زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Protective effects of vitamin D in type II diabetes mellitus

Research Project

Submitted to the Department of (chemistry) in partial fulfillment of the requirements for the degree of B.A or BSc. in (chemistry)

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CERTIFICATE

This project has been written under my supervision and has been submitted for the award of the degree of B.Sc. in **Chemistry** with my approval as supervisor.

Signature  Name: supervisor

Date: / / 2024

I confirm that all requirements have been fulfilled.

Research Project Lecturer

Signature:

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Date: / /2024

Dedication

I dedicate this project to my parents especially my mother, and my dear sisters and brothers. they always support me all the time I want to thank my family from the bottom of my heart. also, I want to thank my friends

Acknowledgment

I am very thankful to my dear supervisor Dr. Luttfia, who was tired with me a lot, and to the department of chemistry

Abstract

Vitamin D deficiency has been shown to alter insulin synthesis and secretion in both human and animal models. It has been reported that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion, and type 2 diabetes mellitus. Vitamin D replenishment improves glycemia and insulin secretion in patients with type 2 diabetes with established hypovitaminosis D, thereby suggesting a role for vitamin D in the pathogenesis of type 2 diabetes mellitus. The presence of vitamin D receptors (VDR) and vitamin D-binding proteins (DBP) in pancreatic tissue and the relationship between certain allelic variations in the VDR and DBP genes with glucose tolerance and insulin secretion have further supported this hypothesis. The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through the regulation of plasma calcium levels, which regulate insulin synthesis and secretion but also through a direct action on pancreatic b-cell function.

Keywords: pathogenesis, type 2 diabetes mellitus, vitamin D, vitamin D–binding protein, vitamin D receptor

Introduction

For many years, a role for vitamin D has been suggested outside bone and calcium metabolism, with beneficial effects suggested in defense against infectious agents, correlations with cancer, and more recently also in the prevention of diabetes [1].

Vitamin D deficiency is associated with metabolic syndrome and type 2 diabetes mellitus (T2DM) in epidemiological studies. It is uncertain whether this relationship is causal or due to confounding. The active metabolite 1α, 25-dihydroxy vitamin D3 (1,25(OH)2D3) influences pancreatic β-cells and insulin secretion, and through other mechanisms, it may influence insulin sensitivity [2]. Although the knowledge of vitamin D has rapidly increased over the last few years, clinicians are nowadays frequently confronted by divergent nations regarding the clinical use of vitamin D. We, therefore, aimed to present an up-to-date on the role of vitamin D in the development of insulin resistance and type 2 diabetes. After a brief introduction to vitamin D metabolism, we summarize mechanistic and observational studies. The main focus of our review is on recent randomized controlled trials (RCTs), which evaluated vitamin D effects on parameters of glucose metabolism and incident diabetes. After some general considerations regarding vitamin D treatment, we present our conclusion [3]' Type 2 diabetes mellitus (T2DM) is characterized by dysregulation of carbohydrate, lipid, and protein metabolism, and results from impaired insulin secretion, insulin resistance, or a combination of both. Of the three major types of diabetes, T2DM is far more common (accounting for more than 90% of all cases) than either type 1 diabetes mellitus (T1DM) or gestational diabetes. Over the past few decades, our understanding of the development and progression of T2DM has evolved rapidly. Its main cause is progressively impaired insulin secretion by pancreatic β-cells, usually upon a background of pre-existing insulin resistance in skeletal muscle, liver, and adipose tissue1 (BOX 1). Pre-diabetes is characterized by any one of the following: impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT), or increased glycated hemoglobin A1c (HbA1c) levels. Individuals with IFG levels are characterized by fasting plasma glucose levels that are higher than normal but do not meet the criteria for the diagnosis of diabetes [4]

Literature Review

1.1 Definition of Vitamins

Vitamins are organic micronutrients mainly synthesized by plants and microorganisms, which do not provide energy. Animals are not able to synthesize them, consequently, these essential micronutrients must be supplied by the diet in small amounts or even trace amounts (micrograms or milligrams per day) for the maintenance of the metabolic functions for protection, for maintenance of health and proper growth of most animal cells [5].

1.2 Classification of Vitamins

Vitamins are classified according to their solubility, into two groups [6].

1. Fat Soluble Vitamins: these are oily and hydrophobic compounds, they are stored in the liver and not excreted out of the body. Bile salts and fats are needed for their absorption. Vitamins A, B, E, and K are fat-soluble

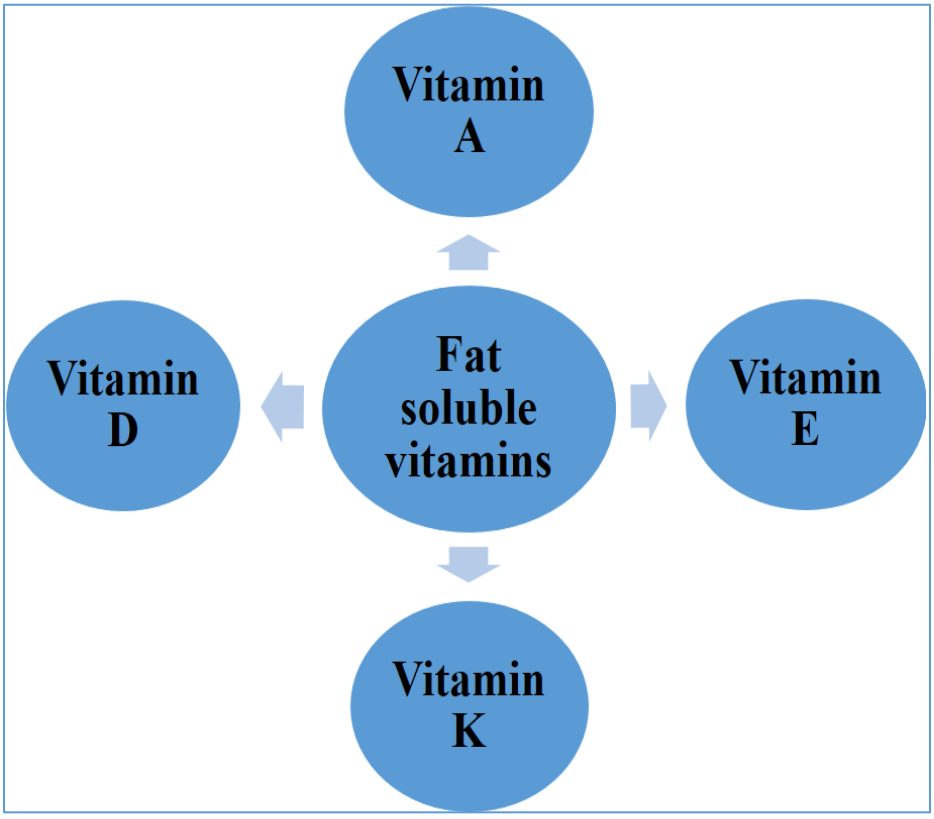

Figure 1: Fat-soluble vitamins [7]

2. Water Soluble Vitamins: Vitamin B complex and Vitamin C are water soluble. They are not stored in the body and, therefore are required daily in small amounts.

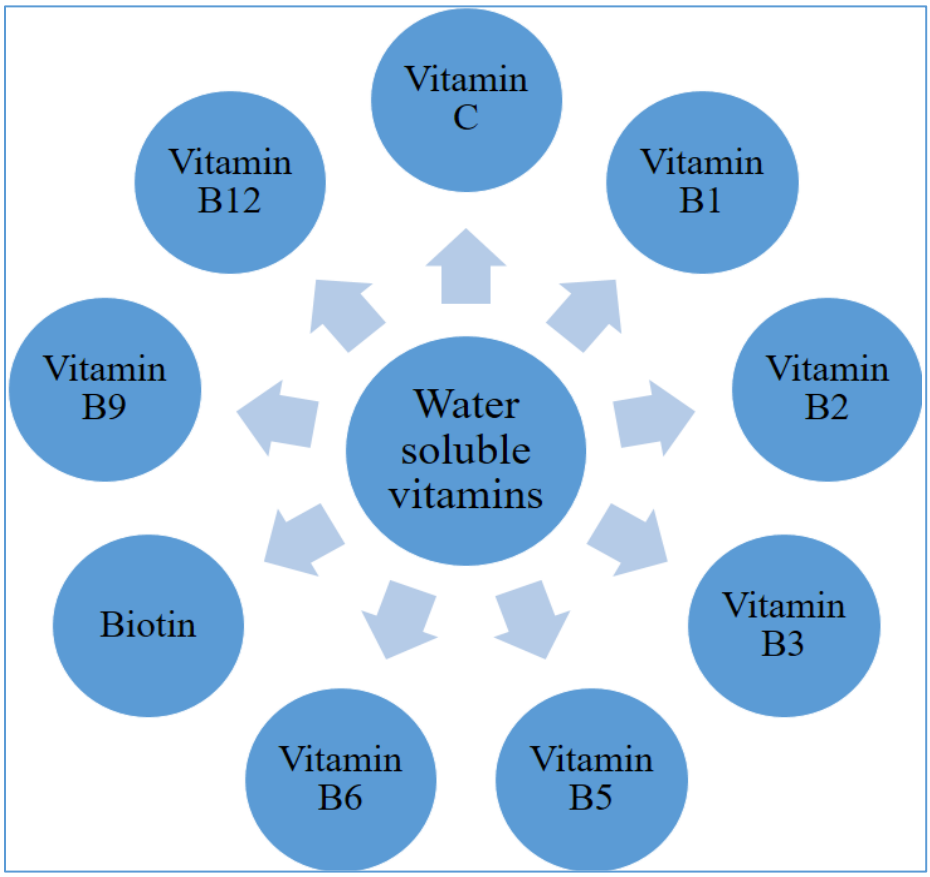

Figure 2: Water Soluble vitamins 7]

1.3 Chemistry of Vitamin D

Vitamin D is represented by cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), which are structurally similar secosteroids derived from the UV irradiation of provitamin D sterols. (Secosteroids are steroids in which one of the rings has broken.) In vertebrates, vitamin D3 is produced in vivo by the action of sunlight on 7-dehydrocholesterol in the skin. Vitamin D2 is produced in plants, fungi, and yeasts by the solar irradiation of ergosterol. Vitamin D3 and vitamin D2 differ structurally only in the C-17 side chain, which in vitamin D2 has a double bond and an additional methyl group [8].

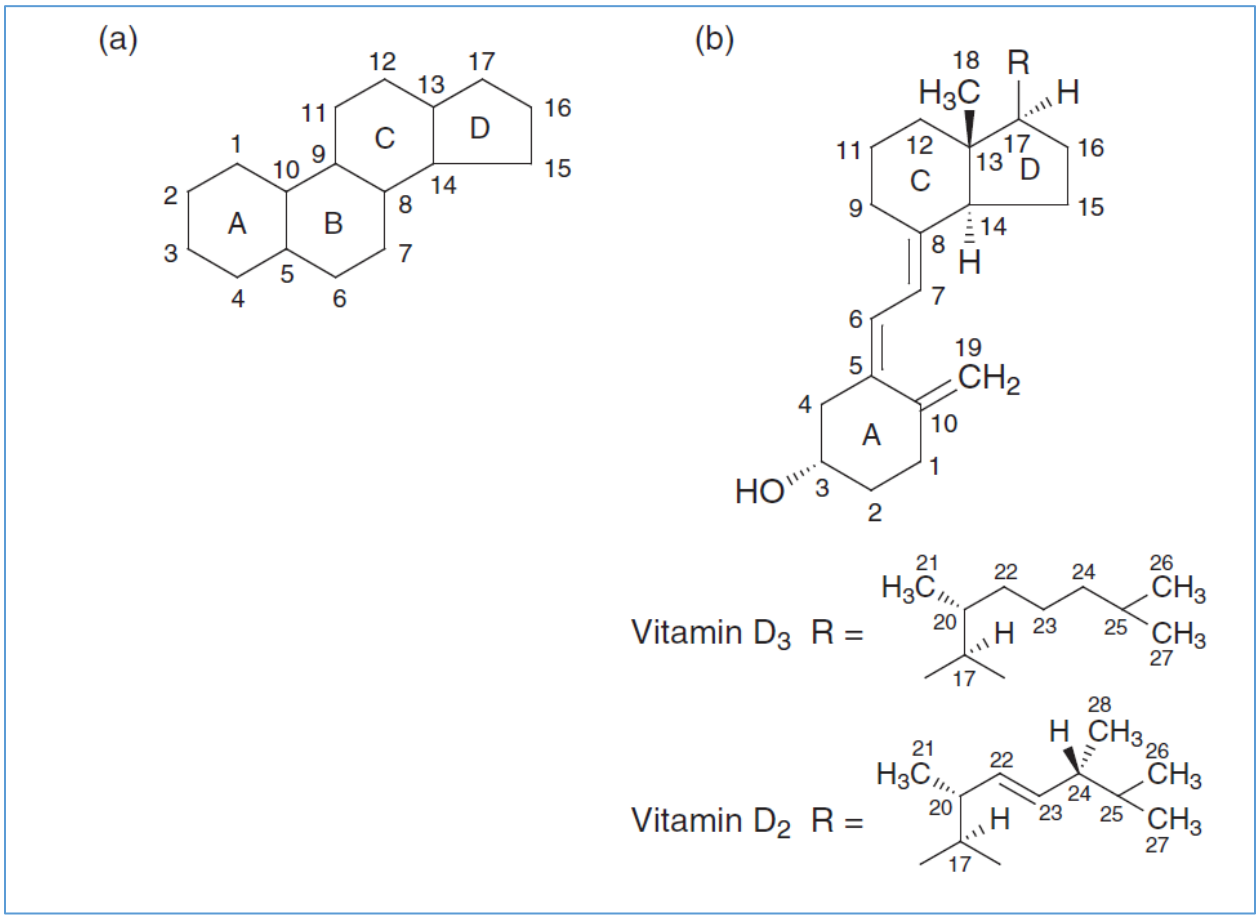

Figure 3: structural relationship of (a) the parent steroid nucleus to (b) vitamin D [9].

1.4 Biological Function Of Vitamin D

Vitamin D acts as a hormone in our bodies, regulating many processes that keep us healthy. One of the main functions of vitamin D is to help balance the levels of calcium and phosphorus in our bodies, which are needed to form our bones and teeth, to help our muscles contract, to help nerves carry messages between the brain and the body and to keep our cells functioning well. Vitamin D is also important to support the healthy function of our immune system. Vitamin D increases the gut uptake of ingested calcium and phosphorus and improves calcium reabsorption by the kidney, thus resulting in the elevation of both mineral elements in plasma. As a consequence, the major biological actions of this vitamin include the maintenance of mineral homeostasis and the regulation of bone remodeling [7]. Also, many other vitamin D targets have been reported, such as heart, stomach, liver, brain, skin, pancreatic islets (b cells), thyroid, parathyroid and adrenal glands, and immune cells (figure). Remarkably, some of these tissues and cell types, including the brain, activated lymphocytes (T and B cells), macrophages, and skin, contain not only the nuclear VDR but also the enzymes required for its synthesis [10].

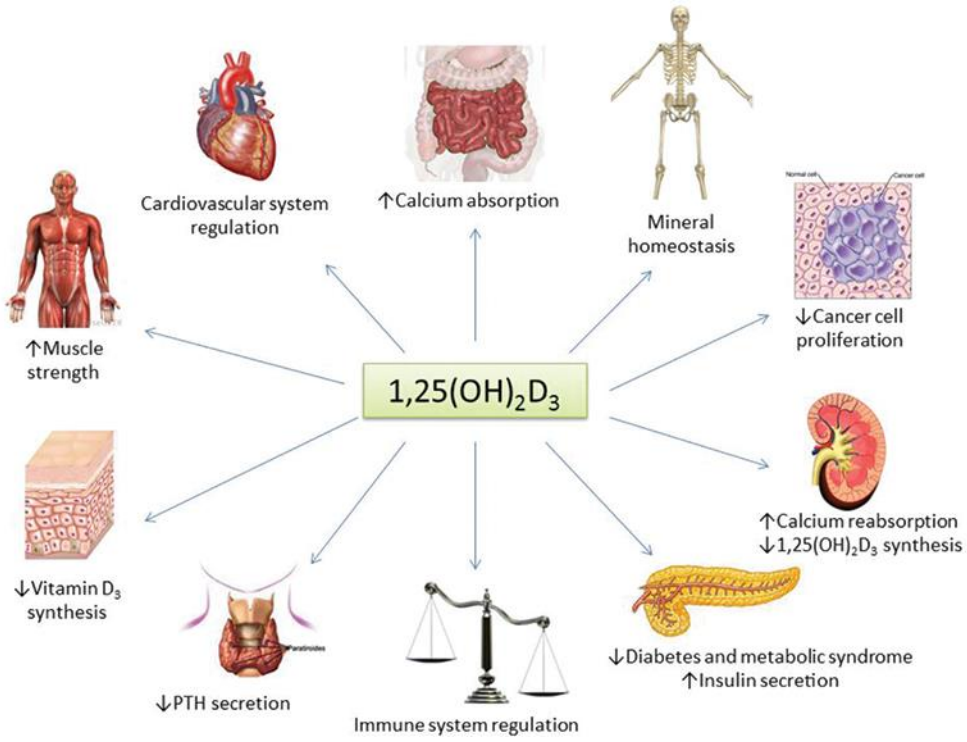

Figure 4: Principal targets and actions of vitamin D [11].

1.5 Metabolism of Vitamin D

Vitamin D can be obtained from food sources of vegetable origin (vitamin D2, also known as ergocalciferol) or animal (vitamin D3, also known as cholecalciferol). The best food sources are fatty fish and their oils. However, small amounts can also be found in butter and egg yolk. Cow's milk and human milk are relatively poor in vitamin D. Skim milk, in particular, often does not contain vitamin D [12].

Therefore, the main source of circulating VD is endogenous synthesis in the skin, where the ultraviolet B (UVB) wavelength of sunlight initiates the conversion of 7-dehydrocholesterol to inactive VD (cholecalciferol). Only small amounts of cholecalciferol are present in some dietary products, so in the absence of adequate sunlight, the supply of VD largely depends on the fortification of dietary products or individual use of oral VD supplements. Cholecalciferol undergoes two hydroxylation steps to form the active VD compound 1,25(OH). The first hydroxylation process takes place in the liver and forms 25-hydroxyvitamin D3 (25(OH)D3), while the second hydroxylation step, which produces the final active metabolite, occurs predominantly in the kidney. These reactions are brought about by 25-hydroxylase in the liver and 1a-hydroxylase in the kidney. The activated form of VD 1,25(OH)2D3 mediates its effect through the VD receptor (VDR) until inactivated by 24-hydroxylation. The table below indicates the factors involved in VD metabolism [13].

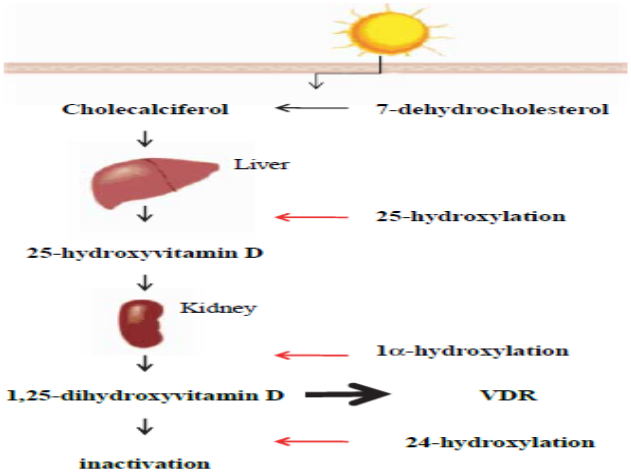

Figure 5: Systemic vitamin D (VD) metabolism [14].

1.6 Definition of Diabetes Mellitus (DM)

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism. [15]

1.7 Classification of diabetes

Three main types of DM are known type I associated with full insulin deficiency, type II-progressive insulin deficiency, and gestational DM which is diagnosed in 2nd or 3rd semester of pregnancy. Currently, although type I cannot be prevented, type II is preventable with good health, exercise, and a healthy diet. Early diagnosis is the key to diabetes management. Nevertheless, type II has affected high population and led to complications in several body parts, heart, nerves, eyes, kidneys, and so on [16]. Diabetes falls into three general categories:

1. **Type I diabetes** is a result of β-cell destruction which customarily provokes complete insulin insufficiency. It was formerly known as insulin-dependent, juvenile, or childhood-onset diabetes and it is occasioned by an autoimmune reaction, in which the immune system invades against the insulin-producing pancreatic beta cells. Type I diabetes is distinguished by deficient insulin production in the body. In such type of DM, the patients require daily administration of insulin to normalize the glucose level in the blood. Have not taken the insulin, their life is threatened and can be fatal. The reason for type IDM is not identified yet being presently not preventable. Albeit, the reasons for type I diabetes are still unclear, changes in environmental risk factors and/or viral infections may have an impact on the appearance of DM. Extreme urination and thirst, continuous hunger, weight loss, vision changes, and fatigue are the main symptoms of this type of DM. More often than not, the number of people who are diagnosed with type I diabetes has escalated [17].

2. **Type II diabetes** which was earlier termed non-insulin-dependent or adult-onset diabetes, is assumed to be a result of a continuous insulin secretory defect on the background of insulin resistance on account of the body's inefficient use of insulin. Type II diabetes is the most typical DM. In this type, the body is capable of producing insulin but becomes so resistant that the insulin is ineffective. By that time, insulin levels could subsequently be turned out insufficient. The causes of high blood glucose levels are both insulin resistance and deficiency. Given that the symptoms (coincidental to type I diabetes symptoms) are generally less noticeable or absent, the illness could be dismissed and be undiagnosed for numerous years, and not until complications have already ascended. For various years, type IIDM was observed only in adults, nowadays it has started to be seen also in children. Until present the exact causes for the development of type II diabetes are unknown, and some significant risk factors are being pointed out. The most significant ones include excess body weight, physical inactivity, and poor nutrition. Other factors that are impacted are ethnicity, family history of DM, history of gestational diabetes, and advancing age [18].

Pancreas

The pancreas is a glandular organ that affects the functioning of the entire body. The pancreas has two essential functions in the body: endocrine (production of hormones that regulate blood sugar levels and glandular secretion) and exocrine (the function of the digestive gland). Endocrine activity is performed by the Langerhans islets and involves the production of hormones such as insulin, proinsulin, amylin, C-peptide, somatostatin, pancreatic polypeptide (PP), and glucagon. Insulin helps to lower blood sugar, and glucagon causes blood sugar to rise [19].

Concepts of Insulin

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid, and protein metabolism, and promoting cell division and growth through its mitogenic effects [20].

Insulin resistance

Insulin resistance is defined as where a normal or elevated insulin level produces an attenuated biological response; classically this refers to impaired sensitivity to insulin-mediated glucose disposal. Compensatory hyperinsulinemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral insulin resistance in muscle and adipose tissue [21].

1.8 Source of Vitamin D

In general, cutaneous synthesis provides most of the vitamin D to the body (80%–100%),19 and with adequate sunlight dietary vitamin D may be unnecessary.20 Most Australians obtain almost all their vitamin D requirements through casual exposure to sunlight. Vitamin D stored in the adipose tissue is available during the winter when sunlight exposure is minimal. However, age, skin color, time spent outdoors, latitude, and angle of the sun can all significantly influence the cutaneous production of vitamin D and therefore affect vitamin D status. Only a few foods contain significant amounts of vitamin D. Rich sources are fish, especially fish with a high fat content, such as sardines, salmon, herring and mackerel Other sources of importance are meat, milk, and eggs, and fortified foods such as margarine [22].

1.9 Deficiency of Vitamin D

Vitamin D deficiency causes rickets in children and osteomalacia in children and adults.1 Rickets is characterized by a failure or delay in endochondral ossification at the growth plates of long bones that, in children old enough to stand, results in characteristic bone deformities of the lower limbs. Osteomalacia is defective mineralization of osteoid on the trabecular and cortical surfaces of bone and is associated with widened osteoid seams and the presence of Looser zones. Both conditions may be associated with pain, hypocalcemic fits, and muscle weakness in the limbs, heart, and respiratory systems. Low vitamin D status, above that associated with clinical deficiency, has also been linked with an increased risk of other diseases, most notably osteoporosis, cardiovascular disease, diabetes, some cancers, and infectious diseases such as tuberculosis[23].

1.10 Relation between vitamin D and diabetes

Type 2 diabetes mellitus is characterized by insulin resistance and altered insulin secretion, although its precise aetiopathogenesis is unknown. Environmental factors are important in such a process, and, aside from their role as triggers, they may also have an accelerating or protective effect. Hypovitaminosis D, owing to depletion or relative vitamin D resistance, has long been suspected to be a risk factor for glucose intolerance. For instance, prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance. Furthermore, hyperinsulin anemia has also been suggested to be associated with increased bone mineral density in subjects with diabetes and without diabetes. On the other hand, the ministration of a single high dose of vitamin D increases blood glucose in patients with diabetes. Further, no benefits in glucose tolerance have been found with vitamin D supplementation in subjects without vitamin D deficiency. Data from several studies have shown that hypovitaminosis D might play an important role in the pathogenesis of type 2 diabetes in human beings. Epidemiological data showed a reduction in serum vitamin D concentration in a London Bangladeshi population at risk for type 2 diabetes compared with subjects not at risk. These patients showed a higher prevalence of type 2 diabetes mellitus than the British Caucasian population, suggesting that vitamin D status might contribute to the pathogenesis of the disease. Short-term vitamin D replenishment in the Bangladeshi Asian population increased insulin secretion without altering glycemia, while longer vitamin D treatment also improved glucose levels. It has also been reported that vitamin D treatment in a Bulgarian population of female patients with type 2 diabetes, with a high prevalence of hypovitaminosis D, partially normalized insulin secretion and action. Also, a study in New Zealand reported that newly diagnosed patients with type 2 diabetes or impaired glucose tolerance had lower 25(OH)D3 levels than matched control subjects. In addition, in elderly Dutch men, vitamin D status was inversely associated with glucose tolerance and insulin secretion. Data from the Third National Health and Nutrition Examination Survey also showed an inverse association between vitamin D status and diabetes in non-Hispanic white and Mexican American people but not in non-Hispanic black people, The prevalence of type 2 diabetes is increased in obesity, which is often associated with hypovitaminosis D. Vitamin D is efficiently deposited in body fat stores where it is no longer bioavailable, which probably explains why a significant proportion of persons with obesity are

chronically vitamin D deficient. Vitamin D deficiency in subjects with obesity is also associated with functional alterations such as elevated PTH levels. This secondary hyperparathyroidism may contribute to the production of glucose intolerance and cardiovascular diseases which, in turn, are also associated with obesity. As stated above, vitamin D stimulates insulin secretion by pancreatic b cells but inhibits PTH synthesis. PTH and insulin increase vitamin D production, and thus, acute insulin deficiency in diabetes mellitus may decrease vitamin D production. In support of this, it is well known that patients with hyperparathyroidism have an increased prevalence of diabetes and insulin resistance. Moreover, after parathyroidectomy, there is a correction of abnormal insulin resistance and glucose intolerance. Thus, the relationship between hypovitaminosis D, altered insulin secretion, and type 2 diabetes may be the result of several related metabolic effects [24].

1.11Vitamin D and B-cell Function

There is ample evidence suggesting a role for vitamin D in insulin secretion, which includes the presence of the VDR in b cells and the vitamin D–-dependent calcium-binding proteins (DBP) in pancreatic tissue. It has been shown in both in vitro and in vivo models that vitamin D itself is essential for normal insulin release in response to glucose and for the maintenance of glucose tolerance. For instance, in diet-induced vitamin D–D-deficient rats, there is glucose tolerance impairment which, together with hyporesponsiveness to exogenous insulin, produces altered insulin sensitivity. Moreover, vitamin D deficiency results in decreased pancreatic insulin secretion, without altering glucagon secretion. Importantly, vitamin D repletion in the early stages of experimental dietary vitamin D deficiency or subjects with vitamin D deficiency leads to a partial improvement in glucose tolerance and correction of insulin secretion in response to glucose. In streptozotocin-induced diabetic rats, plasma calcium levels, DBP, circulating vitamin D, and bone mass are reduced. These defects have been attributed to altered vitamin D metabolism owing to an inhibitory effect of insulin deficiency on the activity of the renal 25(OH)D3 1a-hydroxylase. To further understand the role of vitamin D in b-cell function,

transgenic VDR knockout mice have been generated. However, in this model, one group reported impaired glucose tolerance. others found no effect on glucose tolerance. These contradictory results have been attributed to the different genetic backgrounds of the strains used to generate the transgenic mice.

The effects of vitamin D on insulin secretion may follow several pathways. Evidence exists that vitamin D influences B-cell insulin secretion through a rise in intracellular calcium concentration via non-selective voltage-dependent calcium channels. As a consequence, a major mechanism of action of vitamin D on insulin secretion and synthesis is likely to involve the b-cell calcium-dependent endopeptidases, which produce the cleavage that facilitates the conversion of proinsulin to insulin. Moreover, calcium is not only necessary for insulin exocytosis but also for b-cell glycolysis, which plays a role in signaling circulating glucose concentration. Vitamin D also affects insulin secretion by stimulating its synthesis using activation of protein biosynthesis in pancreatic islets. Several other factors, such as serum phosphorus or the direct action of vitamin D on the b cells of the pancreas, have been proposed to account for the stimulation of insulin secretion by vitamin D treatment. Since serum phosphorus is not altered by vitamin D supplementation, vitamin D has been suggested to be responsible for increased insulin secretion through other mechanisms such as the direct modulation of b-cell growth [24].

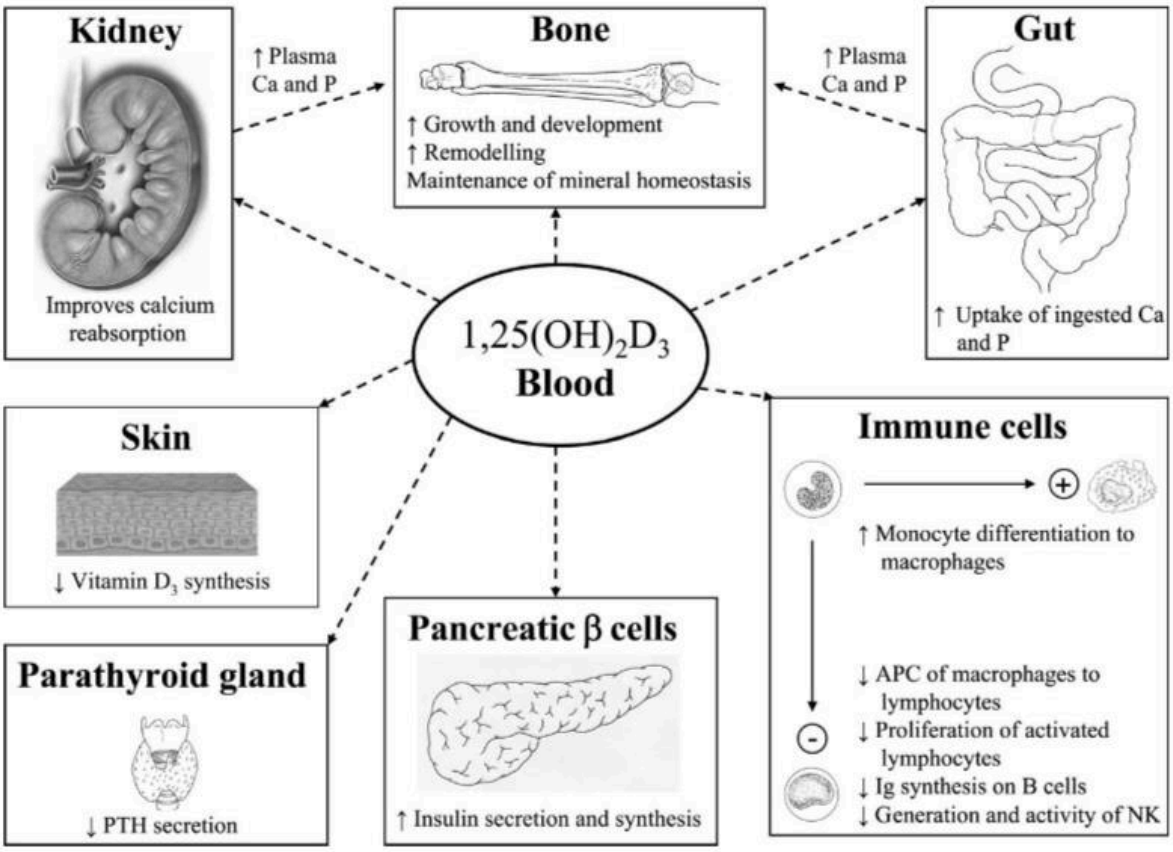

Figure 6: Major targets and actions of vitamin D3 on peripheral tissues. APC, antigen-presenting capacity; Ig, immunoglobulin; NK, natural killer cells; PTH, parathyroid hormone [24].

Discussion

Conclusions and Future Prospects Evidence is accumulating on the possible role of vitamin D in the pathogenesis of type 2 diabetes. Alterations in vitamin D status and/or action may affect insulin sensitivity, b-cell function, or both. Furthermore, several vitamin D–related genes have shown associations with different pathogenetic traits of the disease. Therefore, vitamin D and its related metabolic and immune pathways may be involved in the pathogenesis of type 2 diabetes mellitus at both environmental and genetic levels. The possible role of vitamin D in the pathogenesis of type 2 diabetes mellitus is far from being completely understood. Additionally, further knowledge on this issue may identify new candidate targets in the treatment and prevention of the disease. Therefore, further investigations on this issue are warranted.

Our first finding of note is that vitamin D insufficiency is remarkably common during winter in patients with Type 2 diabetes in Scotland. Our second main finding is that vitamin D supplementation improves endothelial function in this group of patients. Endothelial function is a powerful surrogate marker of cardiovascular risk. Changes in endothelial function are the best available surrogate to predict what effect a new therapy will have on cardiovascular events. Treatment-induced changes in endothelial function have produced a few false positive results (e.g. hormone replacement therapy and antioxidant vitamins) but have not produced a false negative result. Endothelial function is thus a highly sensitive, albeit not perfectly specific, test for predicting which interventions are likely to reduce cardiovascular events. Thus, the improvement in endothelial function seen in this study provides evidence that high-dose vitamin D therapy may be able to reduce cardiovascular events in patients with Type 2 diabetes and merits further study. There are several possible mechanisms by which vitamin D could improve endothelial function. Vitamin D may improve endothelial function indirectly by reducing blood pressure, which may, in turn, be due to its suppressing renin, and/or its decreasing vascular resistance. Vitamin D may favorably alter coronary calcification, which is a precursor of vascular events and a common finding in Type 2 diabetes. This possibility arises because of previous observational data linking low 25-hydroxyvitamin D levels with coronary calcification. Vitamin D supplementation has been shown to reduce levels of tumor necrosis factor (TNF)-α, a proinflammatory cytokine, in patients with chronic heart failure. Vitamin D also reduces the activation of a key cellular component of the atherosclerotic response—the macrophage. Human

endothelial cells can synthesize the active form of vitamin D, which may act at the local level to modulate the effects of inflammatory cytokines on the vasculature. The vitamin D receptor activates a wide variety of other genes, including vascular endothelial growth factor (VEGF). VEGF receptor expression is impaired in patients with Type 2 diabetes, and VEGF in turn promotes nitric oxide synthesis by endothelial cells. It has also been hypothesized that low vitamin D levels and subsequent secondary hyperparathyroidism may promote an acute-phase response which could explain why low levels of vitamin D may be a risk factor for increased cardiovascular events. Many hypotheses are possible and further detailed studies are now warranted to elucidate the pathways by which vitamin D improves endothelial function in patients with Type 2 diabetes[25].

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