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Physiological action of vitamin D3 in health and disease

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ABSTRACT

Vitamin D is the common molecules for every steroid that has the biological effects of cholecalciferol. Vitamin D can be synthesized in the mammalian skin after exposed to ultraviolet (UV) waves and this process occur endogenously. Amongst diverse Vitamins, VitD has powerful effects on the immune system. As major components of the diet, vitamins have essential effects on the innate and acquired immune system. The active form of VitD is calcitriol (1,25(OH)2VitD3). Calcitriol (1,25(OH)2VitD3) is the active form of VitD. Calcitriol regulates antimicrobial peptides productions, comprising defensin and cathelicidin, that controller the natural intestine microbiota floor and supports intestinal barriers. VitD in controlling the immune response in infectious and autoimmune diseases. There is a theory that VitD complements could be beneficial for treatment of COVID-19. Vit D has an important anti-inflammatory function on the immune system by reducing the production of pro-inflammatory cytokines and increasing anti-inflammatory cytokines in immune cells. Also, vitamin D deficiency is closely related to chronic diseases such as osteoporosis, type 1 and type 2 diabetes, hypertension, cardiovascular disease and cancer. In addition, recently it was revealed that vitamin D receptors (VDR) are expressed in many organs such as the testes, and vitamin D may be a adjustable regulator of reproductive function and fertility.

Keyword : vitamin D3, COVID-19, VDR, UV

INTRODUCTION

Vitamin D is an organic molecules and it is considered a vitamin, found in diet and is required in small amounts intended for the health, and is found in the food like egg yolk, salmon, Sardine, mackerel, yogurt, Tuna, fruit juice, Mushroom, milk, and Cereals (Elmaghraby *et al*, 2019). Vitamin D is the common descriptor for every steroid exhibiting the biological action of cholecalciferol. These molecules have the intact A, C, and D- steroid rings (Figure 1), being eventually derived by photolysis of the B ring of 7-dehydroc- holesterol in vivo, this process frees the A- ring from the solid structure of the C and D rings, causing conformational mobility where the A ring under goes quick interconversion between two chair configurations (Combs, 2012). Vitamins D3 and D2 are yellowish to white powders that are freely soluble in petroleum ether, ether and acetone; moderately soluble in oils, ethanol and fats; and insoluble in water. Also, each one exhibits powerful ultraviolet (UV) absorption (with a maximum at 264 nm). Vit. D is sensitive to iodine, light and oxygen. (Combs, 2012).

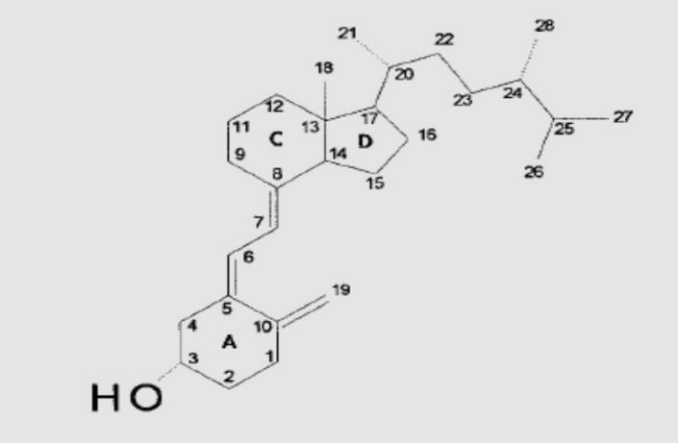

Figure (1): Chemical structures of the vitamin D group (Combs, 2012)

Vitamin D Synthesis and metabolism

Studies conducted from the 1920s and 1930s led to the discovery that vitamin D can be synthesized in the mammalian skin after exposed to ultraviolet (UV) waves and this process occur endogenously (Wolf, 2004). Vitamin D photosynthesis begins with production of the sterol provitamin D3 compound 7-dehydro- cholesterol. This is synthesis in great amount in the skin. In the dermis and epidermis its incorporated into plasma membrane lipid bilayers of cells in humans and most vertebrate animals. After exposure of the skin to sunlight, 7-dehydrocholesterol molecules absorbs UV radiation in the wavelength range between 290–315 nm. The chemical bonds in the 7-dehydrocholesterol molecule were break and rearrange after absorbed energy, resulting in the formation of previtamin D_3. In the skin, previtamin D_3 converts to vitamin D_3 by quick, thermally-induced conversion to vitamin D_3 (Tsiaras and Weinstock, 2011).

After produced, vitamin D_3 and previtamin D_3 persist to absorb UV radiation in a broad range of wavelengths, this process may leads to the breakdown of these compound into biologically inert light products (Tsiaras and Weinstock, 2011), for this cause, during extended exposure to UV- radiation, a stable situation is reached in which just 10–15% of 7-dehydrocholesterol is transformed to previtamin D_3 (Holick, 1995). This photoregulation process is thought to ensure that toxic levels of vitamin D_3 are not synthesized under intense sun exposure (Holick, 2004).

Vitamin D_3 which cutaneously synthesized is liberated from the plasma membrane and enters the circulation after bounding to vitamin D-binding protein (DbP) (Holick, 2004). After 24-28 hours exposure to ultraviolet rays, vitamin D concentrations reach their peak. (Tsiaras and Weinstock, 2011). After that, vitamin D_3 concentration decrease significantly with a serum half-life ranging from 36 to 78 h (Tsiaras and Weinstock, 2011). Because Vit.D_3 is a fat-soluble vitamin, it can be taken up by adipocytes and stored under the skin in subcutaneous or omental fat deposits for later use (Blum *et al.*, 2008). The allocation of vitamin D_3 into adipose-tissues can prolongs its half-life to about 2 months (Jones, 2008).

In the liver circulating- vitamin D_3 was metabolized by the vitamin D-25-hydroxylase enzyme to 25(OH) and this is the main circulating shape of vit. D_3 and the molecule usually estimated by clinicians wishing to evaluate Vit. D_3 status. The extent and rate of the increase of serum 25-(OH)D_3 concentration follow UV-irradiation or Vit. D_3 ingestion is dependent on the regulated the activity of vitamin

D-25-hydroxylase enzyme (Figure 2). The plasma half-life of Vit.25(OH)D_3 is about 15 days (Jones, 2008). 25(OH)D3 is not physically active excluding at very elevated, non-physiological concentration (Vieth, 1999). The process of their activation requires its change to 1,25(OH)2 D3 in the kidney through the enzyme 25(OH) D-1α-hydroxylase and these process firmly regulated by a numeral of factors including serum parathyroid hormone (PTH) and phosphorus. Also, catabolism of 1,25(OH)2 D3 is firmly regulated (Khor *et al.*, 2007).

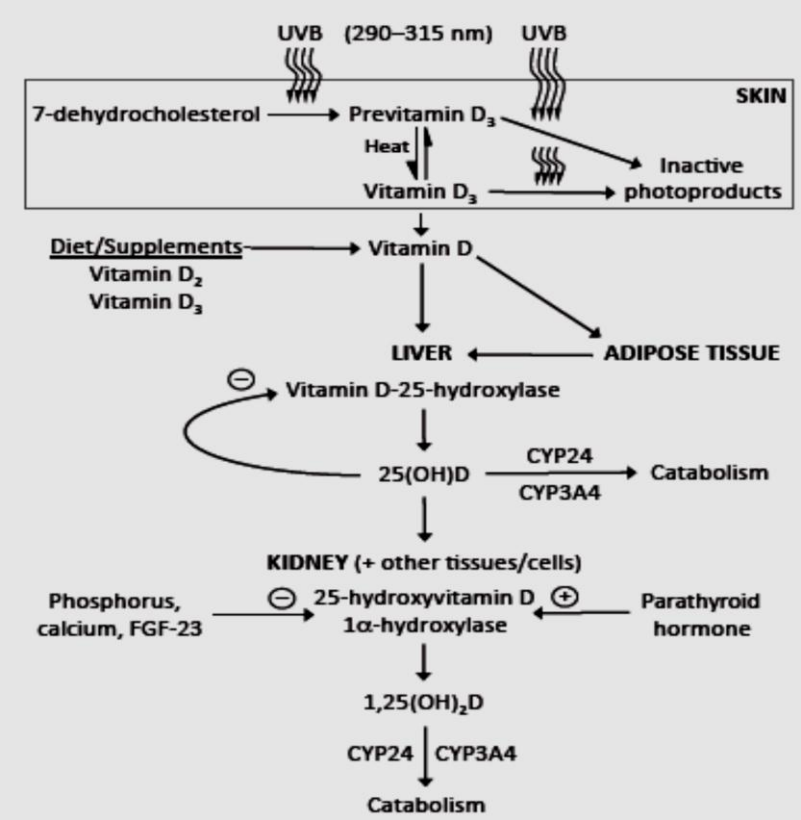

Fig. 2. Synthesis and metabolism of vitamin D.

Gastrointestinal absorption of vitamin D

Following cutaneous synthesis or oral consumption, vitamin D bioavailability is dependent on intestinal absorption, fat storage and metabolism. Dietary vitamin D consists of vitamin D_2 (ergocalciferol) derived from non-vertebrate species (invertebrates, fungi and plants) and vitamin D_3 (cholecalciferol) derived from vertebrates. Vitamins D_2 and D_3 differ only slightly in their chemical structure and both have been used to effectively treat suboptimal vitamin D status, vitamin D deficiency rickets and osteomalacia (Pepper *et al.*, 2009). There is, however, some controversy as to the biological equivalence of these two forms of vitamin D, with some studies suggesting they are differently metabolised (Houghton and Vieth, 2006), and others reporting differential effects on serum 25(OH)D levels (Mastaglia *et al.*, 2006). Vitamins D_2 and D_3 are both relatively non-polar molecules and must therefore be solubilized by incorporation into bile-salt micellar solutions in order to be absorbed to the aqueous phase. Absorption occurs primarily in the proximal small intestine and is influenced by gastric, pancreatic and biliary secretions, micelle

formation, diffusion through the unstirred-water layer, brush-border-membrane uptake, and transport out of the intestinal cell (Tsiaras and Weinstock, 2011).

Vitamin D and the immune system

As the main components of the diet, vitamins have an essential effect on the innate and acquired immune system. Among different Vitamins, VitD has potent effects on the immune system; The active form of VitD is calcitriol (1,25(OH)2VitD3). Calcitriol regulates antimicrobial peptides productions, including cathelicidin and defensin, that control the natural intestine microbiota floor and supports intestinal barriers (Clark and Mach, 2016). Immune system cells such as monocytes, neutrophil, and NK cells produce defensins and cathelicidins as antimicrobial peptides that protect the immune system. In this regard, the expression of the anti- microbial peptide is increased under the influence of VitD (Wang *et al.*, 2004). Furthermore, it protects the respiratory system against infection. It can also increase proteins' expression related to intercellular connections such as connexin-43, tight junctions, and E-cadherin in epithelial barriers, protecting the lungs against infection (Gombart, 2009) . Moreover, VitD improves renal epithelial (Mihajlovic *et al.*, 2017) and cornea epithelial barriers (Yin *et al.*, 2011). It has also been confirmed that receptors of VitD are found on monocytes, macrophages, and it has also been verified that calcitriol leads to enhance mobility and phagocytosis in macrophages. Activated macrophages cause monocytes' differentiation into the tissue macrophages via calcitriol synthesis (Wu *et al.*, 2019). Macrophages increase the generation of TNF cytokine and phagocytosis in the presence of VitD and call and accumulate immune cells such as neutrophils to inflammation sites and stimulate them to kill microbes (Abu-Amer and Bar-Shavit, 1994). Furthermore, VitD controls interferon (IFN) generation; it increases the production capacity of oxidative reactions in macrophages against pathogens. IFNs are considered as immune mediators between innate and acquired immune system. IFN-c, the most potent stimulant for the macrophages' activation, subsequently causes increased cellular immunity, augmented intracellular pathogen elimination, superoxide production, and expression of the inflammatory and anti-inflammatory cytokines genes (Topilski *et al.*, 2004). It also inhibits T cells' proliferation by suppressing the IL-2 production, and it changes the response from Th1 to Th2 cells. VitD implants lymphocytes into the skin and produces chemokines. VitD endeavors in the homing process and production of dermal chemokines in which the precursor form of the VitD3 produced by sunlight.

The role of vitamin D in the prevention of corona

In many people with SARS-COV-2 infection, cytokine storm could be seen as a result of a cytokine overproduction that leads to (Acute Respiratory Syndrome) ARS, organ failure, and finally, death. Researchers have focused on preventing and treating the disease consistently. Nonetheless, no specific vaccine or antiviral drug has been developed for COVID-19 yet. VitD in modulating the immune response in infectious and autoimmune diseases is well known. There is a hypothesis that VitD supplements could be useful for treatment of COVID-19 (Musavi *et al.*, 2020). Also, VitD administration strengthens ACE2, Ang 1–7, and MasR axis expression and, VitD alters the balance among ACE/Ang II/AT1 and ACE2/Ang 1–7 to the appropriate and protective side (Leffa *et al.*, 2019). These effects indicate the decisive role of VitD in protection against lung infection in COVID-19.

VitD function in SARS-COV-2 immunopathogenesis

Based on numerous studies, a significant reason for mortalities in the initial stage of SARS-COV-2 infection is acute respiratory distress syndrome (ARDS). For instance,

based on an examination, in patients with COVID-19 disease, around 14% died due to RDS (T. Xu *et al.*, 2020). The main immunopathological incident in contamination with SARS-CoV-2, SARS-CoV, and MERS-CoV is ARDS (Z. Xu *et al.*, 2020). A high load of different cytokines is considered as an essential mechanism for ARDS. In SARS-CoV infection, secretion of massive levels of cytokines including IFN-a, IFN-c, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb, and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 via immune system cells are leading to high rate mortality. Similarly, the serum concentrations of IL-6, IFN-a, and CCL5, CXCL8, CXCL-10 in persons who had acute MERS-CoV infection were higher than those subjects with the mild-moderate infection (Min *et al.*, 2016). The high levels of cytokines lead to the hyper-inflammatory syndrome, which causes death in the late stage of SARS-CoV-2 infection, which is precisely similar to what happens in SARS-CoV and MERS-CoV infection (Z. Xu *et al.*, 2020).

Vit D inhibits the proliferation of T-cells and suppresses activation of Th1 cells in adaptive immunity. VitD causes cell differentiation into regulatory T cells by reducing inflammatory cytokines such as IL-17 and 21. On the other hand, VitD increases anti-inflammatory cytokines, such as IL-10, that play an essential role in the induction of tolerance in antigen-presenting cells such as dendritic cells (Wu *et al.*, 2019). VitD reduces pro-inflammatory cytokines and increases anti-inflammatory cytokines by activating different immune system cells. Mostly, T-cells differentiate into subsets of helper cells, which lead to increased production of cytokines in cellular immune responses. These cells are often TH1 and TH2 cells. Along with IL-2 and IFN-c production, TH1 cells form immune response against intracellular pathogens. Also, Th2 cells fight against pathogens and extracellular microorganisms through secreting cytokines such as IL-5, IL-4, IL-10, and IL-13. In this regard, VitD suppresses Th1 cell differentiation via the suppression of IL-1 and IFN-c generation (Wu *et al.*, 2019).

VitD might induce body tolerance against the high volume of cytokines during SARS-COV-2 infection by inhibiting cell differentiation to TH17, enhances Treg cells production, and increases anti-inflammatory cytokines like IL-10, and inhibits inflammatory cytokine production from macrophages and monocytes (Kang *et al.*, 2012). Hence, Vit D has an important anti-inflammatory function on the immune system by reducing the production of pro-inflammatory cytokines and increasing anti-inflammatory cytokines in immune cells.

Vitamin D and Chronic Disease

Hypertension and Cardiovascular Disease

The association of vitamin D status and hypertension is particularly strong. Both controlled trials and meta-analyses have shown a protective effect of high calcium intake for both pregnancy-related and essential hypertension (Wang *et al.*, 2008), whereas risk for incident hypertension is inversely related to antecedently measured serum 25(OH)D concentration. Specifically, in a 4-yr prospective study involving both the Health Professionals Follow-up Study and the Nurses' Health Study, Forman *et al*. reported a relative risk for incident hypertension of 3.18 for individuals with 25(OH)D levels <15 ng/ml, relative to those with levels >30 ng/ml (Forman, Curhan and Taylor, 2008). From the Framingham Offspring Study, with 5.4 yr of follow-up, individuals with 25(OH)D values <15 ng/ml were 53% more likely to experience a cardiovascular event than those above that level, and those with values <10 ng/ml were 80% more likely (Wang *et al.*, 2008).

Finally, Giovannucci *et al*., analyzing data from the Health Professionals Follow-up Study, reported a nearly 2.5- fold increase in risk of myocardial infarction for individuals with 25(OH)D levels below 15 ng/mL, compared to those above 30 ng/mL (Giovannucci *et al.*, 2008).

Diabetes

Both type 1 and type 2 diabetes have been associated with low vitamin D status, both current and antecedent (Scragg *et al*., 2004). For example, in a study based in the National Health and Nutrition Examination Survey (NHANES) data, participants without a known history and/or diagnosis of diabetes were much more likely to have high blood sugar values, both fasting and after a glucose challenge, when they had low vitamin D status (Heaney, 2008). In an interesting report from Finland, adults who had received 2000 IU/d vitamin D during the first year of life had an >80% reduction in risk of incident type 1 diabetes, relative to individuals who had not received such supplement (Hyppönen *et al.*, 2001).

Osteoporosis

The role of vitamin D in the pathogenesis and course of osteoporosis involves both its canonical function and the autocrine activity of the vitamin. For the canonical function, facilitation of calcium absorption, it is difficult to dissect apart the respective roles of calcium and vitamin D and probably not relevant. This is simply because one cannot absorb sufficient calcium from plausible diets unless one has reasonably normal vitamin D status, and, at the same time, one cannot absorb sufficient calcium, no matter what the vitamin D status, if calcium intake itself is absolutely low (Heaney, 1997). Therefore, given the prevalence of low intakes of both nutrients, it is not surprising that most of the clinical trials showing fracture prevention with calcium supplementation have involved treatment with vitamin D as well. All such trials show protection against age related bone loss and, in many instances, reduction in fracture risk as well. Where fractures have been reduced, the induced serum 25(OH)D level was in excess of 75 to 80 nmol/L, and dosages that failed to achieve such serum levels generally failed to show fracture reduction (Bischoff-Ferrari *et al.*, 2005). In addition, apparently through an autocrine pathway, vitamin D has been shown to reduce fall risk within only a few weeks of starting treatment, in some trials by as much as 50% (Tsiaras and Weinstock, 2011). It is likely that this effect is partly responsible for the reduced fracture risk ob- served in treatment studies.

Cancer

There is a large body of epidemiologic data showing an inverse association between incident cancer risk and antecedently measured serum 25(OH)D (Abbas *et al.*, 2008). This evidence has been accumulated for such cancers as prostate, colon, breast, lung, and marrow/lymphoma, among others. Risk reduction for breast cancer, for example, is reported to be as much as 70% for the top quartile of serum 25(OH)D (□75 nmol/L) relative to the bottom quartile (<45 nmol/L) (Abbas *et al.*, 2008). Furthermore, there is an even larger body of animal data showing that vitamin D deficiency in experimental systems predisposes to development of cancer on exposure to typical carcinogens (King, 2020). This has been shown both for animals with knockout of the vitamin D receptor and for animals with induced, nutritional vitamin D deficiency. Capping these lines of evidence is a recent randomized, controlled trial of postmenopausal women showing substantial reduction in all-cancer risk, amounting to from 60 to 75%, over the course of a 4-yr study (Lappe *et al.*, 2007).

Vitamin D deficiency and infertility

One of the recently identified target areas of vitamin D is male reproductive function. Expression of the vitamin D receptor (VDR) and vitamin D metabolizing enzymes has been demonstrated in ejaculatory duct, germ cells, and mature spermatozoa, which suggests that vitamin D has an important role in spermatogenesis and sperm function (Blomberg Jensen *et al.*, 2010). It has been shown that 19 of 2,483 testis- specific genes in mouse testis can be upregulated by treatment with the active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] (Hirai *et al.*, 2009). Vitamin D deficiency results in reduced sperm counts in male rats and lower fertility rates in female rats inseminated with semen from vitamin D-deficient male rats (Hirai *et al.*, 2009). The impaired reproductive performance of male rats that is induced by vitamin D deficiency is reversible and seems to be mediated predominantly through calcium imbalance, because it can be corrected either by supplying vitamin D or by normalizing calcium levels (Sun *et al.*, 2015). VDR-knockout mice have significant gonadal insufficiency, with decreased sperm counts and motility, and histological abnormalities of the testis (Kinuta *et al.*, 2000). In VDR-knockout mice, feeding high-calcium diets partly restores fertility and increases the rate of conception but does not normalize the number or weight of viable fetuses (Johnson and DeLuca, 2001).

VDR and the vitamin D metabolizing enzymes are expressed in germ cells, spermatozoa, Leydig cells and the epithelial cells lining the male reproductive tract (Jensen *et al.*, 2012). This expression profile indicates a direct effect on spermatogenesis, sex hormone production and sperm maturation. Certainly, male rodents with vitamin D deficiency have impaired fertility (Jensen, 2012), while mice with global loss of VDR or 1a-hydroxylase have low sperm motility although the phenotype varies from complete infertility to near normality (Sun *et al.*, 2015). VDR regulates synthesis and signaling of estrogens in the reproductive organs of rodents, which has been shown to be important for semen quality (Jensen *et al.*, 2013). However, recent studies have questioned whether the observed reproductive and endocrine effects in VDR and 1a-hydroxylase knockout mice are elicited by direct VDR-mediated effects or by the concomitant hypocalcaemia (Jensen *et al.*, 2013), (Sun *et al.*, 2015). Rescue of the impaired reproductive phenotype in VDR and 1a-hydroxylase knockout models with calcium+estradiol supplementation indicates an impact of such hypocalcaemia-induced changes. However, time to pregnancy and litter size could not be normalized in vitamin D deficient rats supplemented with calcium (Jensen, 2012). This observation, combined with the modest stimulatory effect of 1,25(OH)2D3 on intracellular calcium concentration and motility of human spermatozoa, indicates that VDR also may have a direct regulatory role in the reproductive organs of higher primates (Blomberg Jensen *et al.*, 2011).

CONCLUSION: Vitamin D plays an important role in the prevention of respiratory diseases such as infection with COVID-19 virus and chronic diseases such as diabetes, osteoporosis, hypertention and cancer, in addition to the important role in the functions of the reproductive system and fertility. So, many experts have recommended that increased sun/UVB exposure is an effective and inexpensive approach to maintaining adequate vitamin D levels and VitD supplements could help improve patients with COVID-19 and chronic disease.

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