To the Substantiation of the Joint Use of Vitamin D and the Rest of the 12 Vitamins Necessary for the Creation and Realization of the Vital Functions of its Hormone-Active Form (The Vitamin D + 12 Vitamins Approach)

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Abstract: The realization of the multiple vital functions of vitamin D in a human organism closely depends on the sufficient provision of the rest of the vitamins necessary for the creation of the hormone-active form of vitamin D, as well as on the normal realization of the vital biochemical and physiological processes it controls.

The above report substantiates the expediency of the combined application of vitamin D and a complex including the rest of the 12 vitamins both for the medical treatment and prevention of diseases (the D + 12 vitamins approach).

Keywords: 1α,25-dioxyvitamin D, prevention of diseases, the vitamin D + 12 vitamins approach.

The tremendous success achieved in the last decades in the study of the vitamin D exchange and its underlying mechanisms has clearly demonstrated the vital role of its hormone-active form, 1α,25-dioxyvitamin D. Its importance has not only been demonstrated in rickets prevention among children and osteoporosis prevention among the elderly, but also in decreasing the risk of the most frequently occurring and gravest modern diseases such as cardiovascular diseases, oncologic diseases, diabetes, and a large variety of others, which are the main reasons behind early disability and death among several million people (Table **1**).

This vast amount of data presented in thousands of publications by independent authors has served as the scientific basis for the development of practical proposals on the wide use of vitamin D. These initiatives are aimed at reducing risk factors and preventing the abovementioned diseases. Those proposals were considered by the European Parliament and the US Senate in the spring and summer of 2010.

Both the European Parliament and the US Senate have discussed increasing the recommended daily dose of this vitamin from 200-400 IU (5-10 μg) to 2000 IU (50 μg) per day. However, this proposal has never been formally adopted as a general compulsory practice – at least, until the present time.

Such guardedness is rather understandable, for it is widely known that vitamin D has rather narrow therapeutic amplitude and, if used in doses exceeding one's physiological need, may cause hypercalcemia and metastatic calcification of such vital organs as the heart and kidneys.

In the 1940-1950s, one of the most remarkable pediatricians used to say that an experienced doctor must be able to lead a baby "between the Scylla of rickets and the Charybdis of D-hypervitaminosis."

Now it is not only pediatricians that are facing this problem to its full extent, but many other specialists are now dealing with this issue, primarily nutritionists who deal with adults and older adults on a regular basis.

The duality of the effect produced by vitamin D, which is dose-dependent, has also been discovered by modern studies evaluating the impact of this vitamin on the frequency and outcomes of cardiovascular, oncologic, and other diseases.

One obvious example of such duality can be found in the results of a research study published by a group of authors in October in *The American Journal of Clinical Nutrition*, 2010 [13]. Within 13 years, the authors of the study had monitored the health status of 1194 men ages 71 years and older who had a concentration of 25-oxyvitamin 25(OH)D in their blood serum at the beginning of the study period, which is the most reliable indicator of vitamin D sufficiency in the body.

The authors found that the general mortality during the research period, which was dependent upon the original sufficiency of vitamin D in the bodies of those examined, was characterized by a U-shape (i.e., the

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E-ISSN: 1929-5634/13

Table 1: Physiologic Systems and Processes Reacting to the Hormone-Active Form of Vitamin D and the Character of Responses it Induces (Citation: A. Norman, R. Bouillon, Exp. Biol. Med., 2010; 235(9): 1034-45) [1]

Physiological systems	Physiological processes and the influence of $1,25(OH)_2D_3$	Disturbances and diseases related to vitamin D deficiency
I. Calcium homeostasis	Calcium intestinal absorption, remodeling of the skeleton bones	Rickets, adult rickets, osteoporosis
II. All cells of the organism	Cell cycle regulation Cell proliferation suppression	Reduced risk of the prostate, breast, rectum cancer, leukemia and other types of cancer [2-4]
III. Immune system	Stimulation of the function of scavenger cells and the synthesis of antibacterial peptides [5, 6]	Increased frequency of infectious diseases, including tuberculosis, autoimmune diseases, type I diabetes, disseminated sclerosis, psoriasis [7, 8]
IV. β-cells of the pancreatic gland	Insulin secretion	Deregulation of the insulin secretion, glucose tolerance, diabetes [6]
V. Cardiovascular system	Regulation of rennin-angiotensin system, blood clotting, fibrinolysis, cardiac muscle functioning	Renal hypertension; increased thrombogenesis; increased risk of cardiovascular diseases, heart attack [9]
VI. Muscular system	Skeletal muscles development	Increased frequency of myopathia
VII. Brain	The presence of the vitamin D receptor and 1α-hydroxylase of vitamin D in the human brain tissue [10]	The lack of vitamin D in the period of prenatal development leads to the deregulation of behavior in the adult state (muscular studies); increased risk of Parkinson disease [11] and mental degradation [12] among the older and elderly

mortality rates were definitely higher for the men with both originally low and originally high levels of vitamin D). For instance, approximately 50% higher mortality rates were recorded both among men with an original concentration of 25(OH)D lower than 46 mol/l (<115 ng/ml) in their blood plasma, and among the men with concentrations higher than 98 nmol/l (<245 ng/ml) [13].

Considering the inconsistency of the available information on the admissible limits and possible consequences of increasing the recommended daily vitamin D consumption rate, as well as considering the absence of relevant positive decisions made by the higher European and American governmental bodies, we find it reasonable, at least at this stage, to approach the problem of enhancing the provision of vitamin D to the population masses in a slightly different and, in our opinion, in a more efficient and safer way.

To be more specific, we must try to identify and eliminate the nutritional problems faced by modern man, which are still the biggest obstacles in both the natural transformation of vitamin D into its hormonal form within the human body, and in realizing the abovementioned vital functions of this form.

In this context, we find it reasonable to turn to the results of the research carried out in 1980s and 1990s at the Laboratory of Vitamins and Mineral Substances at Institute of Nutrition RAMS by the then Senior Fellow of the laboratory and the current professor at South Dakota University, Igor Sergeev, together with his young associates: a postgraduate from the Republic of Cuba, Raul Fernandez Reglado, and a postgraduate from North Korea, Kim Ren Ha.

In his research, which served as a basis for his doctoral thesis, I.N. Sergeev has clearly demonstrated the role of a large variety of vitamins both in the biosynthesis of the hormone-active form of vitamin D: $1,25(OH)_2D$ and in the realization of its multiple vital functions [14, 15], based on vast experimental findings. Let us consider these data in more detail.

Table **2** contains information on the specific role of vitamins C, B_2, B_6, PP, folic acid, α-tocopherol and vitamin K in the biosynthesis process, as well as information on the mechanisms of realization of the specific functions of the hormone-active form of this vitamin, $1,25(OH)_2D_3$ [14, 16].

Of importance, ascorbic acid ensures the normal realization of the steroidogenesis processes, including the synthesis of the primary predecessor of vitamin D, cholesterol [17, 18].

Coferment forms of vitamin B_2 (riboflavin) comprise the active center of the flavoprotein monooxigenases, which are responsible for the hydroxylation of vitamin D

Table 2: Role of Vitamins in the Processes of Biosynthesis and the Realization of the Specific Functions of the Hormone Form of Vitamin D (According to I.N. Sergeev, 1991) [14]

Vitamin C	Necessary for the normal realization of the steroidogenesis processes.
Vitamin B_2	In the forms of FMN and FAD, comprises the active centers of flavoprotein monooxigenases responsible for the hydroxylation of vitamin D with the formation of its active oxyforms: 25(OH)D; $1{,}25(OH)_2D$.
Vitamin B_6	In the form of PALF, takes part in the modification of some proteins, including receptors of steroid hormones.
Vitamin PP	In the form of NAD(F)N, is the source of regenerative equivalents in the process of synthesis of the vitamin D oxy derivatives: 25(OH)D; $1{,}25(OH)_2D$ and others.
Folacin (folic acid)	Plays an important role in the biosynthesis of proteins, including the fast-renewed protein receptors of the active forms of vitamin D.
Vitamin E (α-tocopherols)	As an antioxidant, acts as a protector of microsomal and mitochondrial hydroxylases taking part in the formation of active oxyforms of vitamin D: 25(OH)D; $1{,}25(OH)_2D$ and others.
Vitamin К	Takes part in the post-translation modification of the calcium-binding proteins.

in the process of transforming into its hormone-active form $1{,}25(OH)_2$ D [14, 19].

Nicotinomide coferments (derivatives of nicotinamide, such as vitamin PP) are necessary as they act as sources of regenerative equivalents in the abovementioned processes of the hydroxylation of vitamin D with the production of $1{,}25(OH)_2$ of vitamin D [14].

Folic acid is responsible for maintaining the proliferative capacity of cells, including those of bone tissue, in the process of their growth and renewal [14].

Vitamin E is an antioxidant and acts as a protector of the microsomal and mitochondrial hydroxylases, including those that take part in the synthesis of the hormone-active form of vitamin D [14, 20].

Vitamin К participates in the post-translation modification of the calcium-binding proteins, including the one whose synthesis (on a genetic level) is induced by the hormone-active form of vitamin D [21-25].

Table **3** shows the results of the experimental research conducted by I.N. Sergeev and his associates, which demonstrates the certain character and depth of the specific disorders associated with the synthesis and mechanisms of $1{,}25(OH)_2D$. This is especially apparent in conditions related to the deficiency of each of the vitamins mentioned above in the organism [14].

There are good reasons for comparing the information available on the specific roles of the above-listed vitamins in the creation and realization of the vital functions associated with the hormone-active form of vitamin D with the data on the real provision of the abovementioned vitamins to populations in developed countries. Specifically, it is important to compare the results of the mass studies available on the provision of vitamins to large groups of children and adults in

Table 3: Deregulations in the Biosynthesis of Functions of the Hormone-Active Form of Vitamin D in the Conditions of Insufficient Levels of other Vitamins in the Organism (According to I.N. Sergeev, 1991) [14]

Vitamin deficiency	25(OH)D concentration in blood	1(OH) activity of hydroxylase 25(OH)D in liver	$1{,}25(OH)_2D$ concentration in blood	Concentration of $1{,}25(OH)_2D$ used receptors in kidneys
C	↓	↓↓	↓	↓↓
B_2	↓	-	-	-
Folic acid	-	↓	-	↓↓
E	-	↓↓	↓	-
B_6	-	↓↓	↓	↑↑
К	-	-	-	↑

Russia, as pursued by the Institute of Nutrition RAMS both in the 1990s and in the last 5-7 years [26-28], using the most reliable, up to date methods and criteria. These criteria are based on the analytic definition of the concentration of vitamins and on the activity of the corresponding vitamin-dependent ferments in the biological fluids of the organism (blood, urine) [29, 30]. The results of these surveys illustrate that the insufficient consumption of vitamins is the most popular reason behind nutrition-related ailments.

The most serious nutritional problems concern the consumption of vitamins C, B_1 B_2, B_6, folic acid, and beta-carotene, as deficiency is typical among a significant number of children and adults in the Russian Federation population.

For instance, an examination of working class adults was carried out between 1983 and 1992 in cities such as Moscow, Yekaterinburg, Kuzbas, Norilsk, Bashkiria, and Mari El; in regions of Western and Eastern Siberia; as well as among the farm workers of Kuban. The findings of this investigation revealed that vitamin C deficiencies were noted among 88% of these adults (70% of whom suffered from a strong deficiency), deficiencies in the B vitamins (B_1, B_2, B_6) were found among 60%-80% of this sample (30%-47% of whom suffered from a strong deficiency), and folic acid deficiencies were witnessed among 80%-85% of these individuals (25%-30% of whom suffered from a strong deficiency) [27-29, 31-40].

In addition, the examination of preschool and school-aged children of Moscow, Yekaterinburg, Orenburg and other cities, conducted during those same years, revealed deficiencies of vitamin C in 27%-63%, folic acid among 23%-30%, B_1 in 40%-58%, and B_6 in 24%-70% of cases, accordingly. A total of 23%-32% of the examined children suffered from strong deficiencies of vitamins B_1, B_2, B_6, and ascorbic acid [34, 41-43].

According to the March-April 2001 examination of Moscow schoolchildren, 38% of the children had a vitamin C deficiency (according to its observed level in the blood samples taken), 79% had a vitamin B_2 deficiency, 64% had a vitamin B_6 deficiency, 22% had a vitamin E deficiency, and 84% of children had a beta-carotene deficiency.

A similar examination conducted in February 2006 among schoolchildren in the first four grades in St. Petersburg showed that vitamin C and B_1 deficiencies were found among 50%, and vitamin B_2 deficiencies were found among 30% of the examined children. More notably, only 10% of children had a reasonably sufficient level of all three vitamins. Half of the examined population suffered from a combined deficiency of two or all three of the vitamins at once.

In October 2007, specialists from the Laboratory of Vitamins and Mineral Substances at the Institute of Nutrition RAMS, in cooperation with OGK-2 employees, conducted an objective survey of vitamin sufficiency surrounding vitamins C, A, E, B_2, B_6 and beta-carotene among the staff members of various departments of the OGK-2 branch at the Pokrovskaya GRES power plant. This study investigated the levels of vitamins among a total of 174 men and women [2].

Despite the fact that the study took place in the autumn season, which is abundant in fruit and vegetables, the vitamin C deficiency was discovered among 34.8% of the total examined staff; in total, 6 people had a strong vitamin C deficiency and 2 were close to being classified as scorbutic.

The situation turned even worse when examining the B vitamins, which are found not in vegetables but in high-quality meat products. In particular, vitamin B_2 insufficiency was discovered among 47.4% of the examined (82 people of the 174 examined) and vitamin B_6 deficiency was found among 72.6% (126 people). In all, 108 people (62%) had low beta-carotene levels in their blood.

Only 5 women (!) from the 152 men and women who were examined had a sufficient level of all 6 vitamins, while no men were found to be sufficient across all 6 vitamins. Importantly, 64% of women and 84% of men had combined deficiencies of two, three, or four vitamins at once [32].

A September 2010 survey was conducted among children between 11-17 years of age who were going in for swimming programe. This survey was under control of the Nutrition Department for Healthy and Sick Children at the Scientific Children's Health Center RAMS. The findings showed that the level of vitamin E in the children's blood was below the line among 30.8% of children, levels of vitamin B_2 were low among 53.8% of the children, and beta-carotene levels were low among 79.5% of children. The combined deficiency across 2-4 vitamins was found among 73.9% of boys and 56.2% of girls. Only one girl from the 39 examined children had the necessary levels of all the vitamins mentioned above [38].

Thus, summarizing the numerous data from the results of the clinical and biochemical examinations of the representative child and adult groups across various regions of the country, we can characterize the general vitamin situation among the child and adult populations of the Russian Federation in the following way:

1. The revealed deficiencies imply that not one single vitamin is particularly low in the region; however, various combinations of deficiencies among vitamin C, the B vitamins, and carotene are prevalent, which is characteristic of polyhypoavitaminosis.

2. This vitamin deficiency may be found not only in the spring, but also in the summer and autumn periods, which seems to be the most favorable time of the year, and thus is characterized as a permanent negative factor.

Insufficient consumption of the vitamins and a number of the mineral elements found in food is not some specific trait of the food status of the Russian population, but it is a common problem in all of the developed countries. It emerged as an unavoidable consequence of the strong socioeconomic, as well as the scientific and technical progress that has been evidenced in the last century, which has led to the sweeping reduction in energy expenditure and the relevant decrease of the general amount of food being consumed by the modern man as sources of energy.

The human physiologic need to consume vitamins and mineral substances has been formed over the course of the human's evolution as a species, and the human metabolism has gradually adjusted to the amount of micronutrients that he has received with the consumption of large volumes of plain, natural food that has matched the large energy expenditure of our ancestors.

Within the last several decades, the technical revolution and large-scale social changes resulted in the two- to 2.5-fold (or greater) decrease in human energy expenditure. Food consumption has, or must have, decreased accordingly – otherwise, it would lead to overnutrition, an increased prevalence of overweight and obesity, and a spike in the resulting rates of diabetes, hypertensive disease, atherosclerosis, and other "civilized" diseases. However, food is not only a source of energy, but also a source of vitamins, as well as macro- and microelements. By reducing the general amount of food consumed, we inevitably doom ourselves to vitamin hunger, as well as to deficiencies of a number of vital mineral substances.

The calculations show that even the best diet involving the consumption of 2500 kcal per day (which equals the average energy expenditure of a modern Russian) lacks, at least, 20% of most vitamins [28, 36].

Without going into the details surrounding the reasons for and the consequences of this mass polyhypovitaminosis state among the population of the developed countries, and without describing the efficient methods that can be applied for its correction and prevention (which is the subject of our other publication [36]), we would like to underline here that the necessary condition for the successful realization of all the vital functions of vitamin D discussed above is the comprehensive provision of all vitamins responsible for the creation of the hormone-active form of vitamin D, and the successful realization of the multiple processes controlled by this form.

Taking into account the widespread nature of the polyhypovitaminosis state, may suggest that perhaps the reason for some of the inconsistency or the lack of persuasive evidence in a number of studies evaluating the efficiency of vitamin D in the prevention of cardiovascular, oncologic, and other diseases lies not with the absence of such effects surrounding the insufficient doses of vitamin D, but rather with the lack of other vitamins necessary for the normal creation of the hormone-active form of this vitamin and/or the realization of its function in the organism.

In this respect, it becomes clear that both the effective use of vitamin D in rickets prevention and the reduction of risk for the above-mentioned grave diseases require the application of this vitamin in combination with the recommended doses of other vitamins necessary in order to optimize the useful mechanisms and benefits of vitamin D.

These requirements are, to a great extent, met by multivitamins and vitamin-mineral complexes, as well as by vitamin-enriched protective diet products containing not only vitamin D, but the entire variety of the rest of the twelve vitamins in quantities providing 50% to 100% of the recommended daily dose (the D+12 vitamins approach).

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Received on 21-11-2012 Accepted on 11-12-2012 Published on 31-03-2013

DOI: http://dx.doi.org/10.6000/1929-5634.2013.02.01.1