Vitamin D status in patients with nontraumatic transient loss of consciousness (literature review)

Abstract. The article presents an analysis of the recent scientific findings on vitamin D status in patients with different etiopathogenetic varieties of nontraumatic transient loss of consciousness. The results of recent researches suggest that vitamin D may play an indirect and, in some cases, direct role in the pathogenesis of nontraumatic transient loss of consciousness. Data on the cause-effect relationship between a low vitamin D status and syncope are mixed, controversial and ambiguous, which is largely due to the use of different doses of vitamin D, its initial concentration, duration of therapy, genetic differences in the vitamin D receptors, different age groups, physical parameters of the surveyed, medications, peculiarities of nutrition with special supplements, differences in physical activity, peculiarities of the climate and season, and others. Until now there is no convincing evidence of the benefits of using vitamin D in the treatment and prevention of syncope. Most studies are observational and relate mainly to adult populations. Therefore, randomized controlled studies focused on children may be a promising field of research.

Keywords: nontraumatic transient loss of consciousness; reflex syncope; orthostatic hypotension; cardiogenic syncope; epilepsy; psychogenic syncope; vitamin D; review

Introduction

Nowadays it is evident that Vitamin D plays an essential role in the regulation of Calcium (Ca) and Phosphorus (P) homeostasis as well as in the processes related to bone mineralization and bone mass accumulation. Besides the historically-recorded skeletal functions, it has lately been revealed that Vitamin D is directly or tangentially involved in 1250 genes’ regulation, thus performing the extra-skeletal functions [1]. For this reason, Vitamin D’s deficiency may influence not only the locomotor apparatus, but a potentially wide scope of acute and chronic conditions, namely in children. There are scientific proofs that Vitamin D’s deficiency is related to infectious diseases, bronchial asthma, atopic dermatitis, allergic conditions, diabetes mellitus Type 1, inflammatory bowel conditions, celiac disease, metabolic syndrome and obesity, autism, depression and many others [2-7].

Most scientists agree that Vitamin D supplementation has a positive effect on human health. However, there is no conclusive evidence about its deficiency’s promoting disorders. For this reason, a primary hypothesis of reverse causation is widely accepted and supported by a systemic meta-analysis and randomized controlled trials [8, 9]. Ongoing studies point out potential benefits and minimal risks of Vitamin D supplementation, maintaining optimal and safe 25-hydroxy Vitamin D concentration in those groups unable of synthesizing enough Vitamin D in their skins [10].

Despite an extensive evidence base of Vitamin D’s deficiency and insufficiency studies in connection to numerous children’s diseases, many aspects of this connection are left unclear and disputable. In the recent years, there are many reports on Vitamin D deficiency’s implication in children’s syncope pathogenesis [11-13]. In 2018, the European Society of Cardiology (ESC) published the clinical Guidelines for the diagnosis and management of syncope, in which all the nontraumatic transient losses of consciousness were classified according to four principal groups: syncope (reflex, orthostatic hypotension, cardiogenic, epileptic seizures, psychogenic (psychogenic pseudosyncope (PPS), psychogenic non-epileptic seizures (PNES) and some rare diseases.
The aim of the present study is to analyze the recent findings on Vitamin D status in patients with various etiopathogenetic varieties of nontraumatic transient losses of consciousness.

**Reflex vasovagal syncope**

Autonomic nervous system dysfunction affects Calcium turnover-participating genes' expression both before and after nervous cell differentiation, which gives rise to sympathetic and parasympathetic neurons. Autonomic dysfunction in children and adolescents has heterogenic clinical manifestations due to an imbalance of sympathetic and parasympathetic regulation. It has numerous symptoms, including headaches, dizziness with orthostatic intolerance (OI), accelerated heart rate, gastrointestinal dysfunctions, generalized muscle pain and a low tolerance to physical strain [15].

Vitamin D plays a pivotal role in autonomic homeostasis maintenance and may function as a central neuroactive substance. Activated 1,25-dihydroxyvitamin D is able to coordinate additional molecular mechanisms, namely informing about inflammation and biosynthesis of neuromediators in those sites of central nervous system that regulate cardiovascular activities. It’s worthy of mentioning that Calcitriol penetrates the blood-brain barrier (BBB) and binds itself to Vitamin D receptors located in the central nervous system. For instance, mesencephalon and fornix where a number of autonomic nervous neurons are located have a significantly high concentration of Vitamin D receptors, proving a non-Calcium-moderated role of Vitamin D in autonomic nervous system regulation [16].

Studies by Santillan et al. [17] demonstrate that β-adrenergic signal transduction in chicks' myocardial cells increases if the cells are put into the 1,25-dihydroxycholecalciferol medium. Their findings prove that the principal cardiovascular function may be partially attributed to Vitamin D, as arrhythmic signals are perceived not only by the central nervous system, but by the heart as well [17].

Postural orthostatic tachycardia is a prevalent form of autonomic deregulation characterized by an excessive tachycardia after a sudden body rising into an upright position. It may be associated with a pronounced fatigue, headache, accelerated heart rate, sleep disorder, nausea, dizziness and fainting. A study shows that patients with postural orthostatic tachycardia have a 25-hydroxy Vitamin D deficiency in 51% of cases, and insufficiency — in 56% [18].

A clinical case of an adult patient diagnosed with postural orthostatic tachycardia according to the tilt test reveals 1,25-dihydroxycholecalciferol’s deficiency. A further 5-month-long Calcitriol therapy resulted in an improved orthostatic intolerance and heart rate normalization [19]. Studies of serum Vitamin D’s connection with myocardial function of 84 healthy individuals show a weak systolic and diastolic myocardial dysfunction in Saudi Arabian adolescents with a low Vitamin D’s concentration [20].

**Orthostatic hypotension syncope**

A low Vitamin D’s concentration is associated with an increased risk of orthostatic hypotension. Vitamin D’s association with orthostatic hypotension was proved by a meta-analysis of 5 cross-over studies involving 3646 subjects (1270 having hypovitaminosis and 2376 — a normal Vitamin D’s concentration in blood serum). In a group of patients with Vitamin D hypovitaminosis orthostatic hypotension was more prevalent than in the healthy population. Furthermore, orthostatic hypotension patients had a significantly lower Vitamin D level in blood serum [21].

In another study, 329 elderly women had a deficient 25-hydroxy Vitamin D associated with orthostatic hypotension due to a decreased diastolic blood pressure with a sudden body’s rising into an upright position [22]. Furthermore, in a randomized controlled trial it was proved that a continuous 12-month taking high doses of Vitamin D does not affect orthostatic hypotension in elderly patients with an isolated systolic hypertension [23].

There are only a few reports on a deficient 25-hydroxy Vitamin D prevalence in children and adolescents with syncope and orthostatic hypotension in the contemporary medical reference sources. In one such study, a group of adolescents with orthostatic intolerance and fainting had a depreciated autonomic function, and excessive catecholamine and vasopressin release during the tilt test [24].

At present, syncope’s potential mechanisms of development along with orthostatic failure are not yet entirely clear. Vitamin D may play an intermediary role in an orthostatic hypotension’s genesis. This hypothesis is supported by Vitamin D’s influence at the systolic and diastolic pressure level [25, 26]. Furthermore, Vitamin D receptors are located in the vascular smooth muscles, endothelial and cardiac tissues, proving that Vitamin D may influence vasomotor and cardiac response while orthostasis [27].

**Cardiogenic causes of syncopal conditions**

Based on the recent experimental and clinical date, the modern medicine points out several mechanisms explaining a possible association between the Vitamin D deficiency and cardiovascular conditions. The model mice lacking Vitamin D receptors had an increased ventricle mass, higher values of atrial natriuretic peptides, disorder of metalloproteinase and fibroblast homeostasis, resulting in ventricle dilatation and disorder of electromechanical connections in cardiomyocytes [28]. O’Connell et al. demonstrated that Calcitriol increases cardiomyocyte protein levels and cellular sizes and assumed that it induces their hypertrophy. S-Phase cell cycle arrest is a mechanism through which 1,25-dihy-
droxycholecalciferol regulates cardiomyocyte proliferation [29]. One of the cardioprotecting Vitamin D effects is a reduced myocardial hypertrophy mediator expression, namely atrial natriuretic peptide and growth factors stimulating cellular proliferation [30]. A significant discrepancy among Vitamin D level, interventricular septum thickness and left ventricle mass index was revealed after correctional Vitamin D therapy calibrated according to the age, blood pressure rate and serum 25-hydroxy Vitamin D level in a massive retrospective study informing about Vitamin D’s role in a ventricular remodeling [31]. Calcium also takes part in a cellular proliferation and activates protease, inducing myocardial hypertrophy. Calcium levels rise after Vitamin D taking, leading, on its own, to myocardial hypertrophy, cardiomyocyte apoptosis and heart arrhythmia [32]. Recent findings showing Vitamin D’s influence on the left ventricle hypertrophy are not conclusive and representative of its role from the favorable to adverse effect spectrum [33].

But a few studies report on a connection between Vitamin D deficiency and atrial fibrillation [34, 35]. Serum 25-hydroxy Vitamin D level correlated with left atrial diameter, C-reactive protein and pulmonary systolic pressure, to a significant extent being associated with atrial fibrillation in patients with a nonvalvular persistent atrial fibrillation [35].

Direct electromechanical Vitamin D effects on a left atrium were recorded by Hanafy et al., allowing them to prevent and treat atrial fibrillation [36]. However, Rienstra et al., having examined 2930 Framingham Heart study recruits during a 9.9-year period did not find any connection between Vitamin D status and atrial fibrillations. The researchers claim that Vitamin D deficiency does not promote atrial fibrillations [37]. In a recent study of 328 adults, it was shown that Vitamin D prevents post-operative atrial fibrillations only in the patients with a nonvalvular persistent atrial fibrillation [38].

There is a range of studies focused on the possible connection between a low Vitamin D deficiency’s side effects on the epilepsy’s etiopathogenesis [44]. One of the possibilities is a direct Vitamin D’s influence on the brain, resulting in the reduced neuronal sensitivity and seizure frequency. Vitamin D may affect the seizures by maintaining the neuromediator genes’ expression as they take part in the neurotransmission. Furthermore, Vitamin D, being a neurosteroidal agent, may directly interact with GABAx receptors [44].

Starting from 1960s, numerous data prove that anticonvulsants have a negative effect on bone turnover and lead to an increased risk of fractures. This observation incited many studies of anticonvulsants’ effect and Vitamin D metabolism. Cohort studies demonstrate that anticonvulsant enzyme inducer reduces the level of 25-hydroxy Vitamin D compared with non-enzyme inducers, provoking Vitamin D deficiency in epileptic patients [46-48]. Although there are inconsistencies as to how the anticonvulsants provoke Vitamin D deficiency, they may be attributed to study design discrepancies, geographical location or nutritional habits of the studied groups [49].

Vitamin D deficiency’s side effects on the epilepsy’s etiopathogenesis affect Vitamin D metabolism [42]. This assumption proves the importance of further studies in this field.

Epileptic seizures

In children suffering from epilepsy, reduced blood levels of Vitamin D are associated with a tendency of increasing frequency and duration of seizures. Large-scale epidemiological studies report significant seasonal variations in seizure frequency, with the lowest rate observed in the summer and the highest in winter. It is attributed to a low level of 25-hydroxy Vitamin D at the same period [43].

There are 2 pilot studies of Vitamin D’s efficacy against epilepsy of patients with Vitamin D deficiency. This therapy reduced the 30% reduction in seizure frequency among the main group as compared to the controls [50, 51]. At present, there is only one randomized controlled trial of various Vitamin D doses’ efficacy against the children’s epilepsy. It involved 78 children aged 10-18 years on a long-term anticonvulsant therapy. Patients received Vitamin D3 in low (400 IUs / day) or high (2000 IUs / day) doses for 1 year. The study’s findings show the bone mineral density improved irrespective of the initial Vitamin D level, and its mean annual therapeutic dose. However, they did not inform about this therapy’s efficacy against the seizure frequency [52].

Despite the few findings of the studies recommending global screening and Vitamin D therapy to the patients suffering from its deficiency or insufficiency, there are enough references supporting Vitamin D supplementation for children with epilepsy [53]. According to these, guidelines on the necessity of Vitamin D and Calcium
supplementation for every epileptic child treated with anticonvulsants for 2 years or longer [54, 55].

The international medical literature does not report any studies of Vitamin D status in patients with psychogenic pseudosyncope and psychogenic non-epileptic seizures. Taking into account the recent findings on Vitamin D deficiency and its association with mental diseases [56], this field is very promising and undoubtedly opening new vistas of potential effects on human health.

In conclusion, the recent studies allow us to claim that Vitamin D may have a tangential, or in some cases, direct influence on the nontraumatic transient losses of consciousness and their pathogenesis. The data on the cause-effect association between the Vitamin D status and syncope conditions are mixed, inconclusive and contradictory, mainly due to various doses used, its initial concentration, therapy’s duration, genetic differences of Vitamin D receptors, age, physical parameters, medication, nutritional habits and supplementation, physical activity, climatic and seasonal differences. At present, there are no strong arguments in favor of Vitamin D as a means of prevention and treatment of syncope. Most studies are only observational and involve, primarily, adult population groups. In this light, we consider randomized controlled studies focused on children especially promising.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

**References**


Вітамін-D-статус у пацієнтів із транзиторними втратами свідомості нетравматичного генезу (огляд літератури)

Резюме. У статті подано аналіз новітніх наукових досягнень із вивчення проблематики вітамін-D-статусу в пацієнтів із різними етіопатогенетичними варіантами транзиторних втрат свідомості нетравматичного генезу. Результати останніх наукових досліджень дають змогу припустити, що вітамін D може сприяти опосередкованому, а в деяких випадках і прямому дію в патогенезі транзиторних втрат свідомості. Дані щодо причинно-наслідкового зв'язку між низьким статусом вітаміну D та вибірковими показниками рецептора вітаміну D, різним віком, особливостями харчування засвідчують ознаки динамічного характеру.

Ключові слова: нетравматичні транзиторні втрати свідомості; рефлекторні синкопе; ортостатична гіпотензія; кардіогенні синкопе; епілепсія; психогенні синкопе; вітамін D; огляд літератури.