Information of the Union of Pediatricians of Russia

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Joint position of the Russian Association of Endocrinologists, the Union of Pediatricians of Russia and the Russian osteoporosis associations

Expert group
Chairpersons: Academician G.A. Melnichenko [1] , Academician L.S. Namazova-Baranova [2, 3]
Members of the expert group: Doctor of Medical Sciences, Professor O.A. Gromova [4] , corresponding member RAS, Doctor of Medical Sciences, Professor O. M. Drapkina [5] , MD, DSc , Professor T.L. Karonova [6, 7] , Ph.D. K.S. Kulikova [1] , Yu.A. Krupinova [1] , Doctor of Medical Sciences, Professor O.M. Lesnyak [8] , MD N.V. Mazurina [1] , A.A. Panov [9] , senior teacher, d.m.s. E.A. Pigarova [1] , Doctor of Medical Sciences , Professor L.Ya. Rozhinskaya [1] , MD J.E. Belaya [1] , MD, DSc, Professor L.A. Ruyatkina [10] , MD, DSc , Professor L.A. Suplotova [11]

[1] National Medical Research Center of Endocrinology, Ministry of Health of Russia, Moscow, Russian Federation
[2] Russian National Research Medical University. N.I. Pirogov, Moscow, Russian Federation
[3] Research Institute of Pediatrics and Children's Health, Central Clinical Hospital of the Russian Academy of Sciences, Ministry of Science and Higher Education of the Russian Federation, Moscow Russian Federation
[4] Federal Research Center “Informatics and Management” RAS; Big data storage and analysis center, VGBU VPO "Moscow State University named after M.V. Lomonosov ", Moscow, Russian Federation
[5] National Medical Research Center for Therapy and Preventive Medicine Ministry of Health of the Russian Federation, Moscow, Russian Federation
[6] National Medical Research Center named after V.A. Almazov Ministry Healthcare of the Russian Federation, Moscow, Russian Federation,
[7] First Saint Petersburg State Medical University named after academician I.P. Pavlova Ministry of Health of the Russian Federation, St. Petersburg, Russian Federation
[8] North-Western State Medical University named after I.I. Mechnikov Ministry Healthcare of the Russian Federation, St. Petersburg, Russian Federation
[9] National Research University Higher School of Economics, Moscow, Russian Federation
[10] Novosibirsk State Medical University of the Ministry of Health of the Russian Federation, Novosibirsk, Russian Federation
[11] Tyumen State Medical University of the Ministry of Health of the Russian Federation, Tyumen, Russian Federation

Prevention and treatment of deficiency vitamin D: choosing the optimal approach

Interest in the problems of the biological effects of vitamin on D, its role in the development of various human diseases, as well as to the issues of supply and subsidies of vitamin D has risen sharply in the last decade as a medical the scientific community and society as a whole. In work A. Yang et al. demonstrated more than 3 times an increase in the number of scientific publications (from 1500 to more 4500 publications per year), annually placed in the database data from PubMed, in the period from 2007 to 2017 [1].

Attention to this issue is due to scientific mi data that vitamin D in the human body renders both "classic" - bone, and extra- bone effects that are manifested in association vitamin D deficiency with an increased risk of developing and severe course of a number of oncological, endocrine, autoimmune, neurological and infectious diseases levania [2]. These data allow us to consider the defect cit of vitamin D and maintenance of its normal level as a potential reserve of disease prevention her civilization (chronic non-infectious diseases vanii) and infectious diseases [3].

From the point of view of molecular biology, the effects of vit- mine D are mediated by genomic and non-genomic mechanisms mi. A non-genomic mechanism is carried out by regulation enzyme activities (adenylate cyclase, phospholipase C, protein kinase C, tyrosine kinase) of intracellular signaling nal pathways of cells of the immune and nervous systems the form of vitamin D (1.25 (OH) $_2$ D) [2].

The genomic mechanism is implemented through communication calls with a specific nuclear receptor for vitamins mine D (VDR), which regulates gene expression in humans. Significant identified and confirmed the effect of activated VDR on the expression of more than 200 genes, only a small part of which (7-10%) encodes proteins involved in providing phosphorus- calcium metabolism: TRPV6 (provides absorption intestinal calcium), CALB1 (calbindin; provides transport of calcium into the bloodstream), BGLAP (osteo- calcin; provides bone mineralization and calcium homeostasis), SPP1 (osteopontin; regulates migration of osteoclasts).

Vitamin D plays an essential role in absorption calcium and phosphate in the intestine, in the systemic trans- port of mineral salts and in the process of mineralization bones, also regulates the excretion of calcium and phosphates kidneys. The main classical (bone) clinics ical manifestations of vitamin D deficiency are rickets, osteomalacia and increased risk of fractures [2]. Vitamin D also serves as an important component of the treatment osteoporosis.

In addition to the genes of protein regulators of phosphorus-calcium exchange, activated VDR regulates ex- the pressure of genes such as *REN* (renin; provides regulation of blood pressure, being the key an element of the renin-angiotensin-aldosterone system we regulate), *IGFBP* (insulin binding protein a similar growth factor; enhances the effect of insulin growth factor), *FGF23* and *FGFR23* (growth factor fibroblast 23 and its receptor; regulates levels phosphate anion, fibroblast cell division processes stov), *TGFB1* (transforming growth factor beta-1; regulates the processes of cell division and differentiation osteocytes, chondrocytes, fibroblasts and kera- tinocytes), *LRP2* (LDL-receptor-associated protein 2; is a mediator of endocytosis of lipoproteins of low density) and *INSR* (insulin receptor; provides effects of insulin on any cell types) [2].

In a number of epidemiological studies and their meta- Liz associations were shown to be deficient vitamin D with the risk of obesity [4-6], sugar- type 1 diabetes mellitus [7], type 2 diabetes mellitus [8, 9, 10], cardiovascular disease [11], cancer mammary gland [12, 13] and colon [14, 15], etc. However, currently available prospective data interventional clinical trials do not allow are to unambiguously confirm the effectiveness of the donation of vitamins mine D for the prevention of these diseases [16-18].

Additionally, vitamin D is involved in the regulation of immune by modulating cytokine levels and regulating division of T-helper lymphocytes and differentiation ku B-lymphocytes [19], and also stimulates the production of natural immunity factors - cathelecidin and -defensines [20–22]. Relationship between vitamin D levels and the effectiveness of immune defense has been demonstrated as in observational studies, where the deficit vitamin D was associated with an increase in morbidity respiratory infections [23–27], and in the inter- venous studies that have demonstrated reducing the risk of acute respiratory illness infections in the presence of vitamin D supplementation [28, 29].

Protective effects of vitamin D on respiratory infections were prerequisites to active research of the interrelationships between the liver disease with vitamin D, morbidity and cli - nic course of the infectious process caused by with the SARS-CoV-2 virus. In a number of foreign research an inverse relationship was shown between the concentration serum 25 (OH) D and morbidity, the severity of the course and mortality in COVID-19 [30–35]. Domestic study conducted at the Federal State Budgetary Institution "NMITs them. V.A. Almazov "of the Ministry of Health of Russia T.L. Caro- nova et al., confirmed the presence of an association of severe course and mortality in COVID-19 and low concentrations concentration of 25 (OH) D in blood serum [36]. Study FSBI "National Medical Research Center of Endocrinology" of the Ministry of Health of Russia showed found that in patients with COVID-19, a very low cue level of vitamin D, activity of 1-hydroxylase and vitamin D-binding protein increase in acute phase of COVID-19 and recover as [37]. These studies point to an important the role of vitamin D in morbidity and serious complications with this infectious disease.

Diagnosis of vitamin D deficiency is carried out by the determination of its metabolites in the blood serum. The most informative indicator is con- concentration of calcidiol (25 (OH) D) in serum and plasma blood, since it is the main circulating metabolite of vitamin D, has a long period of decay (2-3 weeks) and reflects the intake as an exogenous nogo (food) and endogenous (synthesized in the skin against the background of insolation) vitamin D.

Biologically active calcitriol (1,25 (OH) $_2$ D) circulates in much smaller quantities (its concentration is 1000 times lower), has a short period half-life (4 hours) and does not reflect the state of reserves vitamin D in the body. Calcitriol levels remain normal or may increase against the background of a deficiency that vitamin D due to secondary hyperparathyroidism, and its definition is advisable only when diagnosing congenital or acquired metabolic disorders ma of vitamin D (for example, with a deficiency of 24-hydroxy- lazy) [38]. Thus, currently for establishing the body's supply of vitamin D the concentration of calcidiol (25 (OH) D) should be determined in serum or plasma.

Regarding the limits of normal concentration 25 (OH) D there is some disagreement. So, Institute of Medicine (IOM), USA, National Osteoporosis Society UK and the Endocrinological Society of Australia, an organ- Osteoporosis Australia and the Australian and the New Zealand Society of Bone and Mineral the exchange is taken as the lower boundary of a sufficient 50 nmol / l (20 ng / ml), indicators in the range 30-50 nmol / L (12-20 ng / ml) is regarded as insufficient accuracy, indicators less than 30 nmol / l (12 ng / ml) - as vitamin D deficiency [39–41].

International Endocrinological Society, Fede- Swiss Food Commission, Spanish Society for the Study of Bones and Mineral Metabolism, Central European Vitamin D Committee considers indicator of sufficient security, figures equal to or exceeding 30 ng / ml (75 nmol / L) [41–43].

There are three specialized professional associations in Russia citation (Russian Association of Endocrinologists, Union pediatricians of Russia, Russian Association for Osteopo- rose) took the following boundaries: an adequate level concentration of 25 (OH) D in blood is considered 30 ng / ml (75 nmol / l), deficiency - concentration 21-29 ng / ml (51-72.5 nmol / L), deficiency - <20 ng / ml (<50 nmol / L). These values are used as for adults. lykh and in children [3, 44, 45]. At the same time, the target level 25 (OH) D during therapy should be assessed taking into account possible toxic effects, therefore it is necessary monitor the treatment: concentrate tion of 25 (OH) D should not exceed 55-60 ng / ml.

Vitamin D deficiency and deficiency include to the group of so-called alimentary-dependent diseases levania, namely malnutrition diseases [46]. Within the framework of the International Classification of Diseases of the Russian model of Vitamin D Deficiency and Deficiency are included in class IV "Endocrine diseases, diseases no nutrition and metabolic disease "(Endocrine, nutritional and metabolic diseases), code E55, and within adopted by the World Health Organization in 2019 and the currently actively implemented class sifications ICD-11 belong to class 05 "Endocrine diseases, nutritional diseases and metabolic diseases levania "(Endocrine, nutritional and metabolic diseases), code 5B57. In clinical practice for coding deficiency and deficiency of vitamin D for the purpose of copper Qing statistics should use the specified codes ICD-10 or ICD-11 [47, 48].

Prevalence of HIV deficiency and deficiency - tamin D is high in the world: in recent studies it has been shown that the prevalence of vitamin D deficiency (25 (OH) D level less than 20 ng / ml) in the United States was 24%, in Canada - 37%, in Europe - 40%. In a number of countries (India, Pakistan, Tunisia) reported prevalence with Clinical Recommendations of the Russian Association tion of endocrinologists [45].

Treatment regimens, supportive care and professional lactics of vitamin D deficiency and deficiency in children and adults have been developed and introduced into clinical practice. For the treatment and prevention of vitamin deficiency

severe vitamin D deficiency (concentration 25 (OH) D less than 12 ng / ml) at the level of more than 20% of the population [49].

According to a number of epidemiological studies, held in 2012–2018, in the Russian Federation prevalence of vitamin D deficiency in adults accounted for 64.5–94% of the population, depending on the region she [50, 51]. In 2020, in 10 regions of our country there were a multicenter non-interventional registration a test of the frequency of deficiency and vitamin D deficiency, which will demonstrate found that 72% of those surveyed had a deficit status and vitamin D deficiency (39% - deficiency, 33% - failure) [52].

In the Russian Federation, epidemiological logical studies of the prevalence of deficiency that of vitamin D in children. In the study "SPRING" in the group of 1230 children aged 1–36 months, it was found that 35.5% of children suffered from vitamin deficiency mine D, 23.4% - vitamin D deficiency [53]. E.I. Kondratyev et al. found that in a group of 1501 children and adolescents living in Moscow and the Moscow region, the optimal level is 25 (OH) D was observed in 18.7%, vitamin D deficiency - every third examined child population (30.3%), moderate calcidiol deficiency was registered almost every second person - 43.8%, had a severe 7.2% of children had cit [54].

High prevalence of vitamin D deficiency indicates its insufficient intake from natural sources that include endogenous synthesis in the skin under the influence of ultraviolet radiation and intake with food. Consumption rate the amount of vitamin D in the diet is 400-600 IU / day in accordance with the Methodological Recommendations of the Russian consumer supervision [55] and 600-1000 IU / day in accordance with mine D in children, it is recommended to use a cyberol, and in adults - cholecalciferol for treatment and colecalciferol or ergocalciferol - for phylaxis [3, 44, 45]. In the Russian Federation for designation of the international non-proprietary most change (INN) / grouping (chemical) changes of medicines containing vitamins min D $_3$, usually transliteration is used "Colecalciferol" (Latin name for vitamin D $_3$ - colecalciferolum), while for biologically active food additives (BAA) are traditionally more commonly used option "cholecalciferol", transliteration "kolekal- tsiferol "is used less frequently [56].

Basic treatment and prevention regimens for deficiency vitamin D are presented in the table.

In the Russian multicenter randomized a comparative study has also demonstrated van the effectiveness and safety of the drug colecalciferol in the form of capsules at a dose of 8000 IU / day 2 months and 50,000 IU once a week for 8 weeks in the saturation phase with the transition to the maintenance phase at a dose of 10,000 IU 1 time per week and 2000 IU / day for 12 weeks. Normal values concentrations of 25 (OH) D were achieved in 90% of patients patients who received colecalciferol 50,000 IU 1 time per week, and in 88% of patients receiving colecalc roll at a dose of 8000 IU / day after 8 weeks of therapy [57].

For a number of years for prevention and treatment vitamin D deficiency medications have been used means (drugs) containing colecalciferol or ergo- calciferol as an active ingredient. Along with with drugs on the Russian market were used dietary supplements that contained cholecalciferol in an amount of up to 600 IU.

In 2020–2021 against the background of high interest in Russian society to the problems of vitamin Mr. D and a growing understanding of the importance of maintaining

Table. Basic regimens for the prevention and treatment of vitamin D deficiency and deficiency in adults and children
Table. Basic regimens for preventing and management of vitamin D insufficiency and deficiency in adults and children

	Children	Adults
Medicine	Colecalciferol	Cholecalciferol or Ergocalciferol
Prevention	1-12 months - 1000 IU / day 1-3 years - 1500 IU / day 3 years - 18 years - 1000 IU / day	18-50 years - 600-800 IU / day Over 50 years old - 800-1000 IU / day
Medicine	Colecalciferol	
Treatment	Depending on the level 25 (OH) D 10 ng / ml or less - 4000 IU / day 1 month 11–20 ng / ml - 3000 IU / day 1 month 21-29 ng / ml - 2000 IU / day 1 month followed by control 25 (OH) D and the appointment of a prophylactic dose upon reaching the level of 30 ng / ml or more	Vitamin D deficiency Saturation phase 50,000 IU once a week for 8 weeks or 200,000 IU once a month for 2 months or 150,000 IU once a month for 3 months or 7000 IU / day 8 weeks Vitamin D deficiency Saturation phase 50,000 IU once a week for 4 weeks or 200,000 IU once or 150,000 IU once or 7000 IU / day 4 weeks Maintenance phase 1500-2000 IU / day 6,000-14,000 IU / day

normal level of this vitamin, the appearance of significant amounts of dietary supplements containing vitamin D in solid forms (tablets and capsules) in high doses (from 1000 to 5000 IU of cholecalciferol in one unit dosing) and in liquid forms (oil solutions, sprays, aqueous solutions). On the territory of the Eurasian eco- nomic union, which includes the Russian Federation, as of 06/08/2021 signed and valid there are 1432 State Register Certificates tion (SGR) dietary supplements containing in their composition as one of the active components is vitamin D $_3$ [56].

BAA are available to a wide range of consumers and available without a prescription, both in pharmacies and in non-specialized retail outlets.

According to the information provided in the SGR, sheet kakh-inserts and on the websites of manufacturers of these dietary supplements, most of them are intended to "replenish prevention and treatment. Confirmation of compliance Dietary supplements to the requirements for their quality and safety goes in the form of state registration, within the framework which is a one-time laboratory study safety characteristics (content of toxic substances and pathogenic microorganisms) and quality (active substance content) dietary supplement. Monitoring safety and independent quality control of dietary supplements after state registration are not obligatory and, as a rule, are not carried out [69, 70, 73, 74].

On the contrary, quality, safety and efficiency Drugs at all stages of their circulation (research and development processing, production, registration, circulation on the market ke) are legally regulated on a supranational (acts of the Eurasian Economic Union) and national national levels. The so-called proper established practices that establish minimum requirements

deficiency and insufficiency of vitamin D "[58–67].

Analysis of the registration documentation of these products Tov made it possible to identify a number of features:

- dietary supplements containing colecalciferol in a dose of 1000 IU and more, in pill form, have division risks and should be taken in a daily dose of no more than 500 IU / day, dietary supplements in the form of solutions are recommended for use in a daily dose not exceeding 500 IU / day [58–64];
- all dietary supplements, without exception, have length restrictions reception, the duration of which, as usually correlates with the recorded daily a dose of dietary supplements (from 1 month for 2000 IU to 6 months for 500 IU) [58–67].

Thus, the daily doses and duration of use dietary supplements specified in the *SGR* do not allow effective to treat and prevent deficiency and deficiency the accuracy of vitamin D.

A recent study demonstrates found that the content of the active ingredient in the dietary supplement varies in a much wider range compared to with drugs. Deviations from the stated content vitamin D is in the range of 2.4-10.8% in dietary supplements in the form tablets and 33.3–41.5% for dietary supplements in the form of solutions. At this deviation from the declared content of the ciferol in drugs was 0.6% in tablets and 1.3% - in solution [68]. The results of this study show testify to a less perfect security system quality of dietary supplements in comparison with drugs.

From the point of view of the legislation of the Russian Federation radios, EU countries and the USA dietary supplements are considered as additional natural sources of food and / or biologically active substances of natural origin or substances of artificial origin, pre- prescribed for addition to the diet, and their circulation is governed by the rules of food products [69–74]. Thus, dietary supplements all over the world considered as a type of food products. US and EU legislation note that dietary supplements should not be used and advertised as a means of treating diseases and pathologies mental states in humans. LS, on the other hand, considered are treated as substances or their combinations that used for prevention, diagnosis, treatment diseases or rehabilitation [75, 76].

Requirements for quality, efficiency and safety dietary supplements and drugs proportionally correspond to the areas their application. Legal requirements for dietary supplements provide ensure their hygienic safety and quality, but not the effectiveness and safety of use for requirements for the quality assurance system at each the stage of drug circulation [75–79]. Compliance with requirements good practice is monitored through regular inspections of state bodies (Roszdravnadzor, State Institute of Medicines and Super- lying practices). Confirmation of conformity of each individual drug requirements for quality, efficiency and security is carried out in the form of state registration, during which not only laboratory examination of quality, but also examination efficiency and safety of drugs based on reports mandatory preclinical and clinical research.

The quality of drugs, in contrast to dietary supplements, is controlled by the state authorities (Roszdravnadzor) not only in the process All registration, but also at all stages of drug circulation.

Regular independent quality control is carried out state and routine monitoring of drug safety. Prod- drug drivers are required to organize a pharmacovigilance system zora and carry out constant monitoring of side reactions to drugs during the entire period of circulation of drugs to the market, transmitting the obtained data on side reactions on drugs to the Federal Service for Supervision in the Sphere health care [79].

Thus, the support and control systems the quality of dietary supplements and drugs are fundamentally different nominal level. Requirements for the quality of dietary supplements provide the safety of their use only as one of the components of the diet in a dosage not exceeding the upper permissible level of consumption, but not as a means of prevention and treatment of diseases levaniations. Efficacy and Safety Studies Dietary supplements as a means of treating diseases are not carried out, which does not allow them to be used for medical purposes.

Daily dose of dietary supplements sources of cholecalciferol must meet the daily needs of a person in vitamin D. Established by various documents- mi operating in the Russian Federation, EU countries and the United States, the daily requirement for vitamin D varies they range from 200 to 800 IU / day [38, 55]. In the Russian Of the Federation of the Technical Regulations of the Customs Union for "Food products in terms of their labeling" TR CU 022/2011 dated 09.12.2011 is set by the recommended my daily intake of vitamin D 5 mcg (200 IU) per day [70], while the content is biologically active substances in a daily dose of dietary supplements should not pre- increase the upper permissible level of their consumption, which is set for vitamin D at 600 IU / day. The daily dose of vitamins and minerals in the composition ve dietary supplements for food for children from 1.5 to 3 years old should not be

increase 50% of the daily physiological need, and for children over 3 years old - 100% of the daily physiological your needs. Daily physiological requirement in vitamin D for the Russian Federation is set at the level of 10 μg (400 IU) per day [55].

Thus, the daily dose of dietary supplements sources of vitamin mine D cannot exceed 600 IU / day for adults, 400 IU / day - for children over 3 years old and 200 IU / day - for children from 1.5 to 3 years old. The established limits for dosages of dietary supplements do not allow their use as means of prevention and treatment of vitamin D deficiency.

Considering the use of dietary supplements for treatment and prevention of vitamin D deficiency and deficiency through the prism of legislative regulation of medical activity, it should be noted that the main legal howl act of the Russian Federation in the field of health care (Federal Law of 21.11.2011 N 323-FZ "On the basics protection of health of citizens in the Russian Federation ") [79] regulates, in addition to the provision of medical services, changes in drugs and medical products for medical purposes, the use of medical nutrition in the framework of kah therapy and prevention of diseases in accordance with with the norms determined by the Ministry of Health- of the Russian Federation [80]. Norms of medical nutrition provide for the use of vitamin and mineral complexes in a dose not exceeding 50-100% of the daily needs for vitamins and minerals. Thus, zom, the dose of vitamin D in the composition of medical nutrition is not may exceed 200-400 IU / day. Clinical guidelines below normal, class IV "Endocrine diseases, nutritional diseases and meta- diseases "(Endocrine, nutritional and metabolic diseases), code E55 according to the ICD-10 classification and to class 05 "Endocrine diseases, diseases nutrition and metabolic diseases "(Endocrine, nutritional and metabolic diseases), code 5B57 according to the fication ICD-11. In clinical practice for coding deficiency and deficiency of vitamin D in order to medical statistics should be used indicated- new codes ICD-10 (or in the future - ICD-11).

4. Deficiency and deficiency of vitamin D is widespread common in the Russian Federation among children and adults: the prevalence is on average 80% of the population, regardless of age, region of residence and season.
5. Consensus has been reached in the Russian scientific community regarding approaches to correcting vitamin D levels in adults and children: deficiency and insufficiency of vitamin mine D should be treated with drugs cholecalciferol (which is optimal vitamin D vitamer for this purpose) in high saturating doses (150,000-200,000 IU during 1 month / 392,000-450,000 IU for 2-3 months for the treatment of deficiency / insufficiency in adults and 2000-4000 IU / day for 1 month in children) with after the next transition to maintenance doses (1500–2000 IU / day in adults and 1000-1500 IU / day in children).
6. On the market of the Russian Federation in recent years

Russian professional associations dedicated to associated with the treatment and prevention of vitamin D deficiency, do not contain instructions on the possibility of using dietary supplements for appropriate purposes [3, 44, 45].

Based on the foregoing, dietary supplements as sources of vitamin mine D should only be used for enrichment food ration (to achieve the consumption rate vitamin D).

Treatment and prevention of deficiency and insufficiency vitamin D should be carried out in accordance with the given clinical guidelines by prescribing registered drugs.

Key provisions of the Joint Position

1. Vitamin D is a fat-soluble vitamin, active metabolites of which play an important role in maintaining a number of physiological processes in the human body. The role of vitamin D in regulation phosphorus-calcium metabolism is the best characterized ("classic" effects); Besides, vitamin D is involved in the regulation of immunity theta, proliferation and differentiation processes cells, carbohydrate and lipid metabolism, functional control of the cardiovascular system ("nonclassical effects).
2. A consensus has been reached in the Russian scientific community sus in relation to determining the status of vitamin D: serum concentration of 25 (OH) D is the most a more indicative indicator of vitamin D status. Vitamin D deficiency is defined as the concentration 25 (OH) D <20 ng / ml (<50 nmol / L), insufficient ness - concentration of 25 (OH) D from 20 to 29 ng / ml (from 50 to 72.5 nmol / l), adequate levels - concentralization 25 (OH) D 30 ng / ml (75 nmol / l).
3. In terms of formal classification and terminology deficiency and insufficiency are terminami denoting the same state - drop in serum 25 (OH) D concentration dietary supplements are widely represented - sources of vitamin D, including foods high in vitamin on D in one dosage form (1000-2000 IU / tablet, capsule) that are available to consumers in non-specialized outlets and positions are used by manufacturers as a means of correcting deficiency and deficiency of vitamin D.
7. The scientific community of the Russian Federation does not recommend recommends prescribing dietary supplements sources of vitamin D for treatment and maintenance therapy of deficiency and under- vitamin D deficiency due to the following reasons:

- unlike drugs - drugs colecalciferol products, which are intended for treatment and prevention of disease and pathological conditions of a person, dietary supplements-D are intended for normalization of the composition of the diet in order to ensuring the normal nutritional needs of the body human ma in vitamin D;
- the system of quality control and quality assurance of dietary supplements is not can ensure the effectiveness and safety of changes in dietary supplements in therapeutic and maintenance doses;
- in accordance with applicable law BAA-D in the Russian Federation can be used in doses not exceeding 600 IU / day, which is insufficient but for the treatment and maintenance therapy of deficiency and vitamin D deficiency;
- the basic law of the Russian Federation in the field health care 323-FZ "On health protection of citizens dan "does not allow the use of dietary supplements to provide medical care - treatment and support therapy for vitamin D deficiency and deficiency in this context.

Treatment, supportive therapy and prevention deficiency and deficiency of vitamin D should be give by prescribing drugs containing vitamin D (prerespectfully cholecalciferol) as an active substances.

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