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THE IMPACT OF VITAMIN D DEFICIENCY ON THE MANIFESTATIONS OF METABOLIC SYNDROME IN WOMEN OF REPRODUCTIVE AGE

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Abstract. *This prospective study included 150 outpatient women aged 16–41 years with metabolic syndrome (MS) and 25-hydroxyvitamin D [25(OH)D] levels below 30 nmol /L. All participants underwent anthropometry, bioimpedance measurement of body composition, assessment of carbohydrate and lipid metabolism parameters, and genotyping of* FokI *and* ApaI polymorphisms *of the VDR gene. The treatment protocol included daily intake of cholecalciferol at a dose of 10,000 IU, myo- inositol 4 g, and a low-carbohydrate high-fat (LCHF) diet against the background of standard MS therapy with metformin.*

After 12 weeks, the median 25(OH)D value reached the reference level; body mass index decreased by 7.8% ($p < 0.01$), waist circumference by 6.5% ($p < 0.01$). There was a significant decrease in HOMA-IR (–32%), triglyceride (–18%) and LDL (–11%) concentrations with a simultaneous increase in HDL (+9%). The most pronounced metabolic improvement was noted in carriers of the minor FokI -T *and* ApaI -C alleles.

For the first time in the population of Uzbekistan, a connection between vitamin D deficiency and MS with VDR gene polymorphisms was established, and the high efficiency of complex nutraceutical correction carried out against the background of an LCHF diet was confirmed. Based on the data obtained, a screening algorithm was developed that involves mandatory determination of 25(OH)D and genetic risk markers, which allows for personalization of therapy and increases its clinical and socio-economic effectiveness.

Key words: *metabolic syndrome, 25 (OH) D, VDR gene, body mass index, insulin resistance.*

Introduction. Metabolic syndrome (MS) — a combination of visceral obesity, insulin resistance, arterial hypertension and dyslipidemia — is recognized as one of the leading challenges to global health. According to the latest meta-analytic summary for 2024, the average prevalence of MS among the adult population of the world reaches 28% (95% CI 24–31%). [1] At the same time, vitamin D deficiency (25-hydroxycholecalciferol < 30 nmol /L) remains one of the most common forms of hidden micronutrient deficiency. A systematic review of 190 studies (2000–2022) found the global prevalence of severe vitamin D deficiency to be 15.7%, and hypovitaminosis (<50 nmol /L) to be up to 40% of the world's population. [12]

The proven link between vitamin D deficiency and the development of MS gives the topic particular scientific and clinical significance. A recent (2025) meta-analysis showed that individuals with 25(OH)D levels < 50 nmol /L have a 35% higher risk of developing MS (OR 1.35; 95% CI 1.21–1.50) compared to individuals without deficiency.[11]

Experimental data confirm that the combination of hypovitaminosis D and MS increases systemic inflammation, endothelial dysfunction and myocardial remodeling, which leads to a synergistic increase in cardiovascular complications. Results of modern studies indicate a relationship between reduced serum vitamin D levels and obesity in middle-aged individuals.

The aim of the study. To study the characteristics of metabolic syndrome in women with vitamin D deficiency, to improve the algorithm for diagnosing and treating metabolic syndrome.

Materials and methods. This scientific study included 150 women with metabolic syndrome who were treated as outpatients at the Level Med Clinic and the National Medical Center from 2023 to 2024. The average age of patients was 34 ± 6 years. All patients were informed about the course

of the study and agreed to participate in this study. The study was conducted on the basis of an objective study, which included subjective data and anthropometric assessment, clinical and laboratory data (complete blood count, biochemical blood test, glucose, homocysteine and insulin levels in the blood, HOMA index, lipid spectrum, vitamin D levels in the blood), genetic analysis, which consisted of studying two polymorphisms of the VDR gene, with observance of the stages of the survey of respondents.

Results and discussion. The results of the data obtained on the portrait of women who took part in the study made it possible to identify a number of factors that contribute to the formation of an unfavorable risk of metabolic disorders.

Age, as a modifiable risk factor, has a significant role in increasing the incidence of overweight and obesity. It was found that women aged 35 years and older have a higher risk of obesity (OR=2.52 95% CI 2.12-3.01; OR=6.36 95% CI 4.14-9.66), which is consistent with data on the increase in the number of patients with overweight and obesity in the population aged 35-45 years.

The age factor was also confirmed by the results of our study (Table 1).

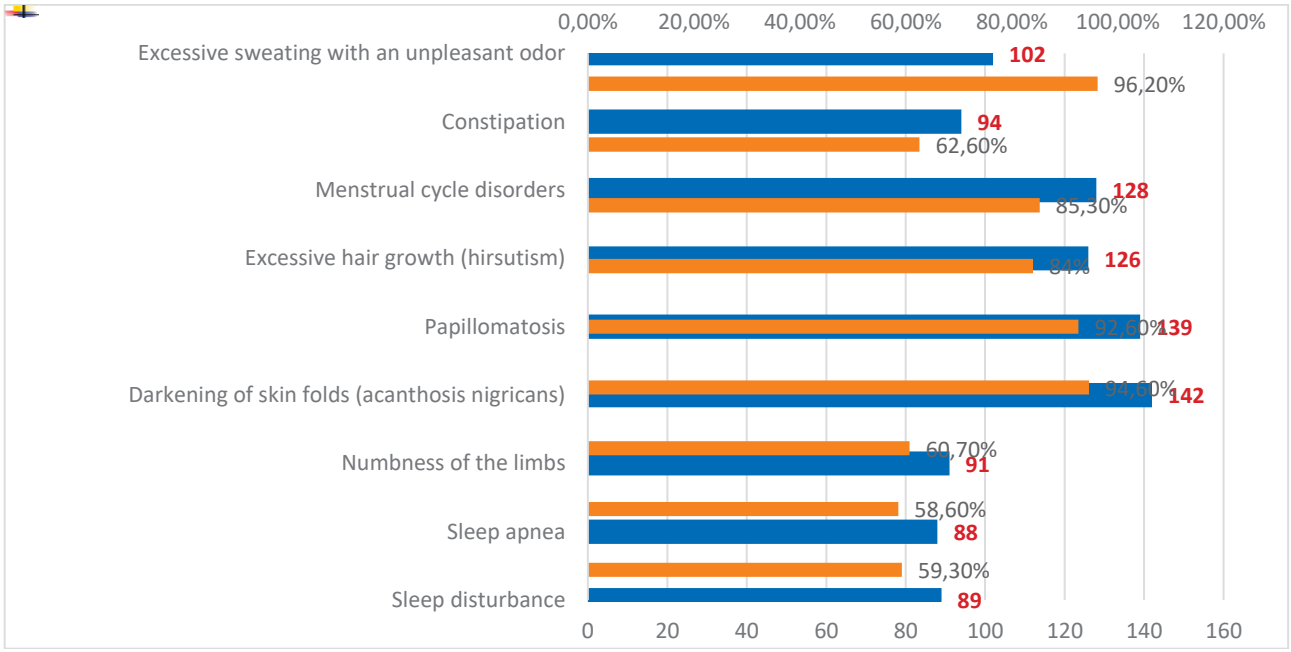
Table 1

Characteristics of patients by age and BMI data

Year of birth	Absl ed		45 years old		40 years old		35 years old		30 years old	
Obesity	79	14.4±3.1	2	10±6.7	14	26.9±6.1	18	2.4±2.3	45	9.1±11.3
Excess body weight	69	45.6±4.45	11	55±11.1	23	44.2±6.8	20	47.6±7.7	17	27.3±10.2
Normal body weight	50	40±4.3	7	35±10.6	15	28.8±6.2	21	50±7.7	7	63.6±9.8
	200	100	20	100	52	100	59	100	69	100

As can be seen, in our study the average age of women with normal body weight was 32.3±4.4 years, which is lower than that of overweight women - 37.7±2.8 years (p=0.035) and obesity - 40.7±4.2 years (p< 0.0001).

Further research showed the importance of the respondents' subjective data (Fig. 1).



** standard deviation 0.05*

Fig. 1. Analysis of subjective complaints other than excess weight of the examined patients (n = 150)

The diagram shows the frequency of the main complaints presented by women of reproductive age who have undergone screening for metabolic syndrome (MS). The values are given as the absolute number of patients (red numbers) and the proportion of the entire sample (%, caption on the right axis).

Key clinical and anamnestic accents:

1. Dermatological markers of insulin resistance. *Acanthosis nigricans* and *papillomatosis* were detected in 94.7% and 92.7% of patients, respectively, which indirectly indicates long-term hyperinsulinemia. In the literature, these signs are considered as a cutaneous equivalent of severe insulin resistance, anticipating the development of MS and type 2 diabetes mellitus. [10]

2. Endocrine and reproductive disorders. The high frequency of oligo-/amenorrhea (85.3%) and clinical hirsutism (84.0%) indicates the phenotype of polycystic ovary syndrome (PCOS) in combination with MS. This is associated with vitamin D deficiency and increased cardiovascular risk, which requires targeted laboratory additional examination (25(OH)D, LH/FSH, total and free testosterone, HOMA-IR index).

3. Somatovegetative manifestations. More than half of the sample had hyperhidrosis, constipation, paresthesia, and sleep disorders/apnea. The complex of these complaints reflects early vegetative dysfunction, as well as obstructive sleep apnea (OSA), which additionally increases insulin resistance and hypertension.

The obtained data demonstrate that pathognomonic skin and reproductive symptoms occur in more than 4/5 of overweight patients, emphasizing the clinical and diagnostic value of their active detection during metabolic syndrome screening and planning of preventive programs.

The anthropometric parameters of the subjects also varied within different limits (Table 2).

Table 2.

Bioimpedance data and BMI of respondents in the main and control groups

No.	Indicators	Main group	Control group	P *
1	Body mass index	31.25	20.73	0.05
2	Waist size	91.32	68.23	0.005
3	Hip volume	99.49	86.25	0.05
4	Fat mass	31	10.1	0.005
5	Skeletal muscle mass	21,22	23.37	0,1

**P - standard deviation*

Analysis of bioimpedance data confirmed that abdominal fat distribution (waist circumference>91 cm) supports the diagnosis of metabolic syndrome, correlating with insulin resistance and increased vascular risk.

Sarcopenic obesity (↓ SMM against the background of ↑ fat mass) indicates an unfavorable prognosis: low muscle mass worsens insulin sensitivity and limits the metabolic "buffering" capacity of the body.

Practical implications:

First: the targeted focus of the intervention is to reduce % fat while simultaneously increasing/maintaining SMM (strength training, adequate protein, vitamin D);

Second: monitoring the dynamics - repeated bioimpedance every 3-6 months, waist monitoring monthly.

The next stage of the research of respondents was laboratory examinations (Table 3).

Table 3.

Analysis of vitamin D levels in the blood depending on the BMI indicators of respondents

No.	Indicators	Vitamin D <20	%	Vitamin D>20	%
1	Excess weight	39	69.6%	17	30.35%*
2	Obesity	94	100%	0	0%
3	Normal body weight	0	0	50	100%

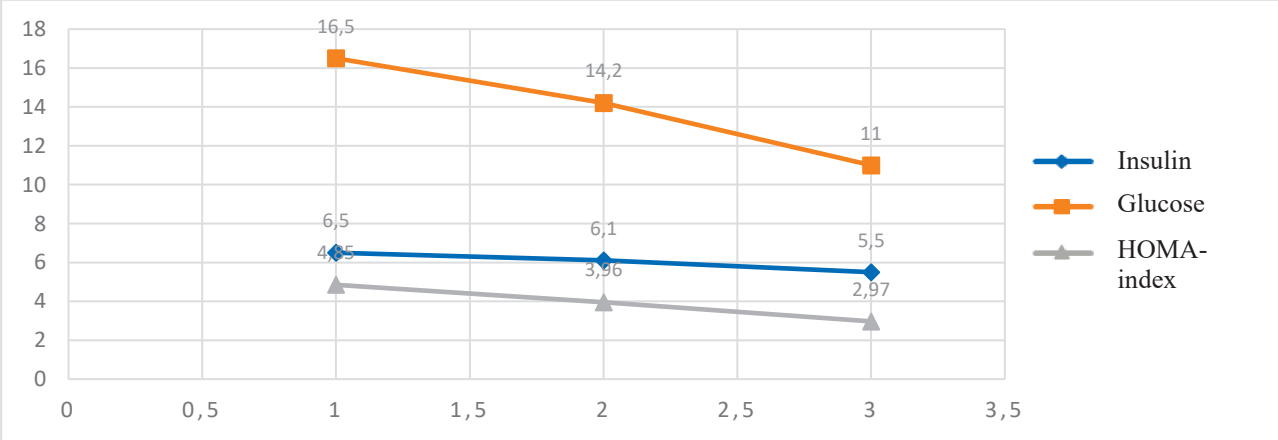
**P-standard deviation = 0.005*

The gradation demonstrates a clear negative relationship between the concentration of 25(OH)D and the severity of excess body weight. The lower the level of vitamin D, the higher the probability of shifting from the normal BMI range towards obesity. In the studied sample, vitamin D deficiency is statistically significantly associated with excess body weight and especially with obesity. The obtained results confirm the need for *targeted screening and timely correction of hypovitaminosis D* as part of the comprehensive prevention and treatment of metabolic syndrome.

Pathophysiological accents:

- Sequestration of D in adipose tissue and expansion of the volume of distribution reduce circulating 25(OH)D.
- In obesity, there is suppression of 1-α- hydroxylase, increased degradation by 25(OH)D-24-hydroxylase and subclinical inflammation, which further reduces the bioavailability of active metabolites.
- Vitamin D deficiency, in turn, disrupts IRS-1/GLUT-4 expression via VDR signaling, increasing insulin resistance and creating a "vicious cycle" of fat accumulation.

The data presented below demonstrate that a decrease in vitamin D concentration is closely associated with an increase in hyperinsulinemia, hyperglycemia, and the HOMA-IR index, which emphasizes the possible pathogenetic role of D deficiency in the formation of carbohydrate metabolism disorders (Fig. 2).



** Three groups were constructed according to the accepted clinical gradation of the level of 25-hydroxyvitamin D in serum.*

*** HOMA-IR = (insulin, mIU /L × glucose, mmol/L) / 22.5; insulin resistance threshold ≈ 2.5–3.0.*

Fig. 2. Correlation of the level of vitamin D provision with carbohydrate metabolism data

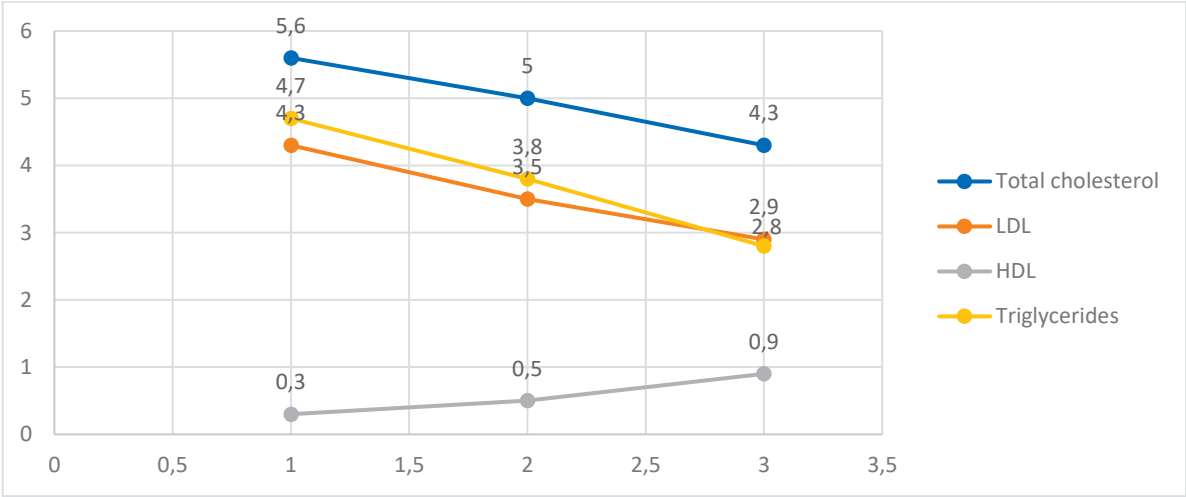
In this diagram, the clear downward trend for all three parameters indicates an inverse correlation between vitamin D concentration and the severity of carbohydrate metabolism disorders: the lower the 25(OH)D, the higher the hyperinsulinemia, hyperglycemia, and HOMA-IR. In the

vitamin D-deficient group, HOMA-IR is almost double the threshold of 2.5-3.0, confirming the pronounced insulin resistance characteristic of metabolic syndrome. Even 10-15 ng /ml of additional 25(OH)D (transition from category 1 to 2) is accompanied by a significant improvement in the parameters, emphasizing the dose -dependent nature of the effect.

Pathophysiological explanation: Vitamin D, interacting with VDR in β-cells and adipocytes, regulates:

- transcription of IRS-1 and GLUT-4 ⇒ increases tissue sensitivity to insulin;
- insulin secretion through modulation of intracellular Ca^{2+};
- systemic inflammation (↓ NF- κB), reducing lipotoxicity.

A correlation was also established between vitamin D deficiency and lipid spectrum (Fig. 3).



**Boundaries correspond to Endocrine Society 2011.*

Fig. 3. Correlation of the level of vitamin D provision with the data of lipid metabolism indicators

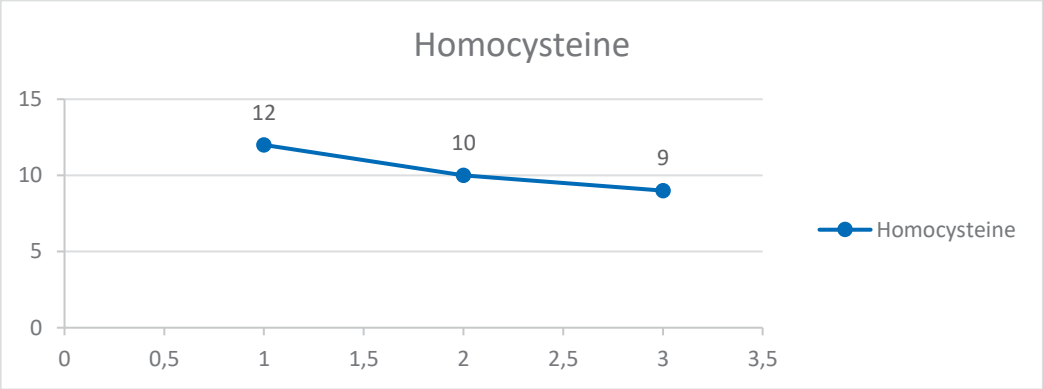
This table demonstrates that vitamin D deficiency is associated with severe atherogenic dyslipidemia, whereas optimal 25-(OH)D levels are associated with decreased LDL, triglycerides and increased HDL, potentially reducing cardiovascular risk in patients with metabolic syndrome.

The downward trend of atherogenic fractions indicates that during the transition from severe deficiency to a sufficient level of vitamin D, total cholesterol ↓ by 23%, LDL ↓ by 35%, triglycerides ↓ by 38%. At the same time, the growth of the antiatherogenic fraction is an indicator that the concentration of HDL increases threefold (0.30 → 0.90 mmol/l), reflecting an improvement in reverse cholesterol transport.

The atherogenic index (TG/HDL ratio) decreases by more than 4.5 times (15.7 → 3.2), which indicates a significant reduction in cardiometabolic risk.

Regulation of lipogenesis via VDR. Active form of vitamin D inhibits transcription of SREBP-1c and de-novo enzymes lipogenesis, reducing triglyceride production in the liver. Increased expression of LDL receptors and lipoprotein lipase promotes plasma clearance of LDL and VLDL. The anti-inflammatory effect (↓ IL-6, TNF-α) prevents lipoprotein oxidation, indirectly increasing HDL levels. The inverse correlation between 25-(OH)D levels and atherogenic lipids emphasizes the pathogenetic role of vitamin D deficiency in the development of dyslipidemia in metabolic syndrome. Maintaining 25-(OH)D ≥ 50 ng / ml can be considered as an inexpensive adjuvant to statins / fibrates, especially in patients with hypertriglyceridemia and low HDL.

OH)D deficiency, homocysteine remains in the “high-normal” zone (≥ 10 μmol /L), which is associated with accelerated atherogenesis and endothelial dysfunction. Reaching ≥ 30 ng /mL lowers the indicator to 9 μmol /L, a level considered metabolically “optimal” and safe for blood vessels (Fig. 4).



** The boundaries are based on the recommendations of the Endocrine Society (2011).*

Fig. 4. Correlation of the level of vitamin D provision with homocysteine

In this diagram, the inverse correlation highlights that correction of D deficiency may be a feasible adjuvant to folate/B_{12} therapy in patients with moderate hyperhomocysteinemia and metabolic syndrome. Even a "modest" increase in 25-(OH)D to ≥ 30 ng /mL moves homocysteine from the borderline atherogenic zone to a safe range, potentially reducing vascular risk. The downward trend: each increase in vitamin D status by one category is accompanied by an average decrease in homocysteine of ~1–2 μmol /L (≈ 17% relative decrease between the extreme groups).

The genotypic pattern of Apa I VDR differs sharply between the groups: the C allele is completely dominant in patients with metabolic syndrome and is virtually absent in the control (Table 4). The data support the hypothesis of direct involvement of the vitamin D receptor pathway in the pathogenesis of insulin resistance and obesity.

- The C-allele and especially the homozygous CC genotype are significantly associated with membership in the main cohort (obesity/metabolic syndrome).
- The AA genotype predominates in the control group (90%) and can be considered protective.

Table 4.

Analysis of APAL polymorphism of the VDR gene in the main and control groups

No.	APA I (VDR rs 7975232) in the main group	n	%	APA I (VDR rs 7975232) in the control group	n	%
1	AA	28	18.66	AA	45	90*
2	AC	65	43.3	AC	5	10**
3	SS	57	38	SS	0	0

**P – standard deviation = 0.013*

***P – standard deviation = 0.005*

According to the table, the VDR Apa I C-allele is a strong genetic predictor of metabolic disorders: carriers have ≈ 28-fold risk compared to carriers of the A-allele.

Apa I is located in the 3'-UTR of the VDR gene and affects mRNA stability. The "C" allele is associated with decreased receptor expression, leading to:

↓ IRS-1 and GLUT-4 transcription → insulin resistance;

↑ expression of lipogenic enzymes SREBP-1c, FASN → hypertriglyceridemia;

↑ proinflammatory IL-6/TNF-α → subclinical inflammation.

The combination of these effects forms the metabolic syndrome with insufficient activation of VDR signaling. However, it is necessary to take into account the polymorphism of FOK I VDR gene (Table 5).

Table 5.

FOK polymorphism analysis I VDR gene in the main and control groups

No.	FOK I (VDR rs 10735810) in the main group	n	%	FOK I (VDR rs 10735810) in the control group	n	%	R
1	AA	91	66,6	AA	0	0	-
2	AG	50	33.3	AG	3	6	-
3	GG	9	6	GG	47	94	0.05

The table interprets that the carriage of the A allele increases the probability of belonging to the main group (obesity/metabolic syndrome) by approximately 100 times compared to G carriers. In the cohort of patients with metabolic syndrome, a sharp shift in the frequencies of Fok I VDR was revealed: the A allele occurs three times more often, and the GG homozygote is practically absent. This emphasizes the critical role of genetic variability of VDR in the formation of energy metabolism disorders and confirms the feasibility of a personalized approach to the correction of vitamin D and metabolic therapy.

Fok I is located in the start codon of the VDR gene. The G allele (often denoted as F) produces a shortened protein (424 aa) with greater transcriptional activity. The A allele (f) shifts the frame by three amino acids → a long isoform (427 aa) with reduced VDR activity. A weak VDR signal reduces the expression of IRS-1 and GLUT-4, reduces lipolysis and enhances the proinflammatory background - the pathogenetic basis for insulin resistance and weight gain.

The study showed that the prevalence of AA/AG (≈ 100% of patients) is a genetic predisposition to metabolic syndrome against the background of hypovitaminosis D. No AA in the control; dominance of GG (94%) G-allele is protective: a more active VDR reduces the risk of obesity and IR. Strategy for managing A carriers is to keep 25-(OH)D at a level of ≥ 40 ng / ml:

• Early initiation of insulin sensitizer or metformin/GLP-1

• Prioritize strength training to compensate for low VDR activity

Conclusions. Among women of reproductive age with metabolic syndrome (MS), severe vitamin D deficiency (25-(OH)D < 20 ng /ml) occurs in more than 90% of obese patients and 70% of overweight patients; it significantly correlates with increased BMI, waist circumference, fasting glucose, HOMA-IR and triglyceride levels, and decreased HDL-C.

Carrying minor alleles C (ApaI, rs7975232) and A (FokI, rs10735810) of the VDR gene significantly increases the risk of developing MS: the frequency of the CC and AA/AG genotypes among patients is 38% and ≈ 100%, respectively, while in the control group it does not exceed 10%.

A combined nutraceutical program (cholecalciferol 10,000 IU/ day + myo- inositol 4 g/ day) against the background of an LCHF diet for 12 weeks resulted in:

• an increase in the median level of 25-(OH)D to a sufficient level (≥ 60 ng /ml);

• reduction in BMI by 7.8% and waist circumference by 6.5%;

• a decrease in HOMA-IR by 32%, triglycerides by 18%, LDL-C by 11% with a simultaneous increase in HDL-C by 9%;

• reducing homocysteine to < 10 μmol /L, confirming the cardiometabolic benefit of the intervention.

The most pronounced metabolic response was observed in carriers of minor alleles of FokI -T and ApaI -C, which emphasizes the importance of genetically determined sensitivity to vitamin D and justifies the need for a personalized approach to the correction of hypovitaminosis.

The proposed management algorithm (25-(OH)D screening, VDR genotyping, targeted high-dose vitaminization and myo- inositol against the background of an LCHF diet) provides a multifactorial improvement in the cardiometabolic profile and can be recommended for widespread

implementation in clinical practice in order to reduce cardiovascular risk and socioeconomic losses associated with MS in women of childbearing age.

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