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Diabetes Mellitus: Impact Due To Vitamin D Deficiency

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ABSTRACT:
Diabetes mellitus is now considered as major metabolic disorder and theVitamin D is also associated with the occurrence of Diabetes mellitus. Vitamin D levels are linked to high blood pressure, neoplastic, and heart disease. A deficiency of vitamin D is linked with the development and progression of diabetes. Although there is an association between vitamin D and insulin secretion, insulin resistance, and beta cell dysfunction in patients with diabetes, the evidence on vitamin D levels and DM is conflicting and poorly controlled. There is increasing evidence that deficiency is a risk factor for diabetes and chronic kidney disease,but it is not clear regarding the death of diabetic patients due to vitamin D deficiency Currently, vitamin D supplementation has not been shown to improve glycemic control or prevent the development of diabetes, but with adequate sample size, study duration, and optimal dose of vitamin D supplementation, further clinical trials are needed. In this articlemajor scenario shown on the mechanisms of primary vitamin D deficiency associated with Diabetes Mellitus, and describes the recent evidence on vitamin Dmedication in patients with these diseases.

Keywords:Diabetes mellitus; Vitamin D supplement, Vitamin D deficiency

I. INTRODUCTION

According to a survey revealed that approximately 85% of the population have vitamin D deficiency. Overall, 62.8% had obesity,42.8%had high BP,18.2% had high FPG, 48.8% had low HDL, 14.2 % had high TG in the local population.[1]International Diabetes Federation 2017, Diabetes and Cardiovascular diseases are top 10 causes of death globally. South Asian countries like India and China are very much affected due to this.[2]A proposed association betweenvitamin D and Diabetes mellitus of type 1were observed in several studies. Treatment with vitamin D has been shown to improve the diabetes and even prevent type 1 diabetes in both humans and animals.These effects are mainly attributed to the immunomodulatory effects of vitamin D. However, little is known about the relationship between vitamin D and type 2 diabetes. Vitamin D deficiency reduces insulin secretion in mice and humans, and instead improves B-cell function and glucose tolerance.[2] Additionally, specific allelic variants in the vitamin D receptor (VDR) and vitamin D binding protein (DBP) can affect glucose tolerance and insulin secretion, suggesting that genes contribute to this risk. Vitamin D can regulate insulin receptor gene expression and insulin secretion, an interesting environmental candidate for the etiology and development of type 2 diabetes.The current review article gave focus in the diabetes mellitus and role of Vitamin D due to its factor, especially its proposed protective role and protective mechanism.[3]

Vitamin D is steroid hormone having fat soluble nature obtained from food and synthesized in the skin after sun exposure. Extra skeletal benefits of vitamin D are on research everywhere in the world. Vitamin D has a significant role in cancer, autoimmune diseases and cardiovascular diseases apart from skeletal benefits. There are mainly two forms of vitamin D in humans which are known as vitamin D2 (Ergocalciferol) and vitamin D3 (Cholecalciferol).It is documented that vitamin D has important functions in the endocrine, paracrine, autocrine systems, and has a significant role in sustaining calcium homeostasis and bone health[4].Ultraviolet B radiation produces Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) while VD3 is produced from provitamin D3 and is converted to VD3 by UV light. [5,6]. Most of the 25-hydroxyvitamin (25 [OH] D) is derived from metabolites found in the skin. Alternative sources are mainly foods obtained from plants or animals.

Vitamin D shows a decrease in action of immune system due to which there is T and B lymphocytes cells produces the immunoglobins and

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cytokines to overcome antigen by cells called macrophages.Vitamin D are converted into its active form which are stored in adipose tissue of skin.[7]Vitamin D metabolism requires two types of hydroxylation to form the active metabolite. The primary degradation of vitamin D occurs in the liver, and vitamin D is metabolized to 25(OH)D by cytochrome P 2R1 (CYP2R1). 25(OH)D binds to vitamin D carrier protein (DBP) and can enter the blood stably. DDBP 25(OH) is excreted in the urine and reabsorbed by megalin proximal polyubiquitin receptors, where the complex is catalyzed by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and 1, the active form of hydroxyvitamin Gene expression CYP27B1 in the kidney is regulated by several factors such as Parathyroid hormone (PTH), hypocalcemia, hypophosphatemia, and calcitonin can affect CYP27B1 activation and increase 1,25(OH)2D levels. On the other hand, 1,25-(OH)2D and fibroblast growth factor 23 (FGF-23) can inhibit CYP27B1 and reduce 1,25(OH)2D levels. Vitamin D affects nuclear receptor (VDR) gene transcription. In general, 1,25(OH)2D increases intestinal absorption of calcium and phosphorus and modulates vascular calcium reabsorption. Because VDR is expressed in various organs such as the heart, liver, blood vessels, and central nervous system, these tissues also express 25-hydroxyvitamin D-1α-hydroxylase.[8] 25(OH)D is the only 1,25(OH)2D product and does not affect individual tissues in dimer is changed to other tissues have 1α-hydroxylase enzymatic activity [9]. However, recent reports have revealed that 25(OH)D has a low ability to bind VDR and affects many tissues of the ear or paracrine. Moreover, the enzymatic activity of 1α-hydroxylase outside the kidney is regulated differently than in tubular cells.

Metabolic and Biological Functions of Vitamin D:

The absorption of the Vitamin D affects the aborptionof calcium and other ions, that's leads to increase the level of minerals in plasma by increase the reabsorption of calcium by the organ kidney. As a result, important biological actions of this vitamin include maintaining mineral homeostasis and regulating bone remodeling.[10] Thus, total vitamin D requirement is met by the photochemical conversion of 7-dehydrocholesterol by sunlight (Figure 1). Industrialization has reduced our exposure to the sun, making us more dependent on dietary sources of vitamin D. Regardless of the source of vitamin D, it must be hydroxylated twice to produce the biologically active form, 1,25(OH)2D3Vitamin D[11].

This metabolite is extracted by the liver to convert into calcidiol which is known as 25-hydroxy vitamin D [25(OH)D]. This 25(OH)D circulates in the blood stream, this specific metabolite is the determinant of person's vitamin D status.

Vitamin D binding protein has anti-inflammatory and immunomodulatory functions which is independent of the carrier of vitamin D. Further, in the proximal tubule of kidneys (predominantly occurs), it covert some amount of calcidiol into calcitriol which is called as 1,25 dihydroxyvitaminD by 1α-hydroxylation process which is the biologically active form of vitamin D.

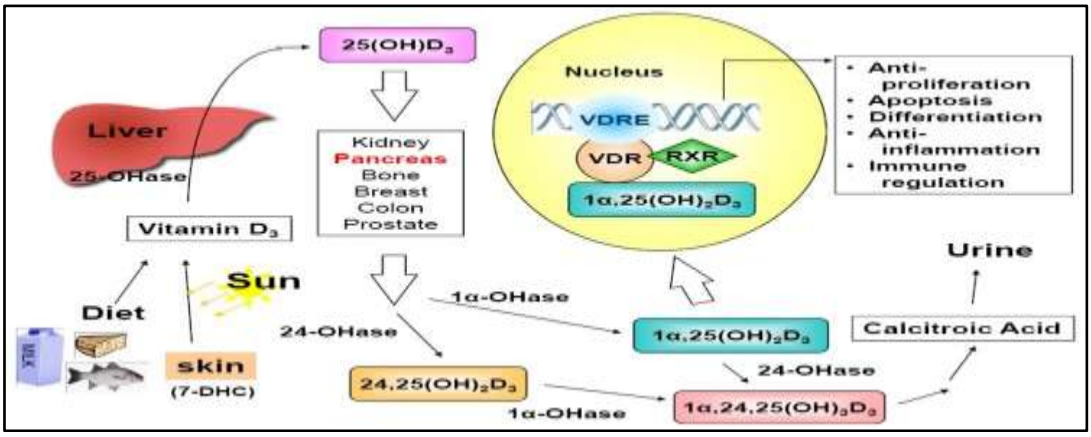

Figure 1: Activation process of Vitamin D3

Vitamin D3 can be obtained directly from diet or by photochemical conversion of 7-dehydrocholesterol to pro-vitamin D3 from sunlight. Provitamin D3 is thermodynamically unstable and is converted to vitamin D3 by heat. Regardless of the source, vitamin D hydroxylation

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must be used three times to produce active organisms. Therefore, the first hydroxylation process occurs in the liver to form 25-hydroxyvitamin D3 (25(OH)D3) and is catalyzed by vitamin D-25-hydroxylase (25-OH). The second hydroxylation step to produce the final active metabolite of vitamin D3 (1,25(OH)2D3) is carried out primarily in the liver by 25-hydroxyvitamin D3 1a-hydroxylase (1-OHase). increase. 1,25(OH)2D3 is then released into the bloodstream where it binds to vitamin D binding protein (DBP) until reaching target tissues via vitamin D receptors (VDR). Vitamin D 24 hydroxylase (24-OH) is an enzyme that acts in the kidneys on hormone metabolism.[12]

Vitamin D effect on Beta Cells:

Several lines of evidence suggest insulin secretion effect due to Vitamin D, by acting on humoral cells and pancreatic tissue as VDR and protein known as Vitamin dependent calcium binding protein.Expression of VDR and CYP27B1 has been reported for many other tissues that can be broadly termed 'barrier sites, indicating that localised responses to vitamin D may be a key feature of these tissues.[3] Both in vitro and biological models have demonstrated that vitamin D itself is essential for maintaining normal glucose responses to insulin secretion and glucose tolerance, and that impaired glucose tolerance is accompanied by insulin resistance. . Variation in insulin sensitivity.[13] Furthermore, vitamin D deficiency reduces pancreatic insulin secretion without altering glucagon secretion. Importantly, vitamin D supplementation in early-stage experimental vitamin D-deficient or vitamin D-deficient individuals partially improves glucose tolerance and insulin secretion in response to glucose.[14] Alterations in vitamin D metabolism due to the inhibitory effect of insulin deficiency on 25(OH)D3 1a-hydroxylase vitamin D per lymphocyte function by Plasma calcium, DBP, circulating vitamin D, and bone mass reduction in streptozotocin-induced diabetic rats.

Effect of vitamin D on diabetes

VD is one of the major hormones to control homeostasis.[11] Type 1 diabetes results from complex autoimmune destruction of pancreatic islet beta cells resulting in complete insulin deficiency.

Diabetes Type 1:

Type I autoimmune DM is characterized by the detection of autoantibodies against pancreatic islet cells and their infiltration by T cells, B cells, and macrophages.[15] Vitamin D also has immunomodulatory properties. Rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel diseaseare known auto immune disorder which are associated with vitamin D deficiency. Since VDR is expressed on human T and B lymphocytes, it is clear that the Th1/Th2 TB profile has changed.[5] Additionally, it was believed that lymph node peace was the first to stop the system's defenses. And the absence of non-diabetics (these and others) showed facts and events in the majority of diabetic patients and the number of losses has decreased. The active form of Vitamin D defense against the inflammation of the pancreas and decreases the severity through several mechanisms action act on immune system and pancreatic cells.[16]

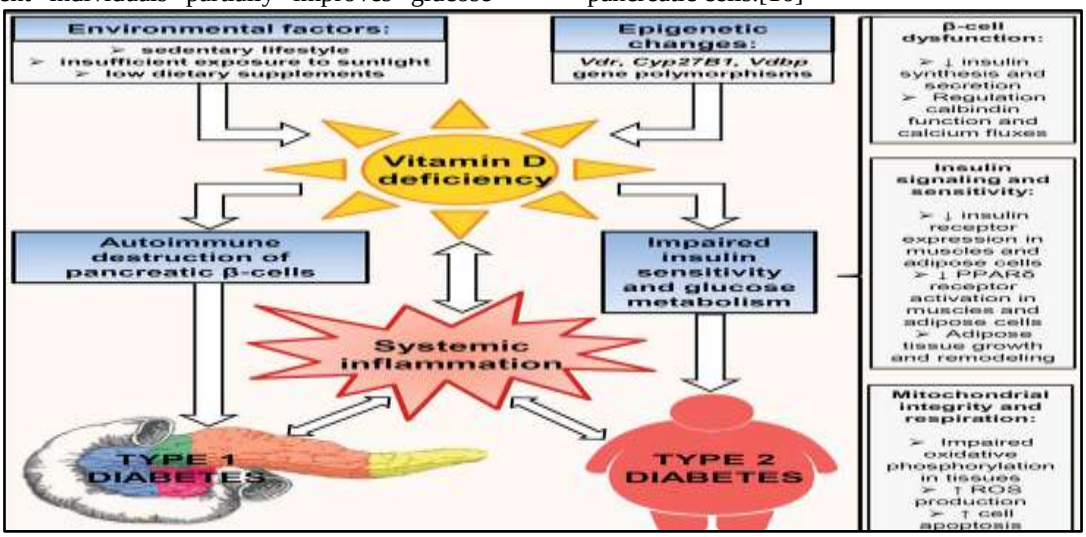

Figure 2: Vitamin D effect on Diabetes Mellitus[17]

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Diabetes Type 2:

Vitamin D and Diabetes mellitus 2 is exactly factor that was not known but is seen in several studies that is characterized by insulin resistancewhich leads to an imbalance of insulin secretion due to Vitamin D deficiency. The main reason was found out to be environmental factors that triggertheprocess of insulin secretion and leads to affects on the protective effect of pancreatic cells.[18]Furthermore, most patients with type 2 diabetes had vitamin D deficiency (<20 ng/ml), indicating that vitamin D deficiency was significantly higher in the diabetic group than in the non-diabetic group. This finding thus confirms the association between vitamin D deficiency and T2DM, possibly due to the presence and distribution of vitamin D receptors in pancreatic β-cells, adipose tissues, and skeletal muscle. When ingested, it raises blood sugar levels in diabetics [19].

Vitamin D supplementation in diabetes:

Furthermore, vitamin D supplementation in non-vitamin D deficient subjects did not show any benefit on glucose tolerance [20]. There are various effects due to genomic also, in this rapid nongenomic mechanism of action of VitaminD presence due to activation of insulin exocytosis by an increase in Ca^{2+} regulation. Inseveral studies suggest that vitamin D deficiency may play an important role in the pathogenesis of type 2 diabetes in humans.[18]Epidemiological data show that Bangladeshi residents in London have lower serum vitamin D levels at risk for type 2 diabetes than non-risk subjects.In showed a high prevalence of type 2 diabetes, suggesting that Vitamin D status may contribute to the etiology of the disease gain.[21,22]

Short-term vitamin D supplementation in the Asian Bengali population increased insulin secretion without altering blood glucose levels, whereas long-term vitamin D treatment also improved blood glucose levels. The meta-analysis reportsuggested that results of clinical trials of vitamin D supplementation on metabolic syndromes are controversial.In addition, a New Zealand study reported that a newly diagnosed patient with type 2 diabetes or impaired glucose tolerance had lower 25(OH)D3 levels in her than matched control subjects.[23]From the various finding, the mice lack on the vitamin D and impaired insulin resistance leads to a decrease in secretion while stimulation with glucose. Furthermore, vitamin D status was inversely correlated with glucose tolerance and insulin secretion in older Dutch men.[24]Data from the Third Annual National Health and Nutrition Survey show an inverse association between vitamin D status and diabetes in non-Hispanic whites and Mexican Americans, but not in non-Hispanic blacks. (OH)D3 was not associated with glucose status in a UK population. These data suggest that vitamin D deficiency may be an important risk factor for impaired glucose tolerance in some populations.[25] The lack of an inverse association between vitamin D status and diabetes in non-Hispanic blacks is surprising, especially given the low vitamin D levels among blood types.

II. CONCLUSION

Current sources emphasize therole of vitamin D in Type 1 and type 2 diabetes mellitus. Several prospective studies have shown a relationship between vitamin D status and chronic diseases such as diabetes and chronic kidney disease. However, there are conflicting results regarding whether restoring normal vitamin D levels alters these diseases' incidence and clinical course. The major and more comprehensive is to determine the role of Vitamin D in the treatment of glucose intolerance progressive prevention in group of high risk of type 2 diabetes mellitus should be studied.

REFERENCES

[1]. Luong K, Nguyen LTH, Nguyen DNP. The role of vitamin D in protecting type 1 diabetes mellitus. Diabetes Metab Res Rev 2005; 21: 338–346.

[2]. Mathieu C, Gysemans C, Guilietti A et al. Vitamin D And diabetes. Diabetologia 2005; 48: 1247–1257.

[3]. The EURODIAB Substudy 2 Study Group. Vitamin Supplement in early childhood and risk for type 1(insulin-dependent) diabetes mellitus. Diabetologia 1999; 42: 51–54.

[4]. Stene LC, Ulriksen J, Magnus P et al. Use of cod liver Oil during pregnancy is associated with lower risk of Type 1 diabetes in the offspring. Diabetologia 2000; 43:1093–1098.

[5]. Mathieu C, Laureys J, Sobis H et al. 1,25-Dihydroxyvitamin D3 prevents insulitis in NOD mice. Diabetes 1992; 41: 1491–1495.

[6]. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest 2006; 116: 2062-2072

International Journal of Pharmaceutical Research and Applications
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[7]. Holick MF. Sunlight and vitamin D for bone health and prevention Of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80: 1678S-1688S
[8]. Christensen EI, Willnow TE. Essential role of megalin in renal Proximal tubule for vitamin homeostasis. J Am Soc Nephrol 1999; 10: 2224-2236
[9]. Verroust PJ, Birn H, Nielsen R, Kozyraki R, Christensen EI. The Tandem endocytic receptors megalin and cubling are important Proteins in renal pathology. Kidney Int 2002; 62: 745-756
[10]. Dusso AS. Kidney disease and vitamin D levels: 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and VDR activation. Kidney Int Suppl (2011) 2011; 1: 136-141.
[11]. Boucher BJ, Mannan N, Noonan K et al. Glucose intolerance and impairment of insulin secretion in relation To vitamin D deficiency in East London Asians. Diabetologia 1995; 38: 1239–1245.
[12]. Iyengar S, Hamman RF, Marshall JA et al. On the role Of vitamin D binding globulin in glucose homeostasis:Results from the San Luis Valley Diabetes Study. Genet Epidemiol 1989; 6: 691–698.
[13]. Pratleyy RE, Thompson DB, Prochazka M et al. An Autosomal genomic scan for loci linked to prediabetic Phenotypes in Pima Indians. J Clin Invest 1998; 101:1757–1764.
[14]. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium 2011 Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press, 2011
[15]. Buchebner D, McGuigan F, Gerdhem P, Malm J, Ridderstråle M, Akesson K. Vitamin D insufficiency over 5 years is associated with Increased fracture risk-an observational cohort study of elderly Women. Osteoporos Int 2014; 25: 2767-2775.
[16]. Ensrud KE, Taylor BC, Paudel ML, Cauley JA, Cawthon PM, Cummings SR, Fink HA, Barrett-Connor E, Zmuda JM, Shikany JM, Orwoll ES. Serum 25-hydroxyvitamin D levels and rate of Hip bone loss in older men. J Clin Endocrinol Metab 2009; 94: 2773-2780.
[17]. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, Treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930
[18]. DeLuca HF. Overview of general physiologic features and Functions of vitamin D. Am J Clin Nutr 2004; 80: 1689S-1696S]
[19]. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D Insufficiency. Lancet 1998; 351: 805-806
[20]. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations Of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006; 84: 18-28 [PMID: 16825677]
[21]. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch PediatrAdolesc Med 2004; 158: 531-537
[22]. Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in Maine are at risk for vitamin D insufficiency. J Am Diet Assoc 2005; 105: 971-974
[23]. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007; 85: 860-868 [PMID: 17344510]
[24]. Jacques PF, Felson DT, Tucker KL, Mahnken B, Wilson PW, Rosenberg IH, Rush D. Plasma 25-hydroxyvitamin D and its Determinants in an elderly population sample. Am J Clin Nutr1997; 66: 929-936 [PMID: 9322570]
[25]. Orwoll E, Riddle M, Prince M. Effects of vitamin D On insulin and glucagon secretion in non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1994; 59:1083–1087.