VITAMIN D AND OPHTHALMOPATHIES. A REVIEW

Hribová P.[1], Sotak Š.[2]

[1]Department of Ophthalmology of the Faculty of Medicine, Pavol Jozef Šafárik University and Louis Pasteur University Hospital in Košice, Slovakia
[2]I[st] Department of Internal Medicine of the Faculty of Medicine, Pavol Jozef Šafárik University and Louis Pasteur University Hospital in Košice, Slovakia

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MUDr. Paulína Hribová

Korešpondenčný autor:
MUDr. Štefan Sotak, PhD., MPH, EMBA, LL.M
I. interná klinika LF UPJŠ a UN LP v Košiciach
Trieda SNP 1
040 11 Košice
E-mail: stefan.sotak@upjs.sk

SUMMARY

The importance of vitamin D3 (hydroxycholecalciferol) as one of the liposoluble vitamins is known in the prevention and treatment of metabolic bone diseases (rickets, osteomalacia, osteoporosis). In recent years, however, information has increased on the importance of vitamin D3 in numerous organ systems and in the pathogenesis of various diseases, e. g. ophthalmopathies. The immunological functions of vitamin D3 are the subject of studies dealing with autoimmune optic nerve disorders and their results appear to have a positive effect on demyelinating diseases. It also plays an important role in maintaining the thickness of the retinal nerve fiber layer, but its additional administration has not been successful. Optical neuritis may be the first sign of multiple sclerosis. It appears that sufficient serum vitamin D3 levels may protect patients from deterioration in the form of a further attack of demyelination. The course of diabetic retinopathy is probably also influenced by vitamin D3, inter alia, by correlating the fact that its receptor and the enzymes of its metabolism are expressed on the retina. Low serum levels of vitamin D3 may even trigger age-related macular degeneration. Conversely, higher dietary intake of vitamin D3 may positively affect neovascularization. The optimal level of hydroxycholecalciferol is between 60 and 200 nmol /l, the severe deficit represents a decrease below 25 nmol/l. The body can normally produce up to 10,000 IU of this vitamin after exposure to sunlight. However, the demonstration of its protective character in connection with the mentioned diseases of the retina and optic nerve will require a sufficient number of studies to confirm the facts found so far about this rediscovered vitamin.

Key words: vitamin D, ophtalmopathias

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INTRODUCTION

The overall concept of vitamins dating back to the end of the 19[th] century is already obsolete. Vitamins were originally defined as "vital amines", i.e. substances that the body cannot synthesise on its own, but must ingest through food, and which are chemically amines. Substances that we do not historically classify as vitamins fulfil this definition, and, conversely, some substances that we have historically classified as vitamins do not fulfil this definition. In the case of vitamin D_3 (cholecalciferol) the terms "vitamin" and "hormone" overlap.

Vitamin D metabolism

The production of the active form of vitamin D is regulated by the requests of calcium and phosphorus. Their decreased plasma levels stimulate the parathyroid glands to produce parathyroid hormone (PTH). PTH binds to osteoblasts in bone, liver and nephrons of the kidney. It stimulates the 1-α-hydroxylase responsible for the production of active vitamin D. It should be emphasised that, in addition to nephrons, 1-α-hydroxylase activity has also been demonstrated in the skin, immune system cells and osteoblasts. This is one of the reasons why extrarenal production of the active form of vitamin D is possible, which also explains its nonskeletal effects [1,2].

Since vitamin D is a substance of a steroid nature, its effects are mediated through the vitamin D nuclear receptor (VDR), which acts as a transcription factor activated by a ligand. It is the distribution of VDR receptors that explains the pleiotropic effects of vitamin D [1,2].

The normal level of vitamin D is between 60 and 200 nmol/l; a decrease below 25 nmol/l [3] represents a severe deficit.

Vitamin D comprehensively affects bone metabolism

and is essential for proper skeletal development. Its deficiency in childhood results in insufficient growth and the development of rickets. In adulthood, vitamin D deficiency leads to the development of secondary hyperparathyroidism with subsequent mobilisation of calcium from the bone. The result is the development of osteoporosis or osteomalacia, and/or their combinations [2].

Vitamin D deficiency is responsible for a senile type of osteoporosis with an extraordinary epidemiological dimension [2].

Vitamin D deficiency also plays an important role in the aetiopathogenesis of Crohn's disease, oncological diseases (breast, ovaries, prostate, pancreas, colon), dyslipidaemia, arterial hypertension, autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, lupus erythematodes, autoimmune thyroiditis and type 1 diabetes mellitus [1,2], polycystic ovarian syndrome [4], SARS-CoV-2 infection [5], and just as importantly, the following ophtalmopathies.

Vitamin D and ophtalmopathies

In ophthalmology, the importance of vitamin D supplementation is mainly investigated in the context of inflammatory autoimmune impairment of the optic nerve, which is associated with central nervous system (CNS) demyelinating diseases. Studies have long focused on the immunological functions of vitamin D in relation to the treatment of these diseases [6]. A study comparing IgG-autoantibodies' levels against protein aquaporin 4 in patients newly diagnosed with optic neuromyelitis (neuromyelitis optica, NMO), using MRI, showed that NMO-IgG-negative patients had significantly higher rates of exposure to sunlight and higher serum levels of hydroxycholecalciferol compared to NMO-IgG-positive patients. Patients with negative NMO-IgG also consumed significantly higher amounts of vitamin D. This study suggests that vitamin D may play an important role in NMO pathogenesis due to its effect on NMO-IgG synthesis [7].

Several studies also suggest a link between serum vitamin D levels and the thickness of the retinal nerve fibre layer (RNFL) or ganglion cell layer (GCL) thickness, measured using optical coherence tomography (OCT). In patients with vitamin D deficiency, significant decreases in both RNFL and GCL were observed after overcoming optical neuritis, compared to patients with sufficient vitamin D. In another study comparing patients at an early stage of diabetic retinopathy with vitamin D deficiency to patients with sufficient vitamin D, the mean thickness of RNFL was significantly reduced in vitamin D-deficient patients compared to patients with sufficient vitamin D, indicating a potential neuroprotective effect of vitamin D [10].

Although some studies indicate a positive effect of sufficient vitamin D in patients with NMO, its administration to patients with low serum vitamin D levels did not produce the expected effect. A study on the effect of vitamin D on RNFL thickness, using OCT, followed 52 patients with confirmed unilateral NMO, aged 15-38 years, with low serum levels of 25-hydroxyvitamin D. In 27 patients given vitamin D (50 000 IU/week) at 6 months, the mean RNFL thickness decreased from 111.3 µm to 91.4 µm. Similarly, 25 placebo patients had a decrease in RNFL thickness from the original 113.7 µm to 96.1 µm. Thus, the addition of vitamin D to standard NMO treatment had no effect on the thickness of the RNFL [11].

A study was also conducted to evaluate the effects of the preventive administration of vitamin D_3 on conversion to SM and changes to MRI in patients with NMO and low serum vitamin D levels. One group of patients received 50 000 IU of vitamin D_3 weekly for 12 months and the other group received a placebo. During follow-up, in only 5 patients taking the placebo there was no further attack of demyelination, while no further attack occurred in the group of patients taking vitamin D_3. In addition, the incidence of new CNS lesions on MRI was significantly lower in the vitamin D group than in the placebo group. Thus, administration of vitamin D may have a protective effect on conversion to MS.

However, further monitoring with a longer duration is needed to confirm this finding. [12]. A recent laboratory study also suggested a possible beneficial effect of vitamin D in improving the effectiveness of glucocorticoids in relapse. Although some indicators of disease activity have been significantly reduced after vitamin D supplementation, the evidence gathered so far is insufficient to draw a definitive conclusion about the effects of vitamin D supplementation on clinical parameters [13].

The conclusions of a number of studies regarding the beneficial effect of vitamin D in demyelinating optic neuritis are still ambiguous. Determining whether vitamin D can serve as prophylaxis for NMO and MS, or even reduce the rate of disability or relapse, requires further investigation [6].

The aforementioned diabetic retinopathy is one of the world-leading causes of blindness. The disease first manifests as a non-proliferative form (NPDR). Increasing damage to the retinal vasculature later leads to vascular leakage and diabetic macular oedema, vascular sclerosis results in ischaemia, angiogenesis and possibly neovascularisation of the retina, a proliferative form of diabetic retinopathy (PDR). Studies in animal models for diabetic retinopathy suggest that calcitriol supplementation protects against retinal neovascularisation. Many other studies also document the antiangiogenic effect of vitamin D, although primarily in tumour models [14]. The potential effect of vitamin D on the retina is supported by evidence that VDR and enzymes involved in its metabolism are expressed in the retina [15]. Meta-analyses in patients showed a significant association between vitamin D deficiency and diabetic retinopathy, as well as a statistically significant difference in mean serum vitamin D levels between patients without diabetic retinopathy. It is also interesting that patients with PDR have significantly lower mean serum vitamin D levels than patients with NPDR [16]. A study

published in 2018 confirmed the protective effect of vitamin D, by significantly reducing the rate of retinal cell apoptosis and vascular permeability in the retinas of diabetic rats. Thus, vitamin D has considerable potential in the treatment of diabetic retinopathy [18].

However, the clinical relevance of the above-mentioned studies remains unclear. There is currently no information in the available literature on the effect of vitamin D supplementation in patients with diabetic retinopathy. However, it is possible that further studies will demonstrate the positive effect of vitamin D supplementation. Vitamin D supplementation as a protective mechanism against the development and progression of this type of retinopathy therefore requires further investigation [14].

The study has also recently focused on the effect of vitamin D on age-related macular degeneration (AMD). The most convincing evidence that vitamin D has a beneficial effect on VPDM is its ability to modulate the immune system, as well as its ability to inhibit inflammation and angiogenesis [17]. Cumulative data from experimental observational studies suggest that low serum vitamin D levels may be a potential risk factor for the development of VPDM. However, although these studies are useful to investigate the possible relationship between vitamin D and VPDM, they are not intended to establish a causal relationship. Intervention studies evaluating the effect of vitamin D supplementation in preventing the onset or progression of VPDM are still lacking. Therefore, there are no specific nutritional recommendations regarding vitamin D intake in relation to primary or secondary prevention of VPDM. However, several studies have examined the relationship between vitamin D in food and VPDM [18]. Such a study published in 2017 confirmed that a higher dietary vitamin D intake was associated with a significantly lower risk of VPDM progression to advanced form. A beneficial effect has been observed mainly in relation to the development of neovascularisation [19].

CONCLUSION

With the current increasing body of evidence indicating the importance of vitamin D in clinical medicine, attention should be focused on this hormone. Of course, there are still a number of unanswered questions left on the issue of the pleiotropic effects of vitamin D, to which answers will surely be sought in the near future. This applies both to target vitamin D levels, and to the refinement of vitamin D dosing in non-skeletal indications, which will probably be different from those in bone indications [1,2].

REFERENCES

1. Jackuliak P. Pleiotropné účinky vitamínu D. MEDICUS news. 2019;1(3):49-52. Slovak.
2. Jackuliak P. Pleiotropné účinky vitamínu D. Lekárnické listy. 2020;22(2):38-39. Slovak.
3. Šterzl I. Vliv vitaminu D na imunitní mechanismy. Interní Med. 2014;16(3):110-112. Czech.
4. Lazúrová I, Figurová J, Dravecká I. Vitamín D a syndróm polycystických ovárií. Vnitř Lék. 2016;62(S3):87-91. Slovak.
5. Smaha J, Kužma M, Jackuliak P, Payer J. Suplementácia vitamínu D ako dôležitý faktor v prevencii a liečbe ochorenia COVID-19: aké máme dôkazy? Vnit Lék. 2020;66:494-500. Slovak.
6. Rodney C, Rodney S, Millis R. Vitamin D and demyelinating diseases: Neuromyelitis optica (NMO) and multiple sclerosis (MS) [internet]. Hindawi Autoimmune Diseases; 2020. [cited 2020 Nov 18]. Available from: //https://www.hindawi.com/journals/ad/2020/8718736/
7. Shaygannejad V, Maljaei MB, Bank SS, Mirmosayyeb O, Maracy MR, Askari G. Association between sun exposure, vitamin D intake, serum vitamin D level, and immunoglobulin G level in patients with neuromyelitis optica spectrum disorder. Int J Prev Med. 2018;9:68.
8. Burton JM, Eliasziw M, Trufyn J, Tung C, Carter G, Costello F. A prospective cohort study of vitamin D in optic neuritis recovery. Mult Scler. 2016;23(1):82-93
9. Burton JM, Trufin J, Tung C, Eliasziw, Costello F. The Role of Vitamin D Status in Optic Neuritis – An Update. Neurology. 2016;80:7.
10. Gungor A, Ates O, Bilen H, Kocer I. Retinal Nerve Fiber Layer Thickness in Early-Stage Diabetic Retinopathy With Vitamin D Deficiency. IOVS. 2015;56:6433-6437.
11. Salari M, Janghorbani M, Etemadifar M, Dehghani A, Razmjoo H, Naderian G. Effects of vitamin D on retinal nerve fiber layer in vitamin D deficient patients with optic neuritis: Preliminary findings of a randomized, placebo-controlled trial. J Res Med Sci. 2015;4:372-378.
12. Derakshandi H, Etemadifar M, Feizi A et al. Preventive effect of vitamin D_3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial. Acta Neurol Belg. 2013;113:257-263.
13. Miclea A, Bagnoud M, Chan A, Hoepner R. A brief review of the effects of vitamin D on multiple sclerosis. Front Immunol. 2020;11:781.
14. Zhang J, Upala S, Sanguankeo A. Relationship between vitamin D deficiency and diabetic retinopathy: a meta-analysis. Can J Ophthalmol. 2017;52(S1):S39-44.
15. Skowron, K, Pawlicka I, Gil K. The role of vitamin D in the pathogenesis of ocular diseases. Folia Med Cracov. 2018;58(2):103-118.
16. Lu L, Lu Q, Chen W, Li J, Li C, Zheng Z. Vitamin D_3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway [internet]. J Diab Res; 2018. [cited 2020 Dec 05]. Available from: //https://www.hindawi.com/journals/jdr/2018/8193523/
17. Kaarniranta K, Pawlowka E, Szczepanska J, Jablkowska A, Błasiak J. Can vitamin D protect against age-related macular degeneration or slow its progression? Acta Biochim Pol. 2019;66:147-158.
18. Layana AG, Minnella AM, Garhöfer G et al. Vitamin D and age-related macular degeneration. Nutrients. 2017;9(10):1120.
19. Merle BMJ, Silver RE, Rosner B, Seddon JM. Associations between vitamin D intake and progression to incident advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017;58(11):4569-4578.