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VITAMIN D – A REMARK ON THE KNOWN AND A SURVEY OF THE LESSER-KNOWN FACTS

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Vitamin D as one of liposoluble vitamins has in clinical practice so far been related to children age and skeletal development. During the last years however, there has been a great deal of new information considering a rather more complicated involvement of vitamin D in a variety of processes and functions of the human body. The influence of vitamin D on the immune system, carcinogenesis, ostheogenesis, management of the depression and other correlations in elders are discussed in this article.

Keywords: Vitamin D, seniors.

Introduction. Vitamin D belongs to the group of liposoluble vitamins and is naturally present in a relatively narrow spectrum of commonly used diet components. The most important source of vitamin D is the ultraviolet component of solar radiation, which triggers the synthesis of vitamin D in our skin. Vitamin D obtained from the diet or synthesised in the skin is biologically inert cholecalciferol, and it has to undergo two further processes of hydroxylation to become active 25-hydroxycholecalciferol – calcidiol, or 1,25-dihydroxycholecalciferol – calcitriol. The former process occurs in the liver, the latter in the kidneys [1].

The main function of vitamin D is support of calcium resorption from the intestine and maintenance of adequate serum levels of calcium and phosphorus as an important precondition for bone growth and normal mineralisation of bone mass. More recently, it was found that vitamin D takes part in the regulation of the activity of osteoblasts and osteoclasts in the process of bone remodelling. Seen from this aspect, deficiency of vitamin D causes rickets in children and osteomalacia in adults; along with lack of calcium the development of osteoporosis and a significant increase of the number of osteoporotic fractures are markedly accelerated [2].

The deepening knowledge of the cellular and subcellular structure and functioning of the human organism lets ensue numerous as yet unforeseen facts. Vitamin D demonstrably becomes involved in immunity processes, in the functioning of the neuron, in insulin reactivity in DNA self-repair, in processes of proliferation, differentiation, and apoptosis. The presence of vitamin D receptors has been proved in many types of tissue cultures, in some of the types even including the ability to convert to active forms of vitamin D [3].

Vitamin D and contemporary population. In the last several years, reports have been appearing on the very low level of vitamin D in the majority of population of the middle geographical area, irrespective of the continent [4,5]. As the most suitable for monitoring vitamin D metabolism has been considered 25OHvit D3, which reflects the amount of the vitamin obtained in the diet and synthesised in the skin and has the corresponding biological half-life of 15 days; it informs us on the tissue deposits of vitamin D. Calcitriol – 1,25$(OH)_2$ vit D – is not a suitable clinical indicator because its level drops only at the moment when the deficit in the organism is already very marked [1]. For the evaluation of the current serum level of vitamin D there exists a standard used in Germany, where the healthy population should reach a serum level between 50 and 200 nmol/l. The US National Institute of Health recommends the lower limit of the standard to equal 37.5 nmol/l, when a level lower than this is already considered as a state when there appear severe disorders of bone metabolism and of the other processes in which vitamin D gets involved. Values over 500 nmol/l are considered to be toxic [3]. According to the first results of testing, the Czech population finds itself situated with its average value just on the borderland between 30 and 40 nmol/l, which means that at least half the population does not meet the level necessary for high-quality remodelling of the bone [5].

The current recommendation concerning the daily uptake of vitamin D differs markedly from the so far customary practice, when maximum attention was given to the uptake of vitamin D in children. At present it has been known and confirmed by numerous studies that supplementation with vitamin D and calcium in older patients in a dose double that recommended for childhood age has a significant positive effect on reduction of the number of falls and fractures in postmenopausal women as well as in the senium, and with deficient serum levels a rise by 1 nmol/l for each 100 IU may be expected [6]; see Table 1.

Table 1

Recommended daily maintenance doses of vitamin D by gender and age

Age	Children	Men	Women	Pregnancy	Lactation
0 to 13	200 IU				
14 to 18		200 IU	200 IU	200 IU	200 IU
19 to 50		200 IU	200 IU	200 IU	200 IU
51 to 70		400 IU	400 IU		
over 70		600 IU	600 IU		

Sources of vitamin D. The diet in the composition usual in the Czech cuisine is an insufficient source of vitamin D, with only a half of the recommended daily dose of 400 IU maximum, i.e. 200 IU being reached. Of the fish products available on our market, significant quantities of vitamin D are contained in salmon, mackerel, and cod liver [7]; see Table 2.

Table 2

The content of vitamin D in 100 g of selected foodstuffs

FRUIT	IU	μg
Fresh avocado	200	5
MUSHROOMS		
Boletus, dried	1120	28
Boletus	124	3.10
Common morel	124	3.10
Chanterelle	84	2.10
Slippery jack	80	2.00
Brown birch boletus	80	2.00
Milk cap	80	2.00
Honey fungus	80	2.00
Field mushroom, grown	78	1.94
Chanterelle (preserved)	48	1.20
Field mushrooms (preserved)	46	1.14
CAKES AND PASTRY		
Walnut pie	44	1.09
Sponge biscuits – spoonful	41	1.02
CREAM AND MILK		
Whole milk, powdered	50	1.24
Whipped cream	44	1.10
CHEESE		
Processed cheese, 45% fat in dry matter (FDM)	125	3.13
Gouda, 45% FDM	50	1.25

FISH	IU	μg
Eel, smoked	3600	90.00
Kipper	1200	30.00
Young herring	1080	27.00
Herring	1068	26.70
Common eel	800	20.00
Anchovy in brine	696	17.39
Herring – fillet in tomato sauce	660	16.50
Salmon	652	16.30
Herring, marinated	520	13.00
Salmon (preserved)	460	11.50
Sardine	430	10.75
Herring, baked	406	10.16
Rollmop	370	9.25
Oyster	320	8.00
Halibut, smoked	172	7.30
Caviar, genuine	235	5.87
Sardines in oil	228	5.71
Caviar, imitation	204	5.10
Halibut	200	5.00

Emmental, 45% FDM	44	1.10
Gorgonzola	40	1.00
Blue cheese, 50% FDM	40	1.00
OILS AND FATS		
Fish oil	12000	300.00
Margarine, low-calorie	100	2.50
Margarine	100	2.50
Margarine, reduced-fat	100	2.50
Butter	50	1.24
Butter, tried	48	1.20
EGGS		
Chicken egg (yolk)	223	5.58
Goose egg	200	5.00
Duck egg	200	5.00
Chicken egg (whole)	117	2.93
OFFAL		
Mutton and lamb liver	80	2.00
Beef liver	68	1.70
Chicken liver	52	1.30
Pork liver	45	1.13

Sole	180	4.50
Common trout	180	4.50
Tuna in vegetable oil	164	4.11
Mackerel	160	4.00
Whitefish	153	3.83
Perch	144	3.60
Golden perch, smoked	136	3.39
Spined loach	125	3.12
Plaice	108	2.70
Carp	108	2.70
Pike	108	2.70
Red perch	92	2.30
Common cuttlefish, fresh, thermally treated	91	2.28
Turbot	72	1.80
Tench	72	1.80
Mackerel, smoked	52	1.31
Atlantic cod (young)	52	1.30
Plaice, smoked	50	1.27

The content of vitamin D in selected kinds of food. Solar radiation of UVB type permeates the human skin and activates 7-dehydrocholesterol found in the skin to D3. The geographical latitude, season of the year, time of the day, quantity of smog, cloudiness, content of melanin in the skin and, last but not least, use of screening filters all affect exposure to solar radiation and the subsequent synthesis of vitamin D. Generally it is reported that latitudes north of 42° N Lat mean insufficient intensity of radiation for vitamin D synthesis in the period from November to February; in the more northerly areas the interval of insufficient exposure makes up to 6 months in the year. Cloudy sky reduces the intensity of radiation by 50 %. Use of sunscreens with a protection factor of over 8 effectively blocks vitamin D-producing rays [1].

What is important, however, is the dilemma between exposure to solar radiation with the aim to ensure delivery of vitamin D and the risk of carcinogenicity of UV radiation. To ensure adequate level vitamin D, it is recommended to expose the face, upper and lower extremities, or the back to sunrays for a period of 5 to 30 minutes in the interval between 10 a.m. and 3 p.m. Unfortunately, reliable data evaluating the cumulative lifelong exposure to solar radiation in the context of the rising risk for the development of skin malignancies are not known as yet.

In the last years, there have been arriving repeatedly alarming results of population studies reporting on tens of per cent of population with vitamin D deficiency. This concerns especially countries of the temperate zone, both on the American and European continents [4]. Particularly endangered groups are formed by seniors with reduced capability of skin synthesis and renal hydroxylation of vitamin D, furthermore people with restricted exposure to solar radiation, people with dark complexion, people with an intolerance to dairy products, patients observing in the long term fat-free diet, patients with malabsorption, extreme obesity, or those after bypass surgery of the stomach [3].

Potential consequences of long-term deficiency of vitamin D

Vitamin D and cognitive functions. Discussions on neuroprotective action of vitamin D have been going on for many years. One of the studies, which attempted to check the relationship between the level of vitamin D and cognitive performance, showed a significant positive dependence between the MMSE score achieved and vitamin D level [8]. A significant difference in the serum levels of vitamin D was observed in a study that compared patients with Parkinson's disease, Alzheimer's dementia, and a control sample. In the group with Parkinson's disease, there were significantly more patients with low level of vitamin D, and the average level in this group was also significantly lower than in the control group. The parameters monitored in patients with Alzheimer's dementia were placed approximately in the middle [9].

Another argument for the existence of a mutual relationship between vitamin D and cognitive affection was provided by the study concerned with polymorphism of the neuronal receptor for vitamin D; the configuration of the receptor reducing the affinity to vitamin D as of a protective factor maintaining the neuronal homeostasis of calcium was significantly more frequent in patients with Alzheimer's dementia [10].

The mechanism of action of vitamin D has been partly explained by its favourable influence on intestinal resorption and by an increase of the serum level of calcium, which leads to a dampening of parathormone secretion and the subsequent lowering of the level of free intracellular calcium as a neurotoxic factor that slows down the neuron's conductivity, damages the cellular membrane of the neuron, and accelerates the neuron's destruction. There has also been described an increased level of free intracellular calcium in neurons which exhibited the presence of neurofibrillary structures and tau protein in Alzheimer's dementia [11].

Vitamin D and depression. As early as since the 1990s references have kept appearing to the favourable influence of vitamin D on seasonal mood disorders, although at the beginning it was not clear if this was an additional effect to the influence of daylight [12].

The effect of the actual vitamin D on mood improvement was confirmed on healthy probands in the winter period by administration of 400 IU, 800 IU of vitamin D3, and placebo in the form of a randomised double-blind study; questionnaires confirmed an improvement of the mood in probands to which active substance was administered [13].

A similarly designed study confirmed the effect of administration of vitamin D in older men living in their own environment, but only doses exceeding 1,000 IU were efficient [14].

The mechanism of action of vitamin D is interpreted by stimulation of tyrosine hydroxylase as an enzyme enhancing the formation of serotonin [15].

Vitamin D and tumours. Vitamin D shows the ability to inhibit mitogen-activated protein kinase (MAPK) and thus negative growth regulation of mammary carcinoma cells both in vivo and in vitro. The mechanism of action is interpreted in two ways: it regulates gene transcription of the gene through the specific intracellular vitamin D receptor (VDR) and, by means of activation of transmembrane transfer, it induces a fast non-transcriptional response of the character of modification of growth factors and peptide hormones [16]. Basing on these activities there occurs an antiproliferative, proapoptotic influence on many cell lines [17].

In a study realised at the Mayo Clinic in the latter half of 2009, women with invasive mammary carcinoma had a significantly lower level of vitamin D, and a significant negative relationship between the oncological type of tumour and vitamin D level [18].

In discussions on the mutual relationship between vitamin D and tumorous growth there frequently appears the theme of exposure to solar radiation as a significant source of vitamin D for man in contrast to the rising occurrence of malignant melanoma, in whose pathogenesis exposure to solar radiation plays indeed an important role. A Swedish study was concerned with the question whether exposure to UV radiation was able to reduce the total tumour morbidity and mortality rates. Exposure to UV radiation through sunrays fulfilled this assumption, whereas exposure to UV radiation in solariums had an opposite effect, even though both groups of probands showed increased serum levels of vitamin D [19].

In discussions regarding the mutual relationship between the vitamin D level and potential antiproliferative action and solar radiation as the principal presumed pathogenetic factor of the development of malignant melanoma, but also as a source of vitamin D, there arises the question of quantity, i.e., what the optimal serum level of vitamin D should be. The authors from the University of Leeds denote values between 70 and 100 nmol/l as optimal, both for patients with malignant melanoma and for the healthy population [17].

Another area of oncology, in which the potential contribution of vitamin D is discussed, is colorectal malignancies. In patients with colonic adenomas, a negative correlation of the frequency of adenomas and the serum level of vitamin D was detected. No such similar association has been corroborated for hyperplastic polyps [20]. On the other hand, in patients with already developed colorectal carcinoma, a highly significant negative dependence has been demonstrated on the serum level of vitamin D; in the case of rectal localisation the dependence was even closer [21].

Vitamin D and immunity. The assumption of a modification of the immune system by vitamin D is based on the detection of production of vitamin D by activated macrophages and on the proved existence of vitamin D receptors on cells of the immune system. In this way vitamin D modifies the local progress of the inflammation in the form of negative feedback. Also, a significant association has been proved between the low level of vitamin D and susceptibility to chronic mycobacterial or viral infections. On the contrary, an adequate level of vitamin D encourages the CD4-mediated cellular and antibody immunity of the surface of skin and mucous membrane – for example, the activity of 1α-hydroxylase has been demonstrated, which is an enzyme generating active vitamin D in the mucous membrane of the respiratory tract, alveolar macrophages, and dendritic cells. Another important area of functioning of vitamin D in human immunity is ensuring and maintaining the tolerance of the actual tissues – it has been demonstrated on model diseases of the type of multiple cerebrospinal sclerosis, insulin-dependent diabetes mellitus, and non-specific intestinal inflammations that vitamin D can strengthen the function of T suppressors and thus improve immunological tolerance of the actual tissue antigens [22,23,24,25].

Vitamin D and the muscle. The favourable influence of vitamin D on the maintenance and new formation of muscular mass and preservation of muscle strength has been demonstrated. The mechanism of action is interpreted by stimulation of the phosphorylation of tyrosine contained in the myoblasts via phospholipase C, which participates in the mobilisation of the intracellular supplies of calcium, and further by protein kinase stimulation [26].

Loss of muscular mass is one of the principal factors influencing the self-sufficiency of seniors; loss of type II muscle fibres means a marked increase of the risk of falls and, in combination with the present osteoporosis, also an increased risk of fractures. According to the results of an Australian study carried out on seniors living in their own environment, individuals with low serum levels of vitamin D exhibited lower muscular mass, lower muscle strength, and generally lower levels of physical activity [27]. The development of sarcopenia is in an essential way modified by the present concurrent diseases and often overlaps with cachexia. Apart from substitution of the low level of vitamin D, references from the practice suggest the possibility of using physical targeted load for the maintenance or recovery of muscle strength and nimbleness especially in those institutions for seniors where patients with Alzheimer's dementia were also successfully involved in the programme [28].

An intervention study of Belgian authors demonstrated an increase in muscle strength, multiplication of muscle mass, and increase of bone density after a 6-month administration of vitamin D at a dose of 880 IU per day. However, neither the administration of double doses of vitamin D nor whole-body vibration training provided any further improvement [29].

With regard to the seriousness of sarcopenia and possible consequences in terms of increased risk of falls, loss of self-sufficiency, and a significant worsening of life quality, recommendations for the management of sarcopenia have even appeared in the official materials of the American Society of Health Institution Directors. Recommendations include training with combined strength and endurance loads, adequate intake of proteins, and supplementation of vitamin D in case of its decreased serum levels [30].

Vitamin D and the bone. The significant positive dependence of bone density and negative dependence of the level of parathormone, frequency of fractures and frequency of falls on the serum level of vitamin D has been demonstrated by many studies. In a number of studies however, the effect of the actual vitamin D and of calcium could not be exactly differentiated from each other. With regard to the senior population, its self-sufficiency, and ability to remain in its own environment, the drop in the frequency of falls and osteoporotic fractures in case of long-time administration of vitamin D in a dose exceeding 700 IU per day and of calcium in a dose exceeding 1,000 mg per day is, however, essential. The above-mentioned favourable influence of vitamin D on the preservation of muscle mass is sure to also take part in the decline of the frequency of falls [6].

In view of the potential undesirable cardiovascular effects of calcium supplementation with a relatively low influence on further reduction of the frequency of fractures compared to the administration of vitamin D alone, there have been lately appearing recommendations for prioritisation of increased supply of calcium through usual diet and not by pharmaceutical preparations [31].

Vitamin D and diabetes mellitus. During the last years, ever more information has kept appearing on the mutual influence of vitamin D and diabetes mellitus of both types 1 and 2. The mechanism is interpreted by the negative influence of low levels of vitamin D on both inborn and acquired immunity and the ensuing worsened tolerance of actual antigens [22,32,33] with the subsequent inflammatory autoimmune reaction. This assumption is also corroborated by the demonstration of increased proinflammatory activity in patients with type 1 diabetes and low levels of vitamin D. These patients had significantly lower levels of vitamin D compared to the control group of healthy individuals and exhibited a significant negative correlation between the serum level of vitamin D and the CRP value [34].

It is true that the multicentric study IMDIAB XIII did not confirm, in a randomised double-blind study, the favourable influence of vitamin D supplementation on the function of pancreatic beta cells or on the levels of glycosylated haemoglobin in recent type-1 diabetics, but the dose applied was only 0.25 μg/day against the commonly recommended dose of 10 μg/day [35].

On the other hand, the study in which type-1 diabetics with serum levels of vitamin D lower than 50 nmol/l were using 4,000 IU of vitamin D per day demonstrated a significant reduction of the value of glycosylated haemoglobin and a drop in insulin consumption [36].

So far, the facts ascertained come from experiments on animals, and/or from observation studies; generally, authors of communications concerned with the relationship of vitamin D and type-1 diabetes mellitus or other extraskeletal diseases of autoimmune character appeal for further studies that would check the hitherto ascertained facts [37].

In relation to type-2 diabetes, vitamin D deficiency has been shown to lead to increased insulin resistance, increased glycaemia, and to a rise in blood pressure. Supplementation with vitamin D leads to an increase in the sensitivity of tissues to insulin, to a drop in glycaemia, and to a drop in blood pressure values. The results of some in vivo studies lack uniformity, most frequently due to methodology; nevertheless, type-2 diabetics are advised to maintain the level of vitamin D around 85 nmol/l all year long [38].

Another unfavourable effect of vitamin D deficiency in type-2 diabetics is endothelial dysfunction with demonstrated insufficient ability of vasodilation, and a drop in the number of circulating endothelial progenitor cells with subsequently increased risk for vascular diabetic complications [39].

Discussion – conclusion. From the review presented above it follows that, along with the introduction of routine examination of the serum level of vitamin D, a variety of issues has been opened of not only technical but also medical character. On the one hand doubts may arise concerning the methodology of examination and rate of relevance of the levels detected for a given sector of population; however, reports on low serum levels coming from numerous countries are similar. Seen from the medical point of view, the often striking discrepancy between the very low serum level of vitamin D and the absolutely intact clinical state of a given patient is sure to cause confusion. However, the problem here is the long-time character of the low-level effect on the given structures and, of course, also the reversibility or irreversibility of already occurred changes.

In this field a great deal of new information is likely to be expected in the near future. With regard to the potential consequences for the present-day middle- and early senior-age population it is highly desirable to introduce positive findings very quickly into practical medicine in the interest of encouragement of the state of health with subsequent prolongation of self-sufficiency of this part of population. If we project for ourselves the image of a senior with advanced geriatric syndromes, that is, one with cognitive disorders, depressive, with instability and falls, with loss of muscle mass and in danger of falls and osteoporotic fractures, susceptible to infections, then the attention given to supply of vitamin D from the middle age might well assist to somewhat mitigate this unfavourable picture.

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ВИТАМИН Д – К ВОПРОСУ ОБ ИЗВЕСТНЫХ И МАЛОИЗВЕСТНЫХ ФАКТАХ

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Витамин Д – один из жирорастворимых витаминов – имеет широкое клиническое применение в детской практике, в т.ч. для остеогенеза. Однако, в последние годы было получено много интересных информативных данных, отражающих новые сведения об участии витамина Д во многих функциях человеческого организма. В настоящей статье обсуждаются вопросы влияния витамина Д на иммунную систему, кардиогенез, остеогенез,, управление депрессией, а также другие влияния в организме людей старших возрастных групп.

Ключевые слова: витамин Д, пожилые люди.