Original Article

Role of Vitamin D in Prevention of Metabolic Syndrome and Cardiovascular Diseases

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Abstract

***Objective*:** About 90% of cardiovascular diseases can be prevented. In recent years, the role of vitamin D in the prevention of cardiovascular disease and components of metabolic syndrome has been actively discussed. The study aimed to investigate the possible influence of vitamin D_3 on the emergence risk of metabolic syndrome and adverse cardiovascular events.

Materials and methods*:** The study enrolled a total of 336 people (170 males and 166 females) aged 50-60 years. For comparative analysis, two groups were formed: Group 1 group involved 150 people treated with placebo, and Group 2 group included 186 people who received vitamin D3 orally in a dose of 2000 IU/day. The duration of treatment and observation was four years. Participants in the study completed a questionnaire developed by the authors of this paper, in which they answered questions about the presence of factors contributing to the development of cardiovascular pathology. ***Results and Discussion: Daily oral intake of vitamin D3 in a dose of 2000 IU/day for four years did not improve laboratory indicators, which are components of MS, namely, the content in the blood of TC, TG, LDL, HDL, AI, fasting and postprandial glycemia, insulin, and insulin resistance index HOMA2-IR ($p>0.05$). Prolonged use of vitamin D3 did not reduce the risk of cardiovascular diseases (myocardial infarcts (RR=0.93, 95% CI [0.21-4.09], p=0.92), strokes (RR=1.24, 95% CI [0.18-8.70], p=0.83), stenting (RR=1,23, 95% CI [0.32-4.88], p=0.76), arterial hypertension (RR=1.12, 95% CI [0.47-2.68], p=0.81), as well as cardiovascular death rates (RR=0.83, 95% CI [0.14-4.88], p=0.83) and death from any other causes (RR=0.93, 95% CI [0.21- 4.09], p=0.92). ***Conclusion**:* Thus, daily prolonged oral administration of vitamin D3 in a dose of 2000 IU/day does not contribute to the improvement of blood lipid spectrum, glycemia, and insulin resistance in metabolic syndrome and does not reduce the risk of adverse (fatal and non-fatal) cardiovascular events.

Keywords: vitamin D for prevention of metabolic syndrome; vitamin D for prevention of cardiovascular diseases; vitamin D and cardiovascular death; vitamin D deficiency.

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Introduction

Cardiovascular disease (CVD) is an urgent problem nowadays, as cardiovascular pathology is the most common cause of death in the world. CVD accounts for about 50% of deaths from non-infectious factors[1] and a third of all deaths.[2] The highest number of deaths from CVD in the countries of South and East Asia is due to high population density, which continues to grow.[3] More than 95% of all deaths from CVD are associated with such conditions as

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coronary heart disease (CHD), hypertension, stroke, cardiomyopathy, atrial fibrillation, and rheumatic heart disease.[2] In 2016, 2.6 million people died from CVD in China, of which 1.7 million - from IHD.[3] In 2017, 19.9 million of CVD new cases were diagnosed in 54 member countries of the European Community of Cardiologists.[4] Approximately 3.9 million people die annually from this heart disorder in Europe, which is about 45% of all deaths in this region. Annual health care costs for CVD treatment in Europe are almost 111 billion euros, and another 54 billion euros are due to productivity losses.[5]

Another condition closely related to CVD is metabolic syndrome (MS). MS represents a complex of clinical, hormonal, and metabolic disorders, which are powerful risk factors for cardiovascular pathology.[6] The pathogenetic basis of MS is insulin resistance and hyperinsulinemia. Hyperglycemia, high blood pressure, obesity, increased blood triglyceride content, and a decrease of high-density lipoproteins (HDL) is traditionally attributed to the MS components. The incidence of MS increases with the worldwide prevalence of obesity.[7] According to epidemiological data, MS affects about 25% of the world population. At the same time, the population of the USA is more vulnerable to MS than Europe, and South-Eastern Asia has a low morbidity rate.[8,9] According to the study conducted in the United States in 2011-2016, the prevalence of MS in the study population was 34.7%(n=17,048), with no statistically significant difference between men and women ($p>0.05$). However, an increase in the prevalence of MS with age was noted, which was 19.5% among people aged 20-39 years and 48.6% among people over 60 years.[10]

According to research data, 90% of CVD cases could be prevented.[2,4] This is why scientists and the medical community around the world are faced with the urgent issue of CVD prophylactic and prevention. Over the last decade, the appropriateness to use vitamin D3 in CVD and MS prevention is evidenced.[11,12] This opinion is based on the fact that the pathogenesis of CVD and MS is based not only on atherogenic dyslipidemia but also on the interaction of various factors: metabolic, genetic, external, and functional disorders. Vitamin D deficiency is one of the factors inciting the MS and CVD appearance.[11-13] that become a pandemic phenomenon lately. Thus, pronounced vitamin D deficiency (<30 nmol/l) is found in 5.9% of the population in the USA, in 7.4% in Canada, in 13% in Europe. The deficit (<50 nmol/l) is recorded in 24% of the population in the USA, 37% in Canada, and 40% in Europe.[14] The reasons for vitamin D deficiency is a decrease in its epidermal synthesis due to lack of insolation through urbanization, prolonged stay indoors, the use of sun-protective means, age factor, a decrease in its bioavailability due to obesity and absorption disorders, as well as increased catabolism due to the use of some drugs, in some diseases, and decreased synthesis of 25(OH) D in liver disorders and 1.25(OH)2D in chronic renal failure, pregnancy, and lactation.[13,15]

Vitamin D is a fat-soluble vitamin, which is contained in small amounts of food and is synthesized in the human body when exposed to sunlight on the skin.[13] However, the form of vitamin D synthesized under the influence of sunlight in the human skin, as well as the one that comes with food or biologically active additives, are biologically inert. This vitamin must undergo two hydroxylation processes to become active, namely, in the liver resulting in the formation of 25- hydroxyvitamin D or calcidiol ([25 (OH) D]), and afterward in the kidneys, where the biologically active 1.25-hydroxyvitamin D or calcitriol (D [1.25 (OH)2D]) is formed.[13,15] It is known that the main function of vitamin D is to participate in phosphorus-calcium metabolism. This vitamin plays an important role in the absorption of calcium in the intestine and is involved in maintaining appropriate levels of phosphate and calcium in the blood. Vitamin D is essential for the work of osteoclasts and osteoblasts, i.e., cells that provide bone growth and their remodeling. Most often, this vitamin is used to prevent rachitis in children, as well as osteomalacia in adults.[13,16]

Besides the regulation of calcium-phosphorus metabolism, vitamin D has many other effects. Thus, vitamin D receptors are present in more than 40 target tissues. External effects of this vitamin are mediated by hydroxylation from 25(OH)D to 1.25(OH)2D. It has been also found to inhibit the proliferation of keratinocytes in the epidermis. During the experiment, it has been established that in animals, for example, the risk of skin malignization due to exposure to ultraviolet radiation in the presence of defects of receptors to vitamin D has increased dramatically. The value of vitamin D in the pathogenesis of some skin diseases, such as psoriasis, ichthyosis, melanoma, atopic dermatitis, acne, photodermatitis, and some skin infections,[16-18] as well as autoimmune diseases like scleroderma, systemic lupus erythematosus, vitiligo, and bubble dermatosis has been studied.[19,20]

Vitamin D plays an important role in the processes of

regulating cell proliferation and differentiation of all organs and tissues, in particular immunocompetent cells and blood cells. Thus, calcitriol receptors were found on macrophages, T-lymphocytes, mature CD-8 cells, and immature thymus lymphocytes. The role of this vitamin in the immune system is proved by the ability to produce 1.25(OH)2D_3 by mononuclear phagocytes.[13]

Also, the neuroprotective action of vitamin D has been examined. This assumption is based on the fact that its metabolites can penetrate through the hematoencephalic barrier, thus gaining access to neurons and clay cells. Its possible role in neuromodulation and neuroprotection may be related to the fact that calcitriol can inhibit the synthesis of inducible NO-synthase, resulting in increased regulation of glutathione, which is part of the body's antioxidant protection system.[15,16]

In recent years, the nephroprotective role of vitamin has been discussed as it is a powerful hormonal inhibitor of renin expression. It was found that vitamin D deficiency is one of the risk factors for kidney disease.[20]

Vitamin D is important for the preservation of reproductive function, as evidenced by the presence of receptors to it on the placenta, endometrium, ovaries, testicles, sperm cells, as well as the pituitary gland. In particular, the development of such conditions as a polycystic ovarian syndrome and a decrease in the quantitative and qualitative characteristics of sperm is also associated with vitamin D deficiency.[21]

In recent years, the function and potential of vitamin D application to prevent CVD and MS have been actively discussed. However, there is no unequivocal opinion on this issue, and the results of studies are very contradictory: there is evidence of the preventive effect of vitamin D on cardiovascular pathology,[11,22-24] while other studies do not confirm such data.[25-28] Issues of cardiovascular pathology, in particular, coronary heart disease, lead to changes in blood lipid levels, reflecting increased lipolysis in metabolic syndrome.[29]

The study aimed to examine the possible effect of vitamin D_3 on the emergence risk of metabolic syndrome and adverse cardiovascular events.

Research material and methods

This study enrolled 336 participants, of whom 170 were men (50.6%) and 166 (49.4%) were women aged 50 to 60 years. The average age of those surveyed was 56.27 ± 2.40 years. The study was conducted from 2012 to 2019 based on primary health care facilities. Under examination were outpatients who had no cardiovascular diseases at the time of inclusion in the study. In the course of the study, two comparison groups were formed randomly, homogeneous by age and sex: Group 1 group involved 150 people treated with placebo, and Group 2 group included 186 people who received vitamin D3 orally in a dose of 2000 IU/day. Also, all patients participating in the study adhered to the recommendations on lifestyle and diet modification. The duration of treatment and observation was four years.

Virtually healthy men and women were included in the study according to the following criteria: age 50-60 years, absence of any CVD in the past and/or at the time of inclusion into the study, absence of obesity, agreement to follow the recommended diet and the regime of physical activity and rest, agreement to refuse additional intake of vitamin D in the form of biologically active supplements and/or multivitamin complexes, and voluntary consent to participate in the study signed by the patient.

Criteria for exclusion involved: age under 50 years and over 60 years, presence of CVD in the past and/or at the time of inclusion in the study, obesity, oncological pathology, additional intake of vitamin D in the form of multivitamin complexes, or biologically active supplements during the last six months before being included in the study, renal insufficiency, cirrhosis of the liver, presence of chronic disease in the decompensation stage, mental illness, hypercalcemia in the history or at the time of inclusion in the study, and the lack of compliance.

To assess the availability of risk factors for CVD, participants filled out a questionnaire developed the authors of the paper, in which they answered questions about heredity and anamnesis of the basic CVD, the presence of harmful habits, professional activities, concomitant pathology, drugs taken at the time of inclusion in studies, etc. Also, all the patients included in the research answered the survey questions concerning the features of nutrition and motor activity. These questionnaires were filled in by individuals at the stage of inclusion into the research and annually during four years of observation. Besides, every year during the entire 4-year follow-up period, each patient completed the questionnaire regarding adherence to the prescribed diet and lifestyle modification, vitamin D3 intake, and the presence/absence of side effects due to intake of the studied vitamin.

When all patients were included in the study, a detailed study of their life history was carried out,

as well as physical examination with obligatory anthropometric research, namely, measurement of growth, waist circumference (WC) and hip measurement (HM), body weight, based on which the body mass index (BMI) and the WC/HM index were calculated. Anthropometric parameters were studied to determine the presence/absence of obesity in a particular patient, which is a component of MS. BMI was calculated using the Kettle formula: BMI = m/h^2, where ***m*** is the body weight (kg), and ***h*** is the height (m). A BMI value of ≥30.0 indicated the presence of obesity.

At the time of inclusion in the study and annually for the next four years, each patient was monitored for some laboratory indicators to determine the presence of MS components and/or CVD risk factors. The obligatory list of laboratory tests included: general clinical blood analysis, indices of carbohydrate metabolism (determination of fasting and postprandial glycemia, insulin, glycosylated hemoglobin, HOMA2-IR index, which was calculated using HOMA Calculator Version 2.2 Diabetes Trials Unit University of Oxford (Great Britain)), lipid panel (total cholesterol (TC), low-density lipoproteins (LDL), triglycerides (TG), high-density lipoproteins (HDL), the Atherogenic Index (AI), which was calculated by the formula: AI=(TC-HDL)/HDL), coagulogram, ionogram (blood content of calcium, potassium, sodium, chloride ions), blood content of vitamin D_3 ($25(OH)D_3$), for monitoring of kidney function - blood content of urea and creatinine, for monitoring of liver function - total bilirubin, blood activity of alanine and aspartate aminotransferase (AAT).

Besides, all patients were submitted to undergo mandatory electrocardiography (ECG) on the SE-601 (Edan, China) apparatus and echocardiography (ECG) on Siemens Acuson X150 (Germany) apparatus.

Statistical data processing was performed using SPSS 13.0 software and Microsoft Excel 2013 (Microsoft, USA). When comparing the mean values, the Student's T-criterion, Fisher's F-criterion, Wilcoxon's T-criterion and U-criterion were used, and at a value of $p< 0.05$, the differences between the studied indicators were believed to be statistically significant. A risk ratio (RR) calculation via the Past program was applied to compare the frequency of cardiovascular events between groups at the end of the observation.

Ethical clearance: The authors declare that the work is written with due consideration of ethical standards

Results

It has been established that the average blood content of vitamin D_3 in the placebo group was (34.72±1.26) ng/ml, in 46 (30.7%) people, its content was within 20-30 ng/ml, and in 11 (7.3%) people - below 20 ng/ml. In the group of people who took vitamin D_3 orally, the initial average blood content was (34.29±1.41) ng/ml, while in 55 (29%) people, its content was within 20-30 ng/ml, and in 16 (8.6%) people - below 20 ng/ml. At the end of the study, the blood content of vitamin D_3 in the group of people who took it daily in the dosage of 2000 UI/day during the four years of observation increased by 1.42 times ($p<0.05$), on average. In contrast, a tendency to a decrease ($p>0.05$) was observed in the placebo group (Table 1).

As for MS indexes (blood TC, TG, LDL, HDL, AI, fasting and postprandial glycemia, insulin, HOMA2-IR index), no statistically significant intergroup difference was recorded at the end of observation

Table 1. Comparative Characteristics of BMI, Vitamin D_3 Content in the Blood, Lipid Panel and Carbohydrate Exchange Indexes between the Group of Vitamin D_3 Intake and Placebo Group

Indicator	Groups for comparison			
	Placebo (n=150)		Vitamin D_3 (n=186)	
	Before treatment	After treatment	Before treatment	After treatment
Vitamin D3, ng/ml	34.72±1.26	33.48±1.09	34.29±1.41	48.65±2.13 */**
BMI***, kg/m2	27.92±1.33	28.95±1.46	28.03±1.50	28.77±1.32
ABP, mmHg	126.10±9.38	129.77±10.24	125.95±7.99	129.63±11.51
TC, mmol/l	5.82±0.29	6.15±0.47	5.97±0.33	6.09±0.44
LDL, mmol/l	3.30±0.26	3.57±0.30	3.38±0.30	3.47±0.26
HDL, mmol/l	1.25±0.09	1.20±0.12	1.27±0.10	1.30±0.08
TG, mmol/l	2.44±0.30	2.63±0.19	2.45±0.17	2.61±0.30
AI, mmol/l	3.68±0.34	4.07±0.28	3.64±0.26	3.70±0.19
Fasting glycemia, mmol/l	5.22±0.51	5.64±0.50	5.19±0.44	5.57±0.37
Postprandial glycemia, mmol/l	7.29±0.66	7.70±0.53	7.25±0.70	7.61±0.64
Insulin, u/L	13.08±0.94	15.37±1.14	13.20±1.03	15.16±1.10
HOMA2-IR Index	1.70±0.04	2.03±0.04	1.71±0.04	2.00±0.06

*Note: * - the difference is significant in comparison with an index before treatment ($p<0.05$); ** - the difference is significant in comparison with the index after treatment in the placebo group ($p<0.05$); *** BMI – body mass index, ABP – arterial blood pressure, TC – total cholesterol, LDL – low-density lipoproteins, HDL – high-density lipoproteins, TG – triglycerides, AI - the Atherogenic Index.*

Table 2. Comparative analysis of cardiovascular events incidence in Group of Vitamin D_3 Intake and Placebo group at the end of the four-year observation

Cardiovascular events	Groups surveyed				RR	95 % CI	p
	Placebo (n=150)		Vitamin D_3 group (n=186)				
	Abs.	%	Abs.	%			
Myocardial infarction	3	2.0	4	2.1	0.93	0.21-4.09	0.92
Stroke	2	1.3	2	1.1	1.24	0.18-8.70	0.83
Stenting	4	2.7	4	2.2	1.24	0.32-4.88	0.76
Arterial hypertension	9	6.0	10	5.4	1.12	0.47-2.68	0.81
Cardiovascular death	2	1.3	3	1.6	0.83	0.14-4.88	0.83
Death due to other reasons	3	2.0	4	2.1	0.93	0.21-4.09	0.92

Also, no statistically significant differences in the incidence of cardiovascular death (RR=0.83, 95% CI [0.14-4.88], p=0.83), and deaths from other reasons (RR=0.93, 95% CI [0.21-4.09], p=0.92) between the comparison groups were established at the end of the observation.

($p<0.05$).

Comparative analysis of unfavorable cardiovascular events and/or diseases incidence revealed no statistically significant difference in the frequency of myocardial infarction ($p>0.05$), stroke ($p>0.05$), arterial hypertension ($p>0.05$), and the frequency of stenting ($p>0.05$) (Table 2).

Discussion

In this study, daily oral administration of vitamin D_3 at a dose of 2000 IU/day for four years did not improve laboratory indicators, which are components of MS (blood TC, TG, LDL, HDL, AI, blood glucose on an empty stomach and 2 h after meal, insulin, and insulin resistance index HOMA2-IR). No statistically significant difference ($p>0.05$) between the placebo group and the group of people who took vitamin D3 was established. At that, a tendency ($p>0.05$) to an increase in these indices at the end of observation in both comparison groups was observed. Also, a tendency ($p>0.05$) to increase in BMI and ABP at the end of a 4-year follow-up was revealed in individuals of both groups compared to the same indicators at the beginning of the study. However, the results did not depend on the initial blood level of vitamin D_3 in the surveyed patients. The data obtained in this study suggest that vitamin D_3 does not have hypolipidemic effects, the ability to improve glucose metabolism, or reduce insulin resistance, which are key indicators of MS, whose growth, in turn, increases cardiovascular risk. Also, the use of vitamin D_3 has not led to a decrease in mortality from cardiovascular events and due to other causes, as evidenced by the absence of a statistically significant difference ($p>0.05$) in their frequency between the placebo group and the group of people who received vitamin D_3. Prolonged use of vitamin D_3 did not reduce the risk of CVD, as evidenced by the absence of statistically significant difference between the placebo group and the group of individuals, who took the studied vitamin, by the frequency of myocardial infarcts (RR = 0.93, 95% CI [0.21-4.09], p = 0.92), strokes (RR = 1.24, 95% CI [0.18-8.70], p=0.83), stenting (RR=1.23, 95% CI [0.32-4.88], p=0.76), and arterial hypertension (RR=1.12, 95% CI [0.47-2.68], p=0.81). The results of this research are similar to the recent large-scale randomized, dual placebo-controlled VITAL study[25] conducted in the United States, which examined the likely effect of vitamin D_3 on reducing the risk of CVD and malignancies. The study involved 25.871 participants, of whom 51% were women over 55 years of age and 49% were men over 50. Patients without cardiovascular or cancer history and/or at the time of the trial were included into the study. Patients were divided into a group that received vitamin D_3 orally in a dosage of 2000 IU per day and a placebo group. The observation period for each patient was 5.3 years, on average. The researchers found that daily ingestion of vitamin D_3 in a dose of 2000 IU/day did not reduce the risk of adverse cardiovascular events (cardiovascular death (RR=0.97, 95% CI [0.85-1.12], heart attack (RR=0.96, 95% CI [0.78-1.19]), stroke (RR=0.95, 95% CI [0.76-1.20])), as well as malignancies (deaths from malignancies (RR=0.83, 95% CI [0.67-1.02] and the occurrence of any invasive malignancy (RR=0.96, 95% CI [0.88-1.06]).[25] Another placebo-controlled trial aimed at studying the effect of high doses of vitamin D_3 on the occurrence of CVD is worth noting. The study enrolled 5.110 virtually healthy patients aged from 50 to 84 years (average age (65.9 ± 8.3) years) who formed a placebo group and a group of individuals who were administered with intravenous vitamin D_3 in a dose of 200.000 IU once in the first month of the study. Then, each patient received a single vitamin D_3 dose of 100.000 IU monthly for the entire period of observation, which was 2.5-4.2 years (3.3

years, on average). According to the results of this study, prolonged oral administration of vitamin D_3 at high doses once a month did not reduce the risk of cardiovascular pathology and/or death: adverse cardiovascular events during the whole period of observation were in 11.5% of placebo individuals and 11.8% of vitamin D_3 group (RR=1.02, 95% CI [0.87-1.20]).[28] In a recent meta-analysis of 21 randomized clinical trials involving more than 83.000 patients, it was found that vitamin D_3 use does not reduce the risk of adverse cardiovascular events (stroke (RR=1.06, 95% CI [0.98-1.15]); p=0.16), myocardial infarction (RR=1.00, 95% CI [0.93-1.08]; p=0.92), cardiovascular death (RR=0.98, 95% CI [0.90-1.07]; p=0.68), and other causes of death (RR=0.97, 95% CI [0.93-1.02]; p=0.23).[27]

However, some studies reported that vitamin D_3 can reduce cardiovascular risk and the risk of MS occurrence.[11,22,23] In particular, one such paper studied the effect of vitamin D_3 on the risk profile of MS in women in the postmenopausal period. In total, the study included 160 women aged 50 to 65 years who were in the postmenopausal period. A part of women (n=80) received vitamin D_3 orally in a dose of 1000 IU for nine months, another part (n=80) comprised a placebo group. It has been established that at the end of nine months of the study, a significant decrease in the blood content of TG by 12.2% (p=0.001), insulin by 13.7% (p=0.008), index HOMA by 17.9% (p=0.007) was observed in the group of people who took vitamin D3 orally compared to the initial one. In the placebo group, the level of fasting glycemia increased by 6.2% (p=0.009). It was found that in women of post-menopause, daily oral administration of vitamin D_3 in a dose of 1000 IU in comparison with placebo reduces the risk of MS (OR=0.42, 95% CI [0.21-0.83], p<0.007>, p<0.007>, p<0.007>) was found.0.05), hypertriglyceridemia (OR=0.43, 95% CI [0.22-0.85], p<0.05), and hyperglycemia (OR=0.23, 95% CI [0.10-0.52], p<0.05).[11] However, it should be noted that the period of observation in the mentioned research was relatively short (only 9 months, in this study - 4 years, in the previously mentioned studies - 4-5 years), and the number of people included in the study was also relatively small (only 160, of which 80 comprised a placebo). Also, only women in post-menopause participated in the study. According to the meta-analysis of 42 studies with a total of 384.248 participants, vitamin D_3 is effective in preventing CVD,[23] but this meta-analysis included studies comparing the effectiveness of vitamin D_3, E, and B. Besides, the duration of observation in each of the studies included in the meta-analysis was different and relatively short, from four weeks to one year.

The assumption that vitamin D_3 may have a beneficial effect on reducing cardiovascular risk and contributing to the prevention of MS is based on the fact that vitamin D_3 receptors are found in almost all cells of the human body, including cardiomyocytes, endothelium, smooth muscle vessels. This provides a reason for argues between the scientists that vitamin D deficiency is a potential risk factor for CVD, MS, obesity, and diabetes.[11,12] According to literature, vitamin D deficiency plays an important role in the pathogenesis of MS risk factors, which, in turn, directly affects the cardiovascular system. It also contributes to the emergence and progression of insulin resistance and disorders in the function of adipose tissue, which results in obesity, stimulates the rennin angiotensin-aldosterone system, and promotes hypertension.[12,16] However, the data available today on this issue are rather contradictory, which does not allow stating unequivocally the positive effect of vitamin D on the reduction of cardiovascular risk and the risk of MS, as well as on the course of the CVD.

Conclusions

Thus, daily oral intake of vitamin D_3 in a dose of 2000 IU/day for four years did not lead to improvement of laboratory indicators, which are components of MS: the content in the blood of TC, TG, LDL, HDL, AI, fasting and postprandial glycemia, insulin, insulin resistance index HOMA2-IR (p> 0.05). Prolonged use of vitamin D3 has not led to a reduction in the risk of cardiovascular disease, as evidenced by the absence of statistically significant difference between the placebo group and the group of individuals who took the studied vitamin, by the frequency of myocardial infarcts (RR = 0,93, 95% CI [0.21-4.09], p=0.92), stroke (RR=1.24, 95% CI [0.18-8.70], p=0.83), stenting (RR=1.23, 95% CI [0.32-4.88], p=0.76), arterial hypertension (RR=1.12, 95% CI [0.47-2,68], p=0.81), as well as cardiovascular death rates (RR=0.83, 95% CI [0.14-4.88], p=0.83) and death from any other causes (RR=0.93, 95% CI [0.21-4.09], p=0.92). Therefore, daily prolonged oral administration of vitamin D_3 in a dose of 2000 IU/day does not contribute to the improvement of blood lipid spectrum, the level of glycemia, reduce

insulin resistance reduction in metabolic syndrome and does not reduce the risk of adverse (fatal and non-fatal) cardiovascular events. Therefore, the use of this vitamin to prevent metabolic syndrome and cardiovascular disease cannot be recommended.

Prospects for further research. The prospect for further research is to study the possibility of using vitamin D3 in patients with skin diseases.

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