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M. I. Isachenko https://orcid.org/0000-0002-3026-1012
O. V. Melnikova https://orcid.org/0000-0002-6807-8440
O. V. Khorolets https://orcid.org/0009-0006-4499-3165

THE IMPACT OF AMINO ACIDS ON CHANGES IN FLUID AND FAT TISSUE CONTENT IN RATS WITH TYPE 2 DIABETES MELLITUS

Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine

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The **aim of the study** was to determine the body composition of rats with experimental type 2 diabetes mellitus, and to assess the impact of amino acid correction on these parameters using bioelectrical impedance analysis.

Materials and methods. Type 2 diabetes mellitus was induced with streptozotocin (30 mg/kg) in rats with insulin resistance. Two experimental subgroups received L-arginine or N-acetyl-L-cysteine, while the diabetic control group received drinking water. Glucose levels, body weight, and body composition were measured.

Results. Streptozotocin administration caused persistent hyperglycemia and body mass reduction, primarily due to fat loss, despite a slight increase in lean body mass. However, the lean body mass remained lower than in the control group. These changes led to overall dehydration caused by reduced extracellular and intracellular fluid volumes, while their ratio was preserved. L-arginine and N-acetyl-L-cysteine reduced glucose levels by 14 % and 13 %, respectively, compared to the untreated diabetic group. Despite the reduction in glucose levels, all diabetic subgroups experienced progressive dehydration, without significant differences in total body weight, fat, or lean body mass mass. The fat-to-lean mass ratio in amino acid-treated groups was 1:5, significantly different from the 1:6 ratio observed in untreated diabetic rats.

Conclusion. Modeling type 2 diabetes mellitus in rats with insulin resistance leads to changes in body composition in rats, including fat mass loss and general dehydration. Amino acid correction reduces glucose levels but does not prevent alterations in water and fat metabolism.

Keywords: bioimpedance analysis of body composition, type 2 diabetes mellitus, L-arginine, N-acetyl-L-cysteine, rats.

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М. І. Ісаченко, О. В. Мельнікова, О. В. Хоролець

ВПЛИВ АМІНОКИСЛОТ НА ЗМІНИ ВМІСТУ РІДИНИ ТА ЖИРОВОЇ ТКАНИНИ У ЩУРІВ ІЗ ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ

Запорізький державний медико-фармацевтичний університет, Запоріжжя, Україна

Метою дослідження було визначення складу тіла щурів з експериментальним цукровим діабетом 2-го типу (ЦД2), а також оцінка впливу корекції амінокислотами на ці показники за допомогою біоімпедансного аналізу.

Для реалізації мети тваринам проводили визначення концентрації глюкози, маси тіла й біоімпедансний аналіз складу тіла.

Моделювання ЦД2 на фоні інсулінорезистентності призводить до змін у складі тіла щурів, включно з втратою жирової маси та загальною дегідратацією. Корекція амінокислотами знижує рівень глюкози, але не попереджає змін у водному та жировому обміні.

Ключові слова: біоімпедансний аналіз складу тіла, цукровий діабет 2-го типу, L-аргінін, N-ацетил-L-цистеїн, щури.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine disorders worldwide, characterized by insulin resistance and impaired insulin secretion [1]. According to data from the World Health Organization, the number of people suffering from this condition is growing year by year, driven by lifestyle changes, particularly insufficient physical activity, unhealthy diets, and rising obesity rates among the population [2].

In the search for new approaches to the treatment and management of T2DM and its complications, researchers are focusing on various pharmacological agents, including amino acids (AA) [3], the most promising of which are L-arginine [4] and N-acetyl-L-cysteine [5]. These compounds demonstrate potential in regulating glucose metabolism, reducing insulin resistance, and improving pancreatic β-cell function [4; 5]. Experimental studies investigating the efficacy of amino acids are important for determining their role in the treatment of T2DM, as they

may offer new strategies for disease management and improving patient condition [6].

One of the common methods for assessing the metabolic status of patients with T2DM is bioelectrical impedance analysis of body composition (BIA) [7]. This method provides an accurate determination of the percentage ratio between muscle and fat mass, as well as the body's hydration level. BIA provides valuable information about changes in the bodies of patients with diabetes that may be associated with the development of complications or the effectiveness of treatment [8].

Studies conducted on animals, such as rats, also play an important role in investigating the mechanisms of T2DM, allowing researchers to detect changes in metabolism and assess the impact of various therapeutic interventions on body composition [9]. Due to its sensitivity and accuracy, BIA can help detect early signs of metabolic disorders, which is critically important for developing new strategies for the treatment and prevention of diabetes [10].

Based on the above, **the aim of the study** was to determine the body composition of rats with experimental type 2 diabetes mellitus, as well as to evaluate the impact of amino acid correction on these parameters using bioelectrical impedance analysis.

Materials and Methods

All studies were conducted at the Educational and Research Medical Laboratory Center with a vivarium at Zaporizhzhia State Medical and Pharmaceutical University (Certificate of Technical Competence No. 181/23 issued by the Ministry of Health of Ukraine on December 21, 2023, valid until December 20, 2028), in accordance with the "General Ethical Principles of Animal Experiments" approved by the 3rd National Congress (Kyiv, 2007), and the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes" (Strasbourg, 1986). During the experiment, the Law of Ukraine "On the Protection of Animals from Cruel Treatment" No. 27, Art. 230, 2006, as amended by Law No. 1759-VI (1759-17) of December 15, 2009, Information of the Verkhovna Rada of Ukraine, 2010, No. 9, Art. 76, General Ethical Principles of Animal Experiments (First National Congress on Bioethics, September 20, 2001, Kyiv), Ethical Principles of Animal Experiments (I National Congress on Bioethics, September 20, 2001, Kyiv), Code of Ethics for Scientists of Ukraine (National Academy of Sciences of Ukraine, 2009), and the approval of the Local Bioethics Committee at ZSMPhU (Protocol No. 2 dated March 15, 2023). The study was conducted as part of ZSMPhU's initiative-based research project on "Pathogenesis and Pathomorphology of Endocrine, Cerebrovascular, Neoplastic, and Non-neoplastic Diseases in Patients and in Experiments" (State registration number 0125U002639), duration: 2025-2029.

Study design

Type 2 diabetes mellitus was induced in normoglycemic, normotensive male Wistar rats aged 16–20 months, which were divided into 2 experimental groups and 3 subgroups (Fig. 1).

Before the induction of T2DM, male Wistar rats with normal blood pressure and glucose levels were subjected to a model of insulin resistance using the appropriate method [11], followed by adherence to the described diet throughout the experiment.

To induce T2DM, a single dose of streptozotocin (Streptozotocin, S0130-1G, Sigma-Aldrich) in 50 mM sodium citrate buffer (pH 4.5) at a dose of 30 mg/kg intraperitoneally, followed by drinking glucose solution according to the following schedule: day 1 – 20 % solution, days 2–3 – 10 % solution, days 4–5 – 5 % solution, and from day 6 onward – drinking pure water. Rats in the control group received only citrate buffer intraperitoneally in the same volume. Two weeks after streptozotocin administration, only animals with a glucose concentration > 15 mmol/L in a blood sample from the tail vein were included in the experiment. Measurements were performed using a Contour Plus glucometer (BAYER CONSUMER CARE AG, Switzerland) and Contour Plus test strips.

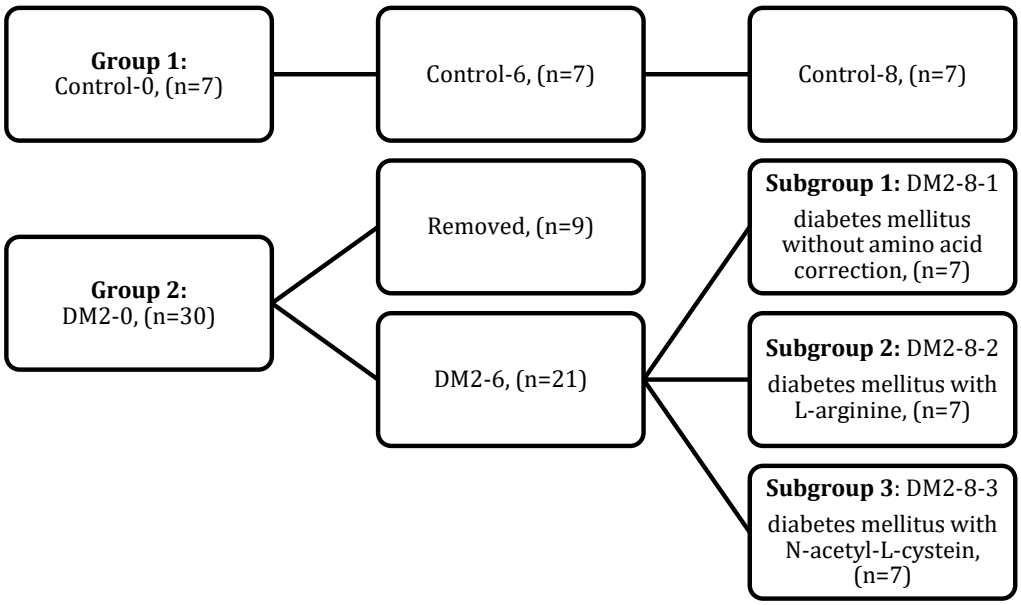

Fig. 1. Study design

The animals were then kept for another 4 weeks under standard conditions with blood glucose monitoring every 2 weeks. Starting from week 7, the rats were divided into 3 subgroups. Subgroup DM2-8-1 consisted of rats with T2DM without amino acid correction; subgroup DM2-8-2 consisted of rats with T2DM to which a solution of L-arginine (2-amino-5-guanidinovaleric acid, C6H14N4O2, CHDA, China) at a dosage of 1.5 g/kg/L per day for 2 weeks, and subgroup 3 – DM2-8-3 – consisted of T2DM rats treated with N-acetyl-L-cysteine (N-acetyl-L-cysteine, C5H9NO3S, China) at the same dosage.

Methodology for conducting bioelectrical impedance analysis of body composition

Prior to performing the bioelectrical impedance analysis (BIA), it was mandatory to enter the animals' biometric data (body weight in grams and rectoanal length in centimeters) into the Vet BIS1 impedance analyzer (ImpediVet, Australia) in accordance with the manufacturer's instructions [12]. The study methodology is detailed in previous articles [11; 13]. The calculated body composition parameters were: total body water (TBW) volume, in milliliters and as a percentage of body weight; extracellular fluid (ECF) and intracellular fluid (ICF) in milliliters and as a percentage of BW; lean body mass (LBM) and fat body mass (FBM) in grams and as a percentage of body weight (Fig. 2) [13]. For anesthesia of the animals, "Medison" (medetomidine hydrochloride) was used, followed by administration of its antidote – "Reverson" (atipamezole hydrochloride) – after the study was completed.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) in the Statistica software (license No. JPZ804I382130ARCN10-J). Continuous variables are presented as the mean (M) ± standard error of the mean (m). All parameters were compared using one-way ANOVA, followed by Tukey's two-sided post-hoc test for multiple comparisons when significant. A two-sided p-value < 0.05 was considered statistically significant for all tests.

Research results and their discussion

The results of the blood glucose concentration measurements in rats of the experimental groups and subgroups are presented in Figure 3 (Fig. 3A–B).

In rats of the DM2 group, a statistically significant increase in glucose concentration was observed compared to control indices at weeks 2, 4, and 6 of the study (Fig. 3A). Administration of L-arginine to rats of the DM2-8-2 subgroup had a significant effect on glucose concentration, leading to a 14 % reduction compared to the untreated DM2-8-1 subgroup, while in the DM2-8-3 subgroup treated with N-acetyl-L-cysteine, only a tendency toward a 13 % decrease was observed (Fig. 3B).

Within 5 weeks following streptozotocin administration to rats with diabetes mellitus, no statistically significant changes in body weight were observed compared to the control group, and neither amino acid had a statistically significant effect on body weight at weeks 7 and 8 of the experiment (Table 1).

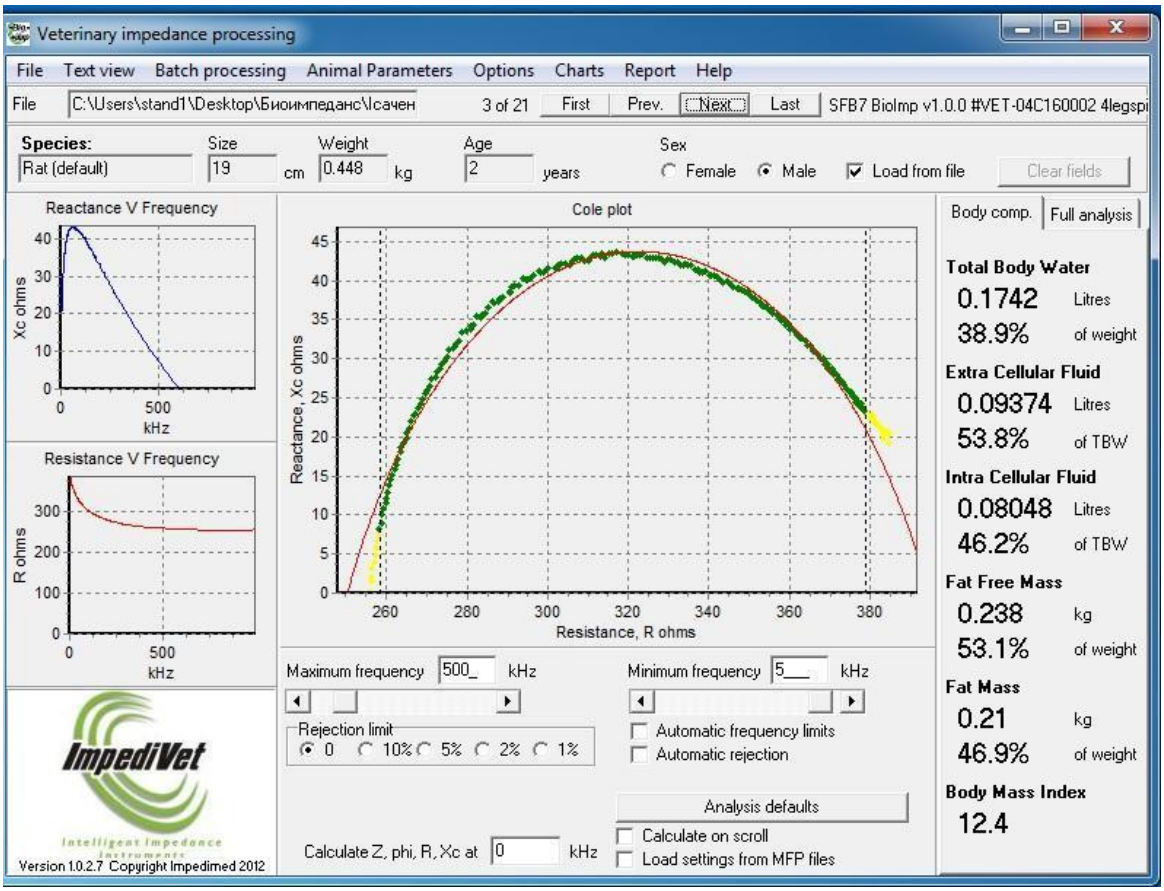

Fig. 2. Analysis of body composition in rats from the T2DM group after Phase 1 and before streptozotocin administration

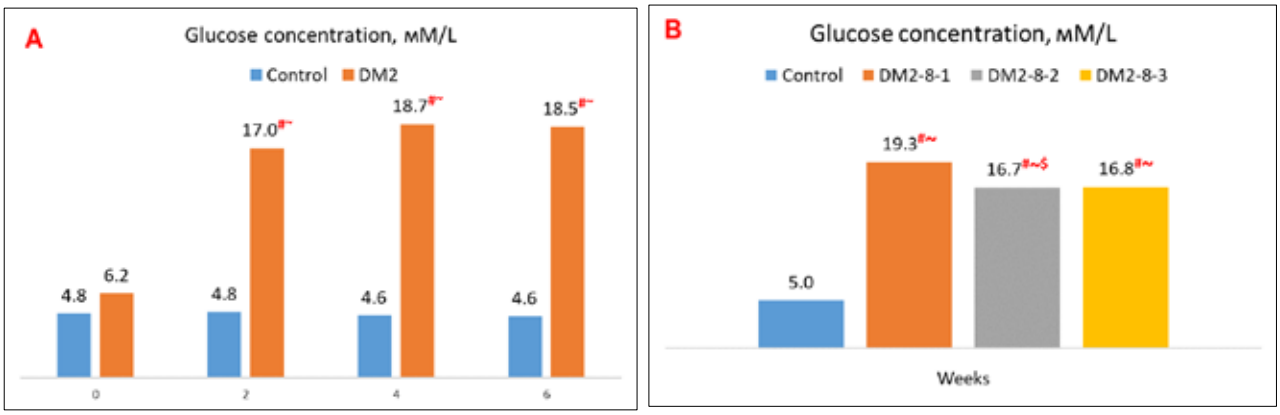

Fig. 3. Changes in glucose concentration in rats from the experimental groups, M ± m

Note 1: # – statistically significant difference in DM2 values compared to those of the control group at the corresponding time point ($p < 0.05$).

Note 2: ~ – statistically significant difference in group parameters at weeks 6 and 8 compared to those of the same group at week 0 ($p < 0.05$).

Note 3: $ – statistically significant difference in parameters of subgroups DM2-8-2 and DM2-8-3 compared to parameters of subgroup DM2-8-1 ($p < 0.05$)

Table 1

Body composition parameters in rats of the experimental groups, M ± m

Groups		0 weeks		6 weeks		8 weeks			
Parameters		Control	DM2	Control	DM2	Control	DM2-8-1	DM2-8-2	DM2-8-3
Rat body mass	g	324 ± 4	352 ± 7#	367 ± 4~	352 ± 6#	377 ± 5~	359 ± 13	362 ± 11	362 ± 11
TBW	ml	0.177 ± 0.007	0.167 ± 0.004	0.211 ± 0.007~	0.160 ± 0.003#	0.212 ± 0.002~	0.137 ± 0.006#~	0.138 ± 0.005#~	0.139 ± 0.003#~
	%	54.5 ± 1.8	47.5 ± 0.7#	57.4 ± 1.3	45.6 ± 0.5#~	56.1 ± 0.5	38.1 ± 0.3#~	38.0 ± 0.6#~	38.4 ± 0.3#~
ECF	ml	0.082 ± 0.003	0.069 ± 0.002#	0.097 ± 0.003~	0.075 ± 0.002#~	0.096 ± 0.001~	0.068 ± 0.003#	0.070 ± 0.002#	0.072 ± 0.002#
	%	46.5 ± 0.7	41.6 ± 1.2#	45.8 ± 0.5	47.1 ± 0.7~	45.2 ± 0.7	49.6 ± 1.6#~	50.8 ± 0.7#~	51.6 ± 0.5#~
ICF	ml	0.095 ± 0.004	0.098 ± 0.003	0.111 ± 0.003~	0.085 ± 0.002#~	0.116 ± 0.002~	0.069 ± 0.004#~	0.068 ± 0.003#~	0.067 ± 0.001#~
	%	53.5 ± 0.7	58.4 ± 1.2#	54.2 ± 0.5	52.9 ± 0.7~	54.8 ± 0.7	50.4 ± 1.6#~	49.2 ± 0.7#~	48.4 ± 0.5#~
FBM	g	0.048 ± 0.001	0.129 ± 0.003#	0.057 ± 0.002~	0.062 ± 0.002~	0.055 ± 0.002~	0.052 ± 0.003~	0.057 ± 0.002~	0.060 ± 0.003~
	%	14.8 ± 0.3	36.7 ± 0.5#~	15.4 ± 0.3	17.6 ± 0.5#~	14.5 ± 0.5	14.6 ± 0.5~	15.6 ± 0.5~	16.6 ± 0.6~$
LBM	g	0.276 ± 0.005	0.223 ± 0.005#	0.312 ± 0.004~	0.290 ± 0.005#~	0.323 ± 0.004~	0.307 ± 0.01~	0.306 ± 0.010~	0.301 ± 0.009#~
	%	85.2 ± 0.3	63.3 ± 0.5#	84.6 ± 0.3	82.4 ± 0.5#~	85.5 ± 0.5	85.4 ± 0.5~	84.4 ± 0.5~	83.4 ± 0.6#~$

Note 1: # – statistically significant difference in the indicators of group DM2 compared to those of the control group at the corresponding time point ($p < 0.05$).

Note 2: ~ – statistically significant difference in the indicators of the groups at weeks 6 and 8 compared to the indicators of the same group at week 0 ($p < 0.05$).

Note 3: $ – statistically significant difference in the indicators of the subgroups DM2-8-2 and DM2-8-3 weeks compared to the indicators of subgroup DM2-8-1 ($p < 0.05$).

As we noted earlier, prior to the induction of T2DM in rats of the DM2-0, obesity had developed, that was accompanied by changes in body composition, a relative deficiency of TBW due to extracellular dehydration, and a redistribution of fluid resulting in intracellular hyperhydration (week 0 values) (Table 1) [11].

Six weeks of T2DM led to a statistically significant 7 % loss in LBM compared to the control group, while changes in FBM showed no significant differences, with the FBM:LBM ratio returning to near-control levels – 1:5. When compared to the animals' condition prior to streptozotocin administration, the changes were more pronounced: a decrease in FBM by a 52 % accompanied by a 30 % increase in LBM. Hyperglycemia, which persisted for 6 weeks, led to generalized dehydration (a 24 % decrease in absolute TBW and a 21 % decrease in relative indicator compared to the control group). These changes occurred due to the loss of both ECF and ICF, with their ratio to TBW remaining within the normal range (1.0 : 1.1) (see Table 1).

The addition of amino acids to drinking water for two weeks had no statistically significant effect on the absolute

values of FBM and LBM in rats of the DM2-8-2 and DM2-8-3 subgroups compared to rats that drank pure water (DM2-8-1) (see Table 1). Analysis of the relative values of FBM and LBM in animals who were administered N-acetyl-L-cysteine (DM2-8-3) revealed a significant decrease in FBM accompanied by an increase in LBM compared to rats without correction (DM2-8-1), but the ratio of FBM to LBM in both treatment subgroups remained at the same level –1:5 versus 1:6 in the DM2-8-1 rats (see Table 1).

Analysis of body water at week 8 revealed a progression of overall dehydration in all three subgroups, with no statistically significant differences when comparing them to one another (see Table 1). The observed changes were caused by an absolute decrease in both ECF and ICF, with no statistically significant influence of amino acids on the studied parameters. A comparison of relative indices revealed a redistribution of fluid relative to TBW toward extracellular hyperhydration. This altered the ECF:ICF ratio, which was 1.0:1.0 in all three subgroups (see Table 1).

In recent years, L-arginine has attracted significant attention as a potential agent for metabolic disorders correction in patients with T2DM [6]. L-arginine is an amino acid that performs several important functions in the body. Studies have shown that L-arginine can lower blood glucose level, which is crucially important for managing this disease. It promotes vasodilation via nitric oxide (NO) that improves glucose uptake by cells. In addition, L-arginine can stimulate insulin secretion by pancreatic β-cells and increase tissue sensitivity to insulin, that contributes to blood glucose decrease [4]. L-arginine may also influence lipid metabolism and inflammatory processes, which often accompany T2DM. Reducing the intensity of inflammation may decrease insulin resistance and improve patients' overall metabolic status. Studies have shown that patients receiving L-arginine demonstrated a significant reduction in HbA1c levels, which is an important indicator of long-term glycemic control [14].

N-acetyl-L-cysteine is also gaining attention as a potential glucose-lowering agent. This compound, known for its antioxidant properties, may significantly influence glucose metabolism and overall health in patients [5]. One of its key mechanisms of action is the ability to increase glutathione levels, a potent antioxidant that protects cells from oxidative stress, and may enhance cellular insulin sensitivity [6]. It has been established that N-acetyl-L-cysteine can modulate glucose metabolism by regulating the activity of enzymes involved in glycolysis and gluconeogenesis. This effect may lead to a reduction in endogenous glucose production in the liver and improving glucose utilization in peripheral tissues [15]. However, our study revealed only a trend toward a decrease in glucose concentration, which is likely due to an insufficient duration of administration or an inappropriate dose.

It is worth noting that, despite the promising findings, research on L-arginine and N-acetyl-L-cysteine in the context of T2DM are currently in the early stages of investigation. Further clinical and experimental studies are required to elucidate their potential mechanisms of action on the pathogenesis of T2DM, as well as to determine optimal dosing regimens, treatment duration, and potential side effects.

The use of BIA provides new opportunities for assessing metabolic changes in body composition in the context of T2DM [7]. The value of this method is based on its low invasiveness and greater informativeness compared to classical mass spectrometry, which allows for the in vivo assessment of changes in metabolic direction in rats in stage 2 following streptozotocin administration. In our experiment, it was found that over 6 weeks, body weight did not change significantly relative to the control and baseline values in the T2DM group of rats. However, the ratio of FBM to LBM changed from 1:2, indicating marked obesity in the animals, and after the induction of hyperglycemia, this ratio shifted to 1:5 due to a predominant loss of fat mass. One of the likely causes of FBM loss is enhanced lipid catabolism, resulting from the use of lipids as a primary energy source. Although such changes may seem positive, they actually indicate metabolic disturbances resulting from endocrine dysregulation [16]. This leads to an increase in free fatty acid levels and triggers inflammatory processes, which, in turn, exacerbate insulin resistance and complicate glucose control. Inflammation may also intensify catabolic processes in muscles, potentially leading to further loss of muscle mass [16]. On the other hand, monitoring body fat reduction may play an important role in a comprehensive approach to T2DM therapy promoting improved insulin sensitivity and enhancing carbohydrate metabolism [17].

In addition, BIA can help detect changes in hydration levels, which is critically important for correcting fluid and electrolyte imbalances and optimizing therapeutic strategies. One of the main causes of dehydration in rats with T2DM is a disruption of glucose-insulin balance. High blood glucose levels lead to osmotic diuresis and glucosuria, which, in turn, result in dehydration. This condition may have serious consequences, including a decrease in circulating blood volume, electrolyte imbalance, and impaired organ function. Moreover, dehydration can result in increased plasma sodium levels, which may impair tissue sensitivity to insulin. This complicates glycemic control and may lead to further progression of T2DM [16].

Conclusions

1. The administration of streptozotocin to insulin-resistant rats induces persistent hyperglycemia, which leads to a decrease in body weight compared to baseline values; however, this difference was not statistically significant compared to the control group. The weight loss occurred due to a reduction in adipose tissue accompanied by an increase in lean body mass; nevertheless, when compared to the control group, this proportion was lower. These changes led to general dehydration due to a decrease in the volume of extracellular and intracellular fluid while maintaining their ratio.

2. Administration of L-arginine led to a 14 % decrease in glucose concentration compared to the subgroup of rats with untreated diabetes; however, administration of N-acetyl-L-cysteine was accompanied only by a tendency toward a decrease. At the same time, progression of total, extracellular, and intracellular dehydration was observed in

all 3 subgroups, without a significant effect on body weight, fat mass, and lean body mass. The fat-to-lean body mass ratio in both subgroups receiving amino acids remained at the same level – 1:5 that differed significantly from the 1:6 ratio in the subgroup of rats without amino acid administration.

3. Modeling of type 2 diabetes mellitus against a background of insulin resistance leads to changes in the body composition of rats, including loss of fat mass and general dehydration. Correction with amino acids reduces glucose levels but does not prevent changes in water and fat metabolism.

Conflict of Interest
None declared.
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