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Role of Vitamin D in Diabetes Mellitus: A Review

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ABSTRACT

Diabetes mellitus (DM), also known as simply diabetes, is a group of metabolic diseases with high blood sugar levels over a prolonged period, which produces the symptoms of frequent urination, increased thirst, and increased hunger. Untreated, diabetes can cause many complications. There are three main types of diabetes mellitus: Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, and Gestational Diabetes Mellitus. The human body is continuously exposed to different types of agents that result in the production of reactive species called free radicals (ROS/RNS), which cause the oxidation of cellular machinery, the body has endogenous antioxidant systems, or it obtains exogenous antioxidants from the diet that neutralizes such species and keeps the homeostasis of the body. Any imbalance between the RS and antioxidants leads to a condition known as oxidative stress. Oxidative stress is increased in metabolic syndrome and type 2 diabetes mellitus. Increased oxidative stress leads to insulin resistance, dyslipidemia, β-cell dysfunction, and impaired glucose tolerance, ultimately leading to T2DM. Vitamin D deficiency has been linked to the onset and progression of DM. The link of vitamin D with insulin insensitivity or abnormal glucose metabolism gained much more scientific attention in the last decade. Several observations or associations were cited, exploring the possible role of altered vitamin D status and its metabolites or altered insulin sensitivity in the pathogenesis of diabetes.

The basic aim of this review was to summarize the basics of oxidative stress in diabetes mellitus and avoid it through Vit D administration.

Keywords: Diabetes mellitus, vitamin D, antioxidants, insulin

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INTRODUCTION

Diabetes mellitus is a disease that has no borders, it manifests itself when the body does not control the amount of glucose (a type of sugar) in the blood and the kidneys make a large amount urine, occurs when the body does not produce enough insulin or does not consume it the way it should (1). The World Health Organization (WHO) states that the number of people with diabetes increased from 108 million in 1980 to 422 million in 2014. The prevalence of this disease continues to increase rapidly in low- and middle-income countries, not behaving in the same way in high-income countries (2,3).

Diabetes mellitus is a group of metabolic disorders characterized by elevated levels of glucose in the blood (hyperglycemia) and insufficiency in the

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production or action of insulin produced by the pancreas inside the body (4). Insulin is a protein (hormone) synthesized in beta cells of the pancreas in response to various stimuli such as glucose, sulphonylureas, and arginine; however, glucose is the major determinant (5). Vitamin D deficiency and *diabetes mellitus* are two common conditions in the elderly population. Vitamin D deficiency is currently a topic of intense interest and is prevalent across all ages, races, geographical regions, and socioeconomic strata. A suboptimal vitamin D status contributes to many conditions, including osteomalacia, osteoporosis, falls, and fractures (6,7).

1. Epidemiology of diabetes mellitus:

It is estimated that 366 million people had DM in 2011; by 2030, this would have risen to 552 million. The number of people with type 2 DM is increasing in every country, with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011 (8). It is estimated that 439 million people will have type 2 DM by the year 2030. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors (9). It is predicted that the prevalence of DM in adults, of which type 2 DM is becoming prominent, will increase in the next two decades, and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years (10).

2. Etiology:

Diabetes mellitus is a chronic metabolic disorder characterized by elevated levels of blood glucose (hyperglycemia) resulting from a combination of genetic and environmental factors. Its etiology is multifaceted and involves two primary forms: type 1 diabetes and type 2 diabetes. Type 1 diabetes is primarily an autoimmune disease, where the body's immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas [11]. Genetic predisposition plays a significant role, and environmental triggers, such as viral infections, may also contribute to its development. Type 2 diabetes, the more prevalent form, typically develops in adulthood, though it can occur in children and adolescents as well. It results from a complex interplay of genetic factors and lifestyle choices, notably obesity, physical inactivity, and an unhealthy diet.

In this form, the body becomes insulin resistant, meaning the cells do not respond effectively to insulin, and the pancreas struggles to produce enough insulin to maintain normal blood glucose levels. While genetics predispose some individuals to diabetes, lifestyle modifications, such as maintaining a healthy weight, engaging in regular physical activity, and adopting a balanced diet, are crucial in preventing and managing this chronic disease. Early diagnosis and appropriate medical care are essential to mitigate its complications and improve the quality of life for those affected [12,13].

3. Types of diabetes mellitus:

1. Type 1 diabetes:

Type 1 diabetes can be characterized by destruction of the pancreatic islets of beta cells and total insulinopenia, according to Ozdemir et al. (14), is one of the most frequent chronic diseases of childhood, the incidence of which is increasing, especially in children under 5 years of age; It significantly affects the health of the population, especially through its chronic or long-term complications, which cause frequent morbidity and significantly reduce life expectancy (15).

2. Type 2 diabetes:

Type 2 diabetes is a chronic, degenerative, and incurable but controllable disease, it is considered one of the chronic diseases with the greatest impact on the quality of life of the world population and constitutes a real health problem; belongs to the group of diseases that cause physical disability due to its various multi-organ difficulties, with an undoubted increase in morbidity and mortality in recent years (16,17).

3. Gestational diabetes mellitus (GSD):

GSD has been defined by Ozdemir et al. (14) as any carbohydrate intolerance diagnosed during

pregnancy. The prevalence of this disease is approximately 2 to 5% of normal pregnancies. However, diabetes is mostly classified into TWO major types: Type I Diabetes (Insulin Dependent Diabetes Mellitus: IDDM) and Type II

Pathophysiology of diabetes mellitus:

Whenever somebody eats a meal, there is a rise in blood glucose levels that stimulates insulin secretion, resulting in an increase in transportation, biotransformation, and storage in muscles and fat tissues. In fasting conditions, the glucose in the blood is provided by the liver and is used by the brain without any dependency on insulin. Besides the storage of glucose, insulin also inhibits the secretion of glucagon and lowers the concentration of serum fatty acids, leading to a decline in liver glucose production (19). Insufficient insulin or resistance to insulin in the body results in reduced tissue uptake of glucose, which results in intracellular hypoglycemia and extracellular hyperglycemia. The intracellular hypoglycemia causes glucogenesis and gluconeogenesis that leads to fats breakdown (causing diabetic ketoacidosis) and decreases protein synthesis and gamma globulins (causing cachexia, polyphagia, and impaired wound healing), while the extracellular hyperglycemia leads to hyperglycemic coma and osmotic dieresis (20).

Diabetes mellitus, a chronic metabolic disorder, encompasses a range of pathophysiological processes that ultimately lead to elevated blood glucose levels. The two primary forms, type 1 and type 2 diabetes, have distinct pathophysiological mechanisms.

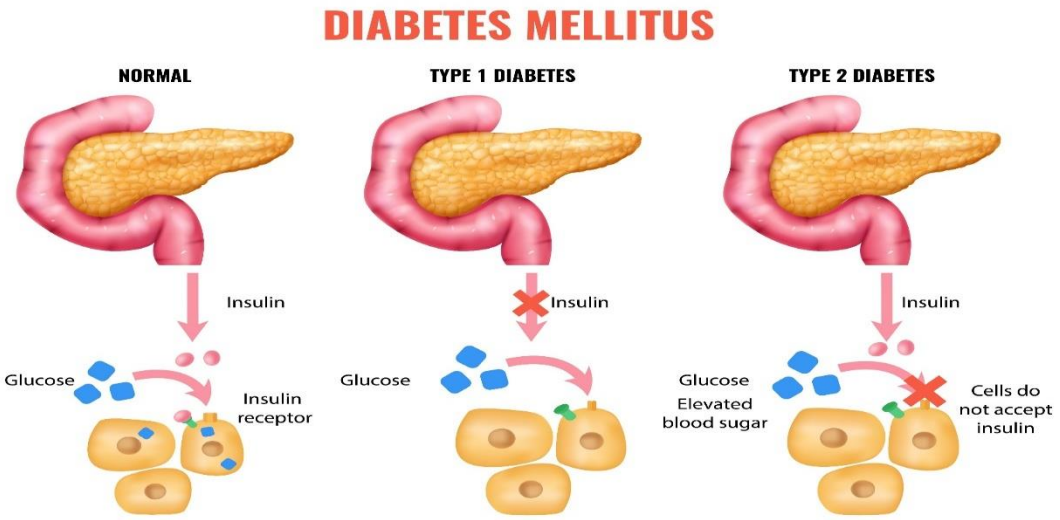

Figure 1. Pathophysiology of diabetes mellitus (18)

Type 1 Diabetes:

Type 1 diabetes is characterized by the autoimmune destruction of insulin-producing beta cells in the pancreas. This process begins when a genetic predisposition is triggered by environmental factors, such as viral infections. Immune cells mistakenly recognize beta cells as foreign invaders, launching an autoimmune attack that leads to their destruction. As a result, insulin production decreases or ceases entirely. Without sufficient insulin, glucose cannot enter cells for energy, leading to hyperglycemia. The lack of insulin in type 1 diabetes causes several pathophysiological effects: Hyperglycemia: Elevated blood glucose levels result from the inability to transport glucose into cells. Ketosis: In the absence of insulin, the body breaks down fat for energy, producing ketones, which can lead to diabetic ketoacidosis. Gluconeogenesis: The liver

produces excess glucose, further contributing to hyperglycemia (21).

Type 2 Diabetes:

Type 2 diabetes primarily involves insulin resistance and impaired insulin secretion. Genetic factors play a significant role, but environmental factors like obesity and sedentary lifestyles are crucial contributors. Insulin resistance means that body cells do not effectively respond to insulin, requiring the pancreas to produce more insulin to maintain glucose control. Pathophysiological processes in type 2 diabetes include Insulin Resistance: Cells, especially in muscle, liver, and adipose tissue, become resistant to insulin's signaling, making it challenging for glucose to enter cells. Beta Cell Dysfunction: Over time, the pancreas may not produce enough insulin, or the insulin it produces is less effective. Excess Gluconeogenesis: The liver continues to produce glucose, contributing to hyperglycemia. Incretin Hormone Dysregulation: Disruption in hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) affects insulin secretion and glucose control. Lipotoxicity: Increased fat deposits in muscle and liver cells lead to impaired insulin action. Chronic Inflammation: Inflammation, often linked to obesity, further exacerbates insulin resistance (22). Understanding the complex pathophysiological processes involved in diabetes is critical for developing effective treatment strategies and preventive measures.

Diabetic Complications:

Diabetes is a sort of disorder in which the patients are at all times at risk of complications. Complications may be macrovascular (coronary heart disease, peripheral vascular disease, and stroke), microvascular (neuropathy, retinopathy, and nephropathy), and both micro- and macrovascular (diabetic foot). The mortality and morbidity of diabetes are associated more with macrovascular degeneration as compared to the risks of microvascular complications in older people (23,24). In general, complications of diabetes mellitus can be categorized into two groups (25).

Metabolic acute complications:

These are short-term and include hypoglycemia, ketoacidosis, and hyperosmolar non-ketotic coma.

1.6.2. Systemic late complications: These are long-term chronic complications that include diabetic nephropathy, microangiopathy, diabetic neuro- and retinopathy, atherosclerosis, and infections.

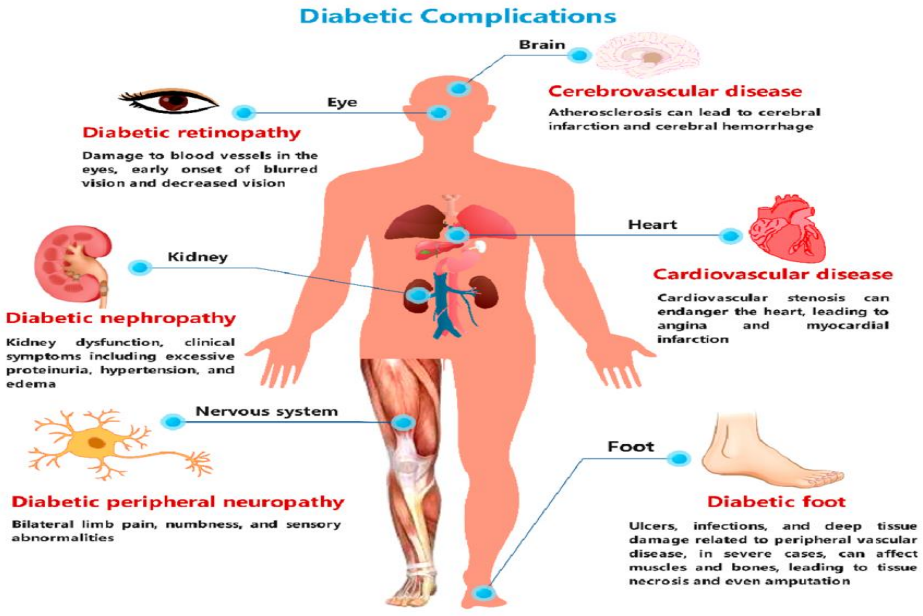

Figure 2. Diabetes mellitus complications (26)

Diagnosis of Diabetes Mellitus:

The classic symptoms of DM (polyuria, polydipsia, polyphagia, and weight loss) are more frequent in DM1 than in DM2. Fifty percent of the cases are asymptomatic or oligosymptomatic (non-specific signs and symptoms: cramps, recurring vulvovaginitis, asthenia), and an important risk factor is obesity. The diagnosis of DM is made through laboratory tests (fasting glycaemia, oral glucose tolerance test, and glycated haemoglobin) (27).

Management of Diabetes Mellitus:

Primary prevention is the main aim of preventing diabetes from occurring in susceptible individuals or the general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes (28-30). Dietary and lifestyle modifications are the main goals of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes is overweight and usually has other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes (31). Insulin replacement therapy is the mainstay for patients with type 1 DM, while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise, or oral medications.

Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors, and thiazolidenediones. Their main goal is to restore normal metabolic disorders, such as insulin resistance and inadequate insulin secretion from the pancreas. Diet and lifestyle strategies are to reduce weight, improve glycemic control, and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes (32).

TREATMENT:

INSULIN:

Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycemia and preventing hypoglycemia between meals (33). The site of administration of insulin injections is equally important for better and safe action of insulin and can be given by intramuscular or intravenous route. Different preparations of insulin are available, such as human insulin, beef insulin, and pork insulin. Insulin therapy is not free from complications and adverse effects. The most important adverse effects are weight gain and hypoglycemia when an inappropriate dose of insulin is taken and when there is a mismatch between meals and insulin injection (34,35). Weight gain after starting insulin therapy for uncontrolled diabetes is an inevitable consequence and is the result of increased truncal fat and muscle bulk. This is also due to reduced energy losses through glycosuria (36,37).

Oral hypoglycemic drugs:

Sulphonyl ureas such as *glibenclamide, glipizide,* and *biguanides* such as *metformin* and *phenformin* are oral hypoglycemic drugs. *Sulfonylureas* cause hypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind *sulfonylurea* (SUR) receptors on the ß-cell plasma membrane, causing the closure of adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane. This, in turn, opens voltage-gated channels, allowing an influx of calcium ions and subsequent secretion of preformed insulin granules. Acute administration of sulfonylureas to type 2 DM patients increases insulin release from the pancreas and may also further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a

functional pancreas was necessary for the hypoglycemic actions of sulfonylureas (38). *Biguanides,* such as *metformin,* are antihyperglycemic, not hypoglycemic (39). It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses (40). It has been shown to increase peripheral uptake of glucose and to reduce hepatic glucose output by approximately 20-30% when given orally but not intravenously. Impaired absorption of glucose from the gut has also been suggested as a mechanism of action (41-43).

Vitamin D:

Vitamin D is a fat-soluble vitamin, whereby more than 90% are obtainable by cutaneous production from sunlight exposure while only approximately 10-20% is obtained by dietary intake (44). Vitamin D is classically known for its role as an important hormone in mineral homeostasis and maintenance of musculoskeletal health (45). However, vitamin D also possesses antioxidant properties as potent as or even better than the classical antioxidant vitamin E (46-49). Furthermore, vitamin D has also been discovered to be a potent hormone that exerts significant biological actions, such as induction of cell differentiation, reduction in inflammation, and immunomodulation (50).

Synthesis of Vit D:

There are two major forms of vitamin D, which differ chemically only in their side chains. Ergocalciferol (vitamin D2) is synthesized by ultraviolet irradiation of plant sterols (ergosterol) and invertebrates, while cholecalciferol (vitamin D3) is photosynthesized endogenously when solar ultraviolet B radiation with a wavelength of 280-320 nm strikes human epidermis. Irradiation stimulates non-enzymatic photolytic conversion of pro-vitamin D (7-dehydrocholesterol) to pre-vitamin D, thereafter undergoing thermal isomerization into vitamin D 3 (45). An alternative source is dietary intake, mainly from foods of plant or animal origin. In general, these include animals and fish, such as oily fish, fortified dairy products, and animal fats. contain vitamin D3, and mushrooms contain vitamin D2 [51].

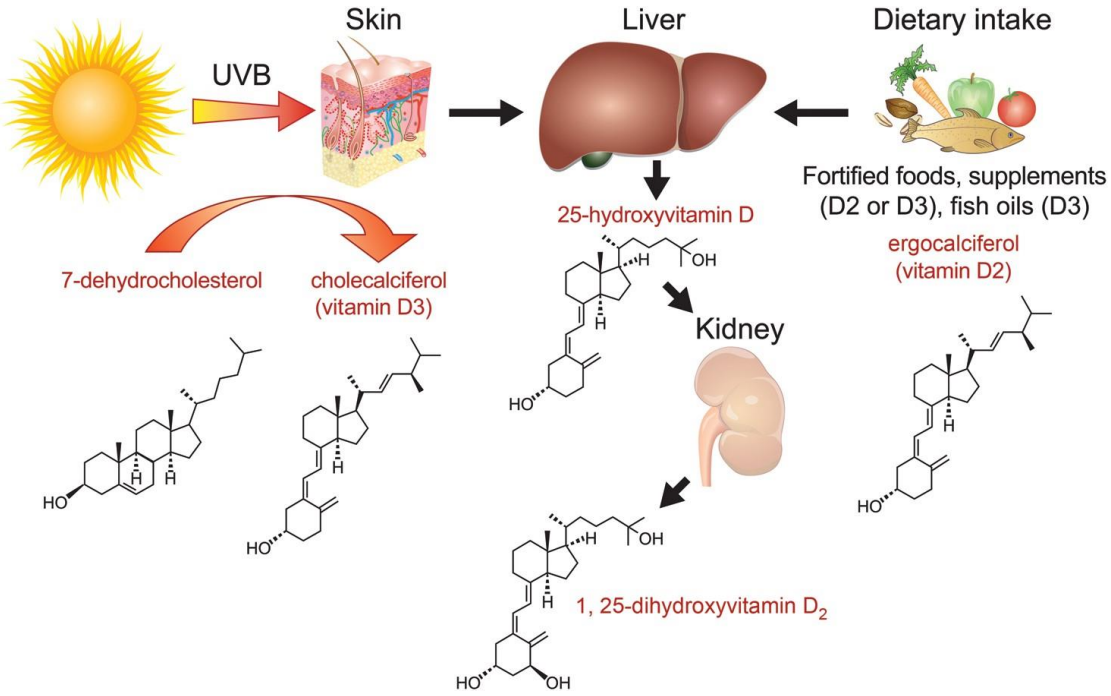

Figure 1 [uploaded by Vin Tangpricha (56)]. Vitamin D synthesis and metabolism. Vitamin D is photosynthesized in the skin and is also acquired by dietary intake. Two hydroxylation steps in the liver and the kidney are required for vitamin D activation, forming 1, 25-dihydroxyvitamin D. UVB, ultraviolet radiation in B-wavelength region (320-290 nm).

Vitamin D Metabolism:

Vitamin D from the skin and diet is either stored in adipose tissue or converted to 25(OH)D in the liver. Vitamin D metabolism requires two hydroxylations to form its active metabolite. The first hydroxylation of vitamin D takes place in the liver, where vitamin D is metabolized to 25(OH)D by cytochrome P 2R1 (CYP2R1). 25(OH)D binds to vitamin D-binding protein (DBP) and can flow into the blood in a stable form. 25(OH)D-DBP complex is excreted into the urine and reabsorbed through megalin, a multiligand scavenger receptor in the proximal tubules [52,53], where the complex is converted by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and changed to its active form 1,25-dihydroxyvitamin (OH)2D, although other tissues have 1α-hydroxylase enzymatic activity [54]. CYP27B1 gene expression in the kidney is mediated by various factors. Parathyroid hormone (PTH), hypocalcemia, hypophosphatemia, and calcitonin affect the activation of CYP27B1 and can increase levels of 1,25-(OH)2D. On the other hand, 1,25-(OH)2D and fibroblast growth factor-23 (FGF-23) inhibit CYP27B1 and can decrease 1,25-(OH)2D levels [55].

Role of vitamin D in diabetes:

Several studies in rats and humans [57,58] have demonstrated that vitamin D deficiency causes reduced insulin secretion and that 1,25(OH)2D3 improves *β*- cell function and, consequently, glucose tolerance [59]. In vitamin D–deficient rats, glucose tolerance and insulin secretion were improved with 1,25(OH)2D3 treatment [60]. In gestational diabetes mellitus, Rudnicki and Molsted-Petersen [61] reported that the glucose level decreased from 5.6 to 4.8 mmol/L after intravenous treatment with 1,25(OH)2D3. This vitamin D also corrects glucose intolerance and normalizes insulin sensitivity in uremic patients [62,63].

Possible Mechanisms by which Vitamin D may influence glucose intolerance and diabetes mellitus:

The development of abnormal glucose tolerance and diabetes mellitus is always preceded by alterations in the function of pancreatic β-cells, insulin sensitivity, and systemic inflammation. Available data suggest that these mechanisms are influenced by vitamin D.

Beta-cell function of the pancreas:

Responses of insulin to glucose load appear to be exclusively influenced by vitamin D. Vitamin D does not appear to affect basal insulin (64,65). A positive role for vitamin D in the modification of the function of β-cells of the pancreas has been reported (66). This role is mediated through several pathways, including direct stimulation of insulin secretion by vitamin D through the presence of vitamin D receptors (VDRs) in β-cells of the pancreas (66) and their expression of 1-α-hydroxylase enzyme (67). Also, 1,25-(OH)2D can activate transcription of the gene of human insulin and thus play an essential role in insulin secretion [68]. In mice, it has been shown that insulin secretory response may be impaired if the functional VDRs are absent (65). Several animal studies have also shown that when those were supplemented with vitamin D, they became able to restore their insulin secretion (64,69-72). Through its regulatory role of the calcium pool of β-cell intracellularly and extracellularly, vitamin D insufficiency appears to affect the normal release of insulin (73), particularly in reaction to a glucose intake since the secretion of insulin is mediated by a calcium-dependent mechanism.

Insulin insensitivity:

Improvement in action of insulin may be mediated by vitamin D directly through the presence of VDRs in skeletal muscles (74), stimulation of expression of insulin receptors in bone marrow cells (75) and through vitamin D activation of peroxisome proliferator activator receptor-δ (76), a transcription factor involved in the control of metabolism of fatty acids in adipose tissue and skeletal muscle (77). The indirect role of vitamin D is *via* the regulation of pools of intracellular and extracellular calcium and

control of the normal influx of calcium through the membranes of cells. Some (78,79) studies have demonstrated a negative association of vitamin D with insulin insensitivity, but this was not shown by others (80).

Inflammation:

In the state of systemic inflammation that T2DM can create, based on a wide range of clinical studies (81-83), the altered function of β-cells triggered by the apoptosis of β-cells can develop due to the presence of elevated cytokines that can also induce insulin resistance directly. Vitamin D can act to lower systemic inflammation in general by interacting with components in the region of promotion of cytokine genes interfering with generation and action of cytokines through impeding the role of factors involved in nuclear transcription (84-86). Specifically, to insulin insensitivity, vitamin D was demonstrated to under-regulate the activation of nuclear factor-κB (84,86,87), which plays a regulatory role for genes of cytokines of pro-inflammation implied in resistance of insulin (88).

Conflict of interest: NIL

Finding: NIL

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