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VITAMIN D AND ITS ROLE IN THE LIPID METABOLISM AND DEVELOPMENT

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Abstract
Vitamin D defciency is a common health problem worldwide. Despite its known skeletal ects, studies have begun to explore its extra-skeletal e.ects, that is, in preventing metabolic diseases such as obesity, hyperlipidemia, and diabetes mellitus. The article explained the relation between deficiency in vitamin D and increase parameters of lipid profile in the serum. Therefore, correction of vitamin D deficiency will lower the lipid profile. Parameters and so protect the heart from diseases.Vitamin D deficiency and its relation to lipid profile. Vitamin D is a steroid hormone classically involved in the calcium metabolism and bone homeostasis. Standard measure of vitamin D sufficiency, total 25OHD (25 hydroxyvitamin) levels, may not be the best measure-at least by itself. Finally, several recent large clinical trials exploring the role of vitamin D supplementation in nonskeletal diseases are briefly reviewed, with an eye toward what questions they answered and what new questions they raised. The major circulating metabolite of vitamin D, 25-hydroxyvitamin D (25(OH) D), is widely used as a biomarker of vitamin D status. Vitamin D intake which vary from 400–1000 IU/d (10–25 µg/d) for an average adult.

Keywords: Metabolism, Vitamin D deficiency, Metabolic disorders, vitamin D supplementation, vitamin D Intake, Triglycerides , LDL , HDL, clinical trials.

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INTRODUCTION

Vitamin D is a steroid hormone which exerts a crucial role in the maintenance of bone and calciumhomeostasis. The discovery dates back to one hundred years ago, but vitamin D has become a hottopic in endocrinology research only in the last decades, and it has recently emerged as a burning issue due to the COVID-19 pandemic, because of the alleged correlation between hypovitaminosis D anhigh risk of chronic pulmonary diseases and mortality [1] . It is now clear that vitamin D displays complex multistep metabolism and acts as a hormone on many extra-skeletal targets [2] .Vitamin D is well knownfor its important role in the maintenance of bone mineral density [3]. However, vitamin D also has an important "nonclassic"modulatory effect on the innate and adaptive immunesystem [4]**.** Vitamin D is essential for normal endothelial function, blood pressure control, increased vascular resistance, and prevention of CVD [5]. Vitamin D deficiency is a major public health problem worldwide in all age groups, even in those residing in countries with sun exposure all year round [6]. While 25(OH) D metabolism forms the backbone of vitamin D physiology, there are other metabolic and catabolic pathways that are now recognised as important for vitamin D function [7]. Several government bodies were requested to derive updated guidelines for the acceptable range of vitamin D intakes for adults, children and infants.

Epidemiology of Vitamin D deficiency

Definition of Vitamin D Deficiency: A central controversy in vitamin D is how to define hypovitaminosis. The blood level of 25(OH) D that is defined as vitamin D deficiency remains controversial. Vitamin D deficiency as defined by SACN, IOM, EFSA, the Endocrine Practice Guidelines and the Australian Working.The prevalence of vitamin D deficiency is 50% in the elderly [8], affecting near of half of adults American population (9) and about 30% of adults in Europe (10), with

increased occurrence in either high- or low-latitude countries [111, 12]. In Saudi Arabian population, vitamin D deficiency is nearby 60% of the population.

2. Studies Linking Vitamin D Deficiency to Impaired Metabolism

Animal Studies

Lower serum glucose levels, improved activities of enzymes related to glucose metabolic pathways, restoration of glucose homeostasis, and reduced pancreatic and liver damage were observed following intraperitoneal injections of vitamin D (7 ng/gm) daily to alloxan-induced diabetic female albino mice for fifteen consecutive days [13].

Human Studies

Vitamin D supplementation was reported to help to improve the metabolic parameters associated with insulin resistance and DM in human subjects [14]. In a double-blinded, randomized, placebo-controlled trial in obese subjects, weekly supplementation with 25,000 IU cholecalciferol orally for 3 months together with hypocaloric diet resulted in improved insulin sensitivity [15]. Women with vitamin D deficiency, however, reported no improvement in insulin resistance or glycemic control following 60,000 IU of oral vitamin D3 supplementation once a month until delivery [16]. Similarly, a randomized, placebo controlled, double-blind trial on women suffering from polycystic ovarian syndrome (PCOS) with vitamin D deficiency demonstrated no significant changes in the fasting serum insulin and FBG levels after supplementation with 50,000 IU oral vitamin D3 once every 20 days for two (2) months [17,18].

Vitamin D Metabolism

As is well known, vitamin D is produced in the skin from 7-dehydrocholesterol (7-DHC) hydrogenated firs t in the liver (and other tissues) to 25 hydroxyvitamin (25OHD), and then in the kidney (and other tissues) to 1,25 dihydroxyvitamin D (1,25(OH)2D), with subsequentcatabolism of both 25OHD and 1,25(OH)2D to their 24 (and 23) hydroxy forms,24,25(OH)2Dand 1,24,25(OH)3D (or 1,23,25(OH)3D).

A7-Dehydrocholesterol Reductase (DHCR7)

Its synthesis in the skin is a step in the Kandutsch-Russell pathway. DHCR7 converts 7-DHC to cholesterol, so its interactivity how much 7-DHC is available for vitamin D production [18]. These patients suffer primarily from the consequences of too little cholesterol, steroids, or bile acids, but they appear to be more sensitive to UVB light, and may present with higher serum 25OHD concentrations than normal subjects [19]. AMPK, a key sensor and regulator of cellular energyhomeostasis and protein kinase A are portent inhibitors of DHCR7, whereas CaMKII has alower inhibitory effect [20].

B. 25-Hydroxylases

The liver is the major if not sole source of 25OHD production from vitamin D. the major role of CYP27A1 is to convert cholesterol to cholicacid and chenodeoxycholic acids such that mutations CYP2R1 25-hydroxylates both D2 and D3 with comparable kinetics,unlike CYP27A1.. Five in CYP27A1 lead to reduced bile acidproduction and increased cholestanol that accumulates in the brain, causing progressive neurologic dysfunction.

C. Cholesterol side chain cleavage enzyme (CYP11A1)

This enzyme is the rate-limiting enzyme in steroid synthesis, but studies from the Slominski laboratory demonstrated that CYP11A1 also metabolizes vitamin D3 to 20(OH)D3 , with subsequent metabolism to additional metabolites that have biologic activity comparable in some cases to 1,25(OH)2 D3 . CYP11A1 is expressed in the skin and cultured keratinocytes as well as better known steroid-producing tissues such as the adrenals, ovary, testes, and placenta.

Mechanisms Underlying the Action of Vitamin D in Improving Impaired Metabolism

Vitamin D Improves Pancreatic β-cell Functions. Functional, pancreatic β-cells play important role in maintaining the blood glucose homeostasis. else cells adapt to an excessive blood glucose level by increasing the insulin secretion, and the latter is further exaggerated in the state of insulin resistance. Chronic exposure to high glucose and free fatty acids (FFA) levels could cause progressive β-cell dysfunction, which may eventually lead to β-cell apoptosis in DM . The role of vitamin D in pancreatic β-cell function is supported by the discovery of 1α-hydroxylase enzyme, which is classically found in the kidney. Insulin release requires calcium influx and the opening of voltage-gated calcium channels (VGCCs) upon glucose stimulation. The active form of vitamin D, calcitriol, regulates extracellular calcium levels and calcium influx into β-cells via VGCC.

Vitamin D Improves Insulin Sensitivity. Firstly, vitamin D modulates the secretion of insulin-sensitizing hormones such as adiponectin and leptin and increases the expression of disulfide-bond A oxidoreductase-like (DsbA-L) protein, a key regulator for adiponectin production . Lower levels of adiponectin have been reported in vitamin D-deficient, obese children, whereas higher adiponectin levels were observed in patients with type 2 DM (T2DM) receiving vitamin D-fortified food containing 500 IU vitamin D3 daily for twelve (12) weeks. Besides, vitamin D maintains the insulin signaling pathway by increasing the expression of insulin receptors (IRs).

Pharmacokinetics of Vitamin D Metabolism

Literature characterising the dose-response curve to vitamin D shows varied results. Clinical studies investigating these relationships vary in dosing regimen, administrative routes, assay methods for 25(OH)D and demographics as well as control of endogenous vitamin D production.

Vitamin D and Skin: from Production to Final Effect

Vitamin D exists in two forms: vitamin D3, which is the most important source in animals and is produced in the skin; and

vitamin D2 which differs from D3 for a methyl group in C24 and a double bond in C22–C23 and is produced by plants. In the skin, vitamin D3 is produced from 7-dehydrocholesterol (7DHC), an intermediate in cholesterol synthesis. Exposure to ultraviolet B (UVB) light, in the range of 290–315 nm. It was only in 2015 that the Kandutsch/Russel pathway was completely elucidated and found to have a high activity in the skin, providing the substrate for VitD3 production.

Vitamin D Catabolism, Metabolites and Transport

More than 50 metabolites of vitamin D have been described in the last decades and some of them display a certain interest because of their biological activity. The final products are the inactive calcitroic acid or 26,23-lactone excreted with bile or urine. CYP24A1 is up-regulated by calcitriol and FGF23 and is inhibited by PTH and hypocalcemia.Idiopathic Infantile Hypercalcemia (IIH, OMIM 143880), a rare disorder due to impaired vitamin D catabolism and subsequent hypercalcemia. In particular, biallelic variants (in homozygosis or heterozygosis) have a severe phenotype with hypercalcemia that may occasionally lead to death in infant age.

MECHANISMS OF ACTION

The VDR is critical for most of the actions of vitamin D, with 1,25(OH)2 D as its major ligand. Vitamin D receptor is a transcription factor found in nearly all cells, although to variable levels. It is a member of the steroid hormone receptor family. Although most actions of VDR involve its role as a transcription factor within the nucleus, the VDR has also been shown to have nongenomic actions via its location in the membrane [21] and perhaps even in mitochondria.

A. Structure

The human VDR is located in chromosome 12 and is comprised of 9 exons. Exon 2 contains the translation start site and the nucleotide sequence encoding the short A/B domain (24 amino acids), to which transcription factors such as TFIIB bind, and the first zinc finger of the DNA binding domain (DBD) (65 amino acids). Exon 3 encodes the second zinc finger of the DBD.

B. Regulation

The regulation of VDR expression is cell specific. For example, 1,25(OH)2 D autoregulates VDR expression in bone cells but not in the intestine. Many factors including 1,25(OH)2 D regulate VDR expression, including growth factors such as FGF, EGF, IGF, insulin, as well as parathyroid hormone, glucocorticoids, estrogen, and retinoic acid in some cases acting via a variety of transcription factors such as AP-1, SP1, C/EBP, CDX2, C/EBPβ, Runx2, cyclic AMP.

Relation between vitamin D and lipid profile

Elevated low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels are independent risk factors for adverse cardiovascular event. lower LDL cholesterol, higher HDL cholesterol, and lower triglycerides were proved.Lipid profile increased total and HDL cholesterol but no change in LDL cholesterol triglycerides.

Hypo-vitaminosis D was shown to be associated not only with adverse effects on TG, total cholesterol, and LDLcholesterol and HDL-cholesterol concentrations but also lowered insulin secretion and sensitivity in a study of healthy people from several racial and ethnic groups [22]. It was found that vitamin D improved serum level of Triglycerides, total cholesterol and LDL in patients with DM type 2 [23].

Vitamin D and lipid profile in pediatrics

It was found that higher serum 25(OH)D is related to a more satisfactory lipid profile in the pediatric age group [24]. Vitamin D is known to be essential for bone metabolism, and low serum 25(OH)D levels increase the risk of rickets, osteomalacia, and osteopenia.

FACTORS AFFECTING RESPONSE TO VITAMIN D SUPPLEMENTATION

Patient-specific factors may further affect the amount of vitamin D required to attain a sufficient concentrationand it is important to substantiate what factors influence subjects' responses to vitamin D supplements. Bodyweight has an influence on the blood volume and amount of muscle and adipose tissue. Higher body fat percentage or higher body mass index (BMI) have been associated with smaller increases in 25(OH) D concentrations in response to vitamin D supplementation.

Pleiotropic Effects of Vitamin D

The classical role of 1,25(OH)2D in calcium/bone metabolism, namely the regulation of intestinal calcium absorption, renal calcium reabsorption and mobilization of calcium and phosphate from bone, has been known for decades and is beyond the aims of the present review.

Pregnancy

Maternal vitamin D status has been investigated as a determinant of offspring bone development. Evidence either supports a role for vitamin D status that can affect bone mineral accrual during the intrauterine period or does not as it did not lead to increased offspring whole-body BMC compared with placebo.

Ultraviolet Radiation and Vitamin D Production

During exposure to sunlight, ultraviolet (UV) B radiation converts 7-dehydrocholesterol to previtamin D3 which in turn is isomerised to vitamin D3. Skin pigment and skintype, sunscreen use, aging, time of day (very little vitamin D3 is produced in the skin in the early morning and late afternoon), season, latitude and altitude can affect previtamin D3 synthesis.The half-life of VDBP is ~1–2 d,94 surprisingly shorter than the half-life of 25(OH)D. There are inconsistencies in the literature in the recommendations for sunlight exposure. Further, there are practical difficulties and detrimental effects of UV exposure, and oral supplementation important in maintaining serum 25(OH)D during winter, and it was likely that the supplement requirement was dependent on sun exposure.

STORAGE SITES FOR VITAMIN D IN THE BODY

Little is known about the quantity and location of vitamin D or its metabolites in the adult human body. In a study using pigs and HPLC for analysis of vitamin D and metabolites, substantial amounts of 25(OH)D were found distributed in the body, principally in fat, muscle and serum.In a further study using dual-energy X-ray absorptiometry for body composition, obese women were shown to have greater adipose tissue storage and the increased amount of vitamin D required to saturate the depot may predispose to inadequate serum 25(OH)D.The relation between stored vitamin D3 and 25(OH)D was investigated in a further study. At typical vitamin D inputs, 25(OH)D constitutes the bulk of vitamin D reserves.

GUIDELINES FOR PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY

Most guidelines recommend oral vitamin D3 as a treatment of choice for vitamin D deficiency. However, vitamin D2 may be preferred by vegetarians and those who prefer to avoid vitamin D from animal origin.Treatment is given either as separate weekly or daily doses over 6–10 w: 50,000 IU (1250 μg) given weekly for 6 w, a total of 300,000 IU (7500 μg); 40,000 IU (1000 μg) given weekly for 7 w, a total of 280,000 IU (7000 μg); 4000 IU (100 μg) given daily over 10 w, a total of 280,000 IU (7000 μg). This is followed by maintenance doses of 800–2000 IU (20–50 μg) daily or on occasion 4000 IU (100 μg) daily given either daily or intermittently at high doses.The principal aim of the therapy is to replenish vitamin D stores following which patients are continued on a maintenance dose.

CONCLUSION

Normal vitamin D levels are associated with normal glucose homeostasis, insulin sensitivity, improved pancreatic β-cell function and insulin secretion, and other improvement in metabolic parameters.. New concepts have emerged in the last years, namely the special role of the skin, the metabolic control of liver hydroxylase CYP2R1, the specificity of 1αhydroxylase in different tissues and cell types and the genomic, non-genomic and epigenomic effects of VDR.There is a lack of data on acceptable 25(OH)D concentrations in infants, children, pregnant and lactating women and certain ethnic groups. Vit D supplementation in vitamin D deficiency and insufficiency is important to correct high levels of LDL and cholesterol and protection from cardiovascular disorders. Clinical trials to address some of these questions have shown that vitamin D supplementation of individuals with normal 25OHD levels on average has a limited impact-at least over the short duration of the trials-on a number of nonskeletal conditions, but subpopulations such as the nonobese and those with low baseline levels of 25OHD may benefit.

AUTHOR CONTRIBUTIONS

All authors are contributed equally

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