
# The role of Calcium and Vitamin D In Type II Diabetes Mellitus

**Eman Tahir Hussein**

emantahir0093@gmail.com
General Directorate of Education, Baghdad, Rusafa, third

ABSTRACT

Several cross-sectional studies have established a connection between vitamin-D deficiency and changes in calcium levels with a higher prevalence of insulin resistance and type 2 diabetes. The present investigation explored a potential association between blood vitamin D and calcium levels in health and type 2 diabetes. The present investigation was a cross-sectional study comprising a total of 40 participants. The study involved the categorization of middle-aged and older individuals into two distinct cohorts based on their health status, namely those diagnosed with type 2 diabetes and those who were deemed healthy. This study employed a simple regression analysis to evaluate serum levels of serum 25(OH)D and calcium levels for measuring function. The findings of this investigation. The potential impact of hypovitaminosis D on glycemic dysregulation in individuals with diabetes is noteworthy, as evidenced by the significant reduction in serum 25(OH)D levels observed in the study results. The restoration of Vitamin D levels has been observed to enhance glycemia and insulin secretion in individuals diagnosed with type 2 diabetes and pre-existing hypovitaminosis D. This finding suggests that Vitamin D may play a important role in the development of type 2 diabetes mellitus. The hypothesis has been reinforced by the existence of vitamin D receptors (VDR) and vitamin D-binding proteins (DBP) in pancreatic tissue, as well as the correlation between specific allelic variations in the VDR and DBP genes and glucose tolerance and insulin secretion. The purported mechanism of vitamin D's impact on type 2 diabetes involves regulating plasma calcium levels, which in turn regulate insulin synthesis and secretion, and directly affect the function of pancreatic beta cells. However, a statistically insignificant reduction was observed in serum Ca levels among the patients compared to the control group. Moreover, various factors, including physical inactivity, inadequate nutrition practices, and obesity, play a significant role in the onset of type 2 diabetes militate findings of this research suggest that the management of calcium and vitamin-D supplements for six months may not have a significant impact on insulin sensitivity or insulin secretion in individuals who are deficient in vitamin D and belong to multiple ethnic groups

Keywords: D-binding proteins [DBP] , vitamin D receptors [VDR] , insulin resistance[IR] Vitamin D deficiency[VDD] , 25-hydroxyvitaminD3[25[OH]D]

## 1.Introduction

Increasing prevalence of Type 2 diabetes nationally and globally, resulting in significant morbidity and mortality [Schmidt *et al*., 2005 and Santulli et al.,2015]. Various modifiable risk factors for type 2 diabetes have been identified, with obesity being the primary factor, as per existing literature [Shukla *et al*.,2012]. Despite the demonstrated efficacy of weight loss in postponing the emergence of type 2 diabetes, its sustainability over an extended period remains challenging [Baier *et*

*al*.,1998]. Consequently, it is necessary to identify modifiable risk factors. that are independent of weight in order to mitigate the increasing prevalence of type 2 diabetes There is accumulating evidence that perturbations .in calcium and vitamin D homeostasis may contribute to the pathogenesis of type 2 diabetes. Cross-sectional studies have indicated a potential association between low serum 25-hydroxyvitamin D concentration and glucose intolerance, diabetes, insulin resistance, and metabolic syndrome, suggesting vitamin D's possible role in these conditions [Baier 1996 and Batt *et al*.,2020]. The potential association between calcium and type 2 diabetes has been indirectly suggested through cross-sectional studies. A negative correlation has been observed between high calcium intake and body weight and fatness [Boucher 1998 and Borrissova *et al*.2003].

Diabetes Mellitus Type 2 (T2DM) is a metabolic disease. that results in various degrees of insulin resistance in the targeted tissues or impairments in insulin secretion from the pancreatic gland [Bouillon et al.,2008]. The disease has been associated with various predisposing factors, such as systemic inflammation, oxidative stress, obesity, lifestyle, diet, and the potential influence of vitamins and minerals [Bouillon *et al*.,2008 and Braun *et al*.,1993]. The topic of interest is the role of functional foods in promoting health and preventing disease. For the past ten years, a correlation has been established between vitamin D and heightened susceptibility to T2DM. It is believed that vitamin D supplements may serve as a viable means of mitigating the risk of T2DM.Several studies on the effect of vitamin-D supplementation on the direction of type2 diabetes mellitus (T2DM) have been conducted in recent years. [Cade and Norman 1986 and Champi *et al*.,2005 ]. According to prior research, pancreatic beta cells contain receptors for Vitamin D, and sufficient levels of this vitamin can enhance insulin sensitivity and secretion [Chang et al.,2004 and Chertow *et al* 1993].

Additionally, vitamin D is essential for the regulation of calcium and, as a result, can indirectly impact the release of insulin from pancreatic beta cells [Chertow *et al*., 1993]. The present study investigates the serum levels of vitamin-D, calcium, phosphorus, and oxidative parameters in healthy individuals and those with diabetes. VDD has emerged as a significant public health concern on a global scale. Several researchers have considered different cut-off values for vitamin D status. However, the majority of them have defined Vitamin D Deficiency (VDD) as a serum 25(OH)D level below 20 ng/mL and insufficiency as a serum 25(OH)D level between 20 and 30 ng/mL. This condition affects almost 1 billion people globally, representing approximately 15% of the world's population. [Chiu *et al*.,2004] Vitamin-D is an essential component in various central homeostatic mechanisms, including bone metabolism, cellular growth, neuromuscular and immune function, and inflammation [Chiu *et al.,*2004]. The presence of down levels of serum vitamin D in an individual can increase their vulnerability to various health complications, including but not limited to multiple sclerosis, autoimmune disorders, infectious diseases, respiratory diseases, cardiometabolic diseases, and cancer, among other conditions [Chiu *et al*.,2004]. The findings of a meta-analysis indicated that vitamin D supplementation did not significantly impact the risk or incidence of T2DM. However, it did reveal a potential dose-response relationship between supplementation and the improvement of glycemia and insulin metabolism in non-T2DM adults. Who suggests that high dose vitamin-D supplementation may offer a potential benefit for preventing T2DM.[ Chiu *et al*.,2001]

The presence of vitamin D receptors in numerous physiological organs indicates that vitamin D is essential for health. that the vitamin D metabolite possesses distinct structural effects. Who is supported by previous research findings [Deepa, 2015]? A vitamin-D receptor has been established in the context of a pancreatic β cell. Who was confirmed by introducing 1,25[oh]2 D3 serum level into a culture medium, stimulating animal pancreatic islets and increasing insulin secretion? Elevated intracellular calcium levels

have been shown to induce augmented insulin secretion [Deepa, 2015]. The presence of calbindin, a protein that binds to calcium, within cells, suggests that calcium serves as a mediator. B-cell growth and differentiation can be modulated by introducing the active metabolite of Vitamin D [Targher *et al*.,2006]. Vitamin D deficiency has been found to result in elevated levels of parathyroid hormone, which can lead to glucose intolerance and secondary hyperthyroidism [Cigolini *et al*.,2006]. Inflammation may contribute to the development of insulin resistance and vitamin D deficiency, as heightened levels of inflammatory markers have been associated with decreased vitamin D levels. A research paper on Mendelian randomization has indicated no causal relationship between c-reactive protein and vitamin D, as evidenced by studies [Cline et al.,1999 and Daiger *et al*.,1975 ].

Research conducted on animals has demonstrated that vitamin D is a fundamental element essential for the proper secretion of insulin [Deluca and Cantorna, 2001 and Fujimato 2000]. It has been suggested that Vitamin D may decrease insulin resistance by modulating calcium and phosphorus metabolism and by upregulating the insulin receptor gene [Gedik and Akahn,1986]. According to a study conducted on 5,677 individuals with impaired glucose tolerance, administering vitamin D resulted in a 54% increase in insulin sensitivity [Giulietti *et al*.,2007]. Several other studies have also reported that enhanced vitamin D consumption improves insulin sensitivity [Harris and Dawson-Hughes1998 and Hirari 1998]. A recent investigation involving 126 individuals in good health has demonstrated a clear correlation between insulin sensitivity and the level of 25[OH]D.

Furthermore, the study revealed that a deficiency in vitamin D harmed the function of β-cells in the pancreas. A longitudinal study conducted for 20 years on a sample of 4,843 individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) revealed that consuming vitamin D was linked to a decreased incidence of T2DM [Holick,2004]. believed that Type 2 diabetes mellitus (T2DM) is arise from a condition characterized by heightened insulin resistance and impaired β-cell function, as per previous research [Holick,2004]. The findings regarding the correlation between insulin secretion and serum 25 [OH]D have been inconclusive in various studies. The present study assessed the impact of vitamin D supplementation on insulin resistance among individuals diagnosed with type 2 diabetes mellitus.

The dietary intake of vitamin D is limited to a minor proportion of 30%, owing to the scarcity of natural sources of this nutrient in food items [Holick,2004]. The synthesis of vitamin D from 7-dehydrocholesterol through photochemical conversion induced by sunlight fulfills the total vitamin D requirements. The process of industrialization has resulted in a decrease in the amount of sunlight exposure, leading to an augmented reliance on dietary sources of vitamin D. The hydroxylation process is essential for the activation of vitamin D, regardless of its origin. Specifically, two hydroxylation processes are required to produce 1,25[OH]2D3, the biologically active form of vitamin D [Hollis , 2005] . The initial hydroxylation process leads to the formation of 25-hydroxyvitamin D3 [25[OH]D3] in the liver.

In contrast, the subsequent hydroxylation step that generates the ultimate active metabolite is primarily carried out in the kidney [Hollis , 2005 and Hu *et al*.,2001 ]. clearance rate slower of serum 25[OH]D3 compared to 1,25[OH]2D3 makes it a superior indicator of vitamin D status, as per sources [Inomata *et al*.,1986 and Hu *et al*.,2001]. Additionally, it has been observed that secondary hyperparathyroidism can lead to high levels of serum 1,25[OH]2D3, rendering it an untrustworthy indicator in such circumstances [Hu *et al*.,2001]. Henceforth, the nomenclature 'vitamin D' will be employed solely to denote the biologically active variant of vitamin D, namely 1,25[OH]2D3, whereas alternative forms will be designated with precise nomenclature. The insufficiency of Vitamin D has been linked to rickets, a condition that causes bone deformities during growth and development. It may lead to osteomalacia and

disrupted muscle metabolism in adults due to the hindrance in calcium equilibrium [Hu *et al*.,2001 and Holick,2004]. The impacts above have also been documented among individuals diagnosed with type 2 diabetes, who may manifest anomalies in the metabolism of vitamin-D and minerals, ultimately leading to the development of osteopenia [Inouye and Sakaki, 2001and In zucchi *et al*.,1998 ]. The role of Vitamin D in modulating the immune response. The correlation between insulin resistance, inflammatory factors and B-cell defeat, which are fundamental characteristics of type 2 diabetes mellitus, has been frequently observed. Type II diabetes is associated with high levels of acute-phase proteins, mediators and cytokines linked to endothelial functional disorder. Aberrations in various markers of systemic inflammation have been detected in individuals with type 2 diabetes mellitus, including but not limited to tumor necrosis factor (TNF-a),(TNF-b), interleukin-6 (IL-6) , C-reactive protein, and plasminogen activator inhibitor-1 [Isaia et al.,2001]. Specific immune mediators, including TNF-a and IL-6, have the potential to impede insulin signaling and induce insulin resistance through various mechanisms [Isaia *et al*.,2001]. The occurrence of inflammatory changes prior to the onset of diabetes has been reported in various studies, leading to the belief that they are contributing factors rather than a result of the disease [Isaia *et al*.,2001].

**1.1 The relationship between Vitamin D and b-cell function.**

Numerous pieces of evidence indicate that vitamin D plays a significant role in insulin secretion. The VDR supports b cells and the presence of vitamin D-dependent calcium-binding proteins (DBP) in pancreatic tissue [Ishida *et al*.,2001 and Ismail A and Namala , 2000]. Research has demonstrated that vitamin D plays a crucial role in the proper insulin freeing in response to glucose and the preservation the tolerance of glucose, as evidenced by both in vitro and in vivo models. Impaired glucose tolerance is observed in cases such as that of rats with vitamin- D deficiency induced by diet. In conjunction together hypo responsiveness to exogenous insulin, this results in altered insulin sensitivity, as evidenced by previous studies [Iyengar *et al*.,1989 and Jacqmain ,2003].

Additionally, it has been observed that a reduction in vitamin D leads to a deficiency in insulin secretion by the pancreas, whereas glucagon secretion remains unaffected [Johnson *et al*.,2003 and Pittas *et al*.,2007]. Significantly, the restoration of vitamin D during the initial phases of experimental dietary vitamin D deficiency [Kadowaki and Norman,1984 and Kahan,2003] or in individuals experiencing vitamin D deficiency results in a partial enhancement of glucose tolerance and rectification of insulin secretion in reaction to glucose [Chiu *et al*.,2004 ,Pittas et al.,2007 ,Kern and Mitmesser, 2018 ]. The research indicates that streptozotocin stimulates diabetic rats exhibit a reduction calcium levels, circulating vitamin D, DBP and bone mass in plasm [Kirk *et al*.,1982 and Klupal *et al*.,1999]. The abnomalities above have been backed to modified vitamin D metabolism, which is caused by the suppressive impact of insulin reduction on the function of the renal 25[OH]D3 1-a-hydroxylase [Klupal *et al*.,1999 ,Kolb and Mandrup-Poulsen,2005].

Transgenic VDR knockout mice have been generated to gain a deeper comprehension of the effect of vitamin-D on b-cell function. In this particular model, it was observed that one group exhibited compromised glucose tolerance [Kumar *et al*.,1994], whereas another group did not demonstrate any impact on glucose tolerance [Leahy, 2005]. The observed inconsistencies have been ascribed to the strains' genetic makeup variations in creating transgenic mice [Inaba *et al*.,1999]. Vitamin D administration has been observed to enhance stimulated insulin secretion in reaction to an oral glucose load in individuals with mild type 2 diabetes mellitus characterized by normal fasting serum glucose levels, as well as in undiabetic healthy individuals and those with vitamin-D insufficiency. This effect has not, however, been observed in patients with established type 2 diabetes. [Chiu *et al*.,2004; Iyenar *et al*.,1989;Libpvitz, 2006; Pittas *et al*.,2007] The phenomenon above is concomitant with a noteworthy elevation the

levels of calcium in serum concentrations and a decline the levels of fatty acids in serum [Iyenar *et al*.,1989]. Research has demonstrated that improving glucose tolerance in patients with vitamin D reduction and enhancing insulin response in women with type II diabetes can be achieved by restoring vitamin D levels [Lee *et al*.,1994; Maestro *et al*.,2002].

Nevertheless, divergent outcomes have been observed in different cohorts, as evidenced by reports indicating that vitamin D supplementation among Asian individuals with both vitamin D deficiency and type 2 diabetes mellitus led to a rise in insulin resistance and deterioration of glycemic regulation [Magkos *et al*.,2022]. The potential impact of vitamin D on insulin secretion may be mediated through various mechanisms. There is available evidence indicating that vitamin-D has an impact on B- cell insulin secretion by increasing intracellular calcium concentration through non-selective voltage-dependent calcium channels [Malecki *et al*.,2002]. Various additional factors, including serum-phosphorus or the direct impact of vitamin-D on the b-cells of the pancreas, have been suggested as potential explanations for promoting insulin secretion through vitamin D therapy [Iyenar *et al*.,1989]. Previous research Iyenar *et al*.,(1989) shows that vitamin D supplementation does not affect serum phosphorus levels. Therefore, it has been hypothesized that vitamin D may enhance insulin secretion through alternative pathways, such as directly modulating b-cell growth. [Snijder *et al*.,2006].

### 1.2 The relationship between Vitamin D Binding Protein and Type II Diabetes Mellitus

Calbindin-D28K is protein, alternatively referred to as DBP, is synthesized by the Gc gene. Its primary role is facilitating the transportation of vitamin D metabolites [Inaba *et al*.,1999 and Mathieu *et al*.,2005] in the bloodstream. Furthermore, it plays a crucial role in the endocytosis and metabolism of vitamin D. Furthermore, it elicits other impacts, such as the binding to globular actin and fatty acids and immunomodulation, as stated in reference 65. DBP is a serum glycoprotein synthesized and secreted by the liver and characterized by high polymorphism, existing as a single chain. This information is supported by Iyenar et al.,(1989). The formation of a complicated between vitamin-D and DBP facilitates the transportation of vitamin D to its intended tissues [Iyenar *et al*.,1989]. Changes in serum DBP concentration are typically accompanied by corresponding variations in the overall vitamin D concentration [Klupal *et al*.,1999].The genetic variations of DBP have been linked to diabetes and prediabetic characteristics in various populations. The analysis of Gc exons revealed the presence of two error polymorphisms at (416) and (420) codons. These polymorphisms result in the formation of three-electrophoretic variables of (DBP) namely (Gc1) fast (Gc1f), Gc1 slow (Gc1s), and (Gc2) [Mathieu et al.,2005;Morrissey *et al*.,1975; Nathan, 2015]. The impact of DBP variants on the presence of active vitamin-D shape in b-cells and their consequent effect on insulin secretion has been proposed [Norman 1989]. Prior research conducted on undiabetic Pima Indians indicated a genetic-linkage among markers located near the (Gc) locus and oral glucose tolerance. However, no such linkage was observed concerning insulin response to oral glucose. This finding is supported by studies [Norman and Powell, 2005; morrisey *et al*.,1975]. Nonetheless, the identical ethnic group did not exhibit any correlation between DBP variations and the incidence of type 2 diabetes [Norman and Powell, 2005; morrisey *et al*.,1975]. The allele (Gc-1) of the DBP gene has been proposed to correlate with typeII diabetes in individuals of Polynesian and Japanese descent, according to studies [nakjaer *et al*.,1999; Nyomba *et al*.,1985]. Additionally, research on subarctic Amerindians has demonstrated a correlation between the (Gc-1) allele, fasting insulin and plasma glucose levels [Nyomba *et al*.,1985]. Furthermore, it was observed that homozygous individuals for Gc 1f-1f exhibited the least amount of insulin fasting in non-diabetic Dogrib Indians from Canada [Osmani and Haseena, 2020]. Despite normoglycemia in both study cohorts, it has

been hypothesized that variances in nutrition between the two groups could potentially explain the absence of correlation between the Gc genotype and glucose homeostasis in the latter investigation [Iyenar *et al*.,1989]. Nevertheless, several investigations conducted on American Caucasian [Palomer *et al*.,2008], French Caucasian Palomer et al.,(2008), and Polish Norman, (1998) populations have reported a lack of correlation among polymorphisms in the (DBP) gene and type II diabetes mellitus. The inconsistent results may be attributable to various genetic backgrounds among the examined populations. Variations in the prevalence of susceptibility alleles may exist among diverse ethnic groups. Previous studies have indicated that there are correlations among DBP polymorphisms and typeII diabetes, but these associations have solely been documented in populations that are not of white ethnicity [morrisey *et al*.,1975; Nykjaer *et al*.,1999; Osmani and Haseena, 2020]. The potential impact variants of DBP on the onset of type2 diabetes could exhibit distinct features among non-Caucasian populations [Palomer *et al*.,2008]. The development of type 2 diabetes is multifactorial, with a complex etiology believed to be influenced by multiple genes. Hence, there may be a multitude of allele combinations present among individuals diagnosed with diabetes. The DBP polymorphisms may significantly impact insulin secretion abnormalities, but only in specific genetic or environmental contexts, as per the findings of previous research [Palomer *et al*.,2008].

**1.3 The pathogenesis of type 2 diabetes mellitus involves insulin resistance.**

In an individual with normal blood glucose levels, the beta cells located in the islets of Langerhans situated in the pancreas will produce and release insulin into the bloodstream biphasically upon increasing blood glucose concentration [Kahn 2003 and Pittas etal.,2007] Insulin is an anabolic hormone that facilitates tissue growth by stimulating glucose uptake and promoting the synthesis of glycogen, triglyceride and protein.[Pfotenhauer and Shubrook,2017] Glut-4,glucose transporters 4, are accountable for facilitating glucose exploiting in to tissues, thereby reducing blood glucose levels to an optimal range of 3.9 to 5.8 mmol/L. However, this physiological process is compromised in individuals suffering from type 2 diabetes mellitus. [Pfotenhauer and Shubrook,2017; Poitout,and Robertson, 2002] The etiology of type2 diabetes mellitus is multifaceted, encompassing a multitude of pathways, organs, tissues, and hormones.[ Rhodes and White,2002] Type2 Diabetes Mellitus is a chronic illness that advances over time. The disease initiates insulin resistance, resulting in amplified hepatic glucose production, and culminates in b-cell dysfunction. Poitout,and Robertson, (2002); Rhodes and White,(2002); Kern and mitmesser, (2018);kirk *et al*.,(1982) Insulin resistance is characterized by the incapacity of specific target tissues to respond effectively to the endogenous insulin secretions of the body, such as adipose tissue and skeletal muscle,. As previously mentioned, the exact mechanisms underlying the reduction in insulin sensitivity in individuals with Type 2 Diabetes Mellitus (T2DM) remain unclear. Nevertheless, some researchers have suggested that hyperglycemia or "glucotoxicity" may be responsible for the observed decrease in insulin sensitivity.[ Ruan and Lodish,2003] Hyperglycemia is believed to worsen insulin resistance by reducing tyrosine-phosphorylation ,increasing serine and threonine phosphorylation of the insulinreceptor, leading to an inhibitory effect. According to estimates, individuals with Type 2 Diabetes Mellitus (T2DM) experience a 50% reduction in autophosphorylation of insulin receptors, which could be attributed, at least in part, to hyperglycemia. Cline et al. conducted a study that demonstrated a reduction in insulin signaling among individuals with T2DM, as evidenced by an 80% decrease in insulin-stimulated glycogen synthesis compared to a healthy control group.[Klupal *et al*.,1999] Furthermore, it has been demonstrated that hyperglycemia can high the generation of ROS, which exhibit advantageous effects at moderate concentrations but harmful effects at levels exceeding physiological norms.[ Kolb and Mandrup-Poulsen,] The activity of crucial

antioxidant enzymes, including superoxide dismutase [SOD] and glutathione reductase, is reduced by hyperglycemia. These enzymes are essential in champions ROS and may have a important function by reducing the low rate inflammation that is a hallmark of T2DM.[ Kolb and Mandrup-Poulsen,2005] Furthermore, it is hypothesized that insulin resistance may be attributed to lipotoxicity' and 'glucotoxicity. Elevated levels of free fatty acids characterize lipotoxicity [FFA] in circulation, attributed to the inhibition of hormone-sensitive lipase [HSL].[ Poitout and Robertson,2002; Kern and Mitmesser,2018 ] In individuals with insulin resistance, inhibiting hormone-sensitive lipase (HSL) by insulin, which typically results in lipolysis, is not as effective as in non-insulin-resistant individuals. The outcome of this phenomenon is an elevation in the breakdown of lipids and an augmentation in the levels of free fatty acids in the bloodstream. whoThis is among the primary reasons excessive weight gain and heightened fat accumulation, especially in the visceral region, are subjects of significant apprehension.[Kumar *et al*.,1994] Visceral adiposity is considered more harmful to an individual's health due to the heightened sensitivity of HSL towards it than subcutaneous adiposity. whoThis may result in a greater likelihood of contributing to insulin resistance.[Kirk *et al*.,1982; Leahy,2005] Furthermore, it is believed that Free Fatty Acids (FFA) can elicit insulin resistance through the facilitation of serine phosphorylation of the insulin receptor, resulting in a subsequent lowering in the efficacy the pathway of the insulin signaling.[ Rhodes and White,2002]The insulin signaling pathway's activation depends on the insulin receptor's phosphorylation of tyrosine amino acids. Without this process, the translocation of GLUT-4 is impeded, resulting in reduced glucose uptake into tissues. whoThis can lead to the development of persistent hyperglycemia or T2DM.[Lee *et al*.,1994] In addition, it is believed that the generation of inflammatory cytokine such as tumor necrosis factor-alpha (TNF-a),This is generated and released by adipocytes and also plays a role in insulin resistance by impeding insulin action.[maestro *et al*., 2002; Batt *et al*.,2020] The presence of heightened TNF-a levels has been detected in obese individuals who exhibit insulin resistance but not Type 2 Diabetes Mellitus (T2DM). This finding implies that the amplified production of cytokines may play a role in the widespread occurrence of insulin resistance and T2DM among this demographic. While not all individuals who are insulin resistant develop Type 2 Diabetes Mellitus (T2DM), it is crucial to recognize the substantial contribution of insulin resistance in the development of T2DM.

**1.4 the function, structure and synthesis of Vitamin-D.**

Vitamin D can be acquired via two primary pathways: dietary consumption or endogenous synthesis. Vitamin D can be sourced from food items, including oily fish such as (salmon, mackerel, egg yolks) and juice. However, it is noteworthy that dietary consumption only contributes to approximately 30% of the total vitamin D acquired.[ Hotamisligil *et al*.,1995] The primary source of vitamin D for individuals is derived from the absorption of ultraviolet B (UVB) radiation with wavelengths ranging from 290 to 315 nm, which is primarily available during the summer season [June-July] in the Northern hemisphere (latitude 42 N). [Inouye and Sakaki , 2001;Inzucchi et al.,1998;–38] The activation of 7dehydrocholesterol (7-DHC), a precursor and synthesized from cholesteroll and located inclose the skin, is initiated by UVB sunlight.[Scragg et al.,1995] The process of 7-DHC activation and its conversion to vitamin D3 within the skin, followed by its isomerization to vitamin D3 (cholecalciferol) and subsequent storage, generates endogenous reserves of vitamin D. Upon undergoing two hydroxylation reactions, these reserves perform a variety of essential physiological functions. Reference 83 is provided.Vitamin D3, whether acquired through dietary intake or endogenous synthesis, lacks biological activity. The activation of vitamin D3 requires two consecutive hydroxylations 25-hydroxylase 25 (OH) from the liver to produce 25(OH) D3 (also referred to as calcidiol), and 25[OH]D3-1a-

hydroxylase [1a[OH]ase from the kidneys to produce 1,25 dihydroxy vitamin-D3 1,25[OH]2D3 (also known as calcitriol).[32–49] Upon formation, the binding of 1,25(OH)2D3 to its vitamin D receptor (VDR) is necessary, resulting in the subsequent formation of a complex with the retinoid X receptor [RXR]. .[Hollis,2005 and Scragg et al.,2004] The VDR has been detected in several cell types, such as, immune cells and intestinal mucosal cells (T and B cells), kidney cells and pancreatic B-cells, and.[ Hollis,2005 ;Ishida *et al*.,1985; Sergeev, I. N., and Rhoten ,1995] The interaction between VDR/RXR and 1,25 [OH]2D3 is complex, followed by the binding of the complex to the vitamin D response element [VDRE] on DNA, results in the upregulation of protein expression. Who that includes calbindin-D28K in pancreatic b-cells and calbindin-D9K in the intestine and, enhancing calcium influx into these tissues.[ Ismail and Namala ,2000; Iyenar *et al*.,1998] Vitamin D, despite its conventional categorization as a vitamin, exhibits physiological actions comparable to a hormone's. The function of 1,25(OH)2D3 in maintaining calcium and phosphorous homeostasis involves enhancing calcium absorption by the intestinal mucosa, reducing calcium excretion by the kidney, and stimulating bone resorption in instances where serum calcium levels fall below optimal levels of 2.25e2.5 mmol/L.[Scragg *et al*.,1995] While a serum concentration of 80 nmol/L of 25[OH]D3 has demonstrated effectiveness in preventing various diseases linked to vitamin D deficiency, it is essential to acknowledge that this value is a subjective threshold. In other words, it may provide adequate sufficiency for some individuals but be significantly deficient for others. The recommendations above rely on data obtained from individuals who do not spend much time outdoors. It is essential to observe that although these individuals may not exhibit any symptoms, these recommendations cannot be assumed suitable for the entire population. Further research is required to determine the appropriate threshold values for different populations.[ Scragg *etal*.,1995] The significance of 1,25[OH]2D3 extends beyond its role in preserving calcium homeostasis, as it has been observed to impact immune function. Furthermore, recent studies suggest its potential involvement in the pathogenesis of T2DM.12,14e17,25,27,29e31 The optimal method for assessing vitamin-D case is to evaluate the concentration of 25[OH]D3 in the serum of, as opposed to 1,25[OH]2D3, owing to the latter's swift clearance rate [Scragg *et al*.,2004].

**1.5 Calcium**

Calcium is ranked fifth in abundance in the human body and is primarily present as a cation. The skeletal system contains 99% of the body's calcium, predominantly in extracellular crystals with an unknown structure. These crystals have a composition that is similar to hydroxyapatite. The study of the chemical processes and structures within living organisms and their functions. The majority of calcium in the bloodstream is found in the plasma, with an average normal concentration of approximately 9.5 mg/L. Calcium is present in three distinct physiochemical states in plasma, wherein roughly 50% is free, and 40% of the protein is bound to plasma proteins, predominantly albumin. Moreover, the remaining 10% is complex with small anions. The free calcium fraction is the biologically active form of calcium, which is subject to tight regulation in plasma by the calcium-regulating hormone PTH and vitamin D. The role of intercellular calcium is crucial in various physiological processes such as muscle contraction, hormone secretion, glycogen metabolism, and cell division.

The etiology of hypocalcemia. Primary hypoparathyroidism refers to a condition characterized by the insufficient production of parathyroid hormone due to glandular aplasia, destruction, or removal. Hypomagnesemia Hypermagnesemia is The condition of having low levels of albumin in the blood, with the caveat that only the total calcium levels are impacted, not the ionized calcium levels. The medical conditions presented include chronic liver disease, nephrotic syndrome, malnutrition, acute pancreatitis, Vitamin D deficiency, renal disease, rhabdomyolysis, and

pseudohypoparathyroidism. The etiology of hypercalcemia: The topic under discussion pertains to primary hyperparathyroidism, specifically adenoma or glandular hyperplasia. *Hyperthyroidism Benign familial hypocalciuria* is a genetic condition characterized by low calcium levels in the urine. The conditions of malignancy and multiple myelomas are being discussed. The administration of Thiazide diuretics and an elevation in vitamin D levels. Extended periods of physical inactivity [Sesti,2006 and Moustafa,20016].

Changes in calcium flow may negatively impact insulin secretion, which is a process that relies on calcium. The restoration of glucose tolerance and insulin secretion in rats with vitamin D deficiency was achieved solely through calcium repletion. The impairment of insulin release is associated with hypocalcemia in individuals who do not have diabetes. Calcium is crucial in insulin-mediated intracellular processes within skeletal muscle, and adipose tissue is insulin-responsive tissue. The optimal range of Ca2+ required for these functions is relatively narrow. Alterations in insulin action are attributed to variations in Ca2+ levels in primary insulin target tissues. The impairment of insulin receptor phosphorylation, which is a calcium-dependent process, results in compromised insulin signal transduction and reduced activity of glucose transporters. Alterations in calcium ion levels impact the metabolic processes of adipocytes, potentially resulting in the buildup of triglycerides through heightened de novo lipogenesis and an incapacity to inhibit insulin-triggered lipolysis, ultimately leading to the accumulation of adipose tissue. Individuals diagnosed with type 2 diabetes mellitus demonstrate compromised regulation of calcium within cells, resulting in deficiencies within skeletal muscle, adipose tissue, and the liver, as reported in reference[ Holick *et al*.,2006]

### 1.6 Glucose

GLUT2 facilitates the transportation of glucose into the beta cell. Upon entry, the initial stage of glucose metabolism involves the process of phosphorylation, which yields glucose-6-phosphate. The catalysis of this particular step is facilitated by hexokinase. It is the limiting factor in glycolysis, and its primary function is to confine glucose within the cellular environment. Adenosine triphosphate (ATP) is generated within the mitochondria during glucose metabolism. The closure of ATP-gated potassium channels in the beta cell membrane results from an ATP: ADP ratio elevation. The beta cell is currently experiencing a restriction in the efflux of potassium ions, which carry a positive charge [K+]. An increase in the positive charge within the beta cell causes depolarization. The opening of voltage-gated calcium channels results in calcium ions [Ca2+] influx into the cell. The elevation of intracellular calcium levels initiates insulin release through exocytosis, as evidenced by previous studies [88-89]. The RyR2, a Ca2+ release channel located on the endoplasmic reticulum (ER), is present in various cell types, such as cardiomyocytes and pancreatic β cells. The significance of RyR2-dependent Ca2+ release in excitation-contraction coupling in cardiomyocytes has been established. However, the functional relevance of RyR2 in insulin secretion of β cells and its association with diabetes mellitus is a topic of debate in the literature [Sun *et al*.,2011 and Szathmarry, 1985].

## 2. The results

### 2.1 $Ca^{+}$ and V.D Serum levels

The results in table ???? shows non-significant decrease in Ca serum levels in patients 9.13 ± 1.1 pg /ml compared to control 9.41 ± 0.77 pg /ml [$P$ = 0.36]. Non-Significant decrease in V.D serum levels in patients 31.80 ± 5.2 pg /ml compared to control 38.60 ± 6.2 pg /ml [$P$ = 0.0015].

**Table1: Serum levels of Ca and V.D in Patients groups compared to apparently healthy control.**

| Interleukins | Patients [No. =20] | Control [No. =20] |
|---|---|---|
| Ca<br>Mean ± S.D. | 9.13 ± 1.1 | 9.41 ± 0.77 |
| *P*-value | 0.36 N.S. | |
| V.D<br>Mean ± S.D. | 31.80 ± 5.2 | 38.60 ± 6.2 |
| *P*-value | 0.001** | |
| ** Significant at < 0.01 | | |

**Receiver Operating Characteristic Curve Analysis [ROC] and Pearson Correlation**

According to the ROC results, false positive results were observed in Ca [AUC = 0.415, $P < 0.3$], true positive results were observed in V.D [AUC = 0.206, $P < 0.001$], [Figure 1, table1].

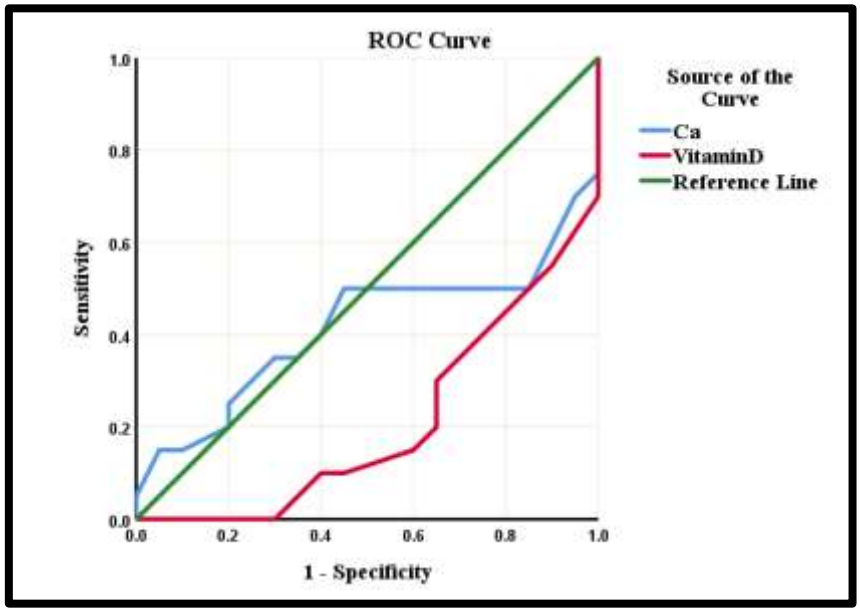


**Figure 1: ROC Curve of Studied Parameters.**

**Table 2: Area under the Curve of Studied Parameters.**

| Test Result Variable[s] | AUC | Cut of Value | *P* value |
|---|---|---|---|
| Ca | 0.415 | 10.45 | 0.3 N.S |
| V.D | 0.373 | 51.00 | 0.16 N.S |

The correlations between the studied parameters illustrated in table 2, weak positive correlation was noticed between Ca with V.D [r= 0.642, *P*= 0.003].

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**Table 3: Pearson Correlation of the studied parameters.**

| Parameters | r- value | *P*-value |
|---|---|---|
| Ca *vs*. V.D | 0.087 | 0.59 N.S. |
| N.S.: Non-Significant. | | |

## 3.Discussion

The objective of this study was to evaluate. vitamin D levels. calcium, phosphorus, and oxidative status in patients with diabetes and those without diabetes. Upon completion of the study, it was observed that the concentration of vitamin D in the group diagnosed with Type 2 Diabetes Mellitus was notably lower compared to the control group. According to the available evidence, vitamin D may substantially regulate blood glucose levels and improve insulin sensitivity by decreasing insulin resistance. [Szathmary, 1987]. Vitamin D is commonly recognized for its prominent application in safeguarding bone health. However, recent studies have initiated an investigation into its multifaceted involvement in various domains of well-being. Empirical evidence suggests that vitamin D insufficiency may share with the onset of Type 2 diabetes. Studies have shown that the pancreas's beta cells responsible for insulin secretion possess both the vitamin D receptor and alpha one hydroxylase enzyme. (Takiishi *et al*.,2010) Calcium has been found to impact the process of insulin secretion indirectly. Vitamin D can regulate extracellular calcium levels, thereby modulating the transmembrane flux of calcium. The reduction of serum vitamin D levels has been observed to impact insulin secretion by calcium, as per previous research [Tanaka *et al*.,1984]. The study findings indicate that no statistically significant difference was observed in the serum calcium and phosphorus levels compared to the control group. Compared to our research, Chen Hui and colleagues have demonstrated that among individuals with Type 2 diabetes, there was a decrease in circulating phosphorus levels and an increase in circulating calcium levels. whoThis was reported in a previous study [Tanaka et al.,1984]. This study examines the serum levels of vitamin D, calcium, phosphorus, and oxidative parameters in healthy individuals and those with diabetes. Inadequate exposure to sunlight, skin type, insufficient dietary intake of vitamin D, increased vitamin D catabolism, and health conditions that reduce the bioavailability of vitamin D are among the factors that can lead to vitamin D deficiency. These factors can result in inefficient synthesis of vitamin D in the skin, decreased absorption, or reduced conversion to the active form.[Tanq et al.,2018]Previous research has indicated that in animal studies, vitamin D can augment the glucose-induced secretion of insulin through the upregulation of insulin receptor expression and the promotion of insulin-mediated glucose transport.[Taylor and Wise,1998] The proposal has been made that there may be a connection between vitamin D and metabolic syndrome, as well as T2DM, due to the impact of vitamin D on insulin release and action, among other factors.

## 4. Conclusion

The findings of this research suggest that the direction of calcium and vitamin-D supplements for six months may not have a significant impact on insulin sensitivity or insulin secretion in individuals who are deficient in vitamin D and belong to multiple ethnic groups, and who are at risk of developing type 2 diabetes, as determined by a diabetes risk questionnaire. Treatment may confer benefits in terms of insulin sensitivity for individuals with prediabetes. It is necessary to conduct randomized controlled trials (RCTs). These trials should focus on individuals with prediabetes, employ gold-standard measures to evaluate surrogate markers of type 2 diabetes and measure the incidence of

type 2 diabetes. It is imperative to assess genetic variations to ascertain potential subpopulations that could derive advantages from this intervention.

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