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Effects of forced treadmill exercise on lipid and carbohydrate metabolism parameters in a mouse model of type 2 diabetes mellitus

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ABSTRACT

Aim. To study the effect of forced treadmill exercise on lipid and carbohydrate metabolism parameters in liver and skeletal muscle tissues of mice with a model of type 2 diabetes mellitus, taking into account age and biological rhythm characteristics.

Materials and methods. To create a model of type 2 diabetes mellitus (T2DM), a high-fat diet was used. Physical activity in the form of forced treadmill exercise was carried out for 4 weeks. Parameters of lipid and carbohydrate metabolism in muscle and liver tissues were determined by Western blotting.

Results. A decrease in glycogen content in the muscles in T2DM was associated with activation of its breakdown rather than with its reduced synthesis. Significant and multidirectional changes were recorded in the content of glycogen phosphorylase in the liver and skeletal muscle tissues. These changes were significantly influenced by both the nature of diet and physical activity. The development of T2DM in mice was accompanied by a decrease in high-density lipoprotein (HDL) content in the liver along with an increase in low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) levels. It is worth noting that physical activity provided partial normalization of the ratio of lipid fractions, despite the fact that the exercises were performed in the context of a high-fat diet.

In the T2DM group, metabolic changes caused by both T2DM modeling and physical exercises were not only quantitative, but in some cases also qualitative. The effects of physical exercises performed at different times of the day on metabolic processes in the liver and muscle tissues varied significantly.

Conclusion. Physical activity can help prevent not only metabolic disorders (obesity and insulin resistance), but also associated complications on the part of the liver and cardiovascular system.

Keywords: liver, skeletal muscles, treadmill running, diabetes mellitus, obesity

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Эффекты принудительных беговых нагрузок на показатели липидного и углеводного обмена у мышей с моделью сахарного диабета типа 2

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РЕЗЮМЕ

Цель: изучалось влияние принудительных физических нагрузок на показатели липидного и углеводного обмена в тканях печени и скелетных мышц у мышей с моделью сахарного диабета типа 2 (СД2) с учетом возрастных и биоритмологических особенностей.

Материалы и методы. Для формирования модели заболевания использовалась высокожировая диета, физические нагрузки в виде принудительного бега проводились в течение 4 нед. Показатели липидного и углеводного обмена в тканях мышц и печени определялись методом вестерн-блоттинга.

Результаты. Снижение содержания гликогена в мышцах при СД2 в большей степени связано с активацией процессов его распада, чем со снижением синтеза. Значительные и разнонаправленные изменения фиксировались в содержании гликогенфосфорилазы в тканях печени и скелетных мышц, на эти изменения существенное влияние оказывали и характер питания, и физические нагрузки. Развитие экспериментального СД2 у мышей сопровождалось снижением содержания липопротеинов высокой плотности в печени параллельно с возрастанием липопротеинов низкой и очень низкой плотности. Важно, что физические нагрузки обеспечивали частичную нормализацию соотношения липидных фракций, несмотря на то что выполнялись они на фоне продолжающейся жировой диеты.

В группе СД2 физические нагрузки носили не только количественный, но в некоторых случаях качественный характер. Эффекты физических нагрузок, применяемых в разное время суток, на метаболические процессы в печени и мышечной ткани значительно различаются.

Заключение. Физические нагрузки могут выступать средством профилактики не только непосредственно метаболических нарушений (ожирение и инсулинорезистентность), но и сопутствующих осложнений со стороны печени и в дальнейшем сердечно-сосудистой системы.

Ключевые слова: печень, скелетные мышцы, беговая нагрузка, сахарный диабет, ожирение

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a serious metabolic disease characterized by insulin resistance and decreased insulin production, resulting in abnormally elevated blood glucose levels. It has been reported that T2DM can induce oxidative stress and inflammatory responses and promote various complications, including liver injury [1, 2].

Fatty liver disease associated with metabolic dysfunction and T2DM are two common metabolic disorders that often coexist and synergistically promote each other's progression [3]. Several pathophysiological pathways are involved in this relationship, including insulin resistance, inflammation, and lipotoxicity, contributing to understanding the complex relationships between these conditions [4]. Dyslipidemia has a significant impact on the risk of developing T2DM and micro- and macrovascular complications, and diabetes significantly contributes to an increased risk of liver fibrosis progression and hepatocellular carcinoma. Moreover, both pathologies have a synergistic effect on cardiovascular events and mortality [5].

The liver helps maintain normal fasting and postprandial blood glucose levels. Insulin loss affects the liver, leading to glycogenolysis and increased hepatic glucose production. Abnormalities in triglyceride storage and lipolysis in insulin-sensitive tissues, such as the liver, are early manifestations of disorders characterized by insulin resistance and are detected earlier than fasting hyperglycemia [2].

One of the models for the development of T2DM is feeding animals with a high-fat diet. High-fat diet can lead to obesity, hyperinsulinemia, and altered glucose homeostasis due to insufficient compensation by the islets of Langerhans. Since obesity in this case is caused by dietary manipulations rather than cytotoxic substances, such models are considered to be more similar to the human diseases [6–8].

Physical activity of varying intensity triggers a large number of biochemical, molecular, genetic, and epigenetic mechanisms underlying adaptive responses of the body to physiological stress [9]. In particular, it has been shown that physical activity has a positive effect on metabolic disorders [10]. Experiments with animals have shown that physical activity increases insulin sensitivity and improves glucose tolerance induced by a high-fat diet not only in the animals themselves but also in their offspring [10]. It has also been shown that circadian rhythms affect the effect of physical exercise. Glucose uptake by muscles and insulin tolerance also have a circadian nature and the effects of physical exercises are associated with the circadian rhythm of these parameters [11].

Therefore, the aim of this study was to investigate the effect of forced treadmill exercise on lipid and carbohydrate metabolism in liver and skeletal muscle tissue in a mouse model of T2DM, taking into account age and biological rhythm characteristics.

MATERIALS AND METHODS

Male mice of the C57bl/6 line were used in the study. The mice were obtained from the vivarium of the Tomsk National Research Medical Center of the Russian Academy of Sciences, Goldberg Research Institute of Pharmacology and Regenerative Medicine. Animal maintenance regime: 12 h /12 h light / dark cycle, with daylight starting at 6 am; free access to food and water; room temperature of 24 °C.

The study was conducted in accordance with the principles of the Basel Declaration and approved by the Bioethics Committee at the Biological Institute of Tomsk State University (Protocol No. 32 of 2.12.2019).

Two groups of mice were used in the experiment: young mice (112 mice aged 4 weeks at the beginning of the experiment) and aged mice (112 mice aged 32 weeks at the beginning of the experiment). The experiment lasted 16 weeks. Until week 12 of the experiment, the mice were divided into 2 subgroups: mice receiving a high-fat diet (56 mice) and mice receiving a standard chow diet (56 mice).

To model T2DM, a high-fat diet was used for 12 weeks, developed specifically for this experiment. The composition and energy value of the feed are described in detail in our previous work [12].

Starting from week 12 of the experiment, each group of animals was divided into two subgroups – animals exposed to (main – 21 animals) and not exposed to (control – 7 animals) forced treadmill exercises.

Different subgroups of mice in the main group performed forced treadmill exercise at different times of the day. Group A performed treadmill exercise in the morning (from 8:00 to 10:00) – 7 animals. Group B did treadmill exercise in the dark phase of the cycle (from 19:00 to 21:00) – 7 animals. In group C, the time of forced treadmill exercise alternated (shift training regime): in the first and third weeks, they performed the exercise in the dark (from 19:00 to 21:00), in the second and fourth weeks – in the morning (from 8:00 to 10:00) – 7 animals.

To normalize physical activity, the BMELAB SID-TM10 treadmill for mice was used [13]. Forced treadmill exercises were performed for 4 weeks. In the first six days, the duration of the exercise was gradually increased from 10 to 60 minutes (the increase by 10 minutes per day) 6 times a week and did not change during the subsequent three weeks. The angle of the treadmill (from 0 to 10°) and its rotation speed (from 15 to 18 m / min) were changed every week. Once a week (every seventh day), the exercise was not performed. Body weight was measured using laboratory scales. The weight of each animal was measured separately. Measurements were performed 11 times during 16 weeks.

The experimental animals were euthanized by decapitation 24 hours after the last exercise. We isolated m.gastrocnemius from both hind limbs and cleared the muscle tissue of connective and adipose tissue. The liver was extracted from the abdominal cavity and also cleared of surrounding tissue. Homogenization of skeletal muscle and liver tissue was performed as follows: before lysis, the tissue was first cut with a scalpel on a glass plate held on ice into small pieces of ~ 1 mm in size. They were then transferred to cold 1X RIPA Buffer (137 mM NaCl, 2.7 mM KCl, 1 mM MgCl2, 0.5 mM Na3VO4, 1% Triton X-100, 10% Glycerol, 20 mM Tris pH 7.8, 1 µg / ml Leupeptin, 0.2 mM PMSF, 10 mM NaF, 1 mM EDTA, 1 mM DTT, 5 mM Na pyrophosphate, 0.5 ml, 1 ml of 100 mM, 1 mM Benzamidine) in tubes with airtight caps and thick walls.

Fifty ml of the buffer was used per 20 mg of wet muscle tissue. The material was kept on ice during processing. Then, 5 mm stainless steel beads (Qiagen, Germany) were placed in the tubes. The tubes were placed in the Digital Vortex-Genie 2 laboratory mixer (Scientific Industries, Inc., USA) for 15 minutes at 4 °C. Then they were left on a mini-rotor shaker (MP-1, Biosan, Latvia) in the refrigerator for 1 hour. Next, they were centrifuged at 13,000 rpm for 5 minutes at 4 °C, after which the clear supernatant was transferred to new tubes with clear markings. Thirty µl were taken to determine the concentration of total protein in the sample (using the Bradford protein assay).

The following parameters were determined in the tissue homogenate. Muscle tissue – glycogen, lactate, glycogen synthase (GYS1), glycogen phosphorylase (PYGM). Liver tissue – liver glycogen synthase (GYS2), liver glycogen phosphorylase (PYGL), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL); alanine aminotransferase (ALT); aspartate aminotransferase (AST).

The analysis was performed using ready-made kits on the Anthos 2010 microplate photometer with software (Biochrom Ltd., UK). Sample preparation, colorimetric analysis, and calculations of the obtained data were carried out according to the manufacturer's protocol. Tissue homogenate was obtained according to the scheme for a sample weighing less than 100 mg. The concentration of total protein in the sample was determined using the modified Bradford protein assay.

PAGE electrophoresis was performed under denaturing conditions and according to the method described previously (Laemmli, 1970) with 5% stacking and 7% separating gels using the electrophoresis system (Mini-PROTEAN Tetra electrophoresis cell, USA) and the current source (PowerPacBasic, USA)). The concentration of total protein applied to each well was 7.5 µg. Using the blotting system (Trans-Blot Turbo, USA), proteins were transferred from the gel to a PVDF membrane (BioRad, USA) followed by blocking with 5% skim milk (BioRad, USA) in 1X TBSt (TBS with the addition of 0.1% Tween-20) for 1 h at room temperature. The target proteins were determined by incubation at 4 °C in 5% dry milk in TBSt overnight at a dilution of 1:1000 with rabbit polyclonal antibodies against citrate synthetase (cat. no. ab96600, abcam, UK) and with a cocktail of Total OXPHOS Rodent WB antibodies (cat. no. ab110413, abcam, UK), containing 5 mouse antibodies, each against the subunits of NDUFB8, SDHB, UQCRC2, MTCO1, ATP5A. The sample was then incubated with HRP-conjugated secondary antibodies (anti-mouse cat. #1706516, anti-rabbit cat. #1706515, BioRad, USA) for 1 h at room temperature in 3% dry

milk in TBSt. Antigen – antibody complexes were visualized using the ECL kit (SuperSigna West Dura, Thermo Scientific, USA) and the documentation system (ChemiDoc-It 2, UVP, UK). The densitometric analysis was performed using ImageJ software.

Immunoblotting. Proteins were transferred from the gel to the PVDF membrane (BioRad, USA) in transfer buffer (25 mM Tris – 192 mM glycine (pH 8.3), 20% ethanol) for 1.5 h at 400 mA. To check the quality of protein transfer to the membrane, the membrane was stained with Ponceau S dye. The dye reversibly binds to proteins, staining them red. To prepare the membrane for immunochemical staining, it was washed several times in a TBS solution (50 mM Tris, pH 7.4, 150 mM NaCl). Then, blocking was performed with 5% dry skim milk (Valio, Finland) prepared in PBST (PBS with the addition of 0.1% Tween-20). Blocking was carried out for one hour at room temperature and constant stirring. The membrane was then transferred into a TBST solution (50 mM Tris, pH 7.4, 150 mM NaCl, 0.1% Tween-20) containing 5% BSA and primary antibodies (1:1000 ratio by volume) and left for 14-17 hours at +4 °C and constant stirring. Next, the membrane was washed three times for 15 minutes with a TBST solution and then incubated at room temperature with constant stirring in a separate container for 1 hour in 10 ml of a TBST solution containing 5% dry skim milk and HRP-conjugated secondary antibodies in a ratio of 1:5000. Then the membrane was washed 3 times with a TBST solution for 15 min.

The bands of the formed protein complexes with primary and secondary antibodies on the membrane were visualized using the enhanced chemiluminescence (ECL) method, using the chemiluminescence kit (SuperSigna West Dura, Thermo Scientific, USA), developing the membranes on a documentation system (ChemiDoc-It 2, UVP, UK). The densitometric analysis was performed using ImageJ software.

Statistical data processing was performed using the GraphPad Prism package (academic license No. 1531155, valid until 21.12.2024). The significance level when testing the hypothesis of equality of two samples was estimated using the Kruskal – Wallis ANOVA test. All data had non-normal distribution of the variables. To compare the groups, two-way analysis of variance with Tukey's multiple comparison criterion and Holm – Sidak adjustment was used. The data were presented as the median and the interquartile range Me (Q_1; Q_3).

RESULTS

In the previous publication [14], we described changes in the body weight of mice during the experiment. Already starting from week 4 of the experiment, a significant increase in the body weight of mice fed with a high-fat diet was observed ($p < 0.05$). At week 12, the differences between the high-fat diet group and the standard chow diet group increased.

From week 12, both groups were divided into 4 subgroups, in which physical exercise was performed at different times of the day (light phase, dark phase, shift regimen). At week 16 (final week) of the experiment, we found that in the group of mice receiving a high-fat diet and in the standard chow diet group, the differences in body weight remained statistically significant ($p < 0.05$).

In the group receiving a high-fat diet, statistically significant differences ($p < 0.05$) in body weight compared to the control group were observed in all 3 subgroups that were exposed to physical activity. The most effective exercise was in the shift training regimen group. In this group, body weight was 1.2 times lower than in the control group.

In the first part of the work, we studied the level of glycogen, lactate, and carbohydrate metabolism enzymes in the tissues of skeletal muscles and the liver. The content of glycogen in the muscles of young animals receiving a high-fat diet decreased by 20%. Physical exercise led to an increase in the glycogen content in muscle tissue in mice receiving a standard chow diet and did not affect this parameter in the group of animals receiving a high-fat diet (Table 1). In aged mice, the content of glycogen in muscle tissue was lower than in young animals by 12%. Receiving a high-fat diet led to a decrease in this parameter by 17%. In both groups, physical activity performed in the morning or in the shift training regimen contributed to an increase in glycogen content, whereas exercise performed in the evening did not affect this parameter (Table 1).

The lactate content in the muscles of young animals fed with a high-fat diet decreased by 9%. Regular physical exercise led to a decrease in the lactate content in muscle tissue in both groups of young mice. In the group of animals fed with a high-fat diet, the decrease was pronounced to a greater extent and reached 50% in the shift training regimen group (Table 1). In aged animals, the lactate content in muscle tissue was lower by 25% than in young animals, while receiving a high-fat diet did not affect the lactate content. In the group of animals fed with

a standard chow diet, regular physical exercise led to a decrease in the lactate content in muscles by 1.5–2 times (the effect of exercises performed in the morning or in the alternating regimen was more pronounced). In aged mice fed with a high-fat diet, the shift training regimen reduced lactate levels by half, while morning or evening exercises had no effect on this parameter (Table 1).

Table 1

Carbohydrate metabolism parameters in skeletal muscle and liver tissues of mice, ng / ml, *Me* (Q_1; Q_3), $n = 6$

Diet	Age	Exercise	Skeletal muscles				Liver	
			GYS1	PYGM	Glycogen	Lactate	GYS2	PYGL
Standard	Young	Control	2172.36 (2137.53; 2364.49)	2.2 (1.6; 2.9)	1.5 (1.47; 1.53)	5.7 (5; 6.35)	4385.71 (4257.14; 4814.29)	18.7 (16.5; 22)
		Morning	2590.34 (2335.28; 2638.65) $p_3 \leq 0.05$	1.6 (1.2; 1.8) $p_3 \leq 0.05$	1.78 (1.78; 1.78) $p_3 \leq 0.05$	5 (4.6; 5.2) $p_3 \leq 0.05$	4700 (4528.57; 4957.14) $p_3 \leq 0.05$	18.7 (15.95; 20.35)
		Evening	2519.55 (2281.35; 2755.51) $p_4 \leq 0.05$	2 (1.8; 24) $p_6 \leq 0.05$	1.72 (1.69; 1.75) $p_4 \leq 0.05$	5.4 (5.1; 5.7)	4750 (4657.14; 4839.29) $p_4 \leq 0.05$	19.8 (18.84; 21.86)
		Shift	2574.61 (2518.43; 2668.99) $p_5 \leq 0.05$	1.4 (0.8; 1.9) $p_5 \leq 0.05$ $p_8 \leq 0.05$	1.78 (1.72; 1.83) $p_5 \leq 0.05$	5 (4.4; 5.6) $p_5 \leq 0.05$ $p_8 \leq 0.05$	4778.57 (4585.71; 4978.57) $p_5 \leq 0.05$	24.2 (23.1; 24.75) $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$
	Aged	Control	2184.72 (2063.37; 2270.11)	1.2 (1.2; 1.6) $p_2 \leq 0.001$	1.33 (1.28; 1.5) $p_2 \leq 0.05$	4.4 (4; 4.8) $p_2 \leq 0.05$	5185.71 (5071.43; 5328.57) $p_2 \leq 0.05$	17.33 (15.81; 19.94) $p_2 \leq 0.05$
		Morning	2652.13 (2595.96; 2747.08) $p_3 \leq 0.05$	2.4 (2.2; 3) $p_2 \leq 0.01$ $p_3 \leq 0.001$	1.72 (1.31; 2.11) $p_3 \leq 0.05$	2 (1.9; 2.1) $p_2 \leq 0.001$ $p_3 \leq 0.001$	5457.14 (4857.14; 5671.43) $p_2 \leq 0.05$	19.25 (19.25; 19.8) $p_2 \leq 0.05$ $p_3 \leq 0.05$
		Evening	2356.63 (2291.46; 2449.89) $p_2 \leq 0.05$ $p_4 \leq 0.05$	2.2 (2; 2.4) $p_4 \leq 0.05$	1.28 (1.19; 1.36) $p_2 \leq 0.05$ $p_6 \leq 0.05$	3 (2.8; 3.2) $p_2 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	4900 (4757.14; 4914.29) $p_6 \leq 0.05$	17.6 (17.6; 19.8) $p_2 \leq 0.05$ $p_6 \leq 0.05$
		Shift	3155.51 (2974.04; 3194.27) $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	2.8 (2.4; 3.2) $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	1.78 (1.67; 2.03) $p_5 \leq 0.05$ $p_8 \leq 0.05$	2 (1.6; 2.8) $p_2 \leq 0.001$ $p_5 \leq 0.05$ $p_8 \leq 0.05$ $p_8 \leq 0.05$	5392.86 (5178.57; 5842.86) $p_2 \leq 0.05$ $p_8 \leq 0.05$	29.7 (29.15; 30.25) $p_2 \leq 0.05$ $p_5 \leq 0.01$ $p_7 \leq 0.01$ $p_8 \leq 0.01$
High-fat	Young	Control	2122.92 (2073.48; 2227.42)	4 (4; 5) $p_1 \leq 0.05$	1.22 (1.17; 1.28) $p_1 \leq 0.05$	5.2 (4.9; 5.53) $p_1 \leq 0.05$	4228.57 (3928.57; 4414.29)	22 (18.7; 23.24) $p_1 \leq 0.05$
		Morning	3100.45 (2761.12; 3165.62) $p_1 \leq 0.05$ $p_3 \leq 0.05$	2 (1.8; 2.8) $p_1 \leq 0.05$ $p_3 \leq 0.001$	1 (0.94; 1.06) $p_1 \leq 0.05$ $p_3 \leq 0.05$	3.2 (2.8; 3.7) $p_1 \leq 0.05$ $p_3 \leq 0.001$	4442.86 (4242.86; 4771.43) $p_1 \leq 0.05$	16.5 (16.5; 17.05) $p_1 \leq 0.05$ $p_3 \leq 0.05$
		Evening	2963.37 (1947.64; 3173.48) $p_4 \leq 0.05$	2.6 (1.3; 2.2) $p_1 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	1.22 (1.11; 1.33) $p_1 \leq 0.05$	4.2 (3.7; 4.7) $p_1 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	4464.29 (3925; 4589.29) $p_4 \leq 0.05$	16.5 (15.4; 16.91) $p_1 \leq 0.05$ $p_4 \leq 0.05$
		Shift	2644.27 (2606.07; 2670.11) $p_7 \leq 0.05$ $p_8 \leq 0.05$	1.8 (0.9; 2.7) $p_5 \leq 0.05$	1.11 (1.06; 1.17) $p_1 \leq 0.05$	2.8 (1.8; 3.8) $p_1 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	4892.86 (4696.43; 5221.43) $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	17.6 (17.05; 19.25) $p_1 \leq 0.05$ $p_5 \leq 0.05$
	Aged	Control	2365.62 (2181.35; 2431.91)	2.8 (2.6; 3) $p_1 \leq 0.05$ $p_2 \leq 0.05$	1.0 (0.74; 1.28) $p_1 \leq 0.05$	4.4 (4.1; 4.8) $p_2 \leq 0.05$	5145.71 (5117.14; 5321.43) $p_2 \leq 0.05$	15.75 (14.06; 16.58) $p_1 \leq 0.05$ $p_2 \leq 0.05$
		Morning	2489.21 (2448.76; 270 9.44) $p_2 \leq 0.05$	2.8 (2.2; 2.8) $p_2 \leq 0.05$	1.22 (0.89; 1.22) $p_1 \leq 0.05$	4.6 (3.9; 5.2) $p_1 \leq 0.05$ $p_2 \leq 0.05$	4985.71 (4707.14; 5250) $p_1 \leq 0.05$ $p_2 \leq 0.05$	15.4 (14.16; 15.95) $p_1 \leq 0.05$

End of table 1

Diet	Age	Exercise	Skeletal muscles				Liver	
			GYS1	PYGM	Glycogen	Lactate	GYS2	PYGL
		Evening	2442.02 (2398.2; 2515.06)	2.6 (2.5; 2.7) $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	1.27 (1.17; 2.5)	5 (4.2; 5.3) $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_4 \leq 0.05$	4814.29 (4575; 5042.86) $p_2 \leq 0.05$	15.68 (13.61; 17.15) $p_1 \leq 0.05$
		Shift	2668.99 (2636.4; 2691.46) $p_1 \leq 0.05$	2.2 (2.1; 2.3) $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	1.26 (1.04; 1.47) $p_1 \leq 0.05$ $p_5 \leq 0.05$	2.4 (2.4; 3.4) $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_5 \leq 0.01$ $p_7 \leq 0.001$ $p_8 \leq 0.001$	4771.43 (4621.43; 4957.14) $p_1 \leq 0.05$ $p_5 \leq 0.05$	19.8 (18.7; 23.65) $p_1 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$

Note. Here and in Table 2: p_1 – significant differences between the standard diet group and the high-fat diet group; p_2 – significant differences between the young and adult mice; p_3 – significant differences between the control group and the morning group; p_4 – significant differences between the control group and the evening group; p_5 – significant differences between the control group and the shift training group; p_6 – significant differences between the morning group and the evening group; p_7 – significant differences between the evening group and the shift training group.

The changes in glycogen synthase levels in muscle and liver tissues were generally similar (Table 1). In young animals fed with a high-fat diet, the levels of this enzyme did not change in either muscle or liver tissues. At the same time, exercise led to a significant increase in enzyme levels in both tissues, with the shift training regimen having the greatest effect. In aged animals, a high-fat diet also had no effect on glycogen synthase levels, but the effects of exercise differed.

In the group of animals receiving a standard chow diet, the levels of the enzyme increased significantly in both muscle and liver tissues. At the same time, in aged animals fed with a standard diet, the glycogen synthase content increased in the muscle tissues, but decreased in the liver tissue. In both cases, the greatest effect was produced by exercises performed in the alternating regimen.

The changes in glycogen phosphorylase levels in muscle and liver tissues, on the contrary, had a number of significant differences (Table 1). In young animals fed with a standard diet, physical exercise led to a significant increase in the enzyme content in the liver and a decrease in the muscle tissue, with the greatest effect produced by exercises performed in the shift training regimen. In young animals receiving a high-fat diet, the content of this enzyme doubled in the muscle tissue and increased only by 10% in the liver tissue. At the same time, physical exercise led to a significant increase in the enzyme content in muscles, while in the liver its content, on the contrary, decreased. In aged animals, a high-fat diet did not affect the glycogen phosphorylase content in the muscles, while in the liver, a decrease of 12% was noted. Regular exercise increased the enzyme levels in both tissue types, but the effect of exercise was greater in the standard diet group. Here, too, the greatest effect was seen with the shift training regimen.

In the second part of the work, we examined the content of HDL, LDL, and VLDL in the liver tissue of mice, as well as the content of aminotransferases (ALT, AST) (Table 2).

In young mice receiving a high-fat diet, the content of HDL in the liver decreased by 20%, while the content of LDL and VLDL increased by 15 and 10%, respectively. Physical exercise led to a reliable decrease in all three parameters in mice receiving a standard diet. In the animals receiving a high-fat diet, we observed a slight increase in the content of HDL in the liver under the influence of physical exercise along with a reliable decrease in LDL and VLDL (Table 2). In all cases, the greatest effect was produced by exercise performed in the morning hours and in the shift training regime.

In aged mice, the content of HDL in the liver was slightly lower, and the content of LDL and VLDL, on the contrary, was slightly higher than in young animals. The effects of physical exercise in the aged groups of animals were greater than in young mice.

The HDL content in the liver increased by 1.5 times, while the LDL and VLDL levels decreased, with the decrease in VLDL being more significant – in some cases, the parameter declined by two times (Table 2). Traditionally, exercises performed in the morning hours and in the shift training regimen were the most effective.

Table 2

Lipid metabolism parameters and the level of aminotransferases in the liver tissue of mice, ng / ml, *Me* (Q_1; Q_3), n = 6

Diet	Age	Exercise	HDL	LDL	VLDL	ALT	AST
Standard	Young	Control	2053 (1771.7; 2420)	1390.8 (1367.8; 1436.8)	6338.4 (5294.2; 7581)	101.6 (85.6; 108.4)	308.8 (306; 332.4)
		Morning	1800 (1540; 1020) $p_3 \leq 0.05$	1282.8 (1282.8; 1340.2) $p_3 \leq 0.05$	4330.8 (3691.2; 4893.2) $p_3 \leq 0.05$	126.2 (114.7; 140.7) $p_3 \leq 0.05$	378 (377.2; 398.2) $p_3 \leq 0.05$
		Evening	1673.8 (1554.3; 1877.9) $p_4 \leq 0.05$ $p_6 \leq 0.05$	1308.1 (1276.15; 1352.9)	5956 (4698.6; 6926.6) $p_6 \leq 0.05$	118 (103.5; 128.4) $p_4 \leq 0.05$	323.4 (296.6; 369.4) $p_6 \leq 0.05$
		Shift	968.8 (937.6; 1234.4) $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	1298.9 (1273; 1344.85) $p_5 \leq 0.05$ $p_8 \leq 0.05$	4691.2 (4180.2; 5250) $p_5 \leq 0.05$ $p_8 \leq 0.05$	154.8 (128.4; 172.4) $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	392.8 (342.8; 397.2) $p_5 \leq 0.05$ $p_8 \leq 0.05$
	Aged	Control	1674 (1586.8; 1739.2) $p_2 \leq 0.001$	2057.4 (2051.7; 2235.6) $p_2 \leq 0.001$	7544.2 (6672.8; 8099.4) $p_2 \leq 0.05$	72 (59.2; 82.8) $p_2 \leq 0.05$	188.8 (166.4; 192.8) $p_2 \leq 0.001$
		Morning	1858.6 (1755.4; 1907.5) $p_3 \leq 0.05$	1155.1 (1054.55; 1272.95) $p_2 \leq 0.05$ $p_3 \leq 0.05$	5985.2 (4930; 6014.7) $p_2 \leq 0.05$ $p_3 \leq 0.05$	63.6 (60.6; 67.8) $p_2 \leq 0.05$ $p_3 \leq 0.05$	160 (134.4; 187.6) $p_2 \leq 0.05$
		Evening	1674 (1608.8; 1717.2) $p_6 \leq 0.05$	1120.7 (1040.25; 1281.6) $p_2 \leq 0.05$ $p_4 \leq 0.05$	6058.8 (5573.6; 6110.2) $p_4 \leq 0.05$	84.4 (169.1; 199.4) $p_2 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	168 (156.2; 180.4) $p_2 \leq 0.05$ $p_4 \leq 0.05$
		Shift	2120 (1932.4; 2140) $p_2 \leq 0.01$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	1195.4 (1103.5; 1290.2) $p_5 \leq 0.05$	4279.4 (3558.7; 4853.1) $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	93.6 (83.4; 97.6) $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$	192.2 (182.5; 236.2) $p_5 \leq 0.05$ $p_7 \leq 0.05$ $p_8 \leq 0.05$
High-fat	Young	Control	1630.6 (1540.3; 1699.1) $p_1 \leq 0.05$	1602.2 (1567.8; 1648.2) $p_1 \leq 0.05$	7029.6 (6956; 7382.4) $p_1 \leq 0.05$	133.8 (123.3; 159.8) $p_1 \leq 0.05$	324.4 (305.6; 347.2) $p_1 \leq 0.05$
		Morning	1708.8 (1632.6; 1774) $p_1 \leq 0.05$	1247.2 (1181.1; 1324.75) $p_3 \leq 0.01$	5073.6 (5029.4; 6308.8) $p_1 \leq 0.05$ $p_3 \leq 0.001$	100.4 (94.1; 103.3) $p_3 \leq 0.05$	243.2 (240.4; 257.2) $p_1 \leq 0.05$ $p_3 \leq 0.05$
		Evening	1741.2 (1681.5; 1789) $p_4 \leq 0.05$	1396.5 (1281.55; 1497.1) $p_4 \leq 0.05$	6647 (6022; 6988.9) $p_1 \leq 0.05$ $p_4 \leq 0.05$ $p_6 \leq 0.05$	119.2 (104.5; 129.9) $p_4 \leq 0.05$ $p_6 \leq 0.05$	316 (280.8; 332.4) $p_6 \leq 0.05$
		Shift	1752 (1710.8; 1795.3) $p_1 \leq 0.05$ $p_5 \leq 0.05$	1206.9 (1181.05; 1224.15) $p_5 \leq 0.05$ $p_8 \leq 0.05$	4926.4 (4625; 6213.2) $p_5 \leq 0.05$ $p_8 \leq 0.05$	99.2 (94.8; 108.4) $p_1 \leq 0.05$ $p_5 \leq 0.05$ $p_8 \leq 0.05$	231.2 (213.9; 243.1) $p_1 \leq 0.05$ $p_5 \leq 0.05$ $p_8 \leq 0.05$
	Aged	Control	1439.2 (1409.2; 1550) $p_1 \leq 0.05$ $p_2 \leq 0.05$	2811.4 (2711.4; 3083.25) $p_1 \leq 0.05$ $p_2 \leq 0.05$	8088.4 (7639.8; 9051.6) $p_2 \leq 0.05$	98.6 (92.9; 101.6) $p_1 \leq 0.05$ $p_2 \leq 0.05$	178.2 (156.3; 205.4) $p_2 \leq 0.05$
		Morning	1695.6 (1489.2; 1695.6) $p_1 \leq 0.05$ $p_3 \leq 0.05$	2195.4 (2091.9; 2264.35) $p_1 \leq 0.01$ $p_2 \leq 0.05$ $p_3 \leq 0.05$	6558.8 (6492.6; 6945.6) $p_2 \leq 0.05$ $p_3 \leq 0.05$	84.2 (69.8; 93.6) $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_3 \leq 0.05$	175.6 (174.6; 176.6) $p_2 \leq 0.05$

End of table 2

Diet	Age	Exercise	HDL	LDL	VLDL	ALT	AST
		Evening	1674 (1625.1; 1695.7) $p_4 \le 0.05$	2172.4 (2155.2; 2287.3) $p_1 \le 0.05$ $p_2 \le 0.05$ $p_4 \le 0.05$	7257.4 (7005.9; 7393.4) $p_1 \le 0.05$ $p_4 \le 0.05$ $p_6 \le 0.05$	77.2 (73.8; 86) $p_1 \le 0.05$ $p_2 \le 0.05$ $p_4 \le 0.05$ $p_6 \le 0.05$	185 (164.5; 207.7) $p_2 \le 0.05$
		Shift	2000 (1934.8; 2040) $p_2 \le 0.05$ $p_5 \le 0.05$ $p_7 \le 0.05$ $p_8 \le 0.05$	2092 (2063.2; 2155.2) $p_1 \le 0.05$ $p_2 \le 0.05$ $p_5 \le 0.05$	5132.4 (4500; 5577.2) $p_1 \le 0.05$ $p_5 \le 0.05$ $p_7 \le 0.05$ $p_8 \le 0.05$	77.2 (77.2; 80) $p_1 \le 0.05$ $p_2 \le 0.05$ $p_5 \le 0.05$ $p_7 \le 0.05$	188.4 (181; 198.9) $p_2 \le 0.05$

In young mice receiving a high-fat diet, the ALT and AST levels in the liver increased by 30 and 5%, respectively. Physical exercises led to a significant increase in the content of both enzymes in the liver of mice receiving a standard chow diet. When performing exercise in the shift regimen, the increase was 30–50%. In the meantime, in the high-fat diet group, we observed a decrease in the content of these enzymes in the liver tissue by 1.5 times. Here, too, the greatest effect was observed exercises performed in the shift regimen (Table 2).

In aged mice, we observed a significant decrease in the ALT and AST levels in the liver. In the animals receiving a high-fat diet, the ALT content in the liver slightly increased. Physical exercise in mice fed with a standard chow diet had opposite effects. Exercise performed in the morning hours contributed to a decrease in the content of both enzymes in the liver tissue, while exercise done in the shift regimen, on the contrary, led to a significant increase (Table 2). In aged animals fed with a high-fat diet, physical exercise led to a decrease in the content of ALT and an increase in the content of AST – the effects of exercise performed in the shift regimen were the most pronounced.

DISCUSSION

The obtained results show that the use of a high-fat diet in mice led to an increase in body weight and the development of obesity (body weight increased by 25% compared to the control group). Forced treadmill exercise had a pronounced effect on metabolism in mice with a model of T2DM. First of all, this was manifested by a decrease in the body weight of animals and depended on the time of the day when the exercise was performed.

As we have already mentioned above, the liver plays an important role in the regulation of carbohydrate and lipid metabolism, therefore, it becomes a target for pathological processes in metabolic disorders, primarily in T2DM [15]. Muscles contain the largest reservoir of glycogen, the depot of which is carefully regulated and affects insulin sensitivity. In our study, we recorded a decrease in glycogen content in the muscles with the development of metabolic disorders. It is important to note that physical exercise is unable to replenish glycogen depot in the context of a high-fat diet, whereas in animals receiving a standard diet, muscle glycogen depot increases significantly against the background of regular physical exercise. According to J. He, D.E. Kelley, a decrease in muscle glycogen correlates with a decrease in the oxidative capacity of mitochondria and the accumulation of lipids in the muscle tissue, and is also directly associated with the level of insulin resistance [16]. The disproportionality of these relationships may play a certain role in the pathogenesis of intracellular metabolic disorders in T2DM. In the meantime, the observed changes in lactate levels after regular physical exercise are most likely associated with the training effect on the cardiovascular system and are weakly associated with metabolic changes in the muscle tissue.

A decrease in the glycogen content is apparently associated with the activation of its breakdown processes rather than with a decrease in its synthesis. This is evidenced by the fact that the content of glycogen synthase in both muscles and liver did not change during the formation of metabolic disorders in mice, but increased during physical activity, primarily in healthy animals. Thus, the effects of this enzyme are more pronounced during physical activity than in the pathogenesis of metabolic disorders.

Yet, significant and multidirectional changes were recorded in the content of glycogen phosphorylase in the liver and skeletal muscle tissue. These changes were significantly influenced by both the nature of nutrition and physical activity. In all likelihood,

this enzyme is involved both in the mechanisms of development of pathological processes and in the mechanisms of adaptive effects of motor activity. This is evidenced by often oppositely directed changes in the content of glycogen phosphorylase in the muscle and liver tissue during physical activity.

The mechanisms of the identified differences in the reaction of carbohydrate metabolism to physical activity in healthy animals and animals with T2DM may be associated with the restructuring of gene expression mechanisms in metabolic disorders. Thus, pathway analysis of differentially regulated genes during exercise revealed upregulation of regulators of GLUT4 (SLC2A4RG, FL0T1, EXOC7, RAB13, RABGAP1, and CBLB), glycolysis (HK2, PFKFB1, PFKFB3, PFKM, FBP2, and LDHA), and insulin signaling mediators in individuals with T2DM compared to healthy controls [17]. It is worth noting that T2DM patients also demonstrated exercise-induced compensatory regulation of genes involved in amino acid biosynthesis and metabolism (PSPH, GATM, NOS1, and GLDC), which responded to differences in amino acid profile (consistently lower plasma glycine, cysteine, and arginine levels).

We have already mentioned above the close association between T2DM and lipid metabolism disorders in the liver. These disorders synergistically promote each other's progression. Several pathophysiological pathways are involved in this association, including insulin resistance, inflammation, and lipotoxicity [3]. Our results are in good agreement with this point of view: the development of experimental T2DM in mice is accompanied by a decrease in the HDL content in the liver in parallel with an increase in LDL and VLDL. It is important to stress that physical exercise provided partial normalization of the ratio of lipid fractions, despite the fact that it was performed in the context of a continuous high-fat diet. Thus, it can be argued that physical activity is able to partially neutralize the pathological effects of a high-fat diet even without dietary adjustments.

The mechanism of such an effect can be associated with increased production of anti-inflammatory myokines under the influence of physical exercise, which are capable of blocking chemotactic factors, such as monocyte chemoattractant protein-1, and/or proinflammatory mediators, such as IL-1β, TNFα, visfatin and plasminogen activator inhibitor-1, and/or increased synthesis of adipokines, such as adiponectin and apelin [17].

An important aspect of our results is the identified numerous differences in the age parameter – in the group of aged mice, metabolic changes caused by both the T2DM modeling and physical exercise were not only quantitative, but in some cases qualitative. In general, a completely expected correlation is observed – in the group of aged animals, disorders in carbohydrate and lipid metabolism were more pronounced, and the corrective effect of physical exercise was weaker in most cases [18]. However, we recorded a number of exceptions that distinguish aged animals from younger ones, such as a decrease in glycogen synthase and an increase in glycogen phosphorylase in the liver tissue. Qualitative differences were also found in liver aminotransferase levels.

It is worth noting that the effects of physical activity on the content of lipid fractions in the liver in aged animals were more pronounced than in young mice. In light of the above hypothesis about the role of myokines and adipokines in these processes, it can be assumed that this feature may be associated with a larger volume of adipose tissue in aged animals.

The explanation for the revealed differences may also be associated with the features of the transcription of muscle genes in response to physical activity. In the work by U. Raue et al., 661 genes were identified whose expression differed when performing exercises with weights in young and elderly people [19].

The results indicating a significant difference in the effects of physical activity performed at different times of the day on metabolic processes in the liver and muscle tissue are of great interest. In almost all cases, the least effective were exercises performed in the evening hours, that is, during the period of natural activity of the animals. The effects of exercises in the period of low activity (morning) were most often higher, but the greatest effect was produced by physical exercise performed in the shift training regimen – for one week in the morning and for another week in the evening. It should be noted that we have previously described similar patterns for the effects of physical activity on body weight and insulin tolerance [14].

There are few works in the literature devoted to the role of circadian rhythms on the effects of physical activity in general, and studies on the role of circadian rhythms in metabolic disorders are isolated. Therefore, there has been no consensus on the mechanisms of this effect yet. A number of authors associate this with the effect of stress, since a greater effect is inherent in exercises performed at an unusual time. This

hypothesis is partially consistent with our data on serum cortisol levels in mice [20].

At the same time, work [11] showed that circadian rhythmicity in insulin tolerance was also observed in the signaling pathways regulating insulin- and exercise-induced glucose uptake in skeletal muscles, including AKT, 5'-adenosine monophosphate-activated protein kinase (AMPK), and phosphorylation of the TBC1 4 domain family. Basal and insulin-stimulated glucose uptake by skeletal muscles and adipose tissues *in vivo* also differed during the day and at night. However, the rhythmicity of glucose uptake differed from the rhythm of insulin tolerance as a whole. Both insulin sensitivity and signaling of isolated skeletal muscles reached a maximum in the dark period. These results indicate that the mechanisms of circadian rhythmicity of carbohydrate metabolism cannot be limited to the stress factor alone.

CONCLUSION

The obtained results allow us to draw several important conclusions:

1. A decrease in the muscle glycogen content in T2DM is associated with the activation of its breakdown rather than with a decrease in its synthesis. This is evidenced by the fact that the content of glycogen synthase in both the muscles and the liver did not change during the formation of metabolic disorders in mice, but increased during physical activity, primarily in healthy animals.

2. Significant and multidirectional changes were recorded in the content of glycogen phosphorylase in the liver and skeletal muscle tissue; these changes were significantly influenced by both the type of diet and physical activity. In all likelihood, this enzyme is involved both in the mechanisms of pathological processes and in the mechanisms of adaptive effects of motor activity.

3. The development of experimental T2DM in mice is accompanied by a decrease in the content of HDL in the liver in parallel with an increase in LDL and VLDL. It is important that physical activity provided partial normalization of the lipid fraction ratio despite the fact that it was performed in the context of a continuous high-fat diet. Thus, it can be argued that physical activity is able to partially neutralize the pathological effects of a high-fat diet even without dietary adjustments.

4. In the group of aged mice, metabolic changes caused by both the T2DM modeling and physical activity were not only quantitative, but in some cases qualitative. In general, a completely expected correlation is observed – in the group of aged animals, carbohydrate and lipid metabolism disorders were more pronounced, and the corrective effect of physical activity was weaker in most cases. However, we recorded a number of exceptions that distinguish aged animals from young ones.

5. The effects of physical activity applied at different times of the day on metabolic processes in the liver and muscle tissue vary significantly. In almost all cases, the weakest effect was shown by exercises performed in the evening hours, that is, during the period of natural activity of rodents. The effects during the period of low activity (morning) were most often higher, but the greatest effect was produced by physical activity performed in the shift regimen – for one week in the morning and for one week in the evening.

The obtained results allow us to conclude that physical activity can act as a means of preventing not only metabolic disorders (obesity and insulin resistance), but also concomitant complications in the liver and, subsequently, the cardiovascular system. Due to the partial normalization of the parameters of carbohydrate and, most importantly, lipid metabolism, they are likely to reduce the risk of both fatty liver disease and vascular disorders.

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Authors' contribution

Milovanova K.G., Zakharova A.N. – significant contribution to conception and design, analysis and interpretation of the data, drafting of the article. Kollantay O.V., Orlova A.A., Shuvalov I.Yu., Popov S.A. – collection of data, analysis of the data, processing and interpretation of the results. Kovalev I.V., Medvedev M.A., Yakimovich I.Yu., Chibalin A.V. – analysis of the data, processing and interpretation of the results, editing of the article. Kapilevich L.V. – research supervision, conception of the study, editing of the article, final approval of the article for publication.

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