationship between hyperglycemia, oxidative stress induced by hyperglycemia, inflammation and the development of T2DM. Various reports have shown that chronic low-grade inflammation is associated with the risk of developing T2DM and that subclinical inflammation contributes to insulin resistance and is associated with the characteristics of the metabolic syndrome which includes hyperglycemia (Nafilah, Zuniarto, & TW, 2022).

In recent years, increasing evidence has shown that T2DM is evolving from a metabolic disorder to an inflammatory disease and that reducing inflammation may have a beneficial effect on insulin resistance. Some evidence has suggested that increased concentrations of circulating inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and high-sensitivity C-reactive protein (hs-CRP), may increase the incidence of DMT2. Interleukin 6 (IL-6) is a multifunctional cytokine involved in the pathophysiology of T2DM. Increased circulating IL-6 is an independent predictor of T2DM and is thought to be involved in the development of inflammation, insulin resistance, and  $\beta$ -cell dysfunction (Karsidin, Wahyuni, & Dwiyantri, 2022).

Vitamin D deficiency is very common in people with T2DM. It has also been reported to impair insulin secretion and increase peripheral insulin resistance as a major

risk factor for the development of T2DM as well as a predictor of abnormalities in most of the variables monitored in patients with the metabolic syndrome (Fauzia, Karsidin, & Dewi, 2021). The biologically active vitamin D metabolite, 1,25-Dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), has been shown to have immunomodulatory or anti-inflammatory effects. Therefore, we conducted a literature review on the pathophysiology, mechanism of IL-6, and the role of vitamin D on IL-6 levels in patients with type 2 diabetes mellitus.

## RESEARCH METHOD

The author conducted a search, selection, and selection of literatures using the literature review method regarding the role of vitamin D on IL-6 in type 2 diabetes mellitus with the keywords Vitamin D, Interleukin-6, and Type 2 Diabetes Mellitus. The literature sources used, namely MDPI, PubMed, ScienceDirect, Wiley, and Hindawi published in the last 5 years, 2017-2021, and clinical trials obtained a number of 53 journals. Writing begins by reviewing the contents of each literature that meets the author's criteria, brainstorming, and cross-checking with other primary sources. The results of the discussion are arranged in an organized format starting from the pathophysiology of T2DM, IL-6, vitamin D, and vitamin D to the levels of IL-6 in T2DM.

## RESULT

Research on the effect of vitamin D on type 2 diabetes mellitus with parameters of IL-6 and blood sugar levels has been carried out both in animal trials and clinically in humans by providing vitamin D supplementation for a certain time. A trial study on mice with poor vitamin D deficiency and T2DM by (Weichao Wang, Zhang, Wang, Wang, & Liu, 2019) which looked at mRNA and protein expression in pancreatic tissue showed high expression of the inflammatory cytokine TNF- $\alpha$ , IL-1 $\beta$ , IL-8 and IL-6 which increase the occurrence of insulin resistance. A 9-week trial in animals that were given 1,25(OH)<sub>2</sub>D<sub>3</sub> with low, medium, and high doses via intragastric gavage showed that fasting blood sugar, CRP, and IL-6 levels decreased significantly compared to a control group that was not given the vitamin D. The results of trials of giving supplementation to experimental animals have the potential to effectively reduce the incidence of T2DM (Ayuditiawati, Zuniarto, Mundzir, & Tamala, 2021).

The intervention treatment using 40,000 IU of cholecalciferol for 24 weeks in individuals with T2DM with complications of peripheral neuropathy found that clinical manifestations, cutaneous microcirculation, and inflammatory markers IL-6 were significantly decreased (2.5 pg/mL vs. 0.6 pg/mL,  $p < 0.001$ ) and an increase in IL-10 (2.5 pg/mL vs. 4.5 pg/mL,  $p < 0.001$ ). However, no change was found in the 5000 IU/week supplementation group (Yuniuswoyo, Mundzir, & Fatullah, 2021). A randomized controlled trial in individuals with T2DM and vitamin D deficiency who were given cholecalciferol 30,000 IU/week for 6 months showed significantly higher levels of vitamin D (25(OH)D) ( $p < 0.0001$ ) and decreased hs-CRP and TNF- $\alpha$  concentrations. significant ( $p < 0.0001$ ) compared to the placebo group, but not significant reductions in IL-6 concentration ( $p = 0.1$ ), fasting blood sugar ( $p = 0.9$ ), and HbA1C levels ( $p = 0.85$ ) Various studies have shown a significant or insignificant decrease in the concentration of IL-6 in T2DM. Based on a systematic review study and meta-analysis of randomized controlled trials in 2018 the effect of vitamin D

supplementation on plasma IL-6 concentrations was evaluated in 5 studies and after intervention, 3 studies had a reduced mean IL-6 concentration in subjects given vitamin D supplementation and 2 studies with only the IL-6 results did not change. Moreover, only one study showed a significant difference and there was no statistical difference in the other studies. Thus, the results showed no significant effect of vitamin D supplementation on plasma IL-6 concentrations (standard mean difference, -0.48 [95% CI -1.36 to 0.41],  $p = 0.29$  when compared to the control group).

Research by (Wang, Zhang, Wang, Wang, & Liu, 2019), showed a negative correlation between serum 25(OH)D levels in T2DM patients and serum TNF- $\alpha$  ( $r = -0.705$ ,  $P < 0.001$ ), IL-1 $\beta$  ( $r = -0.661$ ,  $P < 0.001$ ), IL-8 ( $r = -0.645$ ,  $P < 0.001$ ) and IL-6 ( $r = -0.609$ ,  $P < 0.001$ ) and the involvement of 25(OH)D in increasing inflammation with the incidence of insulin resistance through the NF- $\kappa$ B pathway. IL-6 levels were significantly higher in T2DM patients compared to healthy controls and spearman correlation analysis revealed that PTPN2 was negatively correlated with IL-6 ( $r = 0.2014$ ,  $P = 0.043$ ). Anti-inflammatory effect of vitamin D and resistance training in men with T2DM and vitamin D deficiency, it was found that the concentration of IL-6 ( $p = 0.001$ ) changed significantly in all groups (Vitamin D + resistance training with % -71.73, resistance training with % -65.85, vitamin D with % -61.70). The main effect of the test ( $P = 0.001$ ), group ( $P = 0.001$ ) and the interaction between group and test ( $P = 0.001$ ) in the IL-6 analysis was statistically significant (TW, 2021). The anti-inflammatory effect of the combination of sitagliptin with vitamin D3 on the cytokine profile of T2DM patients stated that no significant changes were found in IL-6, IL-21, and TGF- $\beta$  cytokine levels between patients and control subjects. Tests conducted on hemodialysis T2DM patients who were given vitamin D supplementation did not show any statistically significant changes in IL-6 gene expression. In patients with diabetic retinopathy who were given  $\beta$ -glucan supplementation plus vitamin D, the level of IL-6 did not experience a significant change (2.49 to 2.54 pg/ml) (Haryati & Pratiwi, 2020).

## **DISCUSSION**

Inflammation is one of the pathological mechanisms of insulin resistance. The inflammatory response begins when IL-1 and TNF- $\alpha$  are released from the inflammatory center which results in a cascade of changes including the release of IL-6, acute-phase reactants such as fibrinogen and hs-CRP (Karsidin, Subagja, & Permatasari, 2020). Apart from this, it is known that vitamin D can suppress inflammatory reactions by regulating immunological reactions of macrophages and monocytes, as well as lowering IL-6 concentrations. In vitro, vitamin D can enhance the differentiation of monocytes into macrophages, prevent the release of inflammatory cytokines, and reduce the ability to present antigens to lymphocytes by inhibiting the cell surface expression of class 2 major histocompatibility complex molecules (MHC-II). Vitamin D can also suppress the proliferative and stimulating ability of T cells and monocytes and downregulate proinflammatory cytokines, including C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), and IL-6 in LPS-induced macrophages via the MAPK pathway, IL-1 and IL-8, COX-2, intercellular adhesion molecule (ICAM)1, and B7-1 molecule in macrophages by increasing anti-inflammatory cytokines such as IL-10 (Zuniarto, Nuari, & Nuryana, 2020). Similar observations have also been shown from observational studies in healthy

populations and populations with proinflammatory conditions such as diabetes, arteriosclerosis, and inflammatory polyarthritis (Karsidin, Zakiah, & Biaskawati, 2020).

The acquired vitamin D deficiency may be associated with upregulation of NF- $\kappa$ B activity in T2DM patients (Nafi'ah & Nurulhuda, 2020). This is due to the promotion of inflammation that occurs through an increase in the proportion of p-p65/RelB as a key molecule in NF- $\kappa$ B signaling. In this signaling pathway, p65 protein acts as a pro-inflammatory while RelB has an anti-inflammatory role. Activation of NF- $\kappa$ B begins with the degradation of the I $\kappa$ B protein which gives way to the NF- $\kappa$ B subunits to migrate into the nucleus and induce transcription of proinflammatory genes. Activation of the NF- $\kappa$ B signaling pathway follows-as well as in the regulation of a large number of physiological processes and regulates many genes such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6. Vitamin D downregulates NF- $\kappa$ B transcription dependent on genes encoding proinflammatory cytokines such as IL-6. Recent studies have also shown that 1,25-dihydroxyvitamin D can also inhibit I $\kappa$ B protein degradation and decrease p65 NF- $\kappa$ B expression in adult human adipocytes. In addition, 1,25 dihydroxyvitamin D can also inhibit p65 NF- $\kappa$ B translocation to the adipocyte nucleus. Therefore, vitamin D can reduce the secretion of proinflammatory cytokines. Vitamin D receptors in immune cells can participate in the late stages of hydroxylation, calcitriol formation, and reduce pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 which are often identified as key components in the development of insulin resistance and the incidence of T2DM. The absence of vitamin D receptors has been shown to increase the activity of NF- $\kappa$ B as a transcription factor that plays a key role in inflammation and immunoregulation. Treatment with vitamin D can inhibit NF- $\kappa$ B translocation and attenuate NF- $\kappa$ B activity.

Several investigators have found an inverse relationship between 25(OH) D and inflammatory markers such as CRP, TNF- $\alpha$ , and IL-6 in patients with T2DM. The interventions also showed inconsistent findings. Some have found that vitamin D supplementation has an effect and no effect in reducing CRP, TNF- $\alpha$ , IL-6 and increasing IL-10. Patients with the metabolic syndrome given vitamin D therapy can produce significant reductions in IL-6 but do not alter CRP concentrations. The REGARDS study demonstrated an association between low serum 25(OH)D and elevated levels of IL-6, CRP, and no association with IL-10 was found. At the same time, the active form of vitamin D has been shown to reduce the production of TNF- $\alpha$ , IL-6, and stimulate the production of IL-10 by immune cells. The results of this study appear to be consistent with previously reported data regarding the association between 25(OH)D levels and inflammatory markers, but a significant decrease in IL-6 and an increase in IL-10 was seen only in patients receiving high doses of vitamin D (40,000 IU per week) to reach normal 25(OH)D levels. These findings suggest that normalization of serum 25(OH)D with high-dose cholecalciferol treatment affects inflammatory markers.

Based on, patients with vitamin D deficiency had 23% higher IL-6 levels compared to those with normal vitamin D levels. A number of studies have shown that inflammation appears to be one of the most important factors in the development of diabetic nephropathy closely related to the number of inflammatory cells in the kidney. Increased concentrations of inflammatory cytokines have been previously documented in T2DM patients and a recent study showed that TNF- $\alpha$  and IL-6 levels were found to be higher in patients with nephropathy than in T2DM patients without nephropathy. Vitamin D supplementation can reduce the development of diabetic nephropathy by decreasing the production of TNF- $\alpha$  and IL-6.

Insulin resistance is closely related to obesity. In obesity, adipocyte hypertrophy and hyperplasia cause impaired blood flow which makes the tissue hypoxic, inflamed, and infiltrated by macrophages. This disorder is characterized by increased levels of IL-6, IL-8, resistin, TNF- $\alpha$ , and monocyte chemoattractant (MCP1) as well as changes in adiponectin secretion. Studies have shown that 1,25 dihydroxyvitamin D can increase protein I $\kappa$ B as an inhibitor of NF- $\kappa$ B by increasing mRNA stability and decreasing phosphorylation of I $\kappa$ B, IL-6, MCP-1, and macrophage activation.

Consumption of vitamin D and physical activity can cause significant changes in inflammatory markers. IL-6 has a dual role in the regulation of insulin signaling and glucose metabolism in skeletal muscle. Increased glucose uptake in skeletal muscle by IL-6 occurs with stimulation of AMPK and PI3K activity. Exercise significantly induces the production and release of IL-6 into the circulation via skeletal muscle. An acute increase in plasma IL-6 is followed by an increase in plasma levels of IL-10 and interleukin-1 receptor agonist (IL-1ra), both of which are known to have inhibitory effects on the production of pro-inflammatory cytokines, TNF- $\alpha$  and IL-1. Thus, exercise-induced release of IL-6 has a protective role against systemic inflammation and improves insulin sensitivity globally. It was also found that the induction of SOCS3 expression by IL-6 in skeletal muscle cells did not decrease insulin action as in adipocytes and hepatocytes.

In the study (Dadrass, Mohamadzadeh Salamat, Hamidi, & Azizbeigi, 2019), there was the most significant reduction in inflammation in the group with vitamin D intake combined with resistance training. Therefore, it can be concluded that vitamin D intake combined with exercise training can lead to greater improvement in several inflammatory markers than with one single therapy. Vitamin D supplementation had no significant effect on IL-6 and TNF- $\alpha$  levels in the intervention group, compared to the placebo group. However, cytokine levels in the intervention group decreased after vitamin D supplementation. Although there are studies that show vitamin D has no effect on levels of inflammatory markers, vitamin D deficiency has a pathophysiological relationship with elevated levels of inflammatory markers, particularly IL-6. Findings from a meta-analysis did not show a statistically significant impact of vitamin D supplementation on TNF- $\alpha$  and IL-6. However, from another clinical study, vitamin D supplementation of circulating biomarkers (TNF- $\alpha$ , IL-6) in T2DM patients was reported to be decreased. In addition, *in vitro* studies have shown that vitamin D can inhibit IL-6 production and can be directed against IL-6 to reduce the incidence of T2DM. Unfortunately, in this meta-analysis there was no evidence of changes in TNF- $\alpha$  and IL-6 concentrations in T2DM subjects. Moreover, in the subgroup analysis, there was no significant effect on TNF- $\alpha$  and IL-6 status. This may be due to insufficient data in several randomized controlled trials on vitamin D, TNF- $\alpha$ , and IL-6 supplementation. Therefore, it is hoped that more randomized controlled trials will be conducted in the future to analyze the relationship between vitamin D and IL-6 supplementation in subjects with T2DM.

In the study (Sosale, Chandrashekar, Ramachandra Aravind, Renuka, & Anupama, 2017) a decrease in hsCRP, TNF- $\alpha$ , and IL-10, and an increase in IL-6 were observed in both groups compared to baseline. The lack of unidirectional changes in inflammatory cytokines in the group receiving vitamin D compared to the control group, suggests that vitamin D supplementation has no significant effect on inflammatory cytokine levels. The study by (Borzouei et al., 2019), also found that there was no significant change in the serum levels of IL-6, a cytokine from Th17 cells, in T2DM patients.

Stepanova et al. concluded in a single-center randomized trial that the group receiving 40,000 IU of cholecalciferol per week for a period of six months showed improvement in serum IL-6 ( $p = 0.017$ ). Unfortunately, in the analysis of the study by (Borzouei et al., 2019), vitamin D treatment did not support the hypothesis because the observed changes in IL-6 concentrations were not significant in this DMT2 subject. This could be attributed to the fact that the dose of vitamin D was lower in this study (30,000 IU/week). Vitamin D supplementation for 12 weeks in hemodialysis diabetic patients downregulated IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$  gene expression compared with placebo, but did not affect IL-4 and IL-6 gene expression (Fauzia & Khusnia, 2020).

## CONCLUSION

In conclusion, there is still much debate on the role of vitamin D in modulating IL-6 in T2DM. Further research is needed to determine the optimal dose of vitamin D to reduce inflammation mediated by IL-6, especially in T2DM. Further research is needed to determine the best dose between calcemic and immunomodulating effects given that vitamin D also has hypercalcemic and bone remodeling effects. More specific research can also be done on the role of vitamin D in inflammation, so that it can be used as an effective strategy in the therapy of T2DM. Lastly, a larger sample size in studies is needed to confirm the anti-inflammatory effect of vitamin D. In addition, additional research will help in expanding our understanding of how vitamin D ameliorates inflammation in patients with T2DM.

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