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Extraskeletal activity of vitamin D and a potential association with diabetes mellitus

Vanskeletna aktivnost vitamina D i njegova potencijalna udruženost sa šećernom bolesti

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Introduction

For decades, vitamin D has been characterised with its important role in regulating the serum levels of calcium and phosphorus, as well as in maintenance of bone and mineral metabolism. In addition to its classical action, an increasing amount of available data suggests a possible involvement of vitamin D activity in many other pathophysiological fields, such as inflection of immune response and inflammation, cell proliferation or gene expression [1]. Many experimental and clinical data indicate the impact of vitamin D on different steps in onset and development of diabetes, representing this way its potential beneficial influence on morbidity, glycemic control and the incidence of chronic complications [2].

Metabolism of vitamin D

Vitamin D is a group of sterols with a hormone-like activity, that can be consumed from food or synthesized in the skin [3]. There are two inactive forms of vitamin D: cholecalciferol (also called vitamin D3), that comes from foods of animal origin, and ergocalciferol (also called vitamin D2) which is of plant origin. When the skin is exposed to solar ultraviolet B radiation, cholecalciferol could also be rapidly converted from its precursor, called 7-dehydrocholesterol. After entering into blood stream from guts or skin, these inactive forms of vitamin D, are transported to the liver binded to the vitamin D-binding protein (VDBP). Next step in the activation process, is the hydroxylation at C-25 *via* vitamin D-hydroxylase enzyme, forming 25-hydroxyvitamin D_3 [25 (OH) D, also called calcidiol]. This is the major form of storage and detection of vitamin D. Almost all calcidiol is bound to circulating VDBP and transported to kidneys. At the level of the proximal renal tubul, this metabolite is further hydroxylated by the 1α-hydroxylase enzyme forming 1α,25 dihydroxyvitamin D_3 [1α,25 $(OH)_2D$, also called calcitriol]. This is the active form of vitamin D [3, 4].

Apart from the kidneys, many other tissues have the ability to convert calcidiol into calcitriol, since the enzyme 1α-hydroxylase has been observed in placenta, breasts, colon, prostate, macrophages or monocytes. However, in humans, this extrarenal sources of calcitriol only contribute significantly to circulating levels of this active vitamin D form during pregnancy, in chronic renal failure, in sarcoidosis, tuberculosis, granulomatous diseases and rheumatoid arthritis [5].

The production of calcitriol is regulated by serum calcium and phosphorus levels, plasma parathyroid hormone (PTH) levels and fibroblast growth factor 23 (FGF23). Most of the biological activities of calcitriol are mediated by a high-affinity receptor that acts as a ligand-activated transcription factor. This cytosolic/nuclear vitamin D receptor (VDR) is a transcriptional activator of many genes and is widely distributed in more than 38 types of tissues, controlling bone metabolism, inflammation, oxidative damage or chronic diseases [6]. This distribution becomes especially important in understanding of extraskeletal effects of vitamin

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D. This is due, not only the ability of different tissues to synthesized calcitriol, but also because of widespread distribution of the specific VDR that mediated vitamin D action [4].

Vitamin D effects on the immune process and type 1 diabetes

Type 1 diabetes mellitus is chronic progressive autoimmune disease characterized by mononuclear cell infiltration, dominantly by interleukin (IL)-12-dependent T helper type 1 (Th1) cells of the pancreatic islets, with subsequent β-cells destruction and decreased insulin secretion. After 70−90% of β-cells are destroyed, available insulin is no longer adequate to maintain normal blood glucose level and diabetes may be diagnosed. Thus, an autoimmune destruction process plays a central role in the development of type 1 diabetes, and is mediated by the subjects own genetic susceptibility and by non-genetic factors. Vitamin D deficiency is one of the non-genetic factors that could be associated with an increased risk of developing of autoimmune diabetes. In favor of that, the incidence of type 1 diabetes follows a geographical pattern, with reported association between this type of diabetes mellitus and vitamin D status [7]. Vitamin D has a protective effect on the pancreatic β-cells. VDR is detected in almost all cells of the immune system, especially antigen-presenting cells (dendritic cells and macrophages) and activated T-lymphocytes. These cells are also able to synthesize and secrete calcitriol since they possess the enzyme 1α-hydroxylase. Although multiple, the main effect of calcitriol on the immune system is leading to the generation of tolerance and anergy, rather than immune activation [4]. For instance, at the level of dendritic cells, calcitriol inhibits the surface expression of major histocompatibility complex (MHC) class II-complexed antigen. Thus, these cells do not mature at a subsequent exposure to an antigen, but become tolerogenic. IL-12, the major cytokine managing the immune system towards Th1 development, is almost totally inhibited in the presence of calcitriol. The same goes to several other inflammatory T cell cytokines, such as IL-2, interferon-gamma (IFN-γ), and tumor necrosis factor-alfa (TNFα), while the production of anti-inflammatory cytokines like IL-4 or IL-10 is stimulated. These immunomodulatory effects of calcitriol can lead to the protection of target tissues such as β-cells in type 1 diabetes [8].

Treatment of non-obese diabetic (NOD) mouse, which represents an animal model for human type 1 diabetes, with calcitriol analog, can prevent dendritic cells maturation, decreased IL-12 and IFNγ production and arrests Th1 cell infiltration. These processes lead to the inhibition of *insulinitis* and slow down the progression of type 1 diabetes [9]. Clinical type 1 diabetes can also be prevented in animal models, if calcitriol analogues are administered to NOD mice when the autoimmune disease is already active [10].

Simultaneously to experimental data, there are some clinical studies confirming protective immunological effect of vitamin D supplementation. In 38 patients with new-onset type 1 diabetes, cholecalciferol supplementation led to increased level of regulatory T-cells, serum IL-10 levels and significant increase of monocyte chemoattractant protein-1 (MCH-1) levels. This protective effect might contribute to preservation of residual C-peptide secretion obtained in this study [11]. Several observational clinical studies raised the possibility that vitamin D intake during early life, may prevent the development of type 1 diabetes [12, 13]. The first prospective study of cholecalciferol supplementation in infants was conducted in Northern Finland [14]. This study provides the evidence that high doses of vitamin D [2,000 international units (IU) daily or more], during the first year of life, may reduce the risk for type 1 diabetes, at least in the parts of the world where yearly sunlight is limited. Still, some other studies did not confirm this association [15, 16].

Conflicting results were also observed in studies related to vitamin D deficiency in the fetal period and risk of type 1 diabetes. In a Swedish cohort study, a weak inverse association was observed between maternal vitamin D supplementation and the appearance of diabetes-associated autoantibodies at the age of 1 year, but not at 2.5 years [17]. Maternal intake of vitamin D from food, but not from supplements during pregnancy was associated with a decreased risk of early islet autoimmunity appearance in the offspring [18]. Lower risk of type 1 diabetes in the offspring was observed in women using cod liver oil during pregnancy [19]. On the other hand, Marjamäki et al. [20], found no association between the maternal intake of vitamin D, either from food or from supplements, with the risk of advanced β-cell autoimmunity and type 1 diabetes in offsprings [20]. Similarly, measuring of calcidiol concentrations during the first trimester of pregnancy, showed no difference between mothers whose children later on developed type 1 diabetes, and mothers of "non diabetic" healthy children [21].

Vitamin D effects on insulin secretion, insulin resistance and glucose control in type 2 diabetes

Potential influence of vitamin D on glucose handling is based on experimental data, that include the expression of 1α-hydroxylase enzyme and the presence of VDRs on pancreatic β-cells, as well as the presence of VDR on skeletal muscle. Calcitriol also stimulates the expresion of insulin receptor, activates peroxisome proliferator-activated receptor gamma (PPRγ) and enhances insulin-mediated glucose transport *in vitro* [22]. *In vitro*, calcitriol induces the biosynthesis of insulin in rat pancreatic islet cells and improves glucose uptake in cultured myocytes in a dose-dependent manner. Moreover, calcitriol protects pancreatic ß-cells from immune attacks, directly and indirectly by enhancing dendritic cell maturation, T-cells proliferation and macrophage differentiation [23].

Possible mechanisms od vitamin D activity on insulin secretion or sensitivity include: its effect on intracellular calcium levels, diminishing the expresion of proinflammatory citokines involved in insulin resistance such as IL-1, IL-6 and down regulation of nuclear factor kappa B activity [24]. Obesity is commonly associated with vitamin D deficiency, due to the capacity of adipocytes to store calcidiol, making it biologically unavailable [25]. On the other hand, decreased amount of serum calcidiol, calcitriol and raised PTH, can le-

ad to increased intracellular calcium in adipose tissue, which can in turn stimulate lipogenesis, increasing this way the risk of metabolic syndrome and type 2 diabetes [26].

In spite of the mentioned biological data reffering a potential influence of vitamin D to insulin secretion and action, results of conducted clinical studies are pretty inconsistent.

In healthy volunteers, calcidiol concentrations showed a positive relation to insulin sensitivity, and a negative effect on ß-cell function using the hyperglycemic clamp tehnique [27]. In the group of 157 individuals with prediabetes, serum calcidiol levels had a significant inverse correlation with insulin resistance measured by homeostasis model assessment (HOMA2) index, and a positive correlation with insulin sensitivity [28]. A significant inverse association has been reported between calcidiol levels and oral glucose tolerance test (OGTT) − induced insulin secretion in elderly [29]. Similar results regarding positive relationship between serum calcidiol and insulin sensitivity were reported by some other autors [30–32].

On the other hand, prospective cross sectional study conducted on type 2 diabetics enrolled from the urban Indian population, showed no association of serum calcidiol deficiency, on metabolic control or insulin restistance measured by HOMA of insulin resistance (HOMA IR) [33]. Measuring insulin sensitivity with the euglycemic-hyperinsulinemic clamp tehnique in morbidly obese Cavcasian women before and after bariatric surgery, showed no possitive correlation between D vitamin leveles and periferal glucose uptake [34]. The same goes to some other populations [35, 36]. The reasons for such conflicting results might originate from different optimal serum concentrations of calcidiol for different ethnicity, dissimilar methodological approach in measuring of insulin sensitivity, or relativly small sample size in mentioned studies.

The effect of vitamin D supplementation on glucose homeostasis have been studied in many researches. Oral weekly supplemental vitamin D (dose of 50,000 IU) given for two months, significantly decreased serum fasting plasma glycemia and insulin resistance (HOMA IR) in a group of type 2 diabetic patients [37]. A similar association between vitamin D supplementation and insulin sensitivity and fasting glucose levels was obtained in some other studies [27, 38]. Insulin sensitivity was also improved in nondiabetic patients with monthly suplementation with 120,000 IU of vitamin D [39]. In contrast to these results, cholecalciferol supplementation during 6 months (20,000 IU twice weekly) to apparently healthy subjects with insufficient serum calcidiol levels, did not improve insulin secretion or sensitivity using hyperglycemic clamp technique [40]. Some other studies using HOMA β as insulin secretory outcome, also did not observe significant changes in insulin secretion after cholecalciferol suplementation [41, 42]. Disperities in mentioned studies could be partly explained by using HOMA IR instead of more sensitive clamp tehniques in some studies. Supplementation of vitamin D-sufficient populations could be an additional factor; using calcitriol or/and vitamin D analogues instead of oraly supplemental cholecalciferol, could also contribute to result unsteadiness.

As for prospective studies, it seems that they provide the potentially strongest evidence for the relationship of basal plasma calcidiol values and subsequent glycemic control. In the group of 524 non-diabetic persons, baseline values of calcidiol were inversely associated with a 10-year risk of fasting hyperglycemia, insulin resistance and metabolic syndrome [43]. Similarly, a Finnish cohort study showed an inverse relationship between baseline calcidiol levels and a 17-year risk of type 2 diabetes [44]. Finally, meta analysis of 21 prospective studies, that included nearly 5,000 incident cases of type 2 diabetes and 76,220 nondiabetic controls, confirms a significantly inverse association between calcidiol levels and the incidence of type 2 diabetes. This association did not differ markedly by sex, study size or calcidiol assay method [45].

Vitamin D and chronic complications of diabetes

Vitamin D deficiency rate reported to be higher among patients with both types of diabetes [46, 47]. In contrast to numerous evidence that hypovitaminosis D is associated with higher prevalence of type 1 and type 2 diabetes, data of mutual connections between vitamin D status and chronic diabetic complications are scarce. Vitamin D have several immunomodulatory effects, such as inhibition of the renin-angiotensin system and reduction of inflammatory activity, that can be correlated with pro-inflammatory condition that is typical of diabetes.

Some observational studies in small samples, noticed a significant association between lower calcidiol levels and risk of all-cause or cardiovascular mortality in patients with type 2 and type 1 diabetes [48, 49]. Currently the largest, observational study on 472 men and 245 women with type 2 diabetes confirmed an independent relationship between low calcidiol levels and all-cause mortality, but only in men. This relationship was still significant when two other risk markers for mortality (pulse wave velocity and carotid intima-media thickness) were added to analysis, suggesting the posibility that vitamin D can be used as a surrogate marker of risk for mortality in male type 2 diabetic patients. These results also suggest that potential non-skeletal effects of vitamin D is gender-dependent [50].

In the cross-sectional study on 715 type 2 diabetic patients, there was a significant inverse association between circulating vitamin D levels and the presence of retinopathy and/or nephropathy [46]. This inverse and independent relationship was maintained even when the analysis was confined only to patients with glomerular filtration rate above 60 mL/min/1.73 cm^2. Vitamin D deficiency was associated with increased prevalence of retinopathy in young people with type 1 diabetes and in patients with type 2 diabetes, even after adjustment for potential confounders [51, 52]. Another study on 1,520 type 2 diabetic patients showed that vitamin deficiency is an independent risk factor for retinopathy [53]. The same study showed that the prevalence of sight threatening diabetic retinopathy doubles when the serum vitamin D levels are less than 15,57 ng/mL. In a retrospective study on 557 type 2 diabetic patients, vitamin D deficiency was lower in subjects with more severe diabetic microvascular compli-

cations [54]. On the other hand, some other autors did not confirm this relationship. In the prospective observational study on a cohort of type 1 diabetic patients, severe vitamin D deficiency, independently predict all cause mortality, but not the development of retinopathy or nephropathy [49].

As for neuropathy, one meta-analysis showed that vitamin D deficiency was significantly associated with increased risk of diabetic neuropathy in patients with type 2 diabetes. Vitamin D insufficiency was also associated with reduced parasympathetic function in type 2 diabetes, while the onset of neuropathy can be delayed by vitamin D treatment in type 1 diabetic patients [55−57].

A potential protective effect of vitamin D on the onset and progression of diabetic complications, originates from *in vitro* and *in vivo* experimental studies. Calcitriol is a powerful inhibitor of angiogenesis in mouse models of retinopathy and *in vitro* studies on retinal endothelial cells [58]. High serum calcitriol levels were associated with reduced angiogenesis in transgenic retinoblastoma model and in ischemic retinopathy in mice [59].

There are also some experimental evidence that VDR is a modulator of glomerular injury. Calcitriol decreases the glomerulosclerosis index and urinary albumin excretion (UAE) in animal models, while the combination of VDR-activator and an angiotensin-converting ezyme (ACE) inhibitor protected mice from developing diabetic nephropathy (DN). Vitamin D receptor agonists also reduce expresion of inflammatory mediators by monocyte and T-cells, promote survival of podocytes by preventing their apoptosis. Vitamin D is a potent negative endocrine regulator of the renin-angiotensin system (RAS) and predominantly works as a suppressor of renin biosynthesis. Calcitriol also suppresses hyperglycemia-induced activation of the RAS and transforming growth factor beta (TGFβ) in mesangial and juxtaglomerular cells, acting this way on one of the main mechanisam of renal injury in diabetes [60].

As for clinical studies, it is well-known that patients with chronic kidney disease (CKD), regardless of etiology, have active vitamine D deficiency. Serum calcidiol levels begin to decrease in stages 2 CKD, and its deficiency is prevalent in all subsequent stages of CKD. This could be influenced by the loss of VDBP in urine, ineffective synthesis in skin or reduced nutritional intake [61] . In a prospective follow up study on 168 patients with CKD, calcidiol levels were indipendent inverse predictor of disease progression and death, in patients with stages 2−5 of CKD [62]. This association was the strongest among patients with DN. In the prospective study on 103 patients with type 2 diabetes and DN, vitamin D deficiency was associated with accelerated progression of CKD after a median follow-up of 32 months, even though all patients have been received optimal RAS blockade [63]. Finally, the first clinical study that clearly suggests potential renoprotective effect of vitamin D supplementation was the study of Kim et al. [64]. In the group of 63 type 2 diabetic patients with nephropathy, treatment with oral cholecalciferol for 4 months, significantly decreased UAE and urinary TGF-β1 excretion, which represents the prinicipal mediator of onset and progression of diabetic kidney disease.

Vitamin D supplementation: current recommendations

The most accurate way to determine vitamin D status is measuring of calcidiol. Vitamin D deficiency in adults, is defined as a serum calcidiol level of less than 50 nmol/L (20 ng/mL), while insufficiency is defined as a serum calcidiol level of 50 to 75 nmol/L (20 to 30 ng/mL) [65].

A possible explanation for the actual widespread vitamin D deficiency is the lack of sunlight exposure, since the humans typically obtain 90 percent of vitamin D from skin synthesis. It is thought that 5 to 30 min of sun exposure of face, arms, back or legs, at least twice *per* week is usually adequate for vitamin D synthesis. Other factors contributing to vitamin D deficiency are increased use of sunscreen, pollution, dark or aging skin, seasons, latitude, sedentary lifestyle, obesity and use of some medications like glucocorticoids or anticonvulsants, which can increase catabolism of vitamin D. Furthermore, dermatologists caution against direct sun exposure to avoid risks of skin damage or skin cancer; so the useful alternative is supplemental vitamin D [66].

There is still no universally accepted standard regimen for overal correction of vitamin D deficiency, including diabetic state. Thus, there are no specific recommendations for vitamin D supplementations for diabetic patients or pregnant diabetic women, and the treatment strategy is the same as for the general population.

Current referrals are formed as a result of the previously mentioned clinical studies, taking into account the tolerable upper intake level. It is also important to point out, that the vitamin D supplementation is relatively safe, and that the toxicity have been observed only in patients taking more than 40,000 IU/daily [67].

In contrast to the World Health Organisation (WHO), which has not change its referrals from 2004, the Food and Nutrition Board of the American Institute of Medicine notified its new recommendations for vitamin D supplementation in 2010 [68, 69]. The later organisation recommends daily intake of 600 IU of vitamin D for persons aged 9−70 years; 800 IU daily intake for individuals over 70 years and 600 IU daily intake for pregnancy and lactation. Infants are recommended to intake 400 IU per day during the first 12 months, and 600 IU for everyone older than one year of age [69]. The American Academy of Pediatrics shares the same recommendations [70]. This organisation consider that the safe upper limit for vitamin D is 1,000 to 1,500 IU daily for infants; 2,500 to 3,000 IU daily for children between age of 1 to 8 years and 4,000 IU daily for children over 9 years of age, adults and pregnant women. According to the Endocrine Society Clinical Practice Guidelines, daily regimen for pregnant women includes taking products that contain at least 1,000 IU of vitamin D. For lactating women it is recomeneded to take 1,400−1,500 IU vitamin D every day, and to satisfy infant's requirement, they may need 4,000−6,000 IU/daily, if they choose not to give the infant a vitamin D supplements. They also suggets that obese children and adults sho-

uld be taken at least two or three times more vitamin D for age group to satisfy their body requirement [71]. Unlike these organisations, WHO consider that there is no indications for vitamin D supplementation during pregnancy [72]. Some autors claim that there may be no preventive effectiveness of early supplementation with 400 IU/daily of vitamin D or less, while higher doses of 2,000 IU/ daily could provide stronger protective effect against type 1 diabetes [67]. It should be also provided that all infants and children receive between 200 and 1,000 IU of suplemental vitamin D daily, especially if they have limited sun exposure, exclusively breastfed or, are at increased risk of type 1 diabetes. Guided by the results of previous studies, some other autors assume that vitamin D dose needs to be high enough, above 2,000 IU/daily, to raise blood calcidiol levels above 80 nmol/L, because diabetes risk is the lowest at this level [73].

As for patients with DN and CKD, in the majority of guidelines, vitamin D substitution strategies are based on serum calcidiol, calcium and PTH levels, mainly in order to reduce risk for secondary hyperparathyroidism. According to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, ergocalciferol should be used in CKD stages 3 and 4, when serum level of calcidiol is less than 30 ng/mL [74]. For those with high PTH and calcidiol level more than 30 ng/mL in CKD stages 3 and 4, substitution is recommended with active oral steroids (calcidiol, calcitriol or calcitriol analogues such as paricalcitol). Potential nephroprotective effect of cholecalciferol substitution on diabetic kidney disease is still under investigation, and therefore, has not been included in official recommendations.

Conclusion

Although promising, the data on the association between vitamin D and both types of diabetes are still inconclusive. There is also no clearly defined answer to what are the optimal concentrations of vitamin D for optimal glucose maintenance, or whether vitamin D supplementation may provide better clinical course of diabetes and reduce risk for diabetic complications. In order to resolve this problem, large randomized controlled clinical trials of the effect of vitamin D supplementation on glycemic control and diabetic risk are required, providing this way a simple and inexpensive additional assistance in prevention of diabetes mellitus all over the world.

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