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Diagnosis, prevention and treatment of vitamin D deficiency in adults:

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Abstract. ***Background.*** Vitamin D deficiency (VDD) is widespread in the world; its proportion varies considerably in different populations and depends on many causes. Up to now, there were no National recommendations for the diagnosis, prevention, and treatment of VDD in adults in Ukraine. Their creation became the ***purpose*** of this work. ***Methodology.*** Consensus was created using the Delphi method, voting was conducted using the SurveyMonkey® platform. After approval of the composition of the Consensus Group, agreement on the order of formation and structure of the Consensus, creation and correction of the main statements, and two voting rounds, the main Consensus statements were formed and were successfully voted on. The 15 authors of the article are 15 experts who participated in the voting. The final 14 Consensus statements are presented in this article. Each statement is preceded by a justification based on high-quality evidence available in the current literature. ***Results.*** Despite the reduction of VDD in the Ukrainian population in recent years, experts have recommended increasing the awareness of the medical community and the Ukrainian population about the problem and ways to overcome it, with a screening of the total serum level of 25-hydroxyvitamin D (25(OH)D) in subjects from the groups of risk to achieve the target concentration of 30–50 ng/ml (75–125 nmol/l). To ensure it, we recommend the individual selection of a prophylactic dose of vitamin D (800–2000 IU/d for young healthy persons and 3000–5000 IU/d for patients with diseases and conditions that affect the metabolism of vitamin D). For the treatment of VDD, we recommend short-term intake of higher doses (4000–10,000 IU/d) of vitamin D with control of the 25(OH)D level after 4–12 weeks of treatment and subsequent use of maintenance doses. Also, we recommend the determination of serum 25(OH)D level before the initiation of antiosteoporotic therapy in patients with osteoporosis and its complications to prevent its ineffectiveness and increase the safety profile.

Keywords: vitamin D; consensus; recommendations; diagnosis of vitamin D deficiency, prevention of vitamin D deficiency; treatment of vitamin D deficiency

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Introduction

Vitamin D is a group of biologically active fat-soluble compounds (more than 6 vitamers and 50 metabolites), which are formed in the skin under the action of ultraviolet rays of the B range or enter with food (Appendices 1–3) [1, 2]. The main vitamers of vitamin D are the following: D_1 (ergocalciferol and lumisterol in a ratio of 1 : 1), D_2 (ergocalciferol or ergosterol), D_3 (cholecalciferol), D_4 (2,2-dihydroergocalciferol), D_5 (sitocalciferol or 7-dehydrositosterol) and D_6 (sigma-calciferol). Vitamins D_2 and D_3 show the highest biological activity in the human body. The hormonally active form of vitamin D is 1α,25-dihydroxyvitamin D ($1\alpha,25(OH)_2D$), formed from vitamin D vitamers through 25-hydroxyvitamin D (25(OH)D), which includes $25(OH)D_2$ and $25(OH)D_3$ and is measured in blood serum as total 25(OH)D to assess the body's supply of vitamin D [3–6].

Vitamin D was discovered more than 100 years ago [7] and today its crucial importance for many biological processes has been confirmed, in particular, maintenance of calcium-phosphorus homeostasis, bone mineralization, cell proliferation and differentiation in various organs and systems [8–11]. Numerous genomic and non-genomic mechanisms of the influence of vitamin D in the human body have been established [12–14], which are responsible for the implementation of its skeletal and extraskeletal actions [10, 11], and vitamin D receptors (VDR) are found in the nuclei and cell membranes of almost all human organs and tissues.

In 2011, the Endocrine Society suggested considering vitamin D deficiency (VDD) in children and adults as a clinical syndrome caused by a low level of 25(OH)D in blood serum [15]. For today, in accordance with the ICD-10, VDD is classified under headings E55 (VDD. Excludes: osteomalacia in adults (M83.-), osteoporosis (M80-M81), consequences of rickets (E64.3)) and E55.9 (VDD, unspecified. Avitaminosis D).

The results of numerous studies indicated a high prevalence of VDD in the world [16–21], and its frequency varies depending on the country of residence, age and gender of the subjects, season, when the measurement of 25(OH)D was done, presence and type of concomitant pathologies. The recent data [17] indicated that in general in the world the VDD is about 37 %, the lower level is in the USA (18 %), in contrast to the countries of Europe (40 %) and Africa (34 %). It is one of the largest in Iran and Jordan (90 %), the smallest one in Ghana and the Seychelles (< 7 %). VDD occurs in about 20 % of the population of Northern Europe, while in Western, Southern and Eastern Europe it is 30–60 % [18].

Today, international [19, 22, 23] and national recommendations [24–27], published during recent years, testify to the great relevance of this problem, although the approaches to the diagnosis, prevention and treatment of VDD are different in the world. Until now, there were no national recommendations for overcoming VDD in Ukraine, which determines the necessity of their creation.

Consensus development methodology

For development of this Consensus, an expert group of 15 leading Ukrainian scientists was created, who are various specialists (biologists, biochemists, endocrinologists, rheumatologists, orthopedic surgeons, nutritionists, gynecologists, and allergologist) and experts with an extensive experience in studying the problem of vitamin D and related topics. The first, sixth, and eleventh authors of this article were members of the special Working Group created to select and coordinate the work of the experts.

The process of reaching Consensus was carried out using the Delphi method, which is widely used today to create clinical guidelines [28–30]. The voting was conducted using the SurveyMonkey® platform (https://surveymonkey.com) using a 9-point gradation of agreement with the statements on the basis of which the voting was performed (1 — strongly disagree, 3 — disagree, 5 — neutral attitude, 7 — agree, and 9 — completely agree).

Before the beginning of the voting, it was agreed with the experts that Consensus would be reached if > 75 % of the participants agreed with a statements on a voting scale of 7 points or higher. In case of impossibility of reaching a Consensus regarding a specific issue, voting will be repeated after discussion of the issue by experts and its modification.

After approval of the composition of the Consensus group, agreement on the order of formation and structure of the Consensus document, based on the analysis of modern literary sources with a high level of evidence, members of Working Group created the statements regarding the epidemiology of VDD, its screening, prevention, treatment and monitoring, for which all experts had been voted during January-February 2023.

At the beginning of February 2023, members of the Working Group presented to other experts in online format the results of the first round of voting, formulation of statements and comments. After discussion and making changes and comments from all experts, a second Delphi vote was held at the end of February 2023, as the result of which 14 consensus statements had been formulated that were successfully voted on.

The 15 authors of this article are 15 experts who participated in both rounds of Delphi voting. Each round of voting was conducted on each of the 14 proposed statements. The final Consensus statements are presented in the text of the article and Appendix 4. Each statement is preceded by a justification based on currently available evidence.

Epidemiology of vitamin D deficiency in adults

During last decades, a number of epidemiological studies of the status of vitamin D have been conducted in Ukraine [31–36]. The first epidemiological study (2011) [31] involving 1,575 persons at the age from 20 up to 89 years old from different regions of the country revealed a significant proportion (81.8 %) of VDD in the Ukrainian population. A sufficient level of 25(OH)D in the blood was found only in 4.6 % of the subjects, vitamin D insufficiency (VDI) in 13.6 %. The average level of 25(OH)D in the blood serum of the participants of the study was 34.49 nmol/l (13.80 ng/ml).

Another epidemiological study involving 3,460 persons at the age from 1 up to 92 years old with musculoskeletal disorders [32], published in 2017, revealed higher rates of vitamin D supply compared to the previous study (mean 25(OH)D

level was 26.2 ng/ml) with a decrease in the proportion of VDD (37.3 %) and VDI (30.6 %). One more epidemiological study on the study of the status of vitamin D with the participation of 8,426 adults at the age from 20 up to 99 years old, examined in 2016–2022 [35], demonstrated an increase in the level of 25(OH)D (30.9 ng/ml) in blood serum compared to the results of two previous studies. In addition, the proportion of VDI (27.4 %) and VDD (19.9 %) was smaller.

Regional Ukrainian studies conducted in Bukovina and Prykarpattia [33] and Transcarpathia [34] also confirmed a significant share of VDD. Thus, the analysis of the level of 25(OH)D in 482 subjects at the age18–88 years old revealed a normal status of vitamin D in only 7.7 %, in other cases VDD (46.9 %) or VDI (45.4 %) was observed [33]. The average level of 25(OH)D was 21.6 ng/ml. In another regional study [34] of 1823 children and adults, the average level of 25(OH)D was 22.3 ng/ml in women and 25.8 ng/ml in men.

Analysis of vitamin D status in the Ukrainian population during the past five years revealed significantly higher levels of 25(OH)D during the 2020–2021 COVID-19 pandemic (2020: 36.8 ng/ml; 2021: 35.0 ng/ml) both in comparison with the indices of previously published studies and with the level of 25(OH)D in 2018 (30.2 ng/ml) [35]. The annual average level of 25(OH)D in 2022 (36.0 ng/ml) [36] was not significantly different from the values of the previous two years, but there was a significant decrease in the number of 25(OH)D tests, which was apparently related to the russian invasion to Ukraine and a number of limitations both in the diagnosis of VDD and in its proper supplementation.

All studies conducted in Ukraine have demonstrated the dependence of serum 25(OH)D indices on age, with the lowest indices in older age groups. In addition, seasonal variations in 25(OH)D levels were found, with the highest values in late summer and early autumn and the lowest values in late winter and early spring.

Statement 1 [Consensus voting scale (level of agreement): 9 (100 %)]:

Deficiency and insufficiency of vitamin D in the adult population of Ukraine is widespread, that's why it is necessary to increase the awareness of the public and medical personnel about its skeletal and extraskeletal effects, risk groups that require screening and monitoring of the level of 25(OH)D, adequate doses and schemes for the prevention and treatment of vitamin D deficiency.

Screening for vitamin D deficiency in adults

The main circulating form of vitamin D is 25(OH)D, so its level in blood serum is considered to be the best index [15, 23, 37–39] for assessing the supply and monitoring of the vitamin D status. Determination of 25(OH)D provides measuring the level $25(OH)D_2$ and $25(OH)D_3$ and is defined as 25(OH)D total. It is measured in the morning on an empty stomach, and the results are given in ng/ml or nmol/l (with a conversion factor of *2.5). Measurement of the level of vitamin D in urine, breast milk, synovial and amniotic fluids, separate tissues and cell cultures is used in experimental and clinical studies, but it has no value in clinical practice for assessing the status of vitamin D [40].

For today, measurement of serum 25(OH)D levels is performed using methods based on immunoassays (CLIA, ECLIA, RIA and ELISA) and chromatographic methods (HPLC and LC-MS). The first are more often used in clinical practice due to automation and the ability to obtain results quickly. Chromatographic methods, unlike immunoassay methods, allow to determine the metabolites of vitamin D, although they are more complex due to their technical equipment, time-consuming preparation and evaluation of the samples. Today, special attention is paid to the need of standardization of the obtained 25(OH)D results and assurance of laboratory quality of the measurements [40, 41].

The recommendations of various international societies and the European Food Safety Authority (EFSA) [15, 19, 22–24, 42, 43] use different cut-off values for the determining VDD. Comparative analysis of guidelines [44–48] confirmed this by the specifics of the tasks and the choice of the target population. The results of some [49, 50], although not all studies, demonstrate an inverse interconnection between the levels of parathyroid hormone (PTH) and 25(OH)D at a level of the last one in the blood < 30 ng/ml, which justifies our choice of this particular value, as a limit for the determining of the optimal one. In addition, the use in some guidelines of meta-regression analysis (MRA) using a dose-response interconnection instead of analysis of individual participant data (IPD) of the study (which is less appropriate from the point of view of Cochrane experts [51]) can significantly affect recommended cut-off values.

1α,25-dihydroxyvitamin D ($1\alpha,25(OH)_2D$) is a hormonally active form of vitamin D, which realizes its skeletal and extraskeletal effects outside the site of the main synthesis through genomic and non-genomic mechanisms, however, its determination is not used to test the body's vitamin D supply and screening for VDD. The serum level of $1\alpha,25(OH)_2D$ has clinical value in the assessment of congenital/acquired disorders of phosphate and 25(OH)D metabolism in the patients with chronic kidney disease, hereditary diseases with increased phosphate removal, oncogenic osteomalacia, vitamin D-resistant rickets, chronic granulomatous diseases (sarcoidosis), some types of lymphoma. Determination of the level of $1,25(OH)_2D$ for the diagnosis of hypovitaminosis D is not appropriate and may lead to misinterpretation of vitamin D status, since the levels are often normal or even increased in the persons with VDD as a result, in particular, of increased PTH biosynthesis.

Statement 2 [consensus voting scale (level of agreement): 9 (80 %), 7 (13.3 %), 5 (6.7 %)]:

Total 25(OH)D level in serum is recommended as a laboratory marker for the diagnosis of vitamin D deficiency.

Criteria for vitamin D sufficiency in humans:

— < 20 ng/ml (< 50 nmol/L) — vitamin D deficiency;

— ≥ 20 ng/ml (≥ 50 nmol/L) and < 30 ng/ml (< 75 nmol/L) — vitamin D insufficiency;

— 30–50 ng/ml (75–125 nmol/L) is a sufficient level of vitamin D;

— > 50–60 ng/mL (> 125–150 nmol/L) is a safe but not target level of vitamin D;

— > 60–100 ng/mL (> 150–250 nmol/L) is a zone of uncertainty with potential benefits or risks;

— > 100 ng/ml (> 250 nmol/L) — excess/ toxicity zone of vitamin D.

Despite the increase in the number of tests for 25(OH)D in recent years in the world [52–54], which in particular is related to the increase in knowledge about the positive effects of vitamin D and the COVID-19 pandemic, there is currently not enough confirmation to justify the expediency of general screening of the population for VDD [55–57]. However, enough data have been accumulated as for the increase in the proportion of VDD in persons of older age groups [1, 32, 35], subjects with obesity and metabolic syndrome [1, 32, 58], and dark skin pigmentation [59]. In addition, an increase in VDD has been demonstrated in the patients with metabolic diseases of bone tissue [60], subjects with infectious [61, 62] and autoimmune pathology [63–65], in particular, inflammatory bowel diseases [66, 67], rheumatic pathology [68–71], etc., diseases of the endocrine system, in particular, type 1 diabetes, thyroid pathology [72–76], etc., cardiovascular diseases [77–80], nervous system diseases [81–83], diseases of kidneys [84], oncological diseases [85], long-term use of drugs with a negative effect on vitamin D metabolism [86, 87], as well as a connection with an increased mortality rate from various reasons [88–91]. Therefore, determining the serum level of 25(OH)D in this category of persons can be useful for effective prevention and treatment of VDD [15, 22, 23].

Statement 3 [consensus voting scale (level of agreement): 9 (80 %), 7 (20 %)]:

Determination of the serum level of 25(OH)D in adults is not recommended without clear indications, and screening for vitamin D deficiency should be considered in such individuals or in the presence of the following diseases/conditions:

— older persons (≥ 60 years old);

— older persons with an increased risk of falls and a history of low-traumatic fractures;

— immobilized persons and persons during long-term hospitalization;

— pregnant and lactating women;

— obese persons (body mass index ≥ 30 kg/m²);

— persons with dark skin pigmentation;

— osteoporosis;

— osteomalacia;

— pain in bones and muscles;

— hyperparathyroidism;

— chronic kidney disease (CKD);

— malabsorption syndromes (for example, inflammatory bowel diseases, conditions after bariatric surgery, cystic fibrosis, enteritis after radiation, etc.);

— liver failure;

— long-term use of drugs with a negative influence on vitamin D metabolism (for example, anticonvulsant drugs, glucocorticoids, AIDS drugs, antifungal drugs, hypocholesterolemic agents, etc.);

— chronic autoimmune diseases (for example, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, etc.);

— granulomatous diseases (for example, sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidiomycosis, etc.);

— diabetes;

— oncological diseases.

The positive skeletal effects of vitamin D in the human body are realized, in particular, through its influence on calcium-phosphorus metabolism [5, 10, 92]. In cases of chronic VDD, the absorption of calcium, phosphates and magnesium in the intestine decreases [93], the reabsorption of calcium ions and phosphates in the renal tubules is disturbed. In subjects without kidney disease, the normal level of calcium and phosphorus in the blood serum is maintained mainly due to the interaction of two hormones: the synthesis of calcitriol requires the presence of PTH, while its action on bone tissue requires the presence of vitamin D. In presence of VDD, the level of PTH increases, which causes both the bone resorption with the release of calcium and phosphates into the bloodstream, and the reabsorption of calcium in the kidneys to maintain its normal level in the blood. Simultaneously, VDD is usually accompanied by normal levels of calcium and phosphorus in the blood serum with indices of PTH and total alkaline phosphatase (ALP) within the upper limits of the norm or their increased level, as well as a low rate of excretion of calcium in the daily urine. Subjects with severe and/or long-term VDD and the development of secondary hyperparathyroidism have hypocalcemia and/or hypophosphatemia and a high level of ALP [60, 92]. An increased level of ALP in case of VDD leads to the osteomalacia development, when ALP is produced by osteoblasts of a wide layer of osteoid, which is formed in conditions of impaired mineralization [94].

The effectiveness of the use of vitamin D is significantly reduced with a low level of magnesium in the blood [95]. Magnesium deficiency plays an important role in the development of magnesium-dependent rickets or osteomalacia, some forms of which are resistant to the action of vitamin D, and the taking of magnesium supplements increases the effectiveness of the treatment of VDD [96].

An important index for a comprehensive assessment of the status of vitamin D is also the level of creatinine in blood serum, which reflects the functional state of the kidneys, where the second stage of vitamin D metabolism takes place with the formation of its hormonally active form — $1,25(OH)_2D$. Acute or chronic kidney failure and other kidney diseases can be the cause of an increase in the level of creatinine in the blood. Also, severe VDD is a risk factor for renal hyperfiltration [97].

Statement 4 [consensus voting scale (level of agreement): 9 (80 %), 7 (20 %)]:

In individuals with vitamin D deficiency, 25(OH)D should be interpreted in connection with the determination of the level of calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone, and creatinine in blood serum.

Prevention and treatment of vitamin D deficiency in adults

Considering that vitamin D enters the body with food and is synthesized in the skin, a balanced diet and a healthy lifestyle with an adequate level of physical activity (especial-

ly, to prevent obesity), being outdoors can also be important strategies in the prevention of VDD. The expediency of prescribing prophylactic doses of vitamin D in adults is determined by the season of the year, as well as age, body weight, food preferences, physical activity regime, and the presence of risk factors for VDD.

For the prevention and treatment of VDD and VDI, two of its forms are most widely used — vitamin D_2 and D_3. A lower affinity for the vitamin D-binding protein of the blood plasma of vitamin D_3, a higher rate of 25-hydroxylation in the liver and subsequent hydroxylation in the kidneys with the formation of active metabolites, a higher discrimination coefficient (predominance of activity), that are characteristic for vitamin D_3 [3, 4, 6, 7], determine its higher efficiency, which is also confirmed by modern randomized clinical trials (RCTs) and meta-analyses [98, 99].

For today, vitamin D in Ukraine is available only in oral form with a daily and weekly regimen.

Other regimes are also used in the world (monthly, quarterly, semiannually, and annually). According to many researchers [23, 100, 101], it is the daily and weekly regimens of vitamin D intake that are more appropriate compared to the administration of bolus doses. Vitamin D in Ukraine is represented by various forms (capsules, drops and tablets), which should be chosen individually, taking into account the dietary preferences, depending on the functional state and the presence of gastrointestinal tract (GI) pathology to ensure compliance with its purpose.

Statement 5 [consensus voting scale (level of agreement): 9 (67.7 %), 7 (33.3 %)]:

Oral cholecalciferol (vitamin D_3) is recommended for the prevention and treatment of vitamin D deficiency, and ergocalciferol (vitamin D_2) as an alternative (vegetarianism, veganism, etc.). In order to increase adherence to vitamin D intake, it is recommended to use different regimens (daily, weekly).

To date, most guidelines on VDD [15, 19, 22, 23, 42] recommend that adults at the age from 19 up to 65 years old without risk factors affecting vitamin D metabolism should obtain vitamin D through solar insolation whenever possible (staying at least 15 minutes in the sun from 10:00 a.m. to 03:00 p.m. from May to September) and having a healthy diet. If the above is limited or impossible, additional intake of vitamin D is recommended in different doses depending on season, body mass, and dietary preferences. Taking into account the data of epidemiological studies conducted in Ukraine, regarding seasonal fluctuations of the level of 25(OH)D with lower indices in late autumn, winter and spring, for the development of VDD, it may be appropriate to prescribe its preventive doses from October to April.

According to the recommendations of international guidelines and EFSA [15, 19, 22, 23, 42, 43], there is currently no consensus on the recommended prophylactic doses of vitamin D for additional intake (from 200 to 2000 IU/d). Pharmacodynamic studies demonstrate that taking 100 IU/d of vitamin D leads to an increase in the level of serum 25(OH)D, on average, by ~1 ng/ml (2.5 nmol/l), although a number of external and internal factors can significantly influence on this index [16]. According to EFSA data [43], the recommended intake of vitamin D for persons aged 1 year and older is 600 IU/d, and the upper limit of intake (for children over 11 years and adults) is 4,000 IU.

Current data on differences in the dose of vitamin D to achieve a level 25(OH)D of 50 nmol/L in ≥ 97.5 % of subjects [102] depending on the approach used for their analysis (according to MRA it is 560 IU/d, IDU, respectively, 1040 IU/d), allow recommending a dose of at least 800 IU/d as a target for preventing VDD.

Statement 6 [consensus voting scale (level of agreement): 9 (66.7 %), 7 (26.7 %), 5 (6.6 %)]:

Healthy adults without diseases and conditions that affect the metabolism of vitamin D in the body are recommended to take vitamin D supplements from October to April at a dose of 800–2000 IU/d (depending on body mass) because of decrease in the level of synthesis of endogenous vitamin D in the skin.

To date, it has been proven that the frequency of VDD is higher in subjects of older age groups, which can have a negative impact on the development of a number of skeletal and extraskeletal manifestations. The decrease in the level of 25(OH)D in this age group is justified both by a decrease in the synthesis of vitamin D in the skin with age (due to a thickening of the thickness of its stratum corneum, a decrease in the density of VDR, etc.), and by a violation of its absorption from food. Current recommendations differ as for the recommended doses of consumption for older persons, but most of them, in particular for the population of Ukraine [103], note the need to increase the daily dose of vitamin D. Additionally, immobilization, in particular, and during long-term hospitalization with limitation of functional activity, is associated with a decrease in the synthesis of vitamin D in the skin, which can lead to VDD.

Statement 7 [consensus voting scale (level of agreement): 9 (86.7 %), 7 (13.3 %)]:

Taking vitamin D in a dose of 800–2000 IU/d during a year is recommended for the elderly persons, immobilized persons, and persons during long-term hospitalization with limited functional activity.

Currently, guidelines for overcoming VDD in women during pregnancy and lactation [15, 19, 22, 23, 42] recommend its additional intake, although within wide range (200–2000 IU/d). According to the Order of the Ministry of Health of Ukraine [103], an increase of the dose of vitamin D during pregnancy is not provided, however, taking into account the increased need for vitamin D in pregnant and lactating women, its prophylactic intake under the control of the level of 25(OH)D in the blood serum to maintain the optimal concentration is expedient. If testing is not possible, additional vitamin D intake at a dose of 800–2000 IU/d may be considered, depending on the characteristics of diet, lifestyle, diseases and conditions that make an influence on vitamin D metabolism.

Statement 8 [consensus voting scale (level of agreement): 9 (86.7 %), 7 (13.3 %)]:

Women planning pregnancy should consider taking vitamin D at a dose of 800–2000 IU/d or continue taking it during all pregnancy and lactation period.

In persons with obesity (body mass index > 30 kg/m^2), dark skin color and diseases or conditions, that affect vitamin D metabolism, the prescription of prophylactic doses (800–2000 IU/d) of vitamin D may not be sufficient to maintain the optimal concentration of 25(OH)D in the blood, therefore, the prescription of higher doses of vitamin D (3000–5000 IU/d depending on body weight, dietary preferences, seasons) should be considered for them under individual control of the serum level of 25(OH)D. Also, the results of numerous studies and meta-analyses demonstrate the interconnection between the additional use of vitamin D and a reduction in the risk of a number of diseases and conditions (chronic autoimmune [104], infectious [105], oncological diseases [106, 107], diabetes [108, 109], mortality [85]).

Statement 9 [consensus voting scale (level of agreement): 9 (80 %), 7 (13.3 %), 5 (6.7 %)]:

For the persons with diseases and conditions that affect the metabolism of vitamin D in the body, an individual selection of a preventive dose of vitamin D (3000–5000 IU/d) is recommended to achieve the optimal concentration of 25(OH)D.

If there is a necessity of rapid correction of VDD (osteomalacia, severe VDD (< 10 ng/mL), the need to initiate anti-osteoporotic therapy in a patient with a high risk of fractures, secondary hyperparathyroidism and a low level of serum calcium), it is possible to use higher doses (up to 10,000 IU/d) of vitamin D for several weeks [15, 23], which are effective and safe [110]. The selection of high daily doses of vitamin D should be recommended individually depending on the season, the mode of functional activity, the presence of diseases and conditions that affect the metabolism of vitamin D.

Statement 10 [consensus voting scale (level of agreement): 9 (66.7 %), 7 (26.7 %), 5 (6.6 %)]:

Persons without diseases and conditions that affect vitamin D metabolism, with a diagnosed deficiency of vitamin D, should be treated with higher doses of vitamin D compared to the preventive doses recommended for the general population (4000–7000 IU/d).

Statement 11 [consensus voting scale (level of agreement): 9 (66.7 %), 7 (26.7 %), 5 (6.6 %)]:

For the persons with diseases and conditions that affect vitamin D metabolism in the body, higher doses of vitamin D (up to 10,000 IU/d) are recommended for the treatment of vitamin D deficiency compared to healthy adults without other risk factors.

In many clinical guidelines about the management of VDD [15, 19, 22, 23, 42], a level of 25(OH)D < 20 ng/mL is the cutoff that determines need for the treatment. At the same time, it should be noted about the faster growth of the 25(OH)D level at its initial lower value and the decrease in the curvature of the level of growth of concentration when reaching its optimal values [16].

To date, there is no consensus on the timing of monitoring of serum 25(OH)D levels. According to some authors, re-determination of the level of vitamin D should be carried out 4–12 weeks after the start of the treatment of VDD [24, 39], according to others — after 3–6 months [54]. These differences should be taken into account when planning the monitoring of the serum level of 25(OH)D, the timing of which can be determined both by the severity of VDD and the presence of diseases and conditions that affect the vitamin D metabolism, the form and mode of its administration.

Statement 12 [consensus voting scale (level of agreement): 9 (73.3 %), 7 (20 %), 5 (6.7 %)]:

Treatment of vitamin D insufficiency should be initiated at the level of 25(OH)D in blood < 20 ng/mL (< 50 nmol/L) and continued for 4–12 weeks, depending on its severity and other risk factors, until a target level of 30–50 ng/mL is reached (75–125 nmol/l) with further use to maintain optimal vitamin D status at a dose of 800–2000 IU/d.

In case of vitamin D deficiency (25(OH)D < 30 ng/mL or < 75 nmol/L), the decision on additional appointment of vitamin D should be made individually depending on the need for rapid correction of vitamin D insufficiency and other indices.

Despite the fact that chole- and ergocalciferol are most widely used for the prevention and treatment of VDD, some researchers consider it appropriate to use vitamin D metabolites for this purpose [47]. Calcitriol ($1,25(OH)_2D$) and its analogs (α-calcidol) are associated with a higher risk of hypercalcemia, but may be recommended for the patients with chronic hypoparathyroidism or bone mineral disorders associated with CKD [111].

Statement 13 [consensus voting scale (level of agreement): 9 (60 %), 7 (26.7 %), 5 (13.3 %)]:

Active metabolites of vitamin D are not recommended for the treatment of vitamin D deficiency in persons without diseases or conditions that affect vitamin D metabolism in the body, but are recommended for the patients with chronic hypoparathyroidism or bone mineral disorders associated with CKD.

Nowadays, the numerous studies and meta-analyses have shown a positive effect of additional vitamin D intake together with calcium on bone mineral density, reducing the risk of developing of osteoporosis and osteomalacia [112]. According to modern recommendations for the treatment of postmenopausal osteoporosis in women [113, 114], men [115] and glucocorticoid-induced osteoporosis [116], additional intake of vitamin D (400–800 IU/d) together with calcium is recommended for the patients during anti-osteoporotic treatment. A positive effect of daily administration of vitamin D (800–1000 IU/d) in reducing the risk of fractures and falls was noted, while periodic administration was not effective [117]. Most [118–120], but not all [121] researchers confirm the effectiveness of the combined intake of vitamin D together with calcium compounds in reducing the risk of fractures and falls.

To date, the need to use vitamin D has been demonstrated both to increase the effectiveness of antiosteoporotic therapy, in particular when using bisphosphonates [122] or denosumab [123, 124], and to improve the safety profile, prevention of acute-phase reactions when prescribing bisphosphonates [125, 126]. Therefore, determining the level of 25(OH)D in blood is recommended for the patients with osteoporosis before initiation of antiosteoporotic therapy.

Statement 14 [consensus voting scale (level of agreement): 9 (66,7 %), 7 (26,7 %), 5 (6,6 %)]:

For the patients with osteoporosis and its complications, it is recommended to determine the level of 25(OH)D in blood before initiating antiosteoporotic therapy in order to prevent its inefficiency and increase in the safety profile.

If a deficiency of vitamin D is detected before initiation of anti-osteoporotic therapy, its correction is recommended, with a normal level of vitamin D, it is recommended to take it in a dose of 800–2000 IU/d in combination with calcium (1,000 mg/d of elemental calcium) during the entire course of anti-osteoporotic treatment. Patients with an increased risk of falls or fractures (FRAX in accordance with the Ukrainian version) are recommended to take 800–2000 IU/d of vitamin D during the year.

Authors' contribution. *N.V. Grygorieva* — development of the Consensus concept and design, creation of the Consensus Statements, analysis of the data, writing of the text of the article; *M.D. Tronko* — development of the Consensus concept and design, correction of the text; *V.M. Kovalenko* — development of the Consensus concept and design, correction of the text; *S.V. Komisarenko* — development of the Consensus concept and design, correction of the text; *T.F. Tatarchuk* — voting for the Consensus Statements, editing the text; *N.V. Dedukh* — creation of the Consensus Statements, collection and analysis of data, writing and editing the text; *M.M. Veliky* — voting for the Consensus Statements, writing and editing the text; *S.S. Strafun* — voting for the Consensus Statements, editing the text; *Y.I. Komisarenko* — voting for the Consensus Statements, editing the text; *A.V. Kalashnikov* — voting for the Consensus Statements, editing the text; *V.L. Orlenko* — creation of the Consensus Statements, collection and analysis of data, writing and editing the text; *V.I. Pankiv* — voting for the Consensus Statements, editing the text; *O.V. Shvets* — voting for the Consensus Statements, writing and editing the text; *I.V. Gogunska* — voting for the Consensus Statements, editing the text; *S.I. Regeda* — voting for the Consensus Statements, editing the text.

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Appendix 1

Metabolism of vitamin D and its sources

Vitamin D enters the human body in two ways: due to synthesis in the skin and with food. The average daily human need for vitamin D is 5–10 μg.

In the human body, vitamin D_3 is formed in the dermal layer of the skin from the precursor of provitamin D_3 (7-dehydrocholesterol) under the influence of short-wave ultraviolet radiation of the B spectrum (wavelength 290–315 nm) by the so-called photolysis, primarily turning into previtamin D_3, then under the influence of heat into vitamin D_3. The rate of photosynthesis in the skin is ~15–18 IU/cm^2/g and is a subject to strict regulation. With intense long-term UV irradiation of the human body, the level of 25(OH)D_3 does not exceed 80 ng/ml, intensifying the splitting of a part of previtamin D_3 into inactive molecules.

The synthesis of vitamin D in the skin is influenced by both external (latitude of the place of residence, season, time of day, cloudiness, altitude above sea level, etc.) and internal factors (age, skin type (1–6), surface of clothing, use of sun protective creams, long stay in closed rooms). In addition, vitamin D enters the human body with food products of both animal (D_3) and plant (D_2) origin. Vitamin D_3 plays a much more important role compared to D_2 in human life processes, that's why it is considered the "true" vitamin D, while other representatives of this group have less clinical significance.

After entering the blood, vitamin D still remains an inactive compound that requires a number of transformations to synthesize its active hormonal form — 1,25(OH)$_2$D. There are three main stages of vitamin D metabolism.

The first reaction of vitamin D hydroxylation is carried out in the liver (up to 90 %), which is recognized as the main, if not the only, site of hydroxylation. The process takes place with the participation of the microsomal enzyme 25-hydroxylase with the formation of an intermediate biologically transportable form — 25(OH)D (calcidiol). The 25-hydroxylation reaction occurs quite quickly and leads to an increase in the level of 25(OH)D in the blood serum, the level of which reflects both the formation of vitamin D in the skin and its intake with food, as a result of which it is used as a concentration marker of vitamin D in blood serum. Partially the transport form of 25(OH)D, which enters adipose and muscle tissue, can create tissue depots with an indefinite period of existence.

The further reaction of 1α-hydroxylation of 25(OH)D takes place most intensively in the cells of the proximal tubules of the kidney cortex with the participation of the enzyme 1α-hydroxylase (25-hydroxyvitamin D-1α-hydroxylase, CYP27B1) with the formation of its active hormonal form — 1,25(OH)$_2$D. The level of D-hormone formation in the body of a healthy adult person is approximately about 0.3–1.0 μg/day.

At this stage, the active metabolite 1,25(OH)$_2$D is formed, which interacts with the nuclear VDR of the small intestine, kidneys, and other tissues. In addition, it was established that almost all tissues and cells in the human body have VDR and also demonstrate 25(OH)D-1α-hydroxylase (CYP27B1) activity, which indicates the ability to synthesize 1,25(OH)$_2$D in tissues outside the kidneys [127]. The enzyme CYP24A1, which has both 24-hydroxylase and 23-hydroxylase activity, is also involved in the metabolism of vitamin D. Defects in CYP24A1 lead to a deficiency of 24-hydroxylated metabolites of vitamin D, which is accompanied by impaired endochondral ossification.

Appendix 2

Vitamin D mechanism of action of and its skeletal actions

To date it is known that vitamin D in the form of its active form — D-hormone — is responsible for the implementation of various biological reactions in more than 40 target tissues due to the regulation of VDR-mediated gene transcription (genomic mechanism) and rapid non-genomic reactions that take place through the influence on the system of calcium-phosphate homeostasis and the activation of signaling pathways (wingless (WNT), sonic hedgehog (SSH), STAT1-3 or nuclear factor kappa-B) that modulate several intracellular processes, including the cell cycle, proliferation or immune response [14, 128, 129]. Specific proteins that bind $1,25(OH)_2D$ and are the components of the MARRS receptor (membrane-associated rapid response steroid binding protein) may also be responsible for the rapid non-genomic effects of vitamin D). The identity of the MARRS receptor and ERp57/ERp60/GRp58/PDIA3 has been established, which significantly expands its functions as chaperone proteins, DNA-binding protein and component of the immune system. $1,25(OH)_2D$-MARRS, stimulating non-genomic effects in various types of cells, is simultaneously able to penetrate into the nucleus of the cell and in complex with VDR can provide $1,25(OH)_2D$-mediated regulation of gene activity.

The vitamin D receptor is traditionally considered a nuclear transcription factor that provides the influence of vitamin D on the transcription of genes whose promoters have specific DNA sequences — vitamin D-sensitive elements. The regulatory genomic effects of vitamin D also include an epigenomic influence on the structure of chromatin (changes in chromatin accessibility, manifestation of specific contact features of the VDR-$1,25(OH)_2D$ complex with specific binding sites), which affects transcriptomic changes in cells [10, 12]. The concentration of VDR in blood serum is up to 20 times higher than that of vitamin D metabolites, resulting in the binding of these metabolites to only ~5 % of circulating VDR [130]. Such a significant excess of VDR may provide protection against the toxic actions of vitamin D due to an increase of its concentration in blood serum.

Due to genomic and non-genomic mechanisms D, the endocrine system is involved in regulating of the mineral homeostasis of calcium and phosphates in blood circulation processes. In intestinal enterocytes, VDR activation by the active metabolite of vitamin D $1,25(OH)_2D$ is accompanied by an anabolic effect — an increase in the synthesis of calbindin (9K-calcium-binding protein), which enters the lumen of the intestine, binds calcium ions (Ca^{2+}) and transports it through the intestinal wall into the lymphatic vessels, and then into the circulatory system. The effectiveness of this mechanism is evidenced by the fact that without the participation of vitamin D, only 10–15 % of calcium and 60 % of phosphates are absorbed in intestine. The interaction between $1,25(OH)_2D$ and VDR increases the efficiency of intestinal absorption of Ca^{2+} up to 30–40 %, and of phosphates — up to 80 %. $1,25(OH)_2D$ maintains the necessary levels of calcium and phosphates in the blood to ensure the mineralization of bone tissue and prevention of hypocalcemic tetany. Similar mechanisms of action of D-hormone are the basis of the reabsorption of Ca^{2+} in the kidneys.

Deficiency and insufficiency of vitamin D causes a decrease in the absorption of calcium and phosphates in the intestines, as a result of which the level of PTH increases, secondary hyperparathyroidism occurs, in which the total level of calcium in the blood serum is within the normal range due to the mobilization of calcium from bone tissue and increased excretion of phosphates by the kidneys. Mediated PTH increase in the activity of osteoclasts causes a decrease in BMD, as a result of which osteopenia and osteoporosis are developing.

Vitamin D facilitates the mobilization of calcium in bones, and under certain conditions has a resorptive effect to maintain the level of calcium and phosphates in the plasma of blood [10, 131]. The resorptive activity of vitamin D (under conditions of its norm in blood serum) is realized through its ability to influence the functional activity of osteoblasts and osteocytes [4, 10, 12, 13, 130]. In osteoblasts, the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL) increases, which binds to the receptor activator of nuclear factor kappa-B (RANK), located on preosteoclasts and osteoclasts, which leads to the activation of osteoclasts and increased bone resorption. Vitamin D directly through the VDR receptor expressed in osteoclasts and progenitor cells of osteoclasts can also regulate their differentiation and activity [4].

One of the mechanisms of action of vitamin D is the modulation of $\alpha v\beta 3$ integrin expression and its subcellular organization, which contributes to the differentiation of mesenchymal stem cells into osteoblasts due to increased interaction of $\alpha v\beta 3$ with fibronectin [132]. In addition, calcitriol is an important regulator of RUNX2, a transcription factor that plays a key role in controlling of differentiation and function of osteoblasts. The cooperation of these molecules is manifested by the induction of the expression of osteocalcin, a key protein that regulates the mineralization of bone matrix. Calcitriol also modulates the expression of most genes that are responsible for osteoblast maturation and bone matrix mineralization. Under its action, the expression of genes of type I collagen, LF, matrix protein Gla and osteopontin (the last two are inhibitors of mineralization), bone sialoprotein and osteocalcin increases. Calcitriol in osteocytes induces fibroblast growth factor 23 (FGF23), which encodes a major phosphate-regulating hormone and dentin matrix protein 1 (DMP1), which, like osteopontin, acts as a mineralization inhibitor to prevent hypermineralization.

The effect of vitamin D on bone is not limited only by studies of its active form. Thus, with the use of transcriptional analysis, it was demonstrated that not only calcidiol and calcitriol, but also other hydroxylated metabolites of the latter ($24R,25(OH)_2D_3$ and 1α-$24R,25(OH)_3D_3$) induce gene transcription in cells of the osteoblast line, they increase dose-dependently the biosynthesis of LF, osteocalcin and enhance mineralization [133, 134]. Calcidiol can also bind to VDR, but its affinity is about 1,000 times lower than that of $1,25(OH)_2D_3$ [14].

Phosphaturia caused by secondary hyperparathyroidism leads to a decrease in the level of phosphates in the blood serum to the lower limit of the norm or below the norm. The consequence of this is a violation of the ratio of calcium and phosphates, which leads to the defects in the mineralization of the skeleton. In infants and preschool children, vitamin D deficiency causes rickets, which is characterized by multiple bone deformities. Osteomalacia occurs in adults as a result of vitamin D deficiency. Both diseases are caused by a violation of bone mineralization. However, it is necessary to differentiate the pathogenetic mechanisms that led to osteomalacia, including: deficiency or resistance of vitamin D; calcium deficiency rickets (probably, osteomalacia) regardless of dietary vitamin D status; phosphate depletion caused by a primary or secondary increase in growth factor of fibroblasts-23 and inhibition of mineralization caused by the toxic actions of various drugs [112].

Appendix 3

Food sources of vitamin D

Vitamin D enters the human body with food of both plant (D_2) and animal (D_3) origin. The daily requirement for adults in accordance with the norms of physiological needs for nutrients and energy according to the Order of the Ministry of Health of Ukraine No. 1073 dated September 3, 2017, is 5–10 μg/day. The standard activity of vitamins D_2 and D_3 is expressed in international units (IU). For one IU, it is used to take the activity of 0.025 μg of vitamins D_2 and D_3. Therefore, 1 μg of both vitamins corresponds to 40 IU of their activity.

Food sources of vitamin D are quite limited (Table 1). Its naturally high content is found in fatty marine fish, especially in the liver of certain species, for example, in the liver of cod. Vitamin D in different quantities is found in certain types of mushrooms. In recent years, the practice of growing mushrooms under ultraviolet radiation, which increases their vitamin D content, has become increasingly widespread [135], as well as the fortification of food products using vitamin D.

Table 1. Food products that contain vitamin D

Food name	Vitamin D content (μg) in 100 g/ml of product*	Percentage of the daily requirement**
1	2	3
Fish and seafood		
Fish oil (from cod liver)	225	4500
Rainbow trout	19.3	386
Carp	17.9	358
Mackerel	11.5	230
Salmon (red salmon)	10.9	218
Sea bass	5.65	113
Flounder	5.6	112
Sardines canned in oil	4.83	96.6
Tilapia	2.83	56.6
Atlantic herring	2.8	56
Pike	1.87	37.4
Canned tuna	1.45	29
Perch	1.1	22
Atlantic pollock	0.77	15.4
Red granular caviar	0.08	1.6
Eggs and offal		
Chicken egg, whole, 1 pc	1,1	22
Beef liver	0,85	17
Mushrooms		
Chanterelle mushrooms	5.3	106
Shiitake mushrooms	0.4	8
White mushrooms	0.18	3.6

End of Table 1

Note: * — vitamin D content according to the USDA National Nutrient Database for Standard Reference Release 28 (04.2019); ** — daily requirement for adult men and women in accordance with the norms of physiological needs for nutrients and energy (Order of the Ministry of Health of Ukraine, [102]).

Appendix 4

Consensus Statements

1. Deficiency and insufficiency of vitamin D in the adult population of Ukraine is widespread, that's why it is necessary to increase the awareness of the public and medical personnel about its skeletal and extraskeletal effects, risk groups that require screening and monitoring of the level of 25(OH)D, adequate doses and schemes for the prevention and treatment of vitamin D deficiency.

2. Total 25(OH)D level in serum is recommended as a laboratory marker for the diagnosis of vitamin D deficiency.

Criteria for vitamin D sufficiency in humans:

— < 20 ng/ml (< 50 nmol/L) — vitamin D deficiency;

— ≥ 20 ng/ml (≥ 50 nmol/L) and < 30 ng/ml (< 75 nmol/L) — vitamin D insufficiency;

— 30–50 ng/ml (75–125 nmol/L) is a sufficient level of vitamin D;

— > 50–60 ng/mL (> 125–150 nmol/L) is a safe but not target level of vitamin D;

— > 60–100 ng/mL (> 150–250 nmol/L) is a zone of uncertainty with potential benefits or risks;

— > 100 ng/ml (> 250 nmol/L) — excess/ toxicity zone of vitamin D.

3. Determination of the serum level of 25(OH)D in adults is not recommended without clear indications, and screening for vitamin D deficiency should be considered in such individuals or in the presence of the following diseases/ conditions:

— older persons (≥ 60 years old);

— older persons with an increased risk of falls and a history of low-traumatic fractures;
— immobilized persons and persons during long-term hospitalization;
— pregnant and lactating women;
— obese persons (body mass index ≥ 30 kg/m^2);
— persons with dark skin pigmentation;
— osteoporosis;
— osteomalacia;
— pain in bones and muscles;
— hyperparathyroidism;
— chronic kidney disease (CKD);
— malabsorption syndromes (for example, inflammatory bowel diseases, conditions after bariatric surgery, cystic fibrosis, enteritis after radiation, etc.);
— liver failure;
— long-term use of drugs with a negative influence on vitamin D metabolism (for example, anticonvulsant drugs, glucocorticoids, AIDS drugs, antifungal drugs, hypocholesterolemic agents, etc.);
— chronic autoimmune diseases (for example, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, etc.);
— granulomatous diseases (for example, sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidiomycosis, etc.);
— diabetes;
— oncological diseases.

4. In individuals with vitamin D deficiency, 25(OH)D should be interpreted in connection with the determination of the level of calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone, and creatinine in blood serum.

5. Oral cholecalciferol (vitamin D_3) is recommended for the prevention and treatment of vitamin D deficiency, and ergocalciferol (vitamin D_2) as an alternative (vegetarianism, veganism, etc.). In order to increase adherence to vitamin D intake, it is recommended to use different regimens (daily, weekly).

6. Healthy adults without diseases and conditions that affect the metabolism of vitamin D in the body are recommended to take vitamin D supplements from October to April at a dose of 800–2000 IU/d (depending on body mass) because of decrease in the level of synthesis of endogenous vitamin D in the skin.

7. Taking vitamin D in a dose of 800–2000 IU/d during a year is recommended for the elderly persons, immobilized persons, and persons during long-term hospitalization with limited functional activity.

8. Women planning pregnancy should consider taking vitamin D at a dose of 800–2000 IU/d or continue taking it during all pregnancy and lactation period.

9. For the persons with diseases and conditions that affect the metabolism of vitamin D in the body, an individual selection of a preventive dose of vitamin D (3000–5000 IU/d) is recommended to achieve the optimal concentration of 25(OH)D.

10. Persons without diseases and conditions that affect vitamin D metabolism, with a diagnosed deficiency of vitamin D, should be treated with higher doses of vitamin D compared to the preventive doses recommended for the general population (4000–7000 IU/d).

11. For the persons with diseases and conditions that affect vitamin D metabolism in the body, higher doses of vitamin D (up to 10,000 IU/d) are recommended for the treatment of vitamin D deficiency compared to healthy adults without other risk factors.

12. Treatment of vitamin D deficiency should be initiated at the level of 25(OH)D in blood < 20 ng/mL (< 50 nmol/L) and continued for 4–12 weeks, depending on its severity and other risk factors, until a target level of 30–50 ng/mL is reached (75–125 nmol/l) with further use to maintain optimal vitamin D status at a dose of 800–2000 IU/d.

In case of vitamin D deficiency (25(OH)D < 30 ng/mL or < 75 nmol/L), the decision on additional appointment of vitamin D should be made individually depending on the need for rapid correction of vitamin D deficiency and other indice.

13. Active metabolites of vitamin D are not recommended for the treatment of vitamin D deficiency in persons without diseases or conditions that affect vitamin D metabolism in the body, but are recommended for the patients with chronic hypoparathyroidism or bone mineral disorders associated with CKD.

14. For the patients with osteoporosis and its complications, it is recommended to determine the level of 25(OH)D in blood before initiating antiosteoporotic therapy in order to prevent its inefficiency and increase in the safety profile.

If a deficiency of vitamin D is detected before initiation of anti-osteoporotic therapy, its correction is recommended, with a normal level of vitamin D, it is recommended to take it in a dose of 800–2000 IU/d in combination with calcium (1,000 mg/d of elemental calcium) during the entire course of anti-osteoporotic treatment. Patients with an increased risk of falls or fractures (FRAX in accordance with the Ukrainian version) are recommended to take 800–2000 IU/d of vitamin D during the yea.

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Діагностика, профілактика та лікування дефіциту вітаміну D у дорослих: Консенсус українських експертів

Резюме. ***Актуальність.*** Дефіцит вітаміну D (ДВД) є значно поширеним у світі, його частка істотно варіює в різних популяціях і залежить від багатьох причин. До цього часу національних рекомендацій щодо діагностики, профілактики та лікування ДВД у дорослих в Україні не було. Їх створення і стало ***метою*** даної роботи. ***Методологія.*** Консенсус створювали за допомогою методу Дельфі, голосування проводили за допомогою платформи SurveyMonkey®. Після затвердження складу консенсусної групи, узгодження порядку формування та структури Консенсусу, формулювання і корекції основних положень, двох раундів голосування сформовано основні положення Консенсусу, за які група успішно проголосувала. 15 авторів статті є 15 експертами, які брали участь у голосуванні. Остаточні 14 положень Консенсусу подані в даній статті. Перед кожним положенням наведено його обґрунтування, викладене на основі існуючих у сучасній літературі високоякісних доказів. ***Результати.*** Незважаючи на зменшення ДВД в українській популяції протягом останніх років, експертами рекомендовано підвищення обізнаності медичної спільноти та населення щодо проблеми і шляхів її подолання зі скри-

нінгом сироваткового загального рівня 25-гідроксивітаміну D (25(OH)D) в осіб у певних групах ризику для досягнення цільової концентрації 30–50 нг/мл (75–125 нмоль/л). Для її забезпечення рекомендовано індивідуальний підбір профілактичної дози вітаміну D (800–2000 МО/д молодим здоровим особам і 3000–5000 МО/д — хворим із захворюваннями та станами, які впливають на метаболізм вітаміну D в організмі). Для лікування ДВД рекомендовано короткостроковий прийом більш високих доз (4000–10 000 МО/д) вітаміну D з контролем рівня 25(OH)D через 4–12 тижнів лікування і подальшим використанням підтримуючих доз. Рекомендовано визначення сироваткового рівня 25(OH)D у хворих з остеопорозом і його ускладненнями перед ініціацією антиостеопоротичної терапії для запобігання її неефективності й підвищення профілю безпеки.

Ключові слова: вітамін D; Консенсус; рекомендації; діагностика дефіциту вітаміну D; профілактика дефіциту вітаміну D; лікування дефіциту вітаміну D