**Tratamentul suplimentar cu vitamina D în unele afectiuni maligne**

Aurelian Udristioiu,
Spitalul Judetean de Urgenta Targu Jiu
Universitatea Titu Maiorescu, AMG, Târgu Jiu

**Abstract**

 Vitamin D este mai mult decat o vitamina. Aceasta actioneaza ca un hormon si, spre deosebire de restul micronutrientilor esentiali, sinteza endogena este cel mai mare furnizor de vitamina D in organism. In cantitati mici si insuficiente pentru a acoperi necesarul zilnic, vitamina D se gaseste si in o serie de alimente, printre care se numara pestele gras (somon, etc.), uleiul de cod, drojdia de bere sau in alimentele fortifiate cu vitamina D. Hormonul vitaminei D este un sistem endocrin major cu funcții pleiotropice. Fiziologic, majoritatea conținutului de vitamina D al organismului este derivată din fotosinteză la nivelul pielii în urma iradierii UV și, astfel, nivelurile de vitamina D ale organismului sunt influențate de locațiile geografice, de modificările sezoniere și de pigmentările pielii (Holick, 2018).

 Vitamina D este transformată în hormonul activ 1,25-dihidroxivitamina D (1,25 (OH) 2-D3) prin două etape de hidroxilare: 25-hidroxilare în ficat urmată de 1 a-hidroxilare la rinichi. Activitățile biologice ale 1,25 (OH) 2, vitamiana D3, sunt mediate de receptorul de vitamina D (VDR), un receptor de hormoni nucleari (Haussler și colab., 2013). Intestinul este unul dintre țesuturile din corp care au cea mai abundentă expresie VDR (Wang și colab., 2012), indicând că este o țintă fiziologică majoră a vitaminei D. S-a stabilit de mult că semnalizarea vitaminei D / VDR reglementează transportul duodenal al calciului transcelular (Lee și colab., 2015). Studii recente au demonstrat că VDR epitelial intestinal joacă un rol cheie în protejarea integrității barierei mucoasei (He et al., 2018). Cu toate acestea, se știe puțin despre efectul semnalizării vitaminei D / VDR asupra componentelor imune ale intestinului, inclusiv a imunității înnăscute a intestinului.

În forma sa activă biologic, vitamina D-3 stimulează absorbţia intestinală a calciului, iar încorporarea calciului în matricea osoasă mobilizarea calciul din oase Deficienţa de calciu şi/sau vitamina D induce hipersecreţie de parathormon (PTH). Acest hiper- paratiroidism secundar este urmat de creşterea turnover ului osos, responsabil de fragilitate osoasă şi fracturi. Administrarea de calciu şi vitamină D3 în dozele recomandate produce reducerea secreţiei de Parathormon. Studiile recente ofera informatii valoroase despre rolul Vitaminei D in modularea imuna, protectie anti-tumorala si neuroprotectie .

**Modulare imuna.** Vitamina D, pe ansamblu, reduce productia citokinica a limfocitelor T Helper 1, promoveaza activitatea limfocitelor T Helper 2 si tot ea reduce sinteza de IL-12 si stimuleaza productia de IL-10, ceea ce are ca efect reducerea activitatii limfocitelor T Helper 1 si stimularea limfocitelor T supresoare de tip 1. Desi per ansamblu are actiune de ponderare a imunitatii dobandite, iar 1,25dihidroxivitamina D-3 favorizeaza in schimb imunitatea innascuta, promovand proliferarea monocitara si productia de IL-1 si catelicidina de catre monocite si macrofage.

**Protectie antitumorala.** Vitamina D-3, Calcitriolul a dovedit proprietati antitumorale, in special in anumite tipologii de cancer (cancerul de prostata, carcinom scuamocelular, pulmonar, ovarian, mamar, pancreatic, de vezica urinara,, cancerul de colon si neuroblastomul). Legarea calcitriolului de receptorii nucleari induce expresia unor gene implicate in protectia antitumorala. Astfel, calcitriolul dovedeste actiune antiproliferativa, reducand multiplicarea celulelor tumorale. Calcitriolul favorizeaza expresia mai multor gene antiproliferative: gena CDKN-1A care codifica proteina p21 si opreste cresterea celulara iar sinteza acestei proteine este indusa si de proteina p-53, codificata de gena oncosupresoare TP-53; gena GADD-45A (gena responsabila de oprirea cresterii celulare a carei expresie este indusa de degradarea materialului ADN); gena CCNC (gena antiproliferativa, care codifica ciclina C - implicata in oprirea replicarii celulare.

 De asemenea, Calcitriolul are rol in modularea cailor de semnalizare intracelulara care implica enzime de tipul kinazelor. Favorizeaza apoptoza celulelor tumorale, inhiband expresia proteinelor anti-apoptotice Bcl-2 si Bcl-XL si posibil prin promovarea expresiei genelor pro-apoptotice Bax, Bak, Bad dar si prin inhibarea activitatii enzimei telomeraza revers-transcriptaza. Asigura stimularea diferentierii celulare, ajutand practic celulele tumorale sa recapete o serie din caracteristicile initiale ale tesutului in care au aparut, devenind mai putin maligne. Calcitriolul inhiba si actiunea unor factori proliferativi (factorul de crestere insulin-like (insulin like growth factor), factorul de crestere epidermal (epidermal growth factor)), si stimuleaza si actiunea unor factori anti-proliferativi (transforming growth factor beta). Inhiba neo-angiogeneza, inhiba expresia HIF1 A (factor 1 alpha indus de hipoxie) si implicit cea a factorului endotelial de crestere vasculara (VEGF-vascular endothelial growth factor)iar prin inhibarea NFkB, inhiba sinteza de IL-8.

 De asemenea calcitriolul are rol si in inhibarea metastazarii prin: stimularea expresiei caderinei E, a inhibitorului tisular de metaloproteinaze de tip 1 (TIMP1), inhiibarea activitatii MMP9 (metaloproteinazei proteinelor matriceale de tip 9). Pe baza anumitor studii epidemiologice s-a evidentiat un posibil rol protector al vitaminei D fata de aparitia anumitor tipuri de cancer, fiind sugestiva munca lui Giovannucci si a colaboratorilor sai. Acestia au evidentiat ca un nivel seric crescut de 25 hidroxicolecalciferol (62.5 ng/mL) se asociaza cu o reducere de 50% a riscului de dezvoltare a cancerelor din sfera ORL, a celui esofagian, pancreatic, dar si a leucemiei. Autorii afirma ca nivelul seric al vitaminei D este un marker independent pentru predictia aparitiei cancerului. Dupa ultimile studii, s-a desprins concluzia de a recomanda regulat suplimentarea în cantități moderate a dozelor de vitamina D (600 - 800 UI / zi) la numite personae la care s-a descoperit o deficienta de vitamina D, cu ocazia depistarii unei boli benigne sau maligne. Se recomandă evitarea dozelor unice extrem de mari care ar putea avea efecte adverse**.** Astăzi, unii experți recomandă suplimentarea cu 1000-2000 UI vitamina D pe zi în timpul expunerii insuficiente la soare.

 Efectul benefic al Vitmainei D, administrate in unele afectiuni maligne a dovedit experimental, prin studiile clinice din faza 1 si II, efecte antiinflamatorii si antitumorale, prin modularea raspunsuluui imun

**Supplemental Vitamin D treatment in some malignant diseases**

Aurelian Udristioiu,

Target Jiu County Emergency Hospital
& Titu Maiorescu University, AMG, Targu Jiu
Romania

**Abstract**

Vitamin D is more than just a vitamin. It acts as a hormone and, unlike the rest of the essential micronutrients, endogenous synthesis is the largest supplier of vitamin D in the body. In small quantities and insufficient to meet the daily needs, vitamin D is also found in a number of foods, including fatty fish (somon fish, etc.), cod oil, brewer's yeast or food with fortified vitamin D. Vitamin D hormone is a major endocrine system with pleiotropic functions. Physiologically, most of the body's vitamin D content is derived from photosynthesis in the skin after UV irradiation, and thus, the body's vitamin D levels are influenced by geographic locations, seasonal changes and skin pigmentation (Holick, 2018).

 Vitamin D is converted to the active hormone 1,25-dihydroxyvitamin D (1,25 (OH) 2D3) by two hydroxylation steps: 25-hydroxylation in the liver followed by 1-hydroxylation in the kidneys. The biological activities of 1,25 (OH) 2, and vitamin D-3 is mediated by the vitamin D receptor (VDR), a nuclear hormone receptor (Haussler et al., 2013). The intestine is one of the tissues in the body that have the most abundant VDR expression (Wang et al., 2012), indicating that it is a major physiological target of vitamin D. It has long been established that vitamin D / VDR signaling regulates the duodenal transport of transcellular calcium (Lee et al., 2015). Recent studies have shown that intestinal epithelial VDR plays a key role in protecting the integrity of the mucosal barrier (He et al., 2018). However, little is known about the effect of vitamin D / VDR signaling on the immune components of the intestine, including innate immunity of the intestine.

In its biologically active form, vitamin D-3, calcitriol, stimulates intestinal calcium uptake, incorporation of calcium into the bone matrix, and mobilization of calcium from bone. Depending on the mode of production, the physiological regulation of the mechanism of action, vitamin D-3 can be considered as a precursor of a steroid hormone. Vitamin D status cannot be isolated by intestinal calcium absorption, especially when calcium levels are low, as is common in the elderly. Deficiency of calcium and / or vitamin D induces parathormone (PTH) hypersecretion. This secondary hyper-para-thyroidism is followed by increased bone turnover, responsible for bone fragility and fractures. Administration of calcium and vitamin D3 at the recommended doses results in reduced Parathormone secretion. Recent studies provide valuable insights into the role of Vitamin D in immune modulation, protective, anti-tumor protection and neuroprotection.

**Immune modulation.** Vitamin D reduces cytokine production of T helper 1 lymphocytes and promotes T Helper 2 lymphocyte activity and also reduces IL-12 synthesis and stimulates IL-1 production. 10, which has the effect of reducing the activity of T Helper 1 lymphocytes and stimulating T-type suppressor lymphocytes. Although overall it has a weighting action on acquired immunity, 1,25 dihydroxyvitamin D-3 promotes innate immunity, promoting monocyte proliferation and production. of IL-1 and catelicidine by monocytes and macrophages.

**Antitumor protection.** Calcitriol has been shown to have antitumor properties, especially in certain cancer typologies (prostate cancer, squamo-cellular, pulmonary, ovarian, breast, pancreatic, bladder, colon cancer and neuroblastoma). Binding of calcitriol to nuclear receptors induces the expression of genes involved in antitumor protection. Thus, calcitriol demonstrates anti-proliferative action, reducing tumor cell multiplication.Calcitriol promotes the expression of several antiproliferative genes: the CDKN-1A gene encoding the p21 protein that stops cell growth and the synthesis of this protein is also this effect was induced by the p-53 protein, encoded by the TP53 onco-suppressor gene; GADD-45A gene (gene responsible for stopping cell growth whose expression is induced by DNA material degradation); CCNC gene (antiproliferative gene, which encodes cyclin C - involved in stopping cell replication. Basically, the progression of the cell multiplication process is controlled by cyclin (D) and their interaction with enzymes called cyclin-dependent kinases.

 Also, calcitriol plays a role in modulating intracellular signaling pathways that involve kinase-like enzymes. It promotes apoptosis of tumor cells, inhibiting the expression of anti-apoptotic proteins Bcl-2 and Bcl-XL and possibly by promoting the expression of pro-apoptotic genes Bax, Bak, Bad but also by inhibiting the activity of the telomerase reverse-transcriptase enzyme. It provides the stimulation of cell differentiation, practically helping the tumor cells to regain a number of the initial features of the tissue in which they appeared, becoming less malignant. Calcitriol also inhibits the action of proliferative factors (insulin-like growth factor), epidermal growth factor (epidermal growth factor), and it also stimulates the action of transforming growth factor beta. It inhibits neo-angiogenesis: it inhibits the expression of HIF1 A (hypoxia-induced factor 1 alpha) and implicitly that of the vascular endothelial growth factor (VEGF); also by inhibiting NFkB, it inhibits IL-8 synthesis. Calcitriol also plays a role in inhibiting metastasis by stimulating the expression of cadherin E, the tissue inhibitor of metalloproteinases type 1 (TIMP1), inhibiting the activity of MMP9 (metalloproteinase of type 9 matrix proteins).

Based on certain epidemiological studies, a possible protective role of vitamin D has been shown against the occurrence of certain types of cancer, being suggestive of the work of Giovannucci and his collaborators. They showed that an increased serum level of 25 hydroxy-colecalciferol (62.5 ng / mL) is associated with a 50% reduction in the risk of developing cancers of the ENT, esophageal, pancreatic, but also leukemia. The authors state that the serum level of vitamin D is an independent marker for predicting cancer. Following the latest studies, it was concluded that regular doses of vitamin D (600 - 800 IU / day) should be regularly supplemented in so-called persons with vitamin D deficiency, when they have a benign or malignant disease. It is recommended to avoid extremely high single doses that may have adverse effects. Today, some experts recommend supplementing with 1000-2000 IU vitamin D per day during insufficient sun exposure.

 The beneficial effect of Vitamin D, administered in some malignancies, has been demonstrated experimentally, through clinical trials in phase 1 and II anti-inflammatory, antitumor effects, by modulation of the immune response.