With an advancing age, the humans are facing physiological alterations of organs and systems, and their disease risks are rising. The elderly and old ages are critical for the development of osteoporosis and occurrence of low-energy osteoporotic fractures (associated with falls from one’s own height). Among the latter, fractures of proximal hip are considered the most grievous ones. Furthermore, the life quality deteriorates due to the vertebral osteoporotic fractures, resulting in the back pain and reduced mobility, also very likely to a severe dysmobility. The vitamin D deficiency is considered a compound risk factor, affecting both the bone tissue and falls risk as the key fracture predictors. As such, vitamin D has a pleiotropic function, reflected in the skeletal and extraskeletal manifestations [1].

Vitamin D is a unique hormone; it is required to maintain various systems of the human body, including the skeletal and muscle health. Its deficiency is associated with numerous conditions, namely obesity, arterial hypertension and other cardiovascular diseases, diabetes mellitus and dementia [2]. Underscored by the muscle weakness, the sarcopenia develops, along with the progressive cognitive disorders, promoting an increased frequency of falls.

Among other falls risk factors, our review features the vitamin D deficiency in the elderly people and its influence on the falls frequency.

The search is made within the reference sources of Cochrane Reviews, PubMed, Google and Web of Science, including randomized controlled trials and prospective study results, clinical recommendations, based on the following search words: falls, vitamin D, deficiency, supplementation, muscles, cognitive disorders.

**Vitamin D**

Most vitamin D amount – 90 % - is obtained by insulation and only 10 % by food [1]. The vitamin’s bio-
Falls and vitamin D

A typical ageing-associated syndrome is the frequent falls syndrome, attributed to the extant diseases, medication history, muscle weakness, cognitive impairments etc. The previous studies confirmed a significant association between the low vitamin D level and falls in the elderly subjects [6, 7, 8]. There are also data confirming a further increase of subsequent falls and decreased physical capacity related to the vitamin D deficiency (vitamin D’s level under 25 nmol/l) [9].

There is a discussion going on as to whether it is possible to reduce the falls risk by the vitamin D supplementation. Based on the data of conducted metaanalysis of the randomized clinical trials (26 trials, 45,782 participants, most of them elderly women), the authors concluded that the vitamin D reduces the falls risk in a statistically significant manner (odds ratio (OR) of one fall — 0.86; 95% confidence interval (CI): 0.77–0.96); however, this effect did not depend on its dose [10]. Nevertheless, the reduction of falls risk was most pronounced when there was an initial vitamin D deficiency and a parallel elementary calcium intake of 500-1,200 mg daily, supplementing vitamin D. The importance of this combination may be explained by the fact that, with no vitamin D involved, only 10–15% calcium and up to 60% phosphorus are absorbed, while with vitamin D present, the calcium’s intestinal absorption grows to 30–40% and the phosphorus’ intestinal absorption — to 80% [11].

In a randomized controlled blinded multicenter study, 625 participants (their mean age being 83.4 years) with restricted physical capacities residing at the nursery homes (vitamin D level - 25 – 90 nmol/l) for 2 years received calcium supplements (600 mg daily) and vitamin D supplements (initially 10,000 IU a week, then 1,000 IU daily) [12]. The control group was receiving only calcium carbonate. The group, receiving both calcium and vitamin D, had a lower rate of falls, even if the subjects did not suffer from the initial vitamin D deficiency.

The second study confirmed that calcium (1,200 mg daily) and vitamin D (800 IU daily) supplementation after 2 weeks led to a 2-fold reduction in falls rate, compared to only calcium supplementation [13].

There is a double-blind study involving 242 subjects (their mean age - 77 ± 4 years, with a low level of 25(OH) D in blood serum (78 nmol/l) [14]. During 12 months, the subjects received 1,000 mg calcium or 1,000 mg calcium in combination with 800 IU vitamin D daily. For the next 8 months, there was no treatment performed; however, the study remained blinded. Compared to a calcium monotherapy group, in a combination group after 12 months the number of subjects who experienced falls reduced by 27% (odds ratio (OR) = 0.73; CI = 0.54-0.96), while after 20 months — by 39% (OR = 0.61; CI = 0.34-0.76). Along with this finding, the authors revealed the increase of quadriceps strength by 8%.

Another randomized population open-label trial, OSTPRE-FPS, lasted for 3 years; its participants (n = 1,566) received 800 IU vitamin D$_3$ + 1000 mg calcium carbonate daily, while the control group (n = 1573) did not receive any medications or placebo. There was no difference observed in falls frequency; however, in the main group there was a reduction of multiple falls rate, the ones requiring healthcare provision (odds ratio (OR) — 0.72; 95% CI: 0.53–0.97; p = 0.03) [15]. A further analysis of the subgroup of randomly assigned subjects (593 individuals) on medication, with an additional 25(OH)D evaluation, revealed a reduction in falls frequency by 30% (OR — 0.70; 95% CI: 0.50–0.97;
The study revealed that by adding vitamin D one may reduce the falls risk, especially in those patients suffering from its deficiency.

In a prospective cohort study recruiting women (mean age – 83.7 years), a 20 % reduction in falls risk was recorded, along with a 2-fold increase in vitamin D concentration in the blood serum, compared to the initial values (< 25 nmol/l), during 5 months of treatment [6]. The authors consider a low vitamin D level to be an independent falls predictor.

In 2015, there was a Cochrane review published, where, based on the analysis of 14 clinical trials enrolling 28,135 subjects residing with their families, the reduction in falls frequency and falls risk was not registered, though vitamin D supplementation was provided. However, in a group of patients (260 subjects, 2 trials) with a low vitamin D level, the falls frequency and risk decreased after a similar vitamin D supplementation (OR 0.57, 95% CI: 0.37 – 0.89) [16]. Similar results were recorded after analysis of 4 trials involving 804 subjects (OR 0.70, 95% CI: 0.56 – 0.87).

In 2018, the Cochrane review analyzed the data of nursery home residents and in-house patients [17]. Based on 4 trials (4,512 subjects) of the vitamin D deficiency’s correction, there was a recorded decrease in falls frequency (OR 0.72, 95% CI: 0.55 – 0.95); however, the falls risk remained intact (OR 0.92, 95% CI: 0.76-1.12). It was concluded that vitamin D supplementation is especially effective in case of frail subjects, and patients with low vitamin D levels [7].

The opinions as to the beneficial nature of vitamin D monotherapy are changing. A 5-month study of treated subjects showed that in the placebo group the share of people who experienced falls was 44 %, in the group of daily vitamin D dose being 200 IU – 58 %, in the group of daily vitamin D dose being 400 or 600 IU – 60 %, and in the group of daily vitamin D dose being 800 IU – 20 % [18]. Compared to the placebo group, only the group receiving a daily vitamin D dose of 800 IU revealed a 72 %-reduction of falls (OR 0.28; 95% CI: 0.11 – 0.75).

Based on the findings of randomized controlled studies of vitamin D supplementation’s effect on falls frequency, it was confirmed that a combination of vitamin D and calcium, by contrast to only calcium or placebo, reduced a falls risk of nursery home residents [19].

There are also studies with no results confirming a positive vitamin D effect on falls risk. A 26-62-month vitamin D supplementation in the subjects over 70 years did not reflect on the falls risk [20]. However, this same study enrolled patients who had recently suffered a low-energy fracture, indicating an initially higher falls level and extant dysmobility.

One of the major randomized, double-blind, placebo-controlled studies, ViDA, evaluating the effect of vitamin D supplementation on falls and fractures, was held in New Zealand, enrolling healthy volunteers (5108 subjects) aged 50-84 years [21]. Every month during 2.5-5.2 years, they received an initial oral cholecalciferol dose of 200 000 IU (5.0 mg) with a further monthly introduction of 100 000 IU (2.5 mg) of cholecalciferol or placebo in the form of injection. The mean serum 25(OH)D concentration at the outset was 63 nmol/l; however, 30 % volunteers had a 25(OH)D concentration of under 50 nmol/l. During the study, the falls were recorded in 52 % subjects from the vitamin D group and in 53 % – from placebo group. Thus, the high vitamin D doses did not prevent falls or fractures in the healthy adult subjects. Authors consider further trials to be a necessity, in order to determine the effects of a daily vitamin D and calcium combination.

There are many possible explanations for how vitamin D affects the falls risk.

**Vitamin D affecting the muscle tissue**

Functional capacity of muscles is an important factor of mobility, with its age-related decrease being one of the reasons explaining the growing falls frequency.

Vitamin D is equally important for the muscles’ adequate functioning. Muscle fibers are known to have VDR, present in the myoblasts and skeletal muscles of a grown human. Furthermore, vitamin D receptors express the stromal cells of the muscle tissue, suggesting vitamin D’s capacity for muscle growth control and possibly their regeneration [22]. Vitamin D’s biological activity after the VDR-binding manifests itself in the increased muscle fiber size, reduced muscle loss and increased functional activity [23, 24, 25]. There are also genotypic VDR variations, affecting the muscle function and strength [26].

Vitamin D’s role in metabolism and muscle function regulation was confirmed by the study of 116 volunteers (79 females, 37 males, mean age 20-74 years) based on the detection of 24 (out of 96 studied) genes in charge of m-RNA expression under its influence. However, only 4 genes had their activity correlating with the serum concentrations of the active 1,25(OH)2D3 form, all the other has it correlating with 25(OH)D3 concentration [27]. The scope of 25(OH)D3-produced effects is quite extensive: transmitting signals, regulating the protein biosynthesis, influence on the functional mitochondrial activity, muscle contraction etc. Nevertheless, while interpreting their findings, the authors consider 25(OH)D3 is likely to influence the muscle function indirectly, via adipose tissue.

Another study of the elderly people’s skeletal muscles produced the opposite results, i.e. that a long-term vitamin D use does not affect the skeletal muscle expression. As a result, the authors suggest that the skeletal muscles may not be a direct vitamin D target [28]. According to
the authors, this fact may be associated with a gradual VDR decline with an advancing age, under the influence of sex and comorbidity; however, the body’s sensitivity to calcitriol is retained, and leads to a reduced muscle fiber mass and alteration of muscle function [22].

Besides the direct muscle action (via vitamin D receptors), calcitriol modulates the muscle function tangentially – by affecting the calcium homeostasis and increasing its intracellular concentration via gene regulation and signal pathways [29]. Because of the muscles’ ability to contract and its dependence on the calcium ions present, under the calcitriol deficiency the muscle function decreases.

All in all, the clinical manifestations of vitamin D deficiency (< 25 nmol/l) are associated with myopathy, muscle weakness (mostly of proximal muscle groups) and pain, reflected in the gait disorders, balance dysfunctions and is a falls risk factor, increasing the fracture risk in turn [11, 26, 30, 31, 32, 33, 34, 35]. Other authors reported that people having the vitamin D level at less than 10 nmol/l also suffer from low muscle functionality [36].

The key muscle strength regulator is vitamin D-PTH balance. The secondary hyperparathyroidism (over 4.0 pmol/l) is associated with sarcopenia as a manifestation of a long-term vitamin D deficiency [37]. The involutive changes of muscle tissue also result in sarcopenia. Sarcopenia is a condition characterized by a progressive and generalized muscle strength, mass and its faction’s loss. At the present moment, sarcopenia is included on the ICD-10 list of diseases [38]. The age-related decrease of muscle mass and sarcopenia’s progress is not only caused by the changes in the number of muscle fibers: both slow-twitch (red, type I) and fast-twitch (white, type II), but also by a predominant loss of fast-twitch fibers. The remaining ones demonstrate the atrophy, disorders of cross striation, progressive denervation [39]. There is also a registered expansion of adipose and connective tissue between the muscle fibers, another decisive factor for sarcopenia [40].

Despite the positive vitamin D’s influence on the muscle structure and function, results of clinical studies are debatable. Based on the recent metaanalyses of randomized controlled trials studying the effects of vitamin D, there is a small, though statistically significant, improvement of muscle strength, function and reduction in falls among the elderly people with a low 25(OH)D concentration (under 30 nmol/l or 50 nmol/l) in the blood serum [10, 41, 42]. Replenishing vitamin D deficiency, according to the authors, is more effective in people aged 65 years and older compared with young subjects [41].

In the Korean National Health and Nutrition Examination Survey, cross-sectional study held during 2009-2010, a correlation between sarcopenia’s progress and vitamin D status was studied in relation to the subjects’ sex [43]. 2,258 men and 3,005 women aged over 50 years were examined. Sarcopenia was confirmed if the appendicular lean mass index was under 2 standard deviations. As a result, the authors confirmed only the correlation existing between sarcopenia and vitamin D level in women; however, there was no such confirmed correlation for men. Nevertheless, the women’s risk of developing sarcopenia increased 1.46 times if the vitamin D level was less than 10 ng/ml.

Adding calcitriol (200 mcg during 6 months) improved appendicular muscle mass, functional stamina, gait speed (by the 4-m test) and resulted in a reduced average risk of falls in postmenopausal women, diagnosed with osteoporosis or vitamin D deficiency/insufficiency (25(OH)D < 75 nmol/l) [44]. It was also demonstrated that the vitamin D use in a daily dose of 700—800 IU increased muscle strength and reduced the falls risk; however, according to the authors, the optimal vitamin D dose is yet unclear [45].

The efficacy of calcium and vitamin D use along with their influence on the skeletal muscle mass and frequency of falls in the subjects over 70 years were also studied. At the moment of inclusion, the level of vitamin D was under 78 nmol/l. After 12 months of treatment, a significant increase of muscle strength and function was detected in the principal group compared with the placebo group, and the falls risk decreased by 27 % after 12 months of treatment, by 39 % after 20 months of treatment [46].

In the study published in 2014, a daily vitamin D’s dose of 800 IU was used to treat postmenopausal women with osteoporosis and/or vitamin D deficiency. This dose also promoted a considerable improvement of muscle strength, function and a reduced falls risk [47].

Furthermore, the recent multi-center randomized controlled study of elderly people with sarcopenia demonstrated a significant increase of appendicular muscle mass and physical stamina after treatment with oral calcium and vitamin D supplements [31].

While analyzing the reviews of prospective studies, the authors are overall pointing out a wide discrepancy of subjects’ ages, not every study presents initial vitamin D blood serum concentration, not every one reports indices describing muscle strength; however, the vitamin D’s role in muscle health maintenance and reduction of falls risk is not to be denied [5, 25]. This combination is most effective in case of osteoporosis and sarcopenia, as reduced calcium, along with secondary hyperparathyroidism and advancing hypocalcemia, leads to muscle spasms and falls risk increase.

Nevertheless, while estimating the direct and tangential effects of 1,25(OH)2D3 and 25(OH)D3 on the muscle function and gene expression, the researchers claim that in order to outline the contributive factor of
vitamin D’s deficiency or supplementation in the occurring falls, one should take into account other factors. Furthermore, the authors point out the future trends of research requiring a full analysis of vitamin D metabolites, comprising the so-called “metabolon”, which affects the muscle tissue [27].

In such a way, the structural and functional muscle disorders increases the falls risk, while introducing calcium and vitamin D into the treatment regimen promotes its reduction; however, the findings are contentious [48].

There is another vitamin D’s possible way of influencing falls — and that is via nervous system.

**Vitamin D and neural tissue**

The 21st century studies expanded the scope of humanity’s knowledge on vitamin D and its formerly unclear role in the cerebral functioning and development. The research into vitamin D’s association with neural diseases was prompted by the VDR’s detection inside neurons and glial cells of multiple cerebral regions [49]. Vitamin D receptors are present in the parietal, temporal lobe cortex, cingulate gyrus, as well as in the thalamus and other cognition-involved cerebral regions [3]. Vitamin D’s active metabolites are also found in the spinal liquid. Human brain is especially trained to regulate its active metabolites. Bonekey Rep. 2014;3:479. https://doi.org/10.1038/bonekey.2013.213.

Furthermore, the authors point out the future trends of vitamin D’s active metabolites and convert it into the inactive form [50]. Furthermore, the genes, coding enzymes in Vitamin D’s active metabolites are also found in the spinal liquid. Human brain is especially trained to regulate its active metabolites. Bonekey Rep. 2014;3:479. https://doi.org/10.1038/bonekey.2013.213.

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Дефіцит вітаміну D як фактор ризику падіння в осіб літнього віку

Резюме. Серед людей літнього і старчого віку падіння є серйозною проблемою, пов’язаною з погіршенням якості життя, переломами та підвищеною смертністю. На сьогодні на основі даних наукової літератури чітко простежується зв’язок між дефіцитом вітаміну D в сироватці крові та слабкістю м’язів, когнітивними порушеннями, тобто факторами, що призводять до погіршення рівноваги і підвищують ризик падіння. В огляді проаналізовано особливості впливу вітаміну D на структуру та функцію м’язів, а також оцінено вплив прийому кальцію та вітаміну D на сироватку крові та супроводжувачі падіння у осіб літнього віку. На основі даних літературних досліджень і результатів статистичного аналізу виявлено статистично значиму зв’язок між дефіцитом вітаміну D та падіннями у літніх пацієнтів з когнітивними порушеннями. Зроблені висновки щодо того, що вітамін D має потенційну можливість підвищити рівень стабільності та знизити ризик падіння у осіб літнього віку.

Ключові слова: падіння; вітамін D; дефіцит; підтримуючі дози; м’язи; когнітивні порушення

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Дефіцит вітаміну D як фактор ризику падіння у лиц пожилого возраста

Резюме. Среди лиц пожилого и старческого возраста падения являются серьезной проблемой, связанной с ухудшением качества жизни, переломами и повышенной смертностью. На сегодняшний день на основе данных научной литературы четко прослеживается связь между дефицитом витамина D в сыворотке крови и слабостью мышц, когнитивными нарушениями, то есть факторами, которые приводят к ухудшению равновесия и повышают риск падения. В обзоре проанализированы особенности влияния витамина D на структуру и функцию мышц, а также оценено влияние приема кальция и витамина D на силу мышц и снижение риска падений у лиц пожилого возраста. На основе данных литературы доказана роль витамина D в поддержании нормальной функции головного мозга, оценена частота дефицита витамина D у лиц пожилого возраста с когнитивными нарушениями. Сделан вывод, что данные о терапевтической эффективности дополниительного приема витамина D при когнитивных нарушениях являются неоднозначными. Отмечены вопросы, требующие решения, прежде всего установление граничных значений витамина D в сыворотке крови, необходимость дополнительных исследований для определения оптимальных методов лечения, включая дозу витамина D и продолжительность терапии. Наиболее дискуссионным вопросом является использование высоких доз витамина D. Большинство исследователей на основе анализа считают нерациональным использование повышенных доз витамина D в профилактике падений и в целом отмечают их негативное влияние на здоровье человека. Имеется доказательная база, что наиболее эффективно использование витамина D в сочетании с кальцием. Однако, несмотря на растущее количество научных исследований в этой области, окончательно не установлены.

Ключевые слова: падения; витамин D; дефицит; поддерживающие дозы; мышцы; когнитивные нарушения