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The role of non-drug strategies in reducing the risk of cardiovascular complications in women with metabolic syndrome during the menopausal transition

Berikhanova RR[1]*, Minenko IA[2] and Bondarev SA[3]

[1]Federal State Budgetary Institution "Central Clinical Hospital of Civil Aviation", Moscow, Russia

[2]Department of Integrative Medicine FGAOU VO "First Moscow State Medical University named after I.M. Sechenov", Moscow, Russia

[3]Cardiologist of the Rehabilitation Clinic of the University Clinical Hospital №2 FGAOU VO "First Moscow State Medical University named after I.M. Sechenov", Moscow, Russia

Abstract

Objective: To study the possibilities of non-drug correction of metabolic and endocrine disorders in women with metabolic syndrome (MS) in menopause. Design: Participants are divided into 5 groups depending on the programs used, each of the groups is divided into 2 subgroups - menopausal syndrome (MPS) of mild to moderate degree.

Setting: Estimated levels of follicle-stimulating (FSH), luteinizing (LH) hormones, estradiol, hemostasis, glycemic status, lipid profiles, Green test.

Participants: 330 women aged 45-50 with menopausal syndrome (MPS) and MS.

Interventions: Standard approach, physical therapy, balneotherapy, multivitamins and minerals, physiotherapy (vibrotherapy, chromotherapy, melotherapy, aromatherapy, aeroionotherapy) in various combinations.

Main outcome measures: Mann-Whitney test, criterion Kruskal-Wallis, Wilcoxon criterion.

Results: In patients with mild MPS, when using programs with physiotherapy, HOMA-IR decreased by 50%, the atherogenic index by more than 25%, the INR level increased by more than 4,0%, the total Green score decreased by more than 40,0%. in patients with moderate MPS, the treatment complex with the simultaneous use of vibrotherapy, chromotherapy, melootherapy, aromatherapy and aeroionotherapy had the advantage: HOMA-IR decreased by 50,5%, atherogenic index by 30,5%, INR increased by 5,0%, overall score on the Green scale decreased by 40,0%.

Conclusion: In patients with MPS and MS, non-drug programs using physical therapy have a positive effect on the functioning of the endocrine system, hemostasis, carbohydrate and fat metabolism which helps reduce the risk of cardiovascular events. In case of moderate MPS against the background of MS, the program with simultaneous use of vibrotherapy, chromotherapy, melotherapy, aromatherapy and aeroionotherapy has an advantage.

Abbreviations: AI: atherogenicity index; BMI: body mass index; IR: insulin resistance; HOMA-IR -Homeostasis Model Assessment-Insulin Resistance; FSH: follicle-stimulating hormone; LH: luteinizing hormone; MHT: menopausal hormone therapy; MPS: menopausal syndrome; MS: metabolic syndrome; TS: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

Introduction

The biological process of extinction of reproductive function is associated with the deterioration of physical and mental health, social maladaptation and a decrease in the quality of life of women [1,2]. Currently, menopause is a predictor of MS and a high risk of cardiovascular complications [3,4]. An important role in increasing cardiovascular risk is played by thyroid dysfunction, the frequency of which increases in the menopause [5,6]. Hormonal restructuring during the menopausal transition creates conditions for the redistribution of the subcutaneous fat layer with its emphasis in the abdominal-visceral region and the formation of MS [7- 11]. It is convincingly shown that obesity is a chronic systemic inflammation that triggers insulin resistance (IR), multi-organ metabolic dysfunction, platelet activation, and endothelial stress, which determines a high risk of cardiovascular complications [12-16]. The presence of a woman's metabolic syndrome (MS) exacerbates metabolic and endocrine disorders and subjective symptoms of menopause [17,18]. The dominant role of menopausal hormone therapy (MGT) in the treatment of pathological menopause has been established [19,20], but its metabolic and oncological safety remains debatable [21-23]. If there are contraindications to MGT or a woman refuses it, it is a serious problem to provide effective medical

Correspondence to: Berikhanova Rumisa Ramzanovna, Obstetrician Gynecologist, Central Clinical Hospital of Civil Aviation; Applicant, Department of Integrative Medicine, I.M. Sechenov First Moscow State Medical University, Russia, Tel: 89150120906; E-mail: rumiska07@mail.ru

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care without the use of estrogen-gestagenic drugs, both from the position of relieving subjective menopausal symptoms, and from the position of preventing cardiovascular complication.

Purpose of work: To study the effect of multimodal non-drug programs for correcting menopausal disorders in patients with metabolic syndrome during the menopausal transition on metabolic and endocrine disorders.

Materials and methods

Materials**:** The study, approved by the local ethics Committee of the I. M. Sechenov First Moscow State Medical University, meets international ethical requirements and includes 330 women with infored voluntary consent. By randomization, 5 groups were formed, each of which is divided into two subgroups according to the severity of climacteric syndrome (MPS) on the Greene Climacteric Scale (GCS) [24]: subgroup A - patients with mild MPS (1-11 points), subgroup B - patients with moderate MPS (12-19 points) (Table 1).

The age, social characteristics, and somatic status of the groups did not differ. All patients gave voluntary informed consent inclusion criteria: women 45-50 years old (average age 47.5 ± 3.5 years), who are in the period of menopausal transition; the presence of initial MS, diagnosed according to the recommendations of experts of the all-Russian scientific society of cardiologists for the diagnosis and treatment of metabolic syndrome [25], the prescription of MS from two to five years; the presence of mild and moderate MPS, a typical complicated form (against the background of MS); the absence of MGT in the anamnesis; absence of initial disorders of the thyroid gland. Exclusion criteria: whether a woman has: severe mental disorders; alcohol and drug dependence; acute diseases of the cardiovascular system; acute inflammatory diseases; bleeding and propensity to them; malignant or unverified neoplasms; tumors in the growth stage or in a state requiring surgical treatment; signs of severe organ failure; the presence of initially impaired thyroid function according to hormonal examination; the presence of intestinal dysbacteriosis of the 3 degrees of severity; the presence of diabetes mellitus; the presence of vaginitis; individual intolerance to physical factors and / or components of vitamin and mineral products.

Treatment methods: Basic treatment was applied in all groups and included normalization of lifestyle, sleep, diet therapy, and increased physical activity. Treatment principles: personalized approach, timely implementation of events, continuous diet therapy, lifestyle modification (all patients were motivated to quit smoking). In the presence of arterial hypertension, patients received standard antihypertensive therapy (moxonidine 200 mcg orally once a day continuously).

Basic treatment. Reduction diet based on individual calculation of the main exchange: OO = (0,0342 × M + 3,5377) × 240, where OO - the value of the main exchange (kcal), M - body weight (kg). It was recommended to take a fractional meal 5-6 times a day in small portions at the same time. The diet included foods containing complex carbohydrates (cereals, fruits, vegetables), rich in dietary fiber, restricted the use of simple carbohydrates, saturated fat, salt up to 3 g per day, was not allowed to take coffee, alcohol.

The body mass index (BMI) was calculated using the formula: BMI= body weight (kg) / body length2 (m2). Food diaries were analyzed. The total energy value of the diet was calculated based on standard caloric coefficients in kcal per 1 gram: 4 kcal for protein and carbohydrates, 7 kcal for alcohol and 9 kcal for fat.

Physical activity was recommended taking into account the state of health, were in the zone of good tolerance. Used daily walking in the fresh air for 30 minutes. All the patients were motivated to quit smoking, observe the work and rest regime. Basic treatment was carried out in a continuous mode.

Drinking balneotherapy: Ingestion of mineral water "Essentuki № 4" in the volume of 180-300 ml (3 ml per 1 kg of body weight) at room temperature 30 minutes before meals. The course duration was four weeks, followed by a second course in 3 months.

Therapeutic exercise: We used daily morning hygienic gymnastics for 10-15 minutes, pelvic floor exercise (Kegel exercises), aimed at strengthening the periurethral and perivaginal muscles, anal sphincter, and increasing the functional volume of the bladder [26].

Physiotherapy: The multi-factor physiotherapy unit "Spectra Color SPA System" ("Sybaritic Inc.", USA) was used. General vibration therapy: vibration with varying frequency from 10 to 60 Hz and increasing amplitude up to 7 mm, increasing the frequency of vibration for 8-10 seconds, 15 minutes. Music therapy: relaxing melodies within 30 minutes. Aromatherapy: through a four-channel system, aromatic oils were sprayed inside the capsule: Lavandula officinalis, Foeniculum vulgare. Full spectrum chromotherapy was performed for 30 minutes, with a wavelength from 760 to 400 nm. Selective chromotherapy: green light was applied for 30 minutes, with a wavelength of 530 nm. The face was blown with ionized cool air with a predominance of negative ions for 30 minutes. Inside the capsule, a special individual comfortable microclimate was created. Temperature range 25-30 °C. The contour bed with supporting pads allowed the patient to take the most comfortable and relaxing position. Sessions in the physical therapy facility "Spectra Color SPA System" were held twice a week for 30 minutes, a course of 10 sessions. Repeat the course in 3 months. A total of 20 procedures during observation.

Table 1. Study design

Group	I		II		III		IV		V	
Sub-group	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB	VA	VB
n	32	38	30	29	34	32	36	34	38	37
Treatment methods	Basic treatment Drinking balneotherapy Therapeutic exercise Multivitamins and minerals Aromatherapy Ionotherapy Melotherapy Vibration therapy Chromotherapy		Basic treatment Drinking balneotherapy Therapeutic exercise Multivitamins and minerals Aromatherapy Ionotherapy Melotherapy Vibration therapy		Basic treatment Drinking balneotherapy Therapeutic exercise Multivitamins and minerals Aromatherapy Ionotherapy Melotherapy Chromotherapy		Basic treatment Drinking balneotherapy Therapeutic exercise Multivitamins and minerals		Basic treatment	

Note: subgroup A - mild climacteric syndrome, subgroup B - climacteric syndrome of moderate degree

Vitamins and minerals: 22 balanced components ("Menopace ®", " Vitabiotics Ltd.", Great Britain) and calcium carbonate with colecalciferol (vitamin D3) (Calcium-D3 Nycomed, Nycomed Pharma, Norway). Menopace ® " was taken daily 1 capsule per day during or after meals. The course of treatment is 6 months. "Calcium-D3 nicomed", containing calcium carbonate 1250 mg (equivalent to elementary calcium-500 mg) and colecalciferol (vitamin D3) 5 mcg (200 IU), was taken orally 1 tablet 2 times a day for 1 month, repeated course in 3 months. Survey methods:General blood analysis was performed on a hematological analyzer "CELL - DYN 17002 (Abbott, USA). The levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined using the automatic enzyme immunoassay "NexGen" ("ADALTIS", Italy) in blood serum using a set of reagents "Alcor Bio" (Russia). The level of estradiol was studied using ELISA's diagnostic ELISA kits (DRG, Germany). The concentration of fibrinogen, APTT (activated partial thromboplastin time), prothrombin time, and thrombin time in blood plasma was studied on the "ACL 9000" coagulograph ("INSTRUMENTATION LABORATORY", USA) using reagents from the same company, and the INR (International Normalized Ratio) was determined using the formula: INR = (patient's Prothrombin time) / Normal average prothrombin time)^{ISI}, where ISI (International Sensitivity Index of thromboplastin) is an indicator of the sensitivity of the used thromboplastin, which standardizes it relative to the international standard. Hageman-dependent fibrinolysis was determined (Arkhipov A. G., Eremin G. F., 1985). C-reactive protein (CRP) was determined by the latex immunoturbidimetric method.

A biochemical blood test was performed on an automatic selective biochemical analyzer "Konelab 30" ("Thermo Fisher SCIENTIFIC", Finland) and standard sets of reagents "BioSystems" (Spain), including the determination of glucose, blood lipid spectrum (total cholesterol (TS), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides). The atherogenicity index (AI) was determined: AI = (TS-HDL) / HDL; where AI is the atherogenicity index, TS is total cholesterol (mmol/l), and HDL is high - density lipoproteins (mmol/l).

The concentration of immunoreactive insulin was determined on a microplate reader "Multiscan EX" ("Labsystems", Finland) using reagents from the company " DRG " (USA). To determine insulin resistance, the HOMA-IR (Homeostasis Model Assessment - Insulin Resistance) model was used. The index is calculated using the formula:

HOMA-IR = fasting glucose (mmol/l) x fasting insulin (Mme/l) /22.5 (Matthews D. R., 1985).

Statistical analysis

The sample size was not calculated beforehand. Statistical data processing was performed using the application software packages Statistica 10 ("StatSoft Inc", USA) and SAS JMP 11 ("SAS", USA). Comparisons of the two groups on quantitative scales were made based on the nonparametric Mann-Whitney test. Comparing three or more groups on the quantitative scales were based on nonparametric criterion Kruskal-Wallis. To describe quantitative indicators, the average value and standard deviation in the format "M ± σ"were used. The analysis of dynamics of indicators in the case of comparison of two periods was performed on the basis of nonparametric Wilcoxon criterion. The level of statistical significance was determined at the error probability level of 0,05.

Result

The results of the study: Hormonal profile: It was found that in women with moderate MPS in the period of early menopausal transition, the levels of FSH and LH were higher, and the level of estradiol was lower compared to the corresponding indicators of women with mild MPS, which indicated more pronounced violations of the hypothalamic-pituitary-ovarian axis.

Among patients with mild MPS, the most significant positive changes in the hormonal background were found when using complexes with physiotherapy (complexes I, II and III), which was expressed in a significant decrease in gonadotropins after 3 months of treatment, a significant increase in estradiol. The FSH level is shown in table 2 (Table 2)

The level of FSH decreased in patients of subgroup IA after 3 months of therapy by 11,9% (p=0,0183), and after 6 months of treatment by 23,2% (p<0,0001), respectively in subgroup IIA - by 10,7 % (p=0,0208) and 20.3% (p<0,0001), in subgroup IIIA by 10,4% (p=0,0162) and 19,1% (p<0,0001). Significant regression of FSH was also found in the IVA subgroup - by 6,0% (p=0,0227) and 14,0% (p<0,0001), respectively, but there were statistically significant differences with the IA subgroup. In the VA subgroup, the level of FSH did not change significantly, but there was a tendency for it to increase. Among patients with moderate MPS, the most significant decrease in FSH was observed in subgroups IB, IIB and IIIB: in subgroup IB after 3 months by 11,6% (p=0,0237), after 6 months of treatment by 19,3% (p<0,0001), respectively in subgroup IIB by 8,8% (p=0,0222) and 17,6% (p<0,0001), in subgroup IIIB by 8,6% (p=0,0183) and 16,5% (p<0,0001). In subgroup IVB, the level of FSH significantly decreased after 6 months of treatment by 12.0 % (p<0.0001), but was significantly lower compared to the corresponding indicator in subgroup IB. Attention was focused on a significant increase in the level of FSH in the VB subgroup - by 2,6% (p=0,0008).

Table 2. Dynamics of follicle-stimulating hormone (mMe/ml) levels

Subgroup	M ± S, before	M ± S, 3 months	M ± S, 6 months	P (before - 3 months)	P (before - 6 months)
IA	66,92 ± 30,50	58,98 ± 31,67	51,41 ± 31,78	0,0183	<0,0001
IIA	64,57 ± 30,30	57,65 ± 31,84	51,43 ± 31,34	0,0208	<0,0001
IIIA	66,88 ± 30,67	59,90 ± 32,50	54,08 ± 31,29	0,0162	<0,0001
IVA	68,76 ± 30,73	64,66 ± 31,28	59,15 ± 29,57	0,0227	<0,0001
VA	67,70 ± 30,33	68,26 ± 32,70	70,26 ± 35,23	0,5534	0,9273
IB	88,80 ± 32,38	78,47 ± 31,96	71,67 ± 31,69	0,0237	<0,0001
IIB	85,10 ± 33,21	77,61 ± 31,32	70,12 ± 30,49	0,0222	<0,0001
IIIB	83,55 ± 32,04	76,36 ± 30,55	69,75 ± 30,51	0,0183	<0,0001
IVB	83,38 ± 31,93	80,67 ± 32,73	73,39 ± 31,32	0,0610	<0,0001
VB	82,64 ± 31,81	83,23 ± 32,47	84,82 ± 33,31	0,9875	0,0008

The LH level is shown in table 3. Significant regression was observed in subgroup IA, after 3 months of treatment by 19,6% (p=0,0109), after 6 months of treatment by 25,6%, in subgroup IIA by 18,4% (p=0,0069) and 25,0% (p<0,0001), in subgroup IIIA by 17,1% (p=0,0127) and 23,0% (p<0,0001), respectively, differences between subgroups were not significant (Table 3).

In the IVA subgroup, a statistically significant regression of LH was detected after 6 months of treatment - by 11,7% (p<0,0001), but the indicator significantly differed from that of the IA subgroup. It is important to note that in the VA subgroup, the LH level significantly increased by 12.2% (p<0,0001). Among patients with moderate MPS after 3 months of treatment, only the IB subgroup showed a significant decrease in the level of LH - by 16,3% (p=0,0181). After 6 months, the regression of the LH level in subgroup IB reached 23,9% (p<0,0001), and there was a significant decrease in the indicator in subgroups IIB, IIIB - by 19,4% (p<0.0001), 20,0% (p<0,0001), respectively, and to a lesser extent in subgroup IIIB - by 4,0% (p=0,0404). Attention was drawn to a statistically significant increase in the level of LH in the VB subgroup by 7,4% (p<0,0001).

Table 4 shows the level of estradiol. A significant increase in estradiol was detected after 6 months of treatment in subgroups IA, IIA, IIIA and IVA-by 22,3% (p=0,0084), 18,1% (p=0,0208), 18,3% (p=0,0005) and 11,1% (p=0,0113), respectively (Table 4).

However, there were no significant differences between these subgroups. There was no significant change in the level of estradiol in the VA subgroup, the indicator significantly differed from the indicator in the IA subgroup.

In patients with moderate MPS, there was an increase in the level of estradiol in subgroups IB, IIB, IIIB and IVB, it was not reliable. There was a decrease in the level of estradiol in the VB subgroup, but it was not statistically significant (Table 5).

Body Mass Index: BMI is shown in table 5. Initially, the average BMI in subgroups A was 36,07 ± 0,89, in subgroups B it was significantly higher - 36,48 ± 0,99 (p=0,0045). In patients with mild MPS, BMI regression was 11,8% (p=0,0109) in subgroup IA after 3 months of treatment, 17,0% (p<0.0001) after 6 months of treatment, 11,1% (p=0,0183) and 15.3% (p<0,0001) in subgroup IIIA, 9,2%

Table 3. Dynamics of luteinizing hormone level (mMe/ml)

Subgroup	M ± S, before	M ± S, 3 months	M ± S, 6 months	P (before - 3 months)	P (before - 6 months)
IA	23,87 ± 5,93	19,19 ± 6,71	17,76 ± 6,12	0,0109	<0,0001
IIA	23,47 ± 5,49	19,15 ± 6,83	17,61 ± 6,44	0,0069	<0,0001
IIIA	23,49 ± 6,02	19,48 ± 6,75	18,10 ± 6,25	0,0127	<0,0001
IVA	24,53 ± 5,92	23,39 ± 5,51	21,65 ± 5,99	0,0525	<0,0001
VA	24,47 ± 5,72	25,39 ± 5,61	27,45 ± 4,70	0,0938	<0,0001
IB	29,84 ± 6,01	24,97 ± 7,43	22,70 ± 8,17	0,0181	<0,0001
IIB	29,04 ± 5,50	26,39 ± 7,48	23,39 ± 8,33	0,1358	<0,0001
IIIB	28,41 ± 5,75	26,41 ± 7,00	22,74 ± 8,07	0,1054	<0,0001
IVB	27,97 ± 6,02	27,42 ± 6,49	26,85 ± 5,39	0,2074	0,0404
VB	28,27 ± 5,58	28,71 ± 6,08	30,37 ± 5,09	0,3613	<0,0001

Table 4. Dynamics of estradiol level (pmol / l)

Subgroup	M ± S, before	M ± S, 3 months	M ± S, 6 months	P (before - 3 months)	P (before - 6 months)
IA	113,83 ± 53,71	126,04 ± 65,67	139,17 ± 77,87	0,5168	0,0084
IIA	119,28 ± 54,66	125,48 ± 60,31	140,86 ± 73,85	0,7057	0,0208
IIIA	114,07 ± 54,65	119,33 ± 59,40	134,88 ± 73,78	0,2401	0,0005
IVA	112,18 ± 52,94	114,19 ± 54,73	124,59 ± 64,78	0,8110	0,0113
VA	115,18 ± 55,82	115,42 ± 56,26	118,69 ± 59,59	0,8625	0,7394
IB	83,88 ± 34,03	90,10 ± 41,12	93,06 ± 43,79	0,7368	0,0993
IIB	88,55 ± 35,03	92,23 ± 38,49	94,65 ± 41,14	0,5782	0,1950
IIIB	91,20 ± 36,45	94,34 ± 39,50	98,25 ± 43,29	0,8688	0,1786
IVB	90,29 ± 34,78	92,31 ± 36,92	94,66 ± 39,16	0,7959	0,2759
VB	90,76 ± 35,09	88,63 ± 32,89	88,08 ± 33,16	0,4932	0,1012

Table 5. Dynamics of body mass index (BMI)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	36,15 ± 1,02	31,88 ± 1,98	29,99 ± 1,78	0,0109	<0,0001
IIA	36,14 ± 0,90	32,13 ± 2,28	30,61 ± 2,19	0,0183	<0,0001
IIIA	35,99 ± 0,84	32,68 ± 2,38	30,80 ± 2,39	0,0449	<0,0001
IVA	36,08 ± 0,77	33,12 ± 2,28	31,75 ± 2,28	0,0525	<0,0001
VA	35,98 ± 0,91	34,33 ± 2,55	34,39 ± 2,32	0,1300	0,0723
IB	36,45 ± 0,79	32,73 ± 1,58	30,88 ± 1,66	0,0136	<0,0001
IIB	36,50 ± 1,15	32,93 ± 2,14	31,17 ± 1,52	0,0129	<0,0001
IIIB	36,46± 0,93	32,89 ± 1,80	31,42 ± 1,82	0,0109	<0,0001
IVB	36,51± 1,15	33,08 ± 2,10	31,88 ± 2,61	0,0112	<0,0001
VB	36,48 ± 0,93	35,78 ± 1,94	35,16 ± 1,97	0,7304	0,0929

(p=0,0449) and 14.4% (p<0,0001) in subgroup IVA, 8.2% (p=0,0525) and 12,0 % (p<0,0001). The lowest BMI regression was observed in the VA subgroup: after 3 months of treatment by 4,6% (p=0,1300), after 6 months of treatment by 4,4% (p=0,0723). In patients with moderate MPS, BMI reduction was: in subgroup IB after 3 months of treatment, 10,2 % (p=0,0136), after 6 months of treatment, 15,3% (p<0.0001), respectively in subgroup IIB, 9,6% (p=0,0129) and 14,6% (p<0,0001), in subgroup IIIB – 9,8% (p=0,0109) and 13,8% (p<0,0001), in subgroup IVB – 9,4% (p=0,0112) and 12,7% (p<0,0001). In the VB subgroup, the decrease in BMI was not significant - by 1,9% (p=0,7304) and 3,6% (p=0,0929), respectively.

Hemostasis: It was found that in patients with moderate MPS, the thrombophilic properties of blood were more pronounced compared to patients with mild MPS, as indicated by lower values of INR, APTT, higher platelet levels, and XIIA -dependent fibrinolysis.

In patients with mild MPS, the number of platelets (Table 6) significantly decreased after 3 months of treatment in subgroups IA and IIA - by 4,24% (p=0,0048) and 3,83% (p=0,0005), respectively, and after 6 months of treatment, there was a significant regression of the indicator in subgroups IA, IIA and IIIA - by 5,41% (p<0,0001), 4,11% (p<0.0001) and 1,79% (p=0,0008), respectively. No significant changes were found in subgroups IVA and VA. Among patients with moderate CS, a significant decrease in the number of trombocytes was found after 3 months of treatment only in subgroup IB by 1,23%, and after 6 months of treatment-in subgroups IB and IIB - by 2,17% (p=0.0127) and 1,04% (p=0,0222), respectively. In subgroups IIIB and IVB, the indicator did not change significantly. There was a slight increase in the number of platelets in the VB subgroup, but it was not reliable.

A significant increase in the level of INR relative to the baseline was observed in subgroup IA after 3 months of treatment by 4,0 % (p=0,0142), after 6 months of treatment by 5,0% (p=0,0041). In subgroups IIA and IIIA, a statistically significant decrease in INR was achieved after 6 months of treatment by 4,0% (p=0,0028) and 4,0% (p=0,0206), respectively. Among patients with moderate MPS, a significant increase in INR was recorded only in subgroup IB after 6 months of treatment - by 5,1 % (p=0,0157). In both subgroups of group IV, the level of INR increased slightly, but not significantly relative to the baseline. There was also no significant change in the level of INR in both subgroups of group V (Table 7). At the same time, the indicators significantly differed from similar indicators in group I.

The dynamics of the APTT level is shown in table 8. In patients of subgroups IA, IIA and IIIA, APTT significantly increased after 3 months of treatment - by 1,8% (p=0,0183), 1,5% (p=0,0303) and 1,1% (p=0,0231), respectively, after 6 months of treatment - by 3,2% (p<0,0001), 2,7% (p<0,0001) and 2,3% (p<0,0001), the differences between the subgroups were not statistically significant. In the IVA subgroup, the APTT index significantly increased after 6 months of treatment by 0,8% (p=0,0036). Among patients with moderate MPS, APTT significantly increased after 3 months of treatment in subgroups IB and IIB by 1,6% (p=0,0271) and 0,9% (p=0,0062), respectively. After 6 months of therapy, there was an increase in APTT in subgroup IB by 3,3 % (p<0,0001), in subgroup IIB by 1,2% (p=0,0002), and in subgroup IIIB by 1,1% (p=0,0063). In subgroup IVB, the level of APTT increased by 0,9% after 3 months of treatment (p=0,0112), but after 6 months the indicator did not significantly differ from the initial one. In both subgroups of group V, there were no significant changes in APTT (Table 8).

Initially, there was an inhibition of the activity of the fibrinolytic system in patients with MPS on the background of MS, and more pronounced in patients with moderate MPS compared to patients with mild MPS. The level of XIIA-dependent fibrinolysis is shown in table 9. After 3 months of treatment, the level of XIIA-dependent fibrinolysis significantly decreased in subgroup IA by 13,5% (p=0,0234). After 6 months, a statistically significant decrease was observed in subgroups

Table 6. Analysis of the dynamics of the indicator "Platelets, $x10^3/mm^3$»

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	285,96 ± 2,06	273,84 ± 2,27	270,50 ± 2,66	0,0048	<0,0001
IIA	284,72 ± 2,66	273,82 ± 2,61	273,02 ± 2,43	0,0005	<0,0001
IIIA	285,63 ± 2,97	284,38 ± 2,57	280,49 ± 2,35	0,4788	0,0008
IVA	286,79 ± 2,29	284,89 ± 3,00	284,24 ± 2,34	0,1395	0,0762
VA	285,13 ± 2,66	284,03 ± 2,50	284,07 ± 2,66	0,7831	0,6475
IB	286,26 ± 2,61	282,75 ± 2,78	280,05 ± 2,17	0,0207	0,0127
IIB	287,80 ± 2,24	285,39 ± 2,58	284,82 ± 2,11	0,1118	0,0222
IIIB	285,01 ± 2,24	284,38 ± 2,85	284,08 ± 2,18	0,9394	0,3679
IVB	287,08 ± 3,33	286,12 ± 2,65	284,55 ± 2,74	0,7000	0,0897
VB	285,84 ± 2,76	287,74 ± 2,77	288,23 ± 2,32	0,0327	0,0170

Table 7. Dynamics of INR level (0,84-1,15)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	1,00 ± 0,02	1,04 ± 0,03	1,05 ± 0,03	0,0142	0,0041
IIA	0,99 ± 0,03	1,01 ± 0,03	1,03 ± 0,03	0,2883	0,0028
IIIA	0,99 ± 0,04	1,02 ± 0,03	1,03 ± 0,04	0,2074	0,0206
IVA	1,01 ± 0,04	1,01 ± 0,04	1,02 ± 0,03	0,8518	0,0841
VA	0,99 ± 0,03	0,97 ± 0,03	0,99 ± 0,03	0,2642	0,9407
IB	0,97 ± 0,04	1,00 ± 0,03	1,02 ± 0,03	0,3924	0,0157
IIB	0,97 ± 0,04	0,99 ± 0,03	0,99 ± 0,02	0,2915	0,4382
IIIB	0,97 ± 0,02	1,01 ± 0,03	1,00 ± 0,03	0,0580	0,1054
IVB	0,98 ± 0,02	0,99 ± 0,03	1,00 ± 0,03	0,3787	0,3149
VB	0,98 ± 0,03	0,99 ± 0,04	0,98 ± 0,03	0,5641	0,9384

IA, IIA, and IIIA: 21,3% (p=0,0001), 14,4% (p=0,0014), and 17,7% (p=0,0019), respectively. It should be noted that the differences between these subgroups were not statistically significant. In the IVA subgroup after 6 months, the level of XIIA-dependent fibrinolysis significantly decreased by 9,8% (p=0,0350), but the indicator was significantly higher in comparison with the IA subgroup.

Among subgroups of patients with moderate MPS, the level of XIIA-dependent fibrinolysis significantly decreased after 6 months of treatment in subgroups IB, IIB, IIIB and IVB - by 18,3% (p=0,0470), 16,1% (p=0,0053), 16,5 % (p=0,0014) and 12,8% (p=0,0325), while no significant differences were found between the subgroups. In both subgroups of group V, there was no statistically significant change in the level of XIIA-dependent fibrinolysis.

Significant regression of fibrinogen was recorded after 6 months of treatment in both subgroups of all groups (Table 10). **Markers of inflammation:** The most pronounced decrease in fibrinogen levels was observed in subgroups IA, IIA and IIIA, respectively, by 17,1% (p<0,0001), 14,6% (p<0,0001) and 12,2% (p<0,0001), in subgroups IB, IIB and IIIB, respectively, by 16,3% (p<0,0001), 11,6% (p<0,0001) and 11,6% (p<0,0001). When comparing indicators between similar subgroups of groups I, II and III, no statistically significant differences were found. In the IVA subgroup, the level of fibrinogen significantly decreased after 6 months of treatment by 9,8% (p=0,0005), in the IVB subgroup by 7,1% (p<0,0001). The VA and VB subgroups did not show a statistically convincing decrease in fibrinogen levels. It is noteworthy that the indicators in groups IV and V significantly differed from those in group I. among patients with mild MPS, the level of CRP significantly decreased after 6 months of treatment in all groups (Table 11).

The most pronounced regression of CRP was observed after 6 months of treatment in groups I, II and III: in subgroups IA, IIA and IIIA: respectively by 18,2% (p<0,0001), 14,4% (p=0,0014) and 14,2% (p=0,0038), in subgroups IB, IIB and IIIB - by 17,8% (p=0,0008), 16,2% (p=0,0001) and 15,2% (p=0,0048). In the IVA and IVB subgroups, there was also a statistically significant decrease in CRP after 6 months of treatment - by 9,2% (p=0,0089) and 9,9% (p=0,0066), respectively, while in these subgroups, the level of CRP was significantly higher against the same subgroups of group I. In subgroup VA, the level of

Table 8. Dynamics of the level of APTT, sec (24,0-35,0 sec)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	26,86 ± 0,14	27,34 ± 0,13	27,71 ± 0,15	0,0183	<0,0001
IIA	26,81 ± 0,17	27,21 ± 0,16	27,52 ± 0,16	0,0303	<0,0001
IIIA	27,00 ± 0,13	27,30 ± 0,17	27,62 ± 0,16	0,0231	<0,0001
IVA	27,01 ± 0,12	27,04 ± 0,17	27,21 ± 0,16	0,6729	0,0036
VA	26,90 ± 0,19	26,86 ± 0,15	27,02 ± 0,17	0,7394	0,3967
IB	25,11 ± 0,17	25,51 ± 0,13	25,94 ± 0,13	0,0271	<0,0001
IIB	25,31 ± 0,13	25,54 ± 0,14	25,60 ± 0,16	0,0062	0,0002
IIIB	25,21 ± 0,18	25,30 ± 0,14	25,49 ± 0,15	0,6501	0,0063
IVB	25,31 ± 0,18	25,54 ± 0,13	25,48 ± 0,17	0,0112	0,1175
VB	25,14 ± 0,19	25,02 ± 0,15	24,99 ± 0,15	0,1764	0,1898

Table 9. Dynamics of the level of XIIA-dependent fibrinolysis, min (5-12 min)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	11,16 ± 0,88	9,66 ± 1,21	8,78 ± 0,66	0,0234	0,0001
IIA	11,10 ± 0,99	10,50 ± 0,78	9,50 ± 0,82	0,4564	0,0014
IIIA	11,15 ± 1,21	9,94 ± 1,28	9,18 ± 1,00	0,0743	0,0019
IVA	11,03 ± 1,03	10,61 ± 0,96	9,94 ± 1,17	0,6486	0,0350
VA	11,24 ± 0,91	10,79 ± 1,02	10,61 ± 0,82	0,5534	0,1516
IB	11,27 ± 1,12	9,95 ± 1,08	9,21 ± 1,07	0,3666	0,0470
IIB	11,21 ± 1,18	10,03 ± 0,82	9,41 ± 1,15	0,1233	0,0053
IIIB	11,19 ± 1,15	10,31 ± 1,03	9,34 ± 0,90	0,2441	0,0014
IVB	11,26 ± 0,90	10,71 ± 1,06	9,82 ± 1,29	0,7959	0,0325
VB	11,14 ± 1,18	11,00 ± 0,82	10,97 ± 0,96	0,7969	0,9245

Table 10. Dynamics of fibrinogen level, g/l (2.0-4.0 g / l)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	4,08 ± 0,24	3,72 ± 0,14	3,41 ± 0,15	0,1510	<0,0001
IIA	4,07 ± 0,26	3,83 ± 0,16	3,53 ± 0,17	0,1947	<0,0001
IIIA	4,05 ± 0,26	3,81 ± 0,12	3,62 ± 0,16	0,2759	<0,0001
IVA	4,09 ± 0,34	3,93 ± 0,14	3,73 ± 0,25	0,4101	0,0005
VA	4,08 ± 0,32	3,99 ± 0,17	3,85 ± 0,21	0,7615	0,0655
IB	4,27 ± 0,28	3,84 ± 0,12	3,64 ± 0,17	0,3417	<0,0001
IIB	4,25 ± 0,30	4,01 ± 0,14	3,79 ± 0,14	0,2306	<0,0001
IIIB	4,28 ± 0,29	3,94 ± 0,12	3,82 ± 0,15	0,1644	<0,0001
IVB	4,24 ± 0,22	4,04 ± 0,16	3,94± 0,21	0,3787	<0,0001
VB	4,28 ± 0,30	4,17 ± 0,14	4,08 ± 0,26	0,6838	0,0591

CRP significantly decreased by 8,8% (p=0,0455), but it was significantly higher against subgroup IA. In subgroup VB, the decrease in CRP was 7,6%, but it was not statistically significant (p=0,1637) and significantly differed from subgroups IB, IIB and IIIB, in which physiotherapy was used.

Carbohydrate and fat metabolism: The dynamics of the HOMA-IR level is shown in table 12. Regression of the HOMA-IR level in subgroup IA was significant after 3 months of treatment, amounting to 25,0% (p=0,0496), reaching 54,2% (p<0,0001) after 6 months of therapy. After 6 months of treatment, a significant decrease was observed in subgroups IIA, IIIA and IVA: 49,3% (p<0,0001), 49,7% (p<0,0001) and 38,7% (p<0,0001) of the baseline level, respectively. After 6 months of treatment in subgroups A of groups I, II, and III (using physical therapy), HOMA-IR returned to normal values. It should be noted that the HOMA-IR index did not differ significantly between these subgroups, but after 6 months of treatment it was significantly higher in subgroup A of group IV (in which physiotherapy was not used) against these groups. HOMA-IR index significantly decreased after 3 months of treatment only in the subgroup IB of 22,9% (p=0,0430), and after 6 months of treatment a statically significant decline was demonstrated together with the subgroup IB subgroup IIB, IIIB and IVB in subgroup IB is 50,5 % (p<0,0001) in subgroup IIB by 36,8% (p<0,0001) in a subgroup IIIB 37,2% (p<0,0001) in subgroup IVB 32,0% (p<0,0001). However, among patients with moderate MPS only in subgroup IB, the HOMA-IR index reached normal values by the sixth month of treatment (2,68 ± 0,20). At the same time, the level of HOMA-IR after 6 months of treatment in both subgroups of group V did not significantly change and was significantly higher compared to the other groups.

The study of the lipidogram showed that the regression of the AI occurred due to a decrease in the atherogenic fractions of lipids (mainly triglycerides). The decrease in AI was significant in both subgroups of all study groups after 6 months of treatment (Table 13). However, this indicator decreased most significantly when using therapeutic complexes that include physical therapy: in subgroup IA after 3 months of treatment by 13,6% (p=0,3679), after 6 months of treatment by 31,2% (p<0,0001), respectively in subgroup IIA - by 12,6% (p=0,2480) and 26,5% (p=0,0002), in subgroup IIIA - by 12,7% (p=0,4013) and 28,8% (p<0,0001), differences between subgroups were not reliable. Regression of AI in the IVA subgroup after 3 months of treatment was 10,4% (p=0,1292), after 6 months 22,3% (p=0,0001), in the VA subgroup 7,6% (p=0,2502) and 17,0% (p=0,0007) respectively, while the AI values in the VA subgroup were significantly higher in comparison with the IA, IIA and IIIA subgroups. Among subgroups of women with moderate MPS, the most pronounced positive transformation of the lipid profile was observed in subgroup IB, which was expressed in a decrease in IA after 3 months of treatment by 14,7% (p=0,0993), after 6 months of treatment by 30,5% (p<0,0001). The decrease in AI in subgroup IIB was 7,9% and 25,1% respectively, in subgroup IIIB 11,3% (p=0,8010) and 27,8% (p=0,0003), in subgroup IVB 6,7% (p=0,9110) and 21,0% (p=0,0010), in subgroup VB it decreased the least significantly - by 4,6% (p=0,7072) and 10,9% (p=0,0327). In subgroup VB AI was significantly higher in comparison points against subgroup IB.

Green's Test: The total score on the green's climacteric scale in dynamics is shown in table 14. The initial average score in subgroups A was 10,59 ± 1,06 points, in subgroups b 18,55 ± 1,34 points. A strong correlation was found between the HOMA-IR index and the overall score of the green climacteric scale (r=0,86; p<0.005), between BMI and the overall score of the green climacteric scale (r=0,78; p<0,005). Among patients with mild MPS, regression of climacteric symptoms was detected after 3 months of treatment in subgroup IA by 25,5% (p=0,1419), in subgroup IIA by 20,8% (p=0,1324), in subgroup IIIA by 18,6% (p=0,0867), in subgroup IVA by 14,3% (p=0,0737), but it was not reliable. After 6 months of treatment, a statistically significant decrease was found in these subgroups by 55,3% (p<0,0001), 44,6% (p<0,0001),

Table 11. Dynamics of the level of C-reactive protein, mg / l (0-5, 0 mg/l)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	4,44 ± 0,42	3,88 ± 0,28	3,63 ± 0,29	0,0713	<0,0001
IIA	4,38 ± 0,40	4,05 ± 0,35	3,75 ± 0,36	0,3797	0,0014
IIIA	4,44 ± 0,41	4,02 ± 0,33	3,81 ± 0,34	0,1076	0,0038
IVA	4,36 ± 0,40	4,15 ± 0,37	3,96 ± 0,41	0,5751	0,0089
VA	4,41 ± 0,34	4,19 ± 0,31	4,02 ± 0,39	0,2812	0,0455
IB	4,45 ± 0,50	3,89 ± 0,23	3,66 ± 0,29	0,1953	0,0008
IIB	4,45 ± 0,47	4,05 ± 0,29	3,73 ± 0,28	0,0912	0,0001
IIIB	4,46 ± 0,45	4,07 ± 0,36	3,78 ± 0,41	0,2627	0,0048
IVB	4,44 ± 0,48	4,16 ± 0,28	4,00 ± 0,39	0,2576	0,0066
VB	4,48 ± 0,46	4,30 ± 0,32	4,14 ± 0,40	0,7753	0,1637

Table 12. Dynamics of the HOMA-IR level (norm <2,7)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	5,15 ± 0,70	3,86 ± 0,76	2,36 ± 0,21	0,0496	<0,0001
IIA	4,99 ± 0,79	4,01 ± 0,69	2,53 ± 0,21	0,2883	<0,0001
IIIA	5,11 ± 0,70	4,03 ± 0,86	2,57 ± 0,21	0,4013	<0,0001
IVA	5,06 ± 0,77	4,43 ± 0,68	3,10 ± 0,51	0,5264	<0,0001
VA	4,98 ± 0,64	4,58 ± 0,77	4,21 ± 1,19	0,9992	0,2990
IB	5,41 ± 0,84	4,17 ± 0,68	2,68 ± 0,20	0,0430	<0,0001
IIB	5,38 ± 0,57	4,65 ± 0,78	3,40 ± 0,57	0,1635	<0,0001
IIIB	5,43 ± 0,80	4,64 ± 0,69	3,41 ± 0,51	0,1510	<0,0001
IVB	5,38 ± 0,79	4,87 ± 0,85	3,66 ± 0,90	0,6749	<0,0001
VB	5,34 ± 0,61	5,04 ± 0,60	4,74 ± 0,83	0,5166	0,2340

Table 13. Dynamics of the level of the atherogenicity index (<3)

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	3,35 ± 0,59	2,90 ± 0,31	2,31 ± 0,29	0,3679	<0,0001
IIA	3,43 ± 0,52	3,00 ± 0,35	2,52 ± 0,32	0,2480	0,0002
IIIA	3,48 ± 0,49	3,04 ± 0,37	2,47 ± 0,26	0,4013	<0,0001
IVA	3,55 ± 0,44	3,18 ± 0,35	2,76 ± 0,36	0,1292	0,0001
VA	3,47 ± 0,29	3,20 ± 0,29	2,88 ± 0,40	0,2502	0,0007
IB	3,35 ± 0,35	2,86 ± 0,31	2,33 ± 0,17	0,0993	<0,0001
IIB	3,24 ± 0,45	2,98 ± 0,33	2,43 ± 0,29	0,8010	0,0003
IIIB	3,47 ± 0,51	3,08 ± 0,36	2,51 ± 0,35	0,3679	0,0001
IVB	3,40 ± 0,41	3,17 ± 0,31	2,68 ± 0,35	0,9110	0,0010
VB	3,38 ± 0,39	3,22 ± 0,35	3,01 ± 0,38	0,7072	0,0327

Table 14. Severity of symptoms of climacteric syndrome on the green scale, points

Subgroup	M ± S, Before	M ± S, 3 months	M ± S, 6 months	P Before - 3 months	P Before – 6 months
IA	11,00 ± 1,05	8,19 ± 1,16	4,91 ± 0,70	0,1419	<0,0001
IIA	10,61 ± 1,10	8,40 ± 1,40	5,88 ± 0,87	0,1324	<0,0001
IIIA	10,40 ± 1,08	8,47 ± 1,14	6,20 ± 1,13	0,0867	<0,0001
IVA	10,31 ± 0,99	8,83 ± 1,08	7,42 ± 1,03	0,0737	<0,0001
VA	10,61 ± 1,09	11,95 ± 1,36	12,43 ± 1,08	0,0286	0,0006
IB	18,68 ± 1,27	14,17 ± 1,22	10,96 ± 1,25	0,1219	<0,0001
IIB	18,83 ± 1,49	16,80 ± 1,04	14,75 ± 1,43	0,2229	<0,0001
IIIB	18,36 ± 1,28	16,95 ± 1,53	14,86 ± 1,10	0,2203	<0,0001
IVB	18,21 ± 1,39	17,34 ± 1,53	16,80 ± 1,68	0,1996	0,0041
VB	18,65 ± 1,29	19,34 ± 1,19	20,07 ± 1,53	0,4619	0,0106

40,4% (p<0,0001) and 28,1% (p=0,0007), respectively. Among patients with moderate MPS, the total score of climacteric disorders decreased after 3 months of treatment in subgroup IB by 24,1% (p=0,1219), in subgroup IIB by 10,8% (p=0,22229), in subgroup IIIB by 7,7% (p=0,2203), in subgroup IVB by 4,8% (p=0,1996), but the differences were not significant in comparison with the initial values. After 6 months of treatment, the regression rate was 39,9% (p<0,0001), 19,7% (p<0,0001), 14,5% (p<0,0001) and 6,9 % (p=0,0041), respectively. In subgroups IIB, IIIB, and IVB, the total score on the green scale was significantly higher compared to subgroup IB. It is important to note a significant increase in climacteric disorders in group V, which was expressed in an increase in the total test score in subgroup VA after 3 months of treatment by 12,6% (p=0,0286), after 6 months of treatment by 17,1% (p=0,0006), and in subgroup VB after 6 months of treatment by 7,6% (p=0,0106).

Against the background of treatment, the endometrium, cervical epithelium, breast tissue were not compromised, which allowed us to state the safety of the programs used. High compliance to treatment was noted.

Discussion

In women with MPS and MS, the improvement in the functioning of the hypothalamic-pituitary-ovarian system, indicators of carbohydrate, fat metabolism, hemostasis, regression of the severity of metabolic inflammation and the weakening of subjective climacteric symptoms against the background of a decrease in BMI are more pronounced when using complexes in which, in addition to lifestyle modification, physical therapy, balneotherapy and physiotherapy were included. In patients with moderate MPS, optimal correction of metabolic and endocrine disorders required the use of a whole range of synergistic physiotherapy factors (vibrotherapy, chromotherapy, melotherapy, aromatherapy, aeroionotherapy). Taking into account the focus on comorbid pathology and the similarity of pathogenetic mechanisms of MS and MPS, the therapeutic strategy is based on lifestyle modification [27,28]. Physical therapy promoted the activation of metabolism by reducing adipose tissue and increasing muscle tissue [29,30]. Improvement of the studied parameters was favored by the use of drinking balneotherapy due to the coordination of enteroinsular interactions and a decrease in IR [31,32]. The inclusion of vitamins and minerals in the therapeutic program is based on their antioxidant abilities and their importance in coordinating metabolic processes [33,34]. Music therapy has made adjustments to the state of the psychoemotional sphere by pulsating stimulation of the auditory receptors, limbic system, metabolism, and normalization of the respiratory and cardiovascular systems [35]. Aromatherapy had anti-stress, anti-inflammatory effects, normalized the activity of the endocrine system by affecting the olfactory sensory system and modulating the activity of the limbic complex, pituitary-adrenal system [36-38]. Aeroionization harmonized the work of the relationship's nervous system through a neurohumoral mechanism [39-40]. The inclusion of vibrotherapy in the treatment complex was justified by its ability to improve blood circulation, activate redox processes, and provide anti-inflammatory and analgesic effects by stimulating the receptors with mechanical vibrations [41,42]. The result of photobiomodulating effects of chromotherapy was the restoration of the balance of sympathetic-parasympathetic relationships, antistress effect [43,44]. It is important to note that stress is currently regarded as an independent risk factor for atherosclerosis and fatal cardiovascular complications with corresponding metabolic, inflammatory and hemostatic disorders [45,46].

Conclusion

The combined effects of physical therapy, vitamins and minerals, and polymodal physical factors on the background of lifestyle modification contribute to the normalization of the hypothalamic-pituitary-ovarian system, improving carbohydrate and fat metabolism, reducing

metabolic inflammation, prothrombogenic potential of the blood, and, consequently, reducing cardiovascular risk in parallel with the regression of menopausal disorders in patients with MPS complicated by MS. In patients with moderate MPS, the program with simultaneous use of vibrotherapy, chromotherapy, melotherapy, aromatherapy, and aeroionotherapy has an advantage. It seems promising to use non-drug programs as additional measures in the curation of women with severe menopausal syndrome. However, further research is needed to explore the possibilities of non-drug therapeutic strategies in older women with comorbid pathology.

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