Exercise-induced modulation of the gut microbiome in metabolically dysregulated state

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HOO: Methodology; Investigation; Data curation; Writing — original draft, Visualization.
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The article investigates the effects of exercise modalities on metabolic disturbances and the gut microbiome in women with metabolic syndrome The relevance of the study is determined by the rapidly increasing prevalence of metabolic syndrome and the need for effective non-pharmacological interventions capable of simultaneously targeting systemic metabolism and microbiome-mediated regulatory mechanisms. The aim of the study was to evaluate the effectiveness of a 12-week aerobic and resistance training program in correcting carbohydrate and lipid metabolism parameters and to determine the characteristics of taxonomic restructuring of the gut microbiota depending on the type of muscular activity. The study involved 68 women with clinically confirmed metabolic syndrome. Anthropometric indicators, biochemical blood parameters (glucose, insulin, HbA1c, lipid profile, HOMA-IR), and gut microbiome composition were assessed using quantitative 16S rRNA PCR analysis. Baseline analysis demonstrated pronounced disturbances of glycemic control and lipid metabolism in women with metabolic syndrome, including elevated HbA1c, glucose, total cholesterol, and LDL-cholesterol, as well as microbiome alterations characterized by reduced proportions of *Bacteroidetes* and *Actinobacteria* and increased representation of other taxa, indicating dysbiosis. After 12 weeks of resistance training, a statistically significant restructuring of the microbiome was observed: an 18.4 % increase in *Bacteroidetes*, a 36.8 % decrease in *Firmicutes*, and a 43.5 % reduction in the *Firmicutes/Bacteroidetes* ratio, reflecting restoration toward a eubiotic state. Simultaneously, carbohydrate metabolism improved, evidenced by a 7.9 % decrease in HbA1c and a 14 % reduction in the HOMA-IR index, accompanied by reductions in atherogenic cholesterol fractions. In contrast, aerobic training did not produce pronounced quantitative shifts at the phylum level; however, *Akkermansia muciniphila* and *Bacteroides fragilis* appeared in samples, microorganisms associated with improved metabolic adaptation and anti-inflammatory activity. The most notable changes concerned the lipid profile, including decreased triglycerides, total and atherogenic cholesterol, and a tendency toward increased HDL levels. Overall, the results enabled a comparative evaluation of training effects. Resistance exercise primarily improved insulin sensitivity and glycemic control and substantially modified microbiome structure, whereas aerobic exercise exerted a stronger influence on lipid metabolism and induced qualitative changes in microbial composition.

Key words: carbohydrate metabolism, lipid metabolism, exercise training, metabolic syndrome, gut, gut microbiome

Introduction

The full-scale war has intensified exposure to stressors affecting population health. Research findings indicate that life stress contributes to the development of metabolic disturbances, including insulin resistance and impaired glucose and lipid homeostasis, thereby worsening disease prognosis. Numerous studies have demonstrated that individuals exposed to severe war-related stress have an increased risk of developing metabolic syndrome (MetS) [3, 5, 9, 14].

Metabolic syndrome is regarded as a state of systemic dysregulation that develops as a consequence of impaired integrative interaction between the central and peripheral components of homeostasis. The principal pathogenetic determinants of metabolic syndrome (MetS) are visceral obesity and insulin resistance, which initiate a cascade of disturbances in carbohydrate and lipid metabolism, chronic low-grade inflammation, and endothelial dysfunction [7, 12].

The gut microbiome is considered a regulatory system involved in metabolic, immune, and neurovegetative control through the production of biologically active metabolites and the modulation of bile acid metabolism.

A substantial role in the development of metabolic disturbances is attributed to the gut microbiome, which is viewed as an integral modifier of metabolic homeostasis and an active participant in the etiopathogenesis of MetS. Dysbiosis — characterized by reduced microbial diversity and functional alterations of microbial communities — is associated with increased intestinal barrier permeability, metabolic endotoxemia, and activation of TLR4/NF-κB-dependent signaling pathways that sustain systemic inflammation and insulin resistance [4, 13, 15].

At the same time, microbial metabolites, including short-chain fatty acids, tryptophan derivatives, and secondary bile acids, exert regulatory effects through GPR41/43, AhR, FXR, and TGR5 receptors, thereby modulating gluconeogenesis, lipid metabolism, and the inflammatory milieu [1, 8, 10].

Physical exercise represents a physiologically substantiated non-pharmacological intervention capable of modulating insulin sensitivity, lipid metabolism, systemic inflammation, gut microbiome structure, and autonomic regulation of heart rhythm. However, existing studies predominantly focus on individual components of metabolic syndrome, do not account for type-specific differences between aerobic and resistance muscle work, and provide limited insight into the integrated interactions among metabolic, microbiome-related, and autonomic adaptive mechanisms [2, 6, 11]. The modality-dependent effects of physical exercise on microbiome-mediated metabolic adaptations remain insufficiently elucidated.

This study aimed to evaluate the effects of long-term exercisevtraining of different modalities on the correction of disturbances in carbohydrate and lipid metabolism and the gut microbiome in women with metabolic syndrome.

Materials and Methods

The effects of 12-week aerobic and resistance fitness exercise training on biochemical markers of carbohydrate and lipid metabolism, the taxonomic structure of the gut microbiome were investigated in women in the second period of mature adulthood with metabolic syndrome. The study included 68 women with clinically confirmed metabolic syndrome who were allocated into two training groups and one control group. The experimental groups comprised 50 women performing exercise training of different modalities, while 18 women constituted the non-intervention control group. Medical history data, anthropometric measurements, and clinical-laboratory as well as molecular-genetic assessments were analyzed.

The composition of the microbiota at the level of major bacterial phyla was determined using quantitative real-time PCR with universal primers targeting the bacterial 16S rRNA gene, as well as primers specific for *Actinobacteria*, *Firmicutes*, and *Bacteroidetes*.

Biochemical analyses were performed in the clinical diagnostic laboratory of the V. P. Komisarenko Institute of Endocrinology and Metabolism. The examination complex also included clinical investigations (biochemical blood analysis, complete blood count, carbohydrate and lipid profiles using the enzyme-linked immunosorbent assay (ELISA).

Training sessions with a predominantly aerobic character were conducted three times per week, lasted 55 minutes, and included moderate-intensity aerobic exercise (AT). Low-impact exercises were performed within a heart-rate zone of 65–70 % of HRmax (not exceeding 140 beats·min^{-1}), corresponding to an energy expenditure of approximately 6.0 METs. Load variation was achieved by modifying the type of musical accompaniment, exercise orientation, number of muscle groups involved, duration, and number of repetitions. Each session consisted of a preparatory phase (warm-up), a main phase (Zumba fitness exercises), and a final phase (stretching).

During health-oriented fitness sessions with a predominantly resistance character (RT), exercises targeting major muscle groups were performed using body-weight loading (push-ups, squats, low jumps) and external resistance (dumbbells, medicine balls, resistance bands). Each session consisted of three parts: warm-up, main strength section (6–8 exercises), and a concluding phase (stretching).

Normality of data distribution was assessed using the Shapiro–Wilk test. In cases where the distribution deviated from normality, nonparametric statistical methods were applied: the Mann–Whitney U test was used for comparisons between two independent samples, and the Wilcoxon signed-rank test was used to evaluate within-group changes over time.

Participants were recruited voluntarily through an open invitation disseminated via social media, specialized online platforms, and information partnerships with fitness centers and medical institutions. Prior to inclusion in the study, each participant completed a participant

questionnaire and an informed consent form containing explanations of the study objectives, procedures, expected outcomes, and potential risks of participation. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and current bioethical standards. Participation was voluntary, without financial compensation, and participants had the right to withdraw at any time without providing a reason. Confidentiality of personal data and anonymity of results were ensured. The study was approved by the Biomedical Ethics Commission of the National University of Ukraine on Physical Education (30.09.2020; protocol no. 2).
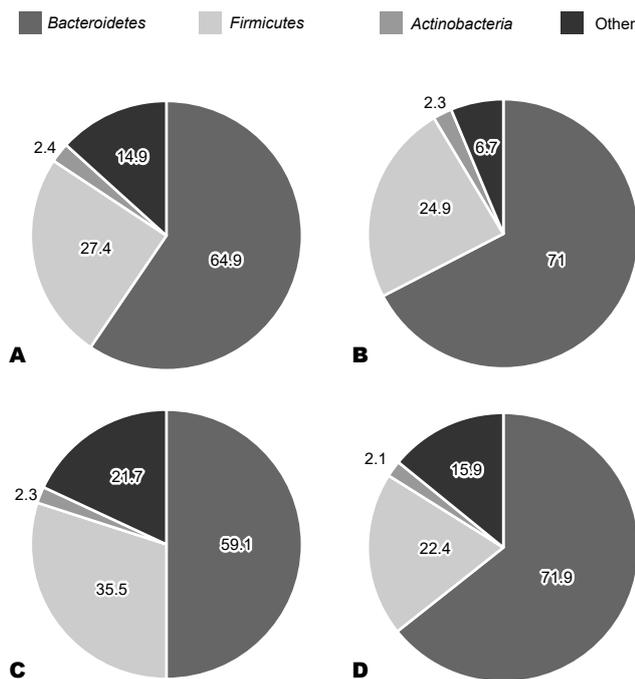

Fig. 1. Taxonomic structure of the gut microbiome under the influence of aerobic and resistance exercise training, % *Note*. A — aerobic training before; B — aerobic training after; C — resistance training before; D — resistance training after.
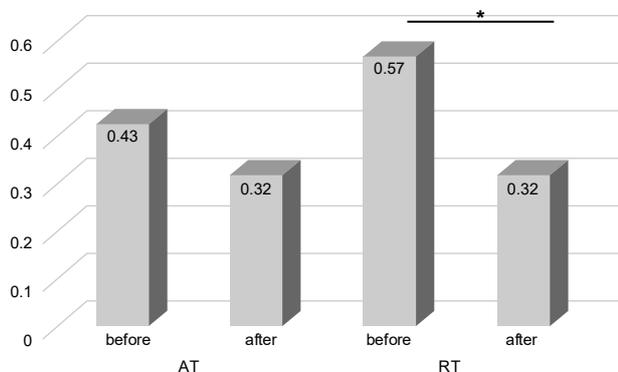

Fig. 2. *Firmicutes/Bacteroidetes* ratio in the resistance and aerobic training groups before and after the intervention *Note*. Statistical significance of differences between pre- and post-intervention parameters was assessed using the Wilcoxon signed-rank test for paired samples. * — difference statistically significant at P<0.05.

Results and Discussion

It was established that women with metabolic syndrome, compared with a conditionally healthy control group, exhibited baseline systemic differences in markers of carbohydrate and lipid metabolism (primarily indicators of glycemic control and atherogenic fractions), anthropometric and somatofunctional characteristics (increased circumferences, BMI, fat mass percentage, biological age, and basal metabolic rate), as well as in the phylum-level composition of the gut microbiome (decreased proportions of *Bacteroidetes* and *Actinobacteria* and an increased "Other" group).

In the metabolic syndrome group, HbA1c was higher by 17.6 % (5.76 % *vs.* 4.90 %; P=0.0003) and fasting glucose by 29.6 % (6.48 *vs.* 5.00 mmol/L; P=0.0046). Total cholesterol was elevated by 29.1 % (6.48 *vs.* 5.02 mmol/L; P=0.0001), LDL-C by 23.9 % (3.47 *vs.* 2.80 mmol/L; P=0.0064), and HDL-C by 25.3 % (1.93 *vs.* 1.54 mmol/L; P=0.0178). ALT was higher by 25.5 % (26.65 *vs.* 21.23 U/L; P=0.0325), whereas differences in insulin, HOMA-IR, TG, AST, and TSH were not statistically significant (P>0.05).

Baseline analysis revealed that in the metabolic syndrome group the relative abundance of *Bacteroides* was 6.8 % lower (63.30% *vs.* 67.90 %; P=0.0385), and *Actinobacteria* was 24.8 % lower (2.18 % *vs.* 2.90 %; P=0.0167), whereas the proportion of "Other" taxa was 3.34-fold higher (12.04 % *vs.* 3.60 %; P=0.0001). *Firmicutes* (P=0.3949) and the F/B ratio (P=0.5023) did not differ significantly.

Exercise training of different modalities (aerobic and resistance), applied over 12 weeks, demonstrated a significant effect on changes in the quantitative composition of the gut microbiome in women with metabolic syndrome, as shown in fig. 1.

According to the results of the detailed comparison of baseline and final data, resistance exercise training in participants led to a significant increase in the relative abundance of *Bacteroidetes* by 18.4 % (P=0.0001), with an elevation of the mean value. This was accompanied by a significant decrease in *Firmicutes* by 36.8 % (P=0.02), which may be interpreted as a favorable shift toward restoration of a eubiotic microbial state.

In contrast, in the aerobic training group only a tendency toward an increase in *Bacteroidetes* content by 8 % (P=0.24) and a simultaneous non-significant decrease in *Firmicutes* (P=0.24) was observed, which did not reach statistical significance.

Thus, the effect of resistance exercise training appeared more pronounced in correcting dysbiotic alterations characteristic of metabolic syndrome compared with aerobic training. In both experimental groups, an inverse correlation between the dynamics of *Bacteroidetes* and *Firmicutes* proportions was detected, moderate during aerobic training (r ≈ −0.2) and stronger during resistance training (r ≈ −0.6). This additionally confirms the presence of a modulatory effect of exercise training on

the gut microbiome, more pronounced under resistance training conditions. Such an effect is likely associated with increased tolerance to physical load and a shift toward a functionally favorable bacterial profile.

Regarding *Actinobacteria*, no significant changes in its representation were detected: stable quantitative values were observed both before and after the intervention.

In the resistance training group, statistically significant changes in the *Firmicutes/Bacteroidetes* ratio were observed, decreasing by 43.5 % (P=0.016) compared with baseline values, as shown in fig. 2. In contrast, in the group performing aerobic exercise training, the *Firmicutes/Bacteroidetes* ratio did not undergo statistically significant changes (P=0.24), although a slight decrease of 3.1 % relative to baseline was observed. This finding may be interpreted as a tendency toward correction of microbial imbalance toward eubiosis under the influence of muscular activity. However, this dynamic was not statistically significant, likely due to a lower intensity or insufficient specificity of the aerobic load for modulation of the intestinal microbiota.

Overall, the obtained results indicate that resistance exercise training exerts a more pronounced modulatory effect on the ratio of key bacterial phyla. The limited effect of aerobic exercise, in turn, highlights the individual variability of microbiome responses and the need for personalized selection of physical activity programs for microbiome correction in individuals with metabolic syndrome.

Additionally, fecal samples from participants in the aerobic training group revealed the presence of *Akkermansia muciniphila*, a microorganism associated with lower fasting glucose levels, greater microbial diversity, and improved metabolic adaptation to exercise. Its appearance may indicate positive shifts in gut microbiome structure under the influence of aerobic training. Along with *A. muciniphila*, *Bacteroides fragilis* — a representative of the obligate colonic microbiota involved in local immune regulation and maintenance of epithelial homeostasis through production of anti-inflammatory polysaccharide A — was also identified. Detection of these taxa may indicate the formation of a more stable and immunologically favorable microbial environment characteristic of a compensated metabolic state.

Comparative analysis of final outcomes between the two groups with different exercise modalities demonstrated that low-intensity aerobic exercise training exerted a more substantial effect on modeling eubiosis than aerobic training.

Based on the obtained results, it was established that a 12-week training program in women with metabolic syndrome was accompanied by positive dynamics in biochemical parameters related to carbohydrate and lipid metabolism, as well as the formation of metabolically relevant associations between metabolic parameters and the taxonomic structure of the gut microbiota. At the same time, the pattern of adaptive response differed substantially depending on the type of exercise

training, allowing resistance and aerobic exercise to be considered distinct non-pharmacological tools for the correction of metabolic disorders.

The correlation analysis demonstrated that after the resistance intervention the most pronounced associations were formed between carbohydrate metabolism parameters and atherogenic components of the lipid profile. Specifically, HbA1c showed a direct correlation with fasting glucose (r=0.61; P<0.01) and HOMA-IR (r=0.32; P<0.05), and was also positively associated with the proportion of the conditionally unfavorable "%other" group (r=0.46; P<0.01), allowing it to be considered a potential microbiota marker of metabolic strain. The HOMA-IR index exhibited strong positive correlations with triglycerides (r=0.69; P<0.01) and VLDL (r=0.63; P<0.01), confirming the pathophysiological unity of insulin resistance and hypertriglyceridemia within the structure of metabolic syndrome.

In the aerobic group, a general tendency toward the formation of a correlation "core" was observed, in which markers of insulin resistance (HOMA-IR) were associated with atherogenic fractions and the triglyceride component, while microbiota indicators (particularly the *Firmicutes/Bacteroidetes* ratio) demonstrated strong interrelations with baseline taxa, reflecting restructuring of the microbial community during metabolic adaptation.

In the resistance training group, the most pronounced changes concerned reductions in atherogenic cholesterol fractions and improvement of carbohydrate metabolism parameters. In particular, significant decreases in total cholesterol and LDL-cholesterol were recorded, reflecting reduced plasma atherogenic potential and forming a biochemical basis for lowering cardiometabolic risk. Concurrently, the carbohydrate profile demonstrated significant shifts in integrated markers of glycemic control and insulin resistance (primarily HbA1c and HOMA-IR), whereas fasting insulin and glucose showed a directed but less pronounced dynamic.

The post-intervention correlation structure confirmed the interrelationship of key carbohydrate and lipid metabolism parameters and their concordance with microbiota characteristics. Specifically, HbA1c showed direct associations with fasting glucose and the HOMA-IR index, while HOMA-IR was associated with parameters of triglyceride-related atherogenicity (particularly triglycerides and VLDL). Simultaneously, associations between the proportion of the conditionally unfavorable "%other" group and glycemic markers were detected, suggesting that this group may serve as a potential indicator of metabolic strain. Overall, resistance exercise in this cohort exerted its effect primarily through improvement of insulin sensitivity and reduction of atherogenic cholesterol fractions, while microbiota associations indicated involvement of the intestinal component in metabolic adaptation.

In the aerobic training group, the most characteristic feature was metabolic efficacy regarding the triglyceride component and atherogenic lipid fractions. Compared with the resistance group, aerobic intervention was accompanied by more pronounced favorable dynamics of

lipid profile parameters, including significant reductions in total cholesterol, LDL-cholesterol, and triglycerides, as well as a tendency toward increased HDL. In the carbohydrate profile, the aerobic program also demonstrated favorable dynamics in glycemic control and insulin resistance indicators, consistent with the physiology of aerobic muscle work, which is characterized by increased fatty acid oxidation, improved insulin sensitivity, and reduced hepatic production of atherogenic lipoproteins.

Comparative analysis showed that resistance training was more strongly associated with improvement in insulin resistance and integral glycemic control indices, whereas aerobic exercise had a more pronounced effect on the lipid profile, particularly triglycerides and atherogenic lipoprotein fractions. In both groups, metabolically relevant relationships between biochemical markers and microbiome taxonomic characteristics were observed, confirming the multicomponent nature of adaptation to exercise.

Thus, after 12 weeks of a resistance training program in women with metabolic syndrome, a statistically significant restructuring of the phylum-level gut microbiome profile was observed. The proportion of *Bacteroidetes* increased by 18.4 % (P=0.0001), *Firmicutes* decreased by 36.8 % (P=0.02), the *Firmicutes/Bacteroidetes* ratio declined by 43.5 % (P=0.016), and the proportion of taxa grouped as "Other" decreased by 26.8 % (P=0.007), while *Actinobacteria* remained stable. Collectively, these changes may reflect a reduction in dysbiotic burden.

Against the background of the 12-week aerobic program, pronounced phylum-level shifts were not observed; however, the appearance of *Akkermansia muciniphila* in fecal samples was recorded as a qualitative indicator of microbiome modulation. This taxon is associated with improved metabolic adaptation and greater stability of intestinal structural and functional integrity. Overall, the resistance fitness program produced quantitatively pronounced phylum-level restructuring, whereas the aerobic program induced predominantly qualitative taxon-specific changes.

Comparison of the effects of the two health-oriented fitness programs in women of the second period of adulthood with metabolic syndrome demonstrated that personalization of non-pharmacological correction should be based on the dominant metabolic profile. When insulin resistance and impaired glycemic control predominate, strengthening the resistance component is more appropriate, whereas in the presence of atherogenic dyslipidemia and hypertriglyceridemia, emphasis should be placed on aerobic exercise. Thus, targeted application of resistance and/or aerobic exercise in women with meta-bolic syndrome may be considered an effective non-pharmacological approach to correcting metabolic disorders, implemented through interconnected mechanisms of normalization of carbohydrate and lipid metabolism and modulation of gut microbiome composition.

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Зміни мікробіому кишки під впливом фізичних вправ в умовах метаболічних порушень

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Стаття присвячена дослідженню впливу фізичних навантажень різної модальності на метаболічні порушення та кишковий мікробіом у жінок із метаболічним синдромом. Актуальність роботи зумовлена стрімким зростанням поширеності метаболічного

синдрому та пошуком ефективних немедикаментозних підходів його корекції, здатних одночасно впливати на системний метаболізм і мікробіом-опосередковані механізми регуляції. Метою дослідження було оцінити ефективність 12-тижневої програми аеробних і силових тренувань щодо корекції показників вуглеводного та ліпідного обміну, а також визначити особливості перебудови таксономічної структури кишкової мікробіоти залежно від типу м'язової роботи. У дослідженні взяли участь 68 жінок із клінічно підтвердженим метаболічним синдромом. П'ятдесят учасниць виконували фізичні вправи та були розподілені на дві групи — аеробних і силових тренувань, тоді як 18 осіб становили контроль без втручання. Тривалість програми становила 12 тижнів. Оцінювали антропометричні показники, біохімічні параметри крові (глюкоза, інсулін, HbA1c, ліпідний профіль, HOMA-IR) та склад кишкового мікробіому методом кількісної ПЛР 16S rRNA. Аналіз вихідних даних показав, що у жінок із метаболічним синдромом спостерігалися виражені порушення глікемічного контролю та ліпідного обміну: підвищення HbA1c, глюкози, загального холестерину і LDL-холестерину, а також зміни мікробіому, що характеризувалися зменшенням частки *Bacteroidetes* і *Actinobacteria* та збільшенням частки інших таксонів, що свідчить про дисбіоз. Після 12 тижнів силового тренування зафіксовано статистично значущу перебудову мікробіому: збільшення частки *Bacteroidetes* на 18,4 %, зменшення *Firmicutes* на 36,8 % і зниження співвідношення *Firmicutes/Bacteroidetes* на 43,5 %, що розцінюється як відновлення еубіотичного стану. Одночасно відбулося покращення вуглеводного обміну — зниження HbA1c на 7,9 % та індексу інсулінорезистентності HOMA-IR на 14 %, а також зменшення атерогенних фракцій холестерину. Аеробні тренування не спричинили виражених кількісних зрушень на рівні філумів, однак у зразках з'явилися *Akkermansia muciniphila* та *Bacteroides fragilis* — мікроорганізми, асоційовані з кращою метаболічною адаптацією і протизапальною активністю. При цьому найбільш виражені позитивні зміни стосувалися ліпідного профілю: зниження тригліцеридів, загального та атерогенного холестерину, а також тенденція до підвищення HDL. Отримані результати дозволили провести узагальнююче порівняння ефектів тренувань. Встановлено, що силові вправи переважно покращують інсулінову чутливість і глікемічний контроль та істотно змінюють структуру мікробіому, тоді як аеробні вправи ефективніше впливають на ліпідний обмін і спричиняють якісні зміни мікробного складу.

Ключові слова: вуглеводний обмін, жировий обмін, фізичні вправи, метаболічний синдром, кишка, кишковий мікробіом