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MORE THAN BONES: ASIDE JOBS OF VITAMIN D

MAS QUE HUESOS: TRABAJOS APARTE O ADICIONALES DE LA VITAMINA D

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Abstract

Vitamin D contributes to maintaining calcium levels in the bloodstream and maintains a good health of our bones. This vitamin activates a cascade of intracellular responses mediated by its nuclear receptor, vitamin D receptor. Interestingly, vitamin D receptor is expressed in almost all cells in our body, suggesting vitamin D could have additional roles. In this article, information about vitamin D and tuberculosis, obesity, diabetes, and cancer are presented.

Keywords: vitamin D, receptor, intracellular, bones.

Resumen

La vitamina D contribuye a mantener los niveles de calcio en el torrente sanguíneo y mantiene una buena salud de nuestros huesos. Esta vitamina activa una cascada de respuestas intracelulares mediadas por su receptor nuclear, el receptor de vitamina D. Curiosamente, el receptor de vitamina D se expresa en casi todas las células de nuestro cuerpo, lo que sugiere que la vitamina D podría tener funciones adicionales. En este artículo se presenta información sobre la vitamina D y la tuberculosis, la obesidad, la diabetes y el cáncer.

Palabras clave: vitamina D, receptor, intracelular, huesos.

INTRODUCTION

Vitamin D was discovered in 1967 when experiments were conducted to identify the responsible molecule present in cod liver oil that could cure rickets (McCollum, 1967). Since then, and with the chemically synthesis of its metabolites (Narwid et al., 1974a; Narwid et al., 1974b; Partridge et al., 1974), the study of vitamin D was oriented towards its physiological roles in calcium and phosphate homeostasis in relation to bone density (Stern et al., 1975).

Currently, it is well-accepted that vitamin D can be initially acquired from the diet (Hribar et al., 2022) or synthesized from cholesterol or ergosterol in the skin upon solar UV-B light exposure (Khanna et al., 2022). This vitamin D, or cholecalciferol or vitamin D_3, is then transferred to the liver where it is converted to calcifediol or 25-hydroxycholecalciferol by hydroxylation of vitamin D_3 by the enzyme vitamin D 25-hydroxylase in the endoplasmic reticulum (Sulimovici et al., 1979). Afterwards, calcifediol is converted to calcitriol or 1,25-dihydroxyvitamin D in the kidney by the cytochrome P450 enzyme 1-alpha-hydroxylase (Miller & Portale, 2000). While the function of hepatic 25-hydroxylase is mainly unregulated, renal 1-alpha-hydroxylase is tightly regulated by the parathormone (Aarskog et al., 1983; Kremer & Goltzman, 1982) controlling the availability of the active circulating hormone calcitriol.

In circulation, cholecalciferol, calcifediol and calcitriol are transported by the vitamin D binding protein (DBP) (Bouillon et al., 2020). In the absence of DBP, the levels of total circulating calcitriol mainly diminish (Zella et al., 2008). Interestingly, DBP gene polymorphisms have been associated with alterations in bone density due to its role in vitamin D bioavailability (Bhan, 2014).

Calcitriol regulates calcium intestinal absorption by increasing the calcium transporter in the apical membrane and calcium ATP-dependent pump in the baso-lateral membrane of the enterocyte (Wasserman & Fullmer, 1989). In addition, calcitriol promotes bone resorption to maintain the 2.5 mM calcium concentration in blood (Brown et al., 2002, p. 2).

Calcitriol activates the transcription of target genes due to its intracellular receptor, vitamin D receptor (VDR) (Carlberg, 2022). Upon binding to calcitriol, VDR dimerizes with retinoid X receptors to activate or repress the transcription of genes containing vitamin D response elements (Abbas, 2017). Importantly, VDR has been detected in almost all types of cells (Carlberg, 2022), opening the question of additional roles of vitamin D beyond bone health. Considering the different cell targets of vitamin D, in this mini-review, novel physiological impacts of vitamin D are presented and discussed.

VITAMIN D AND TUBERCULOSIS

Tuberculosis (TB) is an airborne disease caused by the bacillus *Mycobacterium tuberculosis*. An estimated 10.6 million people fell ill with TB in 2021 (World Health Organization, 2022) and, without treatment, the death rate from TB disease is higher (about 50%) (Menzies et al., 2018). In 2021, there were an estimated 1.4 million deaths among HIV-negative people and 187 000 deaths among HIV-positive people, for a combined total of 1.6 million (World Health Organization, 2022). Some people develop no symptomatology nor spread the bacteria when they get contaged, this is called a latent TB infection (LTBI). It is estimated that 5-15% of the people with LTBI will progress to TB in their lifetime (Cao et al., 2022).

Vitamin D has been proposed to play a role in reducing the susceptibility to LTBI (Ganmaa et al., 2019), the spreading rate in persons that have contact with TB patients (Aibana et al., 2019) and the conversion in tuberculin skin test (Ganmaa

et al., 2012), among others (Martineau et al., 2007). However, the results obtained now are not conclusive and more studies are necessary to acknowledge the real role of Vitamin D in the TB infection.

VITAMIN D AND OBESITY

Due to the molecular composition of vitamin D, the adipose tissue has been considered as the main tissue for its storage (Mutt et al., 2014). Earlier, it was reported that there was a significant inverse correlation between serum calcitriol and body mass index, where obese subjects had significantly lower calcitriol than non-obsese volunteers (Parikh et al., 2004). Thus, the idea of vitamin D negatively regulating adipogenesis was postulated using animal models (Wood, 2008). However, calcitriol was shown to promote adipose differentiation of human subcutaneous preadipocytes (Nimitphong et al., 2012) and to promote adipocyte differentiation of human mesenchymal cells with enhanced lipid accumulation (Narvaez et al., 2013).

To highlight the complex roles of vitamin D in obesity, it has been demonstrated that null expression of 1-alpha-hydroxylase caused lower leptin levels and consequently increased the consumption of food in mice (Narvaez et al., 2009). Recently, experiments on subcutaneous adipose tissue have demonstrated that calcitriol bound VDR inhibits an inflammatory response and adipokine expression in adipocytes (Nimitphong et al., 2021).

These data support the suggestion that vitamin D status may regulate obesity and obesity-related inflammation. Further clinical prospective studies are still required to better understand how vitamin D metabolism affects obesity.

VITAMIN D AND DIABETES

Initially it was proposed that calcitriol could regulate the glucose sensor machinery and stimulate insulin secretion in pancreatic β cells *in vitro* (Bouckenooghe et al., 2003) and in a rat model (Kadowaki & Norman, 1985). Moreover, a meta-analysis study reported that vitamin D deficiency could increase the risk for type 2 diabetes mellitus (Pittas et al., 2007). However, one year supplementation of vitamin D had no effect on insulin levels of prediabetic patients in a randomized placebo controlled clinical trial (Davidson et al., 2013). Also, supplementation with vitamin D3 failed to reduce the risk of diabetes of volunteers with high risk of type 2 diabetes (Pittas et al., 2019). These controversial studies point to the need for more research on the connection between vitamin D and diabetes.

VITAMIN D AND CANCER

The interest in the role of vitamin D in carcinogenesis began when studies in leukemia cells showed that calcitriol could inhibit the promotion of tumor formation of the well-known carcinogenic agent 12-O-tetradecanoylphorbol-13-acetate (Kuroki & Suda, 1983). Since then, several studies have highlighted the role of vitamin D in cancer. In particular, animal models to study this relationship have strongly suggested that vitamin D and/or calcitriol can prevent or cure several types of cancer (VanWeelden et al., 1998; W. Zheng et al., 2012; Y. Zheng et al., 2011). However, it has been difficult to clearly demonstrate this relationship in humans. Thus, recent meta-analyses have shown that low serum calcifediol is associated with reduced survival among female breast cancer patients (Li et al., 2021) and that vitamin D intake can reduce the incidence of pancreatic cancer (Liu et al., 2018). Meanwhile, this association in human subjects has not been observed in prostate cancer (Gilbert et al., 2011) nor basal cell carcinoma of the skin (Hunter et al., 1992).

In vitro and animal studies demonstrate an important role of vitamin D in cancer development and progression. However, other factors seem to be present in human metabolism that modify this

relationship. Therefore, more studies are required to study the role of vitamin D metabolism in human cancer.

CONCLUSION

Different types of normal cells express VDR and 1-alpha-hydroxylase, which indicate that vitamin D metabolism may have a plethora of responses in our body. In addition to the well-established role of vitamin D on calcium metabolism and bone health, interesting novel evidence supports the idea that this vitamin could be beneficial in other tissues and pathologies. More studies in humans are still required to study the impact of vitamin D and its metabolites in human health.

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