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Mini Review

Vitamin D: The black knight.

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The group of vitamin D (VD) consists of 2 molecules, vitamin D2 or ergocalciferol and vitamin D3 called cholecalciferol. The synthesis of these two molecules is a chain reaction. Vit D is a secosteroid produced in the skin under the influence of ultraviolet B (UVB) radiation. Cholecalciferol is classified as a vitamin, but several aspects bring it closer to steroid hormones [1]. VD has been always supposed to play a crucial role in the prevention and treatment of various diseases. Additionally, to its control on calcium and phosphate equilibria, VD is an important modulator of cellular differentiation and proliferation in numerous normal and malignant processes [2]. VD deficiency leads to impaired growth in children. The supplementation before the age of 3 years is significantly associated with the increase of the overall height and the rate of height development. In 1975 Earnest proposed that 25(OH)D, presumably via a specific receptor, was directly stimulating the synthesis of protein, ATP and inorganic phosphate in the rat diaphragm muscle. However, an independent role of vitamin D on skeletal muscle mass and function development during growth remains unclear [1-3]. Some diseases such colorectal cancer, cardiovascular disease, multiple sclerosis, type I diabetes, osteoarthritis, high blood pressure, and allergies have a pathological distribution corresponding to zones of VD deficiency [4].

The lack of sunlight exposure leads to VD deficiency. Higher latitude countries have a high incidence of deficiency. However, despite high exposure to the sunlight, Vitamin D deficiency is well recognized in middle eastern woman, elite gymnasts in Australia, Hawaiian skateboarders, and adolescent girls in England [5,6]. Norman made a major advance in 1969 by discovering vitamin D receptor (VDR), identified on 37 organs of the human body including the dendritic cells. In 2010, he published the first map on the scale of the genome of vitamin D. He revealed that this vitamin is involved in the expression of 229 genes. The VDR gene located on chromosome 12 (12q 13.11) is known to have various polymorphisms including Bsm 1, Fok 1, Apa 1, and Taq 1, which have been associated with various functional outcomes [7].Vitamin D acts on the immune system by stimulating the synthesis of tumor growth factor (TGF), upon expressing on the surface of macrophages, Lymphocytes T, B, monocytes Toll-like receptor 2, VDR and 1 Alpha hydroxylase particularly during bacillus exposure. That could explain the relationship between tuberculosis and VD deficiency [8].

This interference with immune system reactions made the VD low serum level an independent factor to study in several disease. Recent study has confirmed the association of vitamin D deficiency with hypothyroidism, thyroid autoimmunity, increased volume, nodularity, and vascularity of thyroid gland in hypothyroid patients as well as increased HOMA-IR. However, no association between VDR polymorphisms (Fok1 and Apa1) with TSH levels was found [9]. Similar findings were observed in a group of glaucoma patients [10]. VD can regulate proliferation, apoptosis, and cell adhesion at the tumor cell level. It also interferes with tumor angiogenesis, decreases oxidative DNA damage, and limits invasion and metastasis.

According to some studies VD inhibits RCC cell proliferation, angiogenesis, clonogenicity, and metastasis. A preventive role has been also cited in several malignancies. Recent reports found that the homozygous genotype (aa) of the VDR SNP Apa I correlates with total VD serum level in the serum of colorectal cancer patients and that the heterozygous genotype (Tt) of the VDR SNP Taq I significantly associates with serum Ca levels. That may suggest that VD supply would be an easy economical and safe factor in cancer prevention [11,12].

It was also suggested that D-binding protein (DBP) may have a direct impact on carcinogenesis including macrophage activation, apoptosis, and angiogenesis. Prostate cancer cells can express VD metabolizing enzymes and the VDR. Moreover, it is proven that VD3 affects prostate cell differentiation and proliferation. Preclinical and epidemiologic data suggest that VD deficiency may be of great impact in the pathogenesis and progression of prostate cancer (PCa). Furthermore, the protective role of VD in PCa was greater with high-grade than with low-grade PCa [13,14].

Various studies have examined Bladder Cancer (Bc) incidence and serum level of VD. Afzal et al proved that lower plasma VD was associated with higher risk of tobacco-related cancers, including BC [15]. Superficial transitional cell carcinoma of the bladder expresses VDRs, and their polymorphisms were examined in BC. Mittal et al reported that BC risk is higher among patients with VDR rs10735810 polymorphism ('Fok1'), which is known to decrease the receptor's activity [16-18]. Significant antiproliferative VD3 effect on TGCT cells was proven in in-vitro studies [19]. Some other reports ruled out enticing evidence that VD regulates multiple cancer risk and prognosis-relevant pathways, including tumorigenesis in ovarian and breast carcinoma [20]. These results still need to be worked out to get consistency.

Higher VD levels have been associated with lower level of biomarkers of inflammation and oxidative stress in children [21]. VD should have an influence on airway inflammation. The optimal VD status for the prevention of allergic disease is unclear. Based on skeletal health, the institute of medicine recommends 25(OH)VD concentration of > 50 nmol/l and more to be enough [21,22]. However, it is argued that observed associations between VD deficiency and cardiometabolic risks are mediated by underlying adiposity, since 25(OH)D is fat-soluble and its level is lower with greater adiposity [22].

Only few studies have used direct methods such as dual X-ray absorptiometry to measure adiposity or the hyperinsulinaemic-euglycaemic clamp to accurately assess cardiometabolic risk. A meta-analysis demonstrated an almost cross-sectional association between vitamin D levels and cardiometabolic factors [23]. Measurements of serum VD levels (25(OH)VD) show that populations with higher VD levels are less likely to have high blood pressure, cardiovascular or cerebrovascular disease [24]. Over 45 clinical trials have been started to study VD supplementation as a treatment for high blood pressure. Another meta-analysis had highlighted the possibility of a VD induced reduction of systolic blood pressure [25]. The first description of vitamin D independent UV driven-nitrate reduction and vasodilatation mechanism was made by Robert Furchgott for his description of endothelial "Derived Relaxant Factor" that led to his Nobel price award. Today it is known to be the nitric oxide generated by the endothelial cells [26]. The role of vitamin D levels at different stages of pregnancy and different clinical outcomes has been the subject of interest for a long time. It was proven that VD low serum levels is associated with complicated pregnancy and neonatal courses [27].

Key takeaways:

- VD is not only a modulator of the calcium-phosphate metabolism but also an important factor controlling several human processes. This make it probably closer to hormones more than vitamins.
- It is evident that regular cellular proliferation and differentiation depend on VD. The deficiency leads to impaired growth and only early supplementation can make the damage reversible.
- The direct interference of VD low levels or the variation of VDR distribution and polymorphism on malignant process promotion and extension is no more to be ignored. This could be useful in the diagnostic, follow up and prevention of some malignancies.
- The large interference of VD with cardiovascular system should be ruled out in order to open new perspectives in the treatment of related diseases.

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Conflict of interest: none

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