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THE ROLE OF VITAMIN D IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

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ABSTRACT
Vitamin D deficiency has been associated with decreased insulin release, insulin resistance, and type 2 diabetes in experimental and epidemiological studies. Animal studies have shown that 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) stimulates pancreatic cells to secrete insulin. Genetic polymorphisms of vitamin D-related genes may predispose to impaired glycemic control and type 2 diabetes. The aim of this study was to determine the causality of vitamin D to type 2 diabetes. The method used was to search for articles and theories related to vitamin D and diabetes mellitus. Epidemiological studies have shown an association between low serum 25-hydroxyvitamin D3 (25(OH)D3) concentrations and an increased risk of metabolic syndrome and type 2 diabetes. This may be partly explained by increased fat mass. The results of the search for theories and articles indicate that a possible causal relationship between vitamin D deficiency and type 2 diabetes must be proven by randomized clinical trials showing that type 2 diabetes can be prevented or that insulin release and insulin sensitivity can be improved by vitamin D supplementation.

Keywords: diabetes mellitus; resistance; vitamin D

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INTRODUCTION

Vitamin D is one of the important micronutrients needed by the body in certain amounts which functions to regulate most of the coordination of body functions including biochemical and physiological functions to maintain health. Deficiency of this micronutrient is one of the main problems in the health sector in the world because it plays a role in increasing morbidity and mortality rates.(Putri et al., 2024). Various nutrients are needed by the body in certain amounts to meet its needs in the role of development and health conditions. Diet is closely related to a person's health condition. Poor diet will cause the body to experience nutritional deficiency conditions. This condition can be prevented through various methods such as nutritional education, implementing a healthy diet, and through the provision of food supplements.(Godswill et al., 2020).

Vitamin D, a type of fat-soluble prohormone, is synthesized in response to sunlight. Vitamin D undergoes two metabolic conversions, 25-hydroxylation in the liver and 1-alpha-hydroxylation in the kidney, to become the active hormone. The active form, 1-alpha,25-(OH)2D, binds to the vitamin D receptor (VDR) to regulate gene transcription and maintain mineral ion balance. Vitamin D has several roles in the body, including influencing bone health and serum calcium and phosphate levels. In addition, vitamin D can modify immune function, cell proliferation, differentiation, and apoptosis. Vitamin D deficiency has been linked to a variety of health problems, including type 1 and type 2 diabetes.(Basit, 2013).

The prevalence of vitamin D deficiency in Indonesia reaches 50% of the total population from various groups including pregnant and lactating mothers, newborns, adolescents, and health workers. Exposure to sunlight and intake of foods rich in vitamin D determine the status of vitamin D in a person's body. Sources of vitamin D Most of it comes from skin exposed to

sunlight and the rest comes from food. Vitamin D formed by sunlight is in the form of D3 (cholecalciferol) and is synthesized in the human body, while vitamin D2 (ergocalciferol) is found in food. Low vitamin D status inhibits the body's cellular response, which can increase the risk of disease(Rimahardika et al., 2017). In addition, vitamin D deficiency can also cause high susceptibility to falls and fractures and bone deformities. Therefore, vitamin D is very important for maintaining body homeostasis.(Putri et al., 2024).

Diabetes mellitus (DM) is currently a problem in Public Health and is one of four non-communicable diseases that are priority targets for follow-up. The prevalence and number of Diabetes cases have continued to increase over the past few decades.(Godswill et al., 2020). Data from the International Diabetes Federation (IDF) shows that the number of diabetes sufferers in the world in 2021 reached 537 million. This figure is predicted to continue to increase to 643 million in 2030 and 783 million in 2045. According to the IDF, Indonesia is ranked fifth in the country with the highest number of diabetes with 19.5 million sufferers in 2021 and is predicted to be 28.6 million in 2045 (Widiyawati & Sumrahadi, 2024). The aim of this study was to determine the causality of vitamin D to type 2 diabetes.

METHOD

This study is a study by tracing articles and cases that meet the inclusion criteria for the benefits of vitamin D in people with type 1 and 2 diabetes. After several articles were found, conclusions were drawn from several articles by making points related to the inclusion criteria. keywords in the article search are vitamin D, type 1 and 2 diabetes and articles and theories with a search year of no more than 10 years.

RESULT

Diabetes Mellitus type II (DM II) is a worldwide disease with a rapidly growing parallel prevalence and adversities affecting multi-body systems. Hence, it is imperative to treat DM II effectively, maintaining glucose homeostasis to avoid complications such as diabetic nephropathy, peripheral neuropathy, and retinopathy. Vitamin D, among many benefits, has positive outcomes on hemoglobin A1c (HbA1c) control. It aids in insulin secretion and sensitivity. We systematically screened four databases for relevant information; PubMed, Medline, PMC, and Google scholar. Inclusion and exclusion criteria were applied, and quality appraisal was then done using certain checklist tools: Newcastle-Ottawa tool, AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist, SANRA (Scale for the Assessment of Narrative Review Articles) checklist, and Cochrane bias assessment. Data were collected from 14 articles, of which eight are systematic reviews and meta-analysis, one is a narrative review, five are randomized controlled trials and three are general information about DM II and Vitamin D. In addition, this article evaluates the clinical significance of Vitamin D administration in DM II from a glucose homeostasis perspective, and complications such as nephropathy, neuropathy, and retinopathy. Vitamin D had a clinical positive impact on glucose level, particularly on hemoglobin A1c (HbA1c) reduction, alleviation of diabetic neuropathy and nephropathy symptoms, and hyperglycemia induced-oxidative stress on the retinal cells.

Table 1.
Categorization of Vitamin D Levels

<10 ng/ml	Severe deficiency
10-24 ng/ml	Mild to moderate deficiency
25-80 ng/ml	Optimal Levels
>80ng/ml	Toxicity possible

Table 2.

Current DRI Recommendations for Vitamin D

The following are recommendations for vitamin D in DRIs developed by the Food and Nutrition Board at the Institute of Medicine. DRIs are a general term for a set of reference values used to plan and assess nutrient intakes for healthy people. These values, which vary by age and sex, include: Recommended Dietary Allowance (RDA): The average daily intake level sufficient to meet the nutritional needs of almost all (97-98%) healthy people. Adequate Intake (AI): Established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.	
Infant	
0-6 months	AI: 400 IU (10 µg/day)
7-12 months	AI: 400 IU (5 µg/day)
Children	
1-3 years	AI: 600 IU (15 µg/day)
4-8 years	AI: 600 IU (15 µg/day)
Older Children and Adults	
9-70 years	AI: 600 IU (15 µg/day)
Adults>70 years	AI: 800 IU (20 µg/day)
Pregnancy and Lactation	AI: 600 IU (15 µg/day)

DISCUSSION

Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disease with hyperglycemic manifestations caused by impaired insulin secretion, insulin function, and both. The diagnosis of Diabetes mellitus is based on fasting Blood Sugar Levels (KGD) ≥126 mg/dl, or KGD ≥200 mg/dl 2 hours after the Oral Glucose Tolerance Test (OGTT), or random KGD ≥200 mg/dl with classic complaints of hyperglycemia (polyuria, polydipsia, polyphagia), and HbA1c ≥6.5%(Mutmainna, 2019).

Vitamin D

There are two main forms of vitamin D: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by plants (especially fungi and yeast), while vitamin D3 is synthesized in the skin when exposed to ultraviolet B rays from sunlight.Vitamin D3 is also found in some foods such as fatty fish.. Unfortunately, it is very difficult to get enough vitamin D from food sources alone. Both vitamin D2 and vitamin D3 can be made synthetically and used to enrich foods such as dairy products, margarine, and soy milk as well as to make dietary supplements.The synthetic form of vitamin D3 comes from animal sources and is currently the most commonly used form of vitamin D in supplements and fortified foods.. Dietary forms of vitamin D are absorbed in the small intestine along with dietary fat and other fat-soluble vitamins, whereas vitamin D3 enters the circulation after being synthesized nonenzymatically in the skin during exposure to ultraviolet light from sunlight. Neither vitamin D2 nor vitamin D3 has a biological function in the body until they undergo a two-step metabolic process. Metabolism of the various forms of vitamin D requires conversion in the liver and kidneys, and the active form, 1,25-dihydroxyvitamin D (calcitriol), must bind to the vitamin D receptor (VDR) before biological action can occur.Therefore, diabetic patients with liver or kidney problems are at high risk for deficiency, as are patients with digestive tract disorders such as celiac disease, pancreatitis, low bile levels, or sprue. (Safarpour et al., 2020).

In the past, the main source of vitamin D for humans was exposure to sunlight. One common cause of vitamin D deficiency today is lack of exposure to sunlight.Another cause is the lack of food sources containing vitamin D.. Since the industrial revolution, few people have been exposed to sunlight while working. Other barriers to sun exposure include fear of skin cancer, leading to increased use of sunscreen, hats, and other sun protection. For some, religious

beliefs require that their skin be covered. Environmental factors such as pollution and lack of sunlight exposure during the winter (especially in northern latitudes around∼37°) also reduces vitamin D synthesis from sun exposure.35 In addition, aging skin and darker skin require longer sun exposure to initiate vitamin D synthesis. It has been suggested that∼5–30 minutes of sun exposure between 10:00 a.m. and 3:00 p.m. at least twice a week on the face, arms, back, or legs (without sunscreen) is usually sufficient for vitamin D synthesis. Skin exposed to sunlight indoors, for example through a glass window, will not produce vitamin D.(Wijayanti et al., 2021). The most accurate way to determine vitamin D status is to measure 25-hydroxy vitamin D [(25(OH)D)]. The optimal range is 25–80 ng/ml.(Khan et al., 2018).

The Food and Nutrition of The Institute of Medicine (IOM) recently updated the Daily Reference Intake (DRI) for vitamin D. The IOM recommends 600 IU/day of vitamin D for individuals aged 9–70 years and 800 IU/day for those aged >70 years. However, it has been recommended that supplementation with vitamin D3 should be prescribed with the goal of achieving serum 25(OH)D levels of at least 40 ng/mL, possibly as high as 60 ng/mL.(Yu et al., 2018).

Vitamin D Deficiency and Diabetes

Vitamin D deficiency has been widely reported to be associated with several diseases including DM. Some evidence suggests that vitamin D has an effect on the pathogenesis of DM due to insulin resistance and pancreatic beta cell dysfunction.(Kartika & Wibowo, 2020). Vitamin D deficiency can be caused by low vitamin D intake, decreased vitamin D synthesis in the skin, and decreased absorption of vitamin D in the intestine. In immune cells, vitamin D works as an immunomodulator that affects various levels of immune response. Administration of vitamin D can reduce the expression of pro-inflammatory cytokines through the Nuclear Factor-Kappa Beta (NF-Kb) pathway, so that the levels of pro-inflammatory cytokines such as TNF α, IL-1 β, and IL-6 can decrease. Vitamin D also functions to lower blood glucose by increasing insulin sensitivity, peripheral tissue glucose uptake, and glycogen synthesis in the liver. Vitamin D will specifically be bound in plasma by alpha 2-globulin protein(Kokoroko & Sanda, 2019).

Hydroxylation in liver microsomes forms 25-hydroxy-cholecalciferol (25(OH)D), this form will stimulate the enzyme 1 alpha hydroxylased kidney (proximal tubule mitochondria) to convert into its active form of 25-hydroxy-cholecalciferol to 1,25-dihydroxy-cholecalciferol (1,25(OH)2D). The active form of 1,25 OHD will bind to pancreatic beta cells vitamin D receptors which will stimulate insulin receptors to increase insulin sensitivity and pancreatic beta cell resistance, thereby reducing proinflammatory cytokines and insulin resistance which has an impact on decreasing blood glucose levels.(Kalra et al., 2020).

Vitamin D deficiency is common in people with Diabetes which can cause uncontrolled Diabetes. However, giving vitamin D supplementation to people with Diabetes can help in achieving better control of blood glucose levels. The results of several studies on the effects of vitamin D supplementation in patients with Diabetes showed a significant increase in serum insulin. The mechanism may be due to the presence of vitamin D receptors on pancreatic cells and the expression of 1 alpha-hydroxylase in them. Meta-analysis studies have shown that vitamin D supplementation is associated with decreased fasting blood sugar and HbA1C levels in people with type 2 Diabetes who are deficient in vitamin D(Kartika & Wibowo, 2020). Vitamin D can inhibit NF-KB activity by increasing IκKB expression and also suppressing TNF-α production. Zittermann et al. argued that high 25(OH)D3 concentrations are needed to maintain adequate calcitriol concentrations, which can also

suppress proinflammatory cytokines, thus resulting in decreased blood glucose levels.(Safarpour et al., 2020).

In a meta-analysis study aimed at looking at the results of vitamin D supplementation on blood sugar levels in diabetes patients, researchers found that vitamin D supplementation with a minimum dose of 100μg/hr (4000 IU/hr) significantly reduced fasting blood glucose, HbA1c, and insulin resistance index, and increased insulin sensitivity in DM patients.(Prasetia et al., 2021). After conducting a meta-analysis and review of the impact of vitamin D and calcium on blood sugar control in patients with type 2 diabetes, vitamin D and calcium deficiencies appear to impair blood sugar control and that supplementation of both nutrients may be necessary to optimize glucose metabolism.(Kardina et al., 2021). An observational study from the Nurses Health Study involving 83,779 women aged > 20 years found an increased risk of type 2 diabetes in those with low vitamin D status. A combined daily intake of > 800 IU vitamin D and 1,000 mg calcium reduced the risk of type 2 diabetes by 33%. The National Health and Nutrition Examination Survey (NHANES) III study between 1988 and 1994 showed a strong inverse association between low 25(OH)D levels and the prevalence of diabetes.(Dewi & Syagata, 2024). Low vitamin D levels have also been shown to predict future development of type 2 diabetes. One study showed that increasing serum vitamin D levels to normal reduced the risk of developing type 2 diabetes by 55%. As with most diseases and vitamin D, prospective studies of vitamin D supplementation and diabetes are scarce and limited. Prospective trials of vitamin D and diabetes to date have either been too small or used inadequate amounts of vitamin D.(Larasati, 2023).

Mechanism of action of vitamin D

Based on growing evidence, vitamin D deficiency may be a contributing factor in the development of both type 1 and type 2 diabetes. First, insulin-secreting β cells in the pancreas have been shown to contain the vitamin D receptor (VDR) as well as the enzyme 1-alpha hydroxylase. Evidence suggests that treatment with vitamin D improves glucose tolerance and insulin resistance. Vitamin D deficiency results in reduced insulin secretion. Supplementation with vitamin D has been shown to restore insulin secretion in animals. Researchers have also found an indirect effect on insulin secretion, possibly through the effect of calcium on insulin secretion. Vitamin D contributes to the normalization of extracellular calcium, ensuring normal calcium flux through cell membranes; therefore, low vitamin D levels may reduce the ability of calcium to influence insulin secretion.Other potential mechanisms associated with vitamin D and diabetes include enhancing insulin action by stimulating insulin receptor expression, enhancing insulin response to glucose transport, having indirect effects on insulin action, possibly through the effects of calcium on insulin secretion, and ameliorating systemic inflammation through direct effects on cytokines. (Apriliana Setyo Hadi et al., 2020).

Vitamin D and the Immune System

The classic function of vitamin D is to enhance intestinal calcium absorption by regulating several calcium transport proteins in the small intestine. However, various cells express the vitamin D receptor (VDR) and the vitamin D-activating enzyme 1-α-hydroxylase. Various cells of the immune system also express the VDR and 1-α-hydroxylase. Thus, cells of the immune system respond to vitamin D in a paracrine or autocrine manner. Immune system cells that express the VDR and 1-α-hydroxylase are macrophages, T cells, dendritic cells, monocytes, and B cells. Vitamin D is involved in the regulation of innate immunity by enhancing the organism's defense system against microbes and other pathogenic organisms and modulating the adaptive immune system through direct effects on T-cell activation, phenotype, and function of antigen-presenting cells.(Setyawati & Lestarini, 2022).

Vitamin D and Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is a chronic disease with early onset and is the result of immune-mediated destruction of pancreatic β cells. There is variation in incidence. Studies have shown a higher incidence of vitamin D deficiency in patients with type 1 diabetes. One environmental factor that is thought to play a protective role against the development of type 1 diabetes mellitus is early supplementation with vitamin D.(Chang et al., 2000). Several large case-control studies have shown a significantly reduced risk of type 1 diabetes mellitus in infants supplemented with vitamin D compared with those not supplemented. In addition, the incidence of type 1 diabetes was found to be lower in infants born to mothers given cod liver oil during pregnancy. A Finnish cohort study evaluated the effect of vitamin D supplementation on rickets and the development of type 1 diabetes mellitus. An 80% reduction in the risk of developing type 1 diabetes mellitus was found in children receiving >2000 IU of vitamin D/day compared with those receiving less or no vitamin D supplementation. Vitamin D supplementation can prevent type 1 diabetes mellitus, but once pancreatic beta cell destruction has occurred, it has no therapeutic role in reversing type 1 diabetes mellitus.(Apriliana Setyo Hadi et al., 2020).

Observational studies have also shown that low vitamin D status may be associated with an increased risk of type 1 diabetes. Hypponen et al. conducted a cohort study in northern Finland. They collected data over a 1-year period on 10,821 children regarding the dose of vitamin D supplementation and the presence of rickets suspected of being associated with the development of type 1 diabetes. Their findings were significant and surprising; children who took 2,000 IU of vitamin D daily had an 80% lower risk of developing type 1 diabetes.This suggests that it is important for all children to take vitamin D supplements during their first year of life to avoid the development of type 1 diabetes. (Indriyani & Tjahjono, 2018).

Another study regarding vitamin D conducted by(Zipitis & Akobeng, 2008)showed that vitamin D supplementation in early childhood reduced the risk of developing type 1 diabetes by 29% compared to children who were not given vitamin D supplements. In addition, the researchers found evidence indicating a dose-response effect. Because β-cell damage typically begins in infancy or early childhood and continues until type 1 diabetes is diagnosed, studies such as this are interesting in the context of vitamin D use in people with type 1 diabetes.It is hoped that starting vitamin D supplementation soon after birth may be a protective strategy against the development of type 1 diabetes. (Indriyani & Tjahjono, 2018). However, studies are lacking regarding the appropriate dose and duration of vitamin D supplementation in infants and children. Currently, 400 IU of vitamin D3 is recommended for supplementation in all infants until sufficient formula, milk, or other food sources are consumed to meet the 400 IU/day requirement.Although it seems prudent and reasonable to provide vitamin D supplements to infants, children, and adolescents to prevent deficiency, there is a discrepancy in the recommended doses of vitamin D. (Kusumastuty et al., 2021).

Currently, evidence supports that maintaining adequate vitamin D status during pregnancy, lactation, infancy, and childhood may help prevent type 1 diabetes. However, it is still unknown whether genetic factors for type 1 diabetes increase the risk of vitamin D deficiency or conversely, whether vitamin D deficiency increases the risk of type 1 diabetes.(Septiana & Tjahjono, 2015). In addition, studies supporting the use of vitamin D to enhance the treatment of type 1 diabetes after diagnosis are lacking.Only a few intervention studies have evaluated the impact of vitamin D supplementation in reversing type 1 diabetes, and the results have been inconclusive.

CONCLUSION

It was concluded that Vitamin D acts in numerous ways on different systems, and its receptors present in many organs. Upon reviewing several studies, the role of Vitamin D was found to be beneficial in DM II for controlling blood glucose level and hemoglobin A1c level. It increases both insulin sensitivity and insulin secretion. Vitamin D suppresses the inflammatory state in DM II, which in diabetic peripheral neuropathy is crucial. Also, Vitamin D improves nerve conduction and hastens wound healing in cases of diabetic foot. Moreover, it acts as a potent analgesic. In case of diabetic nephropathy, it is very important to maintain its control as it can lead to end-stage renal disease. It was noted that in post-Vitamin D administration urinary albumin excretion decreased.

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