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Review/ Praca poglądowa

Vitamin D and cognition

Witamina D i zdolności poznawcze

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ABSTRACT

It has been recognized that the importance of Vitamin D far exceeds its long-known role in mineral homeostasis. In this review its importance in various normal and pathological processes such as muscle work, cardiovascular health, diabetes and some neurological diseases is briefly presented. In particular, the role of Vitamin D in brain functioning and cognition is summarized. The association of Vitamin D level and cognition has been recognized by numerous authors. Whether the administration of vitamin D could improve existing cognition deficits concomitantly with raising the vitamin level remains to be elucidated. Most authors claim that randomized clinical trials are still needed to clarify this question.

It is estimated that a substantial proportion of the population worldwide is presently deficient in vitamin D. The importance of its supplementation is emphasized.

Vitamin D is in fact a hormone, because it can be synthetized in an organisms in the skin. It originates from 7-dehydrocholesterol, which gets transformed photochemically into provitamin D by light in the 290–315 nm wavelength (the UV light range), after which thermic isomerization cholecalciferol (calcyol) is formed. Cholecalciferol is also delivered by food. Cholecalciferol undergoes two hydroxylation steps: the first through hydroxylase 25 in the liver (carbon 25 forming calcidiol), the second through hydroxylase 1 taking place, mostly in the kidney, adding the hydroxyl group to carbon 1 thus forming calcitriol – 1.25-dihydroxyvitamin D, which is the active form of the vitamin – vitamin D_3. Both hydroxylases are cytochrome P450 enzymes.

Ergocalciferol (vitamin D_2), which is present in diet and fungi, is also metabolized into calcitriol. Skin-synthetized vitamin D undergoes a twofold-longer retention in the organism as compared with vitamin D delivered from diet [1, 2].

Most of the biological activities of vitamin D are mediated by a high-affinity receptor (vitamin D receptor – VDR) that acts as a ligand-activated transcription factor. The major steps involved in the control of gene transcription by the receptor include ligand binding, heterodimerization with retinoid X receptor (RXR), binding of the heterodimer to vitamin D response elements (VDREs), and recruitment of other nuclear proteins into the transcriptional preinitiation complex [3].

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The Vitamin D receptor has been shown to exist in many tissues of rodents and higher animals. The receptor gene in humans is localized in chromosome 12 [4]. A unique deleterious mutation in the receptor causing Vitamin D resistant rickets – a rare monogenetic disease gene – has been described [5]. The association of various common polymorphisms in the VDR gene with common diseases were studied [3, 6]. One of the polymorphisms – the Fok1 polymorphism – consists in T-to-C change in the start codon of exon 2, and leads to the synthesis of a shorter and more active form of the protein [4]. Analysis of the haplotype, i.e. the block of alleles, has also been studied and it has been stated that European populations differ in this respect from African ones [7].

It has long been known that Vitamin D plays a crucial role in phosphate homeostasis, bone mineralization and the regulation of calcium levels. Accumulating data shows its previously unsuspected role beyond the classical one in mineral homeostasis, namely in muscle work, cardiovascular health, diabetes, cancer prevention as well as in brain development and in neuroprotection. It is estimated that Vitamin D controls the expression of more than 200 genes [8].

The subject of the present article will concern mainly the role of Vitamin D in brain functioning and cognition.

Some facts show an especially important role of Vitamin D in nervous tissue. The role played by Vitamin D in the brain development of rodents has been described [9]. The Vitamin D receptor is widely represented in the brain in neurons and in glial cells in various parts of the brain: in pontine-midbrain, cerebellum, thalamus, hypothalamus, basal ganglia, hippocampus, olfactory system and the temporal, orbital and cingulated cortices [10].

The important role of Vitamin D as a neuro-immunomodulator has been emphasized. It regulates the nerve growth factor and other neurotrophic factors [11, 12], thus affecting neuronal plasticity processes. It inhibits the synthesis of inducible nitric oxide synthase (iNOS) – an enzyme that is raised in brain-cells insults [11–13] – and causes the elevation of cholinesterase activity in the brain [14]. The upregulation of gamma glutamyltranspeptidase increases the amount of glutathione – the innate antioxidant protecting oligodendrocytes – and the integrity of the nerve conduction pathway [14].

Vitamin D diminishes the toxicity of reactive oxygen species (ROS) which appear in oxidative stress [15]. It is also active in β-amyloid clearance (one of the two main pathological elements which accumulate in Alzheimer's disease) [16].

It has long been known that Vitamin D is a preventive factor in experimental autoimmuno encephalomyelitis – an animal model of multiple sclerosis (SM) [17]. Vitamin D deficiency has also been associated with increased risk of developing SM in humans; however its role in disease prevention is not yet clear [18]. It has been suggested that a diminished Vitamin D level is also connected with other neurological diseases: Parkinson's disease [19], epilepsy [12], depression [20] and schizophrenia [21].

The connection of Vitamin D with dementia is strongly suggested because of its influence on numerous processes playing an important role in dementia development, such as cardiovascular disease and diabetes. These relations were summarized by Grant [22].

The role of Vitamin D in cardiovascular disease was examined in a prospective study of 1739 Framingham Offspring Study participants and showed an increased risk of cardiovascular disease in persons with various degrees of Vitamin D deficiency [23]. A case-control study of over 18,000 men aged 40–75 years, who were free of cardiovascular disease, followed up 10 years later, showed an increased risk of developing myocardial infarction or fatal coronary heart disease in those deficient in Vitamin D relative to those with a sufficient level [24]. It has also been observed that one of Vitamin D's actions is the blunting of the deleterious effect on endothelial cells of advanced glycatiom endproducts (AGE), which are formed in diabetes [25].

Alzheimer's disease shows many similarities in its pathogenesis with diabetes DM2. These were summarized by Li et al., 2015 [26]. In both pathological states insulin resistance and inflammation take place. In individuals with metabolic syndrome and particularly with diabetes DM2 (both are states with insulin resistance) Alzheimer's disease occurs more frequently as compared with persons free of disturbances in their carbohydrate metabolism. Teergarden, et al. showed that Vitamin D status as assessed by its serum levels is inversely associated with diabetes. Vitamin supplementation improved insulin sensitivity [27]. Vitamin D and calcium supplementation prevented diabetes type 2 development in persons with glucose intolerance [28]. Alzheimer's disease has been termed by some authors as Diabetes 3 – a form of insulin resistance concerning the brain.

Multiple studies concern Vitamin D's role in neurocognitive dysfunction [29].

The global prevalence of dementia was estimated in 2005 at 24.3 million people [30].

Alzheimer's (AD) is the most common cause of dementia in older people. The second most common type is dementia of vascular origin (VaD). Several symptoms occur in both types and some authors use the term ‘vascular cognitive impairment’ [31]. With age the skin's ability to synthesize Vitamin D decreases significantly [32]. What is more, in old age malnutrition is a frequent phenomenon. Therefore one can expect that low Vitamin D levels could be often observed in elderly persons, who are mostly at risk of developing dementia.

Some studies have not found an association of low vitamin D levels with impaired performance on various psychometric measures [33, 34]; however, most population studies have shown such an association [35].

The data of the Health Survey for England 2000 – a nationally representative population-based study of 1766 adults aged 65 years and over (12% of them cognitively impaired as shown by the abbreviated Mental Test Score) – suggested that low serum 25-hydroxyvitamun D was associated with increased odds of cognitive impairment [36].

A prospective study conducted in Italy between 1998 and 2006, with follow-up assessment every 3 years (the InCHIANTI population-based study concerning 858 adults 65 years old and older) showed substantial cognitive decline,