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HEALTH OUTCOMES OF VITAMIN D. PART II. ROLE IN PREVENTION OF DISEASES

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ABSTRACT

Apart from the classic role of vitamin D, its hormonal active form, calcitriol is also characterized by pleiotropic effects on various organs and tissues. For the last several years, many researchers have shown an association between deficiency of vitamin D and the risk of type 2 diabetes mellitus (T2DM). Recent investigations suggested the need of vitamin D supplementation in T2DM prevention. It was shown that vitamin D deficiency decreases insulin secretion. It was also observed that proper vitamin D supplementation may improve the ability of the cells of the islets of *Langerhans* to synthesize many proteins de novo and to convert proinsulin to insulin. Apart from regulating bone metabolism and also calcium and phosphate homeostasis, 1,25(OH)2D3 exerts antiproliferative and pro-differentiating effects on a wide variety of cell types. It also induces apoptosis of cancer cells and slows their proliferation. In a number of major studies the relationship between low vitamin D levels and increased risk of various cancers was observed. It concerns colorectal, lung, prostate, breast and ovarian cancer. It was observed that in patients with low serum vitamin D concentrations such disorders as ischemic heart disease, heart attack, stroke, cardiac arrhythmia, and hypertension were more frequent and mortality was significantly higher. These results led the researchers to consider vitamin D deficiency as a potential risk factor for cardiovascular diseases. The possible mechanism in the pathogenesis of cardiovascular diseases that may be related to low levels of vitamin D, is its adverse effect on the renin-angiotensin-aldosterone system (RAAS). Calcitriol is also an important determinant of muscle cell proliferation and differentiation, as well as inhibition of apoptosis. Vitamin D is synthesized in the skin. However, there are only a few food products that are rich in vitamin D3, e.g.: fish oils, fish and fortified-products, such as dairy products and margarines. Individuals who are vulnerable to vitamin D deficiency should be supplemented.

Key words*: vitamin D, diabetes mellitus, deficiency of vitamin D, cancer, cardiovascular diseases, muscle physiology*

STRESZCZENIE

Poza klasyczną rolą witaminy D, jej hormonalna postać – kalcytriol wykazuje plejotropowe działanie na różne tkanki i narządy w organizmie. W ciągu ostatnich lat, wielu badaczy wykazało związek pomiędzy niedoborem witaminy D a ryzykiem wystąpienia cukrzycy typu 2 (T2DM). Wyniki badań sugerują potrzebę jej suplementacji w profilaktyce T2DM. Udowodniono związek między niedoborem witaminy D a upośledzonym wydzielaniem insuliny. Zaobserwowano również, że prawidłowa jej suplementacja poprawia zdolność komórek wysp *Langerhansa* do syntezy *de novo* wielu białek oraz przekształcania proinsuliny w insulinę. Poza regulowaniem metabolizmu kości i utrzymaniem homeostazy wapniowo-fosforowej, $1,25(OH)_2D_3$ reguluje procesy proliferacji i różnicowania różnych komórek. Ponadto indukuje apoptozę komórek nowotworowych i zwalnia tempo ich proliferacji. W wielu badaniach zaobserwowano związek pomiędzy niskim poziomem witaminy D a zwiększonym ryzykiem wystąpienia różnych nowotworów. Dotyczyło to raka jelita grubego, płuc, prostaty, piersi i jajników. U pacjentów z niskimi stężeniami witaminy D w surowicy zaobserwowano częstsze występowanie schorzeń takich jak choroba niedokrwienna serca, zawał serca, udar mózgu, zaburzenia rytmu serca, nadciśnienie tętnicze oraz wyższą umieralność. Wyniki tych badań skłoniły do uznania niedoboru witaminy D za potencjalny czynnik ryzyka rozwoju chorób sercowo-naczyniowych. Możliwym mechanizmem w ich patogenezie, mogącym tłumaczyć omawiane zjawisko, jest wpływ witaminy D na układ renina-angiotensyna-aldosteron (RAAS). Kalcytriol jest także ważnym czynnikiem, który determinuje proliferację i różnicowanie komórek mięśniowych, jak również hamowanie ich apoptozy. Witamina D jest syntetyzowana w skórze. Niewiele jest jednak produktów spożywczych, które są dobrymi jej źródłami. Są to głównie: oleje rybne, ryby oraz produkty wzbogacane w witaminę D, takie jak produkty mleczne i margaryny. Osoby, które są szczególnie narażone na niedobór tej witaminy powinny stosować jej suplementację.

Słowa kluczowe*: witamina D, niedobór witaminy D, cukrzyca, nowotwory, choroby sercowo-naczyniowe, fizjologia mięśni*

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INTRODUCTION

In the first part of the paper metabolic pathways and classic role of vitamin D were described [32]. It was shown that calcitriol exerts pleiotropic effect in various tissues and organs. In this part of the article its non-classic effects and the role in prevention of type 2 diabetes, cancer, cardiovascular diseases and sarcopenia are described.

TYPE 2 DIABETES MELLITUS

Nowadays, a pandemic of diabetes mellitus, especially of type 2, is observed. Its morbidity rates are very high in many countries worldwide. The high diabetes prevalence results from inadequate lifestyle, including improper diet, which leads to obesity [33].

Type 2 diabetes mellitus (T2DM) is characterized by high blood glucose in the presence of insulin resistance and relative insulin deficiency. This metabolic disease is very strongly related to diet and lifestyle that influence its development [10]. Recent investigations have suggested the need of vitamin D supplementation in T2DM prevention. In animal studies published in 70thies a pancreatic receptor for the active metabolite of vitamin D – $1,25(OH)_2D_3$ was identified. It was shown that vitamin D deficiency decreases insulin secretion. It was observed that proper vitamin D supplementation may improve the ability of the cells of the islets of Langerhans to synthesize many proteins *de novo* and to convert proinsulin to insulin [34]. In animal models it was shown that vitamin D effect on insulin secretion is related rather to the stimulated than the basal glucose secretion. Since that time numerous human studies of vitamin D in T2 diabetes mellitus have been published but the mechanism of this phenomenon is still not well understood.

There are a few mechanisms that can explain the relationship between vitamin D levels and the risk of diabetes. First of all, pancreatic β-cells, that produce insulin, similarly to the immune system, express the vitamin D receptor (VDR) and the vitamin-D-binding protein (DBP). Furthermore, vitamin D promotes calcium absorption and utilization by β-cells, what is necessary for their function and insulin secretion. In addition, allelic variations in genes involved in vitamin D metabolism and in VDR synthesis are associated with glucose intolerance, reduced insulin secretion and sensitivity and also enhanced inflammation [1, 29]. Although, all these mechanisms suggest the great role of vitamin D in the pathogenesis of diabetes mellitus, it is still questionable if increasing vitamin D status would reduce the risk of diabetes.

In a large epidemiological study that included 4,097 healthy Finnish men and women, who were followed for 17 years, an inverse relationship between serum vitamin D levels and the risk of type 2 diabetes was shown. The similar association was also found by *Forouhi* et al. in the cohort study performed in the English town of Ely, that compared baseline measures of the blood 25(OH) D and the subsequent glycemic status. It was confirmed that low baseline serum 25(OH)D concentration was inversely associated with 10-year risk of hyperglycemia, insulin resistance and metabolic syndrome [13, 19].

However, in the recent large study by *Pittas* et al., the lower incidence of type 2 diabetes mellitus in the highest versus the lowest vitamin D status group was reported. However, several trials found no effect of vitamin D supplementation on glycemia or incidence of T2DM. Potential reasons of this inconsistency include various vitamin D baseline levels, different doses used in supplements, and also differences in study designs [24, 25].

All these associations are important for understanding the etiology of abnormal glucose metabolism, but further studies are necessary to confirm the independent vitamin D role in reduction of the risk of type 2 diabetes mellitus.

CANCER

Apart from regulating bone metabolism and also calcium and phosphate homeostasis, $1,25(OH)_2D_3$ exerts antiproliferative and pro-differentiating effects on a wide variety of cell types. It also induces apoptosis of cancer cells and slows their proliferation. These characteristics attributed to vitamin D contribute to anticancer protection [16].

In a number of major studies the relationship between vitamin D levels and a risk of various cancer diseases was observed. In the recent Czech study [8], serum $25(OH)D_3$ concentrations were measured in 215 healthy individuals and in 170 patients with colorectal, lung, prostate and pre- and postmenopausal breast cancers. Researchers have shown that vitamin D levels were significantly lower in cancer patients when compared to the control group. What is more, 64% of patients with lung cancer, 35% of patients with breast cancer, 29% of patients with colorectal cancer and 18% of patients with prostate cancer had $25(OH)D_3$ concentrations below the cut off value (47,5 nmol/L) [8].

Researchers found that the incidence of ovarian cancer is higher in northern countries, the geographical areas with lower exposure to sunlight. This supports the hypothesis that vitamin D may act as a protective factor against ovarian cancer. In the recent Polish study vitamin D deficiency in patients with ovarian cancer was observed [30]. In a group of 72 patients who participated in the study, vitamin D levels were measured before optimal cytoreduction surgery. The results were

Table 1. Vitamin D_3 in food products [17, 27]

Food product	Amount I.U. / 100 g or 100 ml
Fish oil, cod liver	10 001
Fish, herring, Atlantic, raw	1628
Fish, eel, raw	1200
Fish, Herring Atlantic, pickled	680
Fish, salmon, pink, canned, solids with bone and liquid	540
Fish, sardine, Pacific, canned in tomato sauce	480
Fish oil, sardine	332
Margarine „Rama"	300
Fish, mackerel, Atlantic, cooked, dry heat	252
Fish, tuna, light, canned in oil	236
Egg, yolk, raw, fresh	107
Fish, cod, raw	44
Cheese, edam	36
Human breast milk	1,5-8
Cow milk	0,4-1,2
Milk-rice porridge BoboVita (of dry product)	200
Milk-rice porridge BoboVita (of ready meal)	92
Milk Infant Formula	40-50
Milk Follow-on formula	40-80

Table 2. Dietary reference intake for vitamin D according to the Polish and American recommendations [5, 14]

Level / Life stage group	Polish recommendations AI (I.U. per day)	American recommendations RDA (I.U. per day)
Infants	200	–*
Children to 18 years old	200	600
19-50 years old (males)	200	600
51-65 years old (males)	400	600
>65 years old (males)	600	800**
19-50 years old (females)	200	600
51-65 years old (females)	400	600
>65 years old (females)	600	800**
Pregnant women	200	600
Lactating women	200	600

* Without reference to 1 year of age
** After 70 years of age

compared with the control group. The researchers found that the concentrations of $25(OH)D_3$ in the group of patients with ovarian cancer were in the range of deficiency and the mean level was significantly lower than in the control group (12.5±7.75 vs. 22.4±6.5ng/ml). In addition, in the subgroup of patients with levels of $25(OH)D_3$ below 10 ng/mL the overall survival was significantly shorter than in patients with levels above 10 ng/ml [30].

The American Cancer Society's Cancer Prevention Study (CPS) II Nutrition Cohort involved 120 000 men and women. Researchers analyzed the diet, medical history, and lifestyle of the participants. The men with the highest intakes of vitamin D, from both food and dietary supplements (>525 IU/day) had an insignificantly lower risk of colorectal cancer than men who had the lowest vitamin D intakes. However, this association was not observed in women [21].

In the group of 16818 participants of the Third National Health and Nutrition Examination Survey an association between plasma levels of vitamin D and reduced mortality from colorectal cancer was observed. Subjects with higher vitamin D blood levels (≥80 nmol/L) had a 72% lower risk of colorectal cancer death than those with lower vitamin D blood levels (< 50 nmol/L) [7].

Recent epidemiologic studies suggest the possible association between blood levels of vitamin D and the risk of various types of cancer. However, the data are inconsistent and the further investigation is required.

CARDIOVASCULAR DISEASES

Discovery of the vitamin D pleiotropic activity was followed by creation the concept of the relationship between its deficiency and cardiovascular diseases. In the recent years numerous reports based on epidemiological studies that demonstrated enhanced risk of cardiovascular diseases and incidents in patients with low levels of vitamin D were published. It was observed that in patients with low vitamin D concentrations such disorders as ischemic heart disease, heart attack, stroke, cardiac arrhythmia, and hypertension were more frequent and mortality was significantly higher [18]. It was also shown that the prevalence of cardiovascular risk factors, such as hypertriglyceridemia, hypercholesterolemia, diabetes and high body mass index was increased. These results led the researchers to consider vitamin D deficiency as a potential risk factor for cardiovascular disease.

In the Danish Study [23] researchers from the University of Copenhagen and the Copenhagen University Hospital investigated the association between low concentration of vitamin D and ischemic heart disease and death. In a large group of 10 000 Danes they observed that low levels of vitamin D (<15 nmol/L), compared to optimal levels (≥50 nmol/L), were related to increased risk of ischemic heart disease by 40%, heart attack by 64%, and premature death by 57%.

A total of 1 739 participants of the Framingham Offspring Study were free of cardiovascular disease (CVD) at baseline. In 28% of the studied subjects low levels of vitamin D (25(OH)D <15ng/mL) were found. In this group, during the mean follow-up period of 5.4 years, the higher rate of the major CVD events was shown (HR 1.62, 5% CI 1.1-2.36, P=0.01*)*. However, it was relevant only in the group with hypertension (HR

2.13, 95% CI 1.30-3.48), but not in the participants with normal blood pressure (HR 1.04, 95% CI 0.55-1.96). Cardiovascular risk increased across categories of 25(OH)D. In subjects with the levels 10 to <15 ng/mL it was raised by 53%, and in those with the levels <10 ng/mL by 80%. [18,22].

In a survey of 27 000 patients from the Intermountain Healthcare System vitamin D deficiency (≤30 ng/ml) was found in 60% participants. The prevalence of vitamin D deficiency was highly significantly ($p<0.0001$) associated with the increased risk of type 2 diabetes mellitus, dyslipidemia and hypertension. What is more, vitamin D deficiency was strongly related also to coronary heart disease (CHD), myocardial infarction, heart failure, and stroke, as well as total mortality [18].

In the Health Professionals Follow-up Study 18 225 men were observed for 10 years. It was found that low levels of 25(OH)D were associated with higher risk of myocardial infarction. In another recent multicenter epidemiological study it was found that 96% of patients admitted to hospital with acute coronary syndrome had low 25(OH)D levels (<30 ng/ml) [22].

Important role in the pathogenesis of cardiovascular disease that may be related to low levels of vitamin D is attributed to the renin-angiotensin-aldosterone system (RAAS) [22]. In many experimental animal models an increased activity of renin in individuals without a gene for vitamin D_3 converting enzymes or its receptor was demonstrated. In mice without 1αhydroxylase enzyme activity the development of hypertension and left ventricular hypertrophy were observed. The both disorders normalized after treatment with $1,25(OH)_2D_3$. Similarly, the decrease in RAAS activity was also found in patients with hypertension and chronic kidney disease who were treated with vitamin D_3 [22].

Apart from the role in the regulation of renin expression, vitamin D and its analogues exert also their direct effect on the function and structure of the vascular wall [22]. It results from their anti-adhesive, anti-inflammatory and antioxidant activities. However, despite of numerous studies supporting this role of vitamin D_3, there are some investigations that question its effect on vasodilation but indicate rather its activity leading to increased vascular resistance and increased sensitivity to factors that raise blood pressure [22].

Low concentration of serum calcium and hyperparathyroidism, that are secondary to low levels of vitamin D_3, are considered as other mechanisms which play an important role in the pathogenesis of cardiovascular disease. Low level of calcium negatively affects vascular smooth muscle tension, and is regarded as a potential pathogenic factor of hypertension. What is more, high parathyroid hormone level, resulting from deficiency of vitamin D_3, has proven adverse effects on the vascular smooth muscle. Consequently, it results in increased vascular stiffness and resistance of peripheral vessels [6].

There is also another mechanism that may contribute to the link between obesity on one side and hypertension and insulin resistance on the other. Low levels of vitamin D_3 may be related to obesity. Increased body fat tissue mass binds vitamin D_3, which is soluble in fats, what results in its sequestration and reduction of bioavailability [22].

There are a lot of data from intervention and epidemiologic studies that evaluated the impact of vitamin D_3 supplementation on cardiovascular risk. Although the most researchers suggest a negative effect of vitamin D_3 deficiency on the morphology and function of peripheral vessels, it may be presumed that vitamin D_3 deficiency can also be secondary to vascular pathology resulting from immobility and low exposure to sunlight [22].

MUSCLE PHYSIOLOGY - ROLE IN SARCOPENIA

Apart from parathyroid hormone and calcitonin, vitamin D_3 is a major regulator of calcium level in the human body. Calcium is essential for bone and muscle tissues. In the bone calcium is the main building material, whereas in the muscle it determines contraction and relaxation processes [3].

Vitamin D_3 through its active metabolite - $1,25(OH)_2D_3$, promotes absorption of calcium and phosphate in the intestine and kidney. Calcitriol activation depends on the PTH but also on calcium, phosphate, and magnesium levels. It was shown that vitamin D_3 extends lifetime of osteoblasts through inhibition of their apoptosis [3]. Already in 70s some authors described cases of osteomalacia associated with myopathy that weakened mainly the force of the proximal muscles. This effect was initially attributed to osteomalacia, but not to deficiency of vitamin D_3. However, many subsequent studies showed that vitamin D_3 supplementation may increase muscle strength. What is more, it was found that regular physical activity is less effective in subjects with vitamin D_3 deficiency than in those with its normal level [3].

The above-described studies show that vitamin D_3 plays an important role in muscle physiology. It results from the fact that vitamin D_3 activates a number of metabolic processes in the muscle tissue. These functions are mediated by two receptors: the nuclear receptor, associated with the genes activation and the membrane receptor. The nuclear receptor was found in the each type of muscle tissue in both humans and animals. Vitamin D metabolic action is triggered by its active form, $1,25(OH)_2D_3$. After binding to the receptor calcitriol activates transcription of genes that leads to

the synthesis of many proteins in the bone, including: osteocalcin, osteopontin, calcium-binding protein (CaBP), IGFBO-3, and in muscles – to the synthesis of CaBP that is crucial for metabolism of phospholipids and intracellular transport of calcium, that is followed by muscle contraction. The nuclear effect of vitamin D is coactivated by the protein complex: the retinoid-X--receptor (RXR) and the Steroid Receptor Coactivator 3 (SCR). Studies in mice have shown that defect of one of the complex components results in the decrease in length of muscle fibers by 20% [3].

The role of the membrane receptors is less known. Myocyte activation by this sort of receptor is nongenic, reduces the signal transmission process, and is referred to as rapid nongenomic actions. It results in intracellular flow of calcium and regulation of its intra- and extracellular levels [3].

Calcitriol is also an important determinant of muscle cell proliferation and differentiation, as well as inhibition of apoptosis. These effects are mediated by acceleration of action of specific kinases through the activation of mitogen-activated protein kinase (MAPK) [3].

Vitamin D_3 plasma level decreases with age. This phenomenon coexists with other characteristics of ageing – increased intensity of catabolism, osteoporosis, atrophy of nerve tissue, decrease of the hormones activity, and also sarcopenia [20, 28]. Sarcopenia is defined as dysfunction of muscles which is characterized by the decrease in their mass, function and strength that is associated with age [20]. Sarcopenia is an essential component of frailty syndrome - a condition of increased susceptibility to endogenous and exogenous stressors, resulting from the reduction in physiological reserve. It is a consequence of the reduced capacity of multiple systems and multiple-dysregulation, which limits the ability of the body to maintain homeostasis and also its response to stress. Decrease of the vitamin D_3 activity is one of the results of ageing, and also one of the causes of sarcopenia.

In many cases of rickets the coexistence of myopathy that subsided after supplementation with vitamin D was found. Similarly in adults, a number of cases of severe vitamin D deficiency, complicated with muscle weakness, especially that of proximal muscles of upper and lower extremities, were described. Mechanisms that are responsible for the effect of vitamin D deficiency on the development of sarcopenia are variable. One of them is peripheral nerve dysfunction that is often observed in subjects with low plasma vitamin D concentration. It might impair muscle control and coordination. Even mild vitamin D deficiency (<20 ng/ml) decreases skeletal muscle strength. Vitamin D supplementation may result in the increase of functional efficiency, reduction of the risk of falls and acceleration of the recovery after fractures in patients who undergo rehabilitation. It may support the effectiveness of regular physical activity. Regular exercises, that improve leg strength, yielded a much better result in the increase of muscle mass and strength in patients with higher levels of 25(OH)D_3 ($\geq$ 46 ng/ml) than in those with lower levels ($\leq$ 32 ng/ml). Similar results were observed regardless of the age [4].

MAJOR SOURCES OF VITAMIN D

Vitamin D_3, cholecalciferol, is a fat-soluble compound which may be derived from two natural sources. One of them is the skin synthesis, in which the ultraviolet radiation triggers cholecalciferol production from 7-dehydrocholesterol that is stored in the skin [15]. Skin synthesis of vitamin D depends on many factors including: exposure time, the intensity of sun exposure, latitude, time of the day, thickness of cloud cover, the level of air pollution, surface of the exposed part of the body, attendance of tanning salon, skin complexion, age, body mass, amount of body fat [31].

In geographical areas with a high intensity of sun radiation the skin synthesis is the main source of vitamin D_3. In other regions, with low insolation, a well--balanced diet with high-content vitamin D_3 should be the main source of vitamin D_3. There are only a few products that are rich in vitamin D_3, e.g.: fish oils, fish and fortified-products. Currently, due to the high prevalence of vitamin D deficiency and the risk of the related diseases, in many countries there is a statutory duty to enrich certain products. It concerns mainly dairy products, especially milk and other dairy drinks, and also margarines. Another group of products which are enriched with vitamin D_3 are nutritional products for infants and children, because few products in their diet contain vitamin D_3. It should be emphasized that the vitamin D_3 content in breast milk is relatively low [2, 10].

Vitamin D is relatively stable and does not decompose under the influence of heat or during long-term storage. It may be destroyed by ultraviolet radiation. Under aerobic conditions in aqueous medium it may undergo autoxidation [11].

Nowadays, vitamin D deficiency is considered a pandemic because it affects all age groups in almost all geographical regions. It was shown that the percentage of people diagnosed with low levels of 25(OH)D levels doubled in the period of 1994-2004 [12]. This situation is the result of changes in lifestyle of modern societies that involve decrease in time spent outdoors, the widespread use of sunscreens, and also air pollution. All these factors contribute to insufficient exposure to sunlight, and thus reduced skin synthesis of vitamin D. Other factors that probably increase the risk of deficiency of this vitamin are: aging of populations and the resulting

decline of vitamin D synthesis in the skin, low intake of vitamin D with the diet, and the obesity epidemic [9].

It is assumed that a well-balanced diet should provide all the essential nutrients, minerals and vitamins. However, there are groups of people who are particularly vulnerable to deficiency of vitamin D, e.g. children, adolescents, pregnant and nursing women and the elderly. The supplements should be used when sun exposure and the diet are not able to cover the needs of the organism.

The form of vitamin D, currently used in the Polish preparations, is cholecalciferol. Its effect is the most pronounced in the presence of other vitamins and minerals, such as vitamin A, C, calcium, choline, and phosphorus. Vitamin D_3 may be present in a preparation alone or in combination with other compounds. It is used in supplements in doses of 100-500 I.U. in complex formulations, in dose of 1000 I.U. in capsules, and in dose of 15 000 and 300 000 I.U. (the loading dose) per 1 ml of drops [11].

The current Polish recommendations concerning vitamin D intake [12] are presented in the table 2. The established adequate intake (AI) is much below the levels of the American standards expressed in Recommended Dietary Allowance (RDA) [5]. The Polish standards do not specify the level of RDA. The European Food Safety Authority (EFSA) recommends for women over 50 years of age the daily dose of vitamin D of 800 I.U. (RDA) [26].

CONCLUSIONS

1. There is a growing body of evidence that vitamin D plays a role in prevention of type 2 diabetes.
2. It seems that it may also reduce the risk of cancer and cardiovascular diseases.
3. Vitamin D can probably contribute to the maintenance muscle strength.
4. It is reasonable to provide the proper amount of vitamin D by skin exposure to sunlight, regular fish consumption and/or supplementation.

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