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Original Article

The combined effect of magnesium and chromium citrates on the blood plasma lipid profile in rats under the conditions of alloxan-induced diabetes mellitus

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Abstract

The aim was to study the combined effect of magnesium and chromium citrate on the content and profile of lipids in the blood plasma of rats under alloxan-induced diabetes mellitus (DM) to develop new approaches to correcting metabolic disorders. Four groups of rats (control and three experimental, five male Wistar rats per group) included negative control (CG, no DM), positive DM control (EG1) and two treatments – DM rats fed with combined supplemental magnesium and chromium (EG2 and EG3) daily for 30 consecutive days. Alloxan-induced diabetes (EG1, EG2, EG3 groups) was inflicted on day 21 after dietary supplementation started, and all animals were sacrificed on day 30. The blood samples were analyzed for total lipids, phospholipids, cholesterol, cholesterol esters, di- and tri-acyl glycerols, and free fatty acids. The content of both total blood lipids and their certain classes increased in DM rats. In particular, the increase in cholesterol was due to the oxidative stress caused by pancreatitis, where the intensive oxidation of monoacylglycerols and diacylglycerols occurred. The combined use of magnesium and chromium citrates has led to a partial normalization of lipid content indicators. The prophylactic combined magnesium and chromium use contributed to a decrease in total lipids' content and the percentage content of phospholipids, cholesterol, diacylglycerol and free fatty acids in the blood plasma under alloxan-induced DM.

Keywords: diabetes mellitus, magnesium citrate, chromium citrate, lipids.

Introduction

One of the most dangerous diseases today is diabetes mellitus (DM), which is accompanied by disturbances and deep changes in the metabolism of carbohydrates, proteins and lipids. Statistical studies indicate that the number of people with DM doubles every 13–15 years. As a result, by 2040, the number of patients may reach more than one billion [1, 2].

Since DM is a heterogeneous clinical syndrome, it significantly complicates the search for pathogenetic treatment in each specific case. Medical help for DM patients should be comprehensive, and in addition to selecting adequate hypoglycemic therapy and achieving the desired degree of disease compensation, it requires the implementation of many additional measures aimed at eliminating risk factors for its occurrence or further complications [3–5].

Recently, there has been growing interest in the possible protective role of certain essential chemical elements through their involvement in metabolic processes that undergo significant changes in DM. Among these are magnesium (Mg) and chromium (Cr), although not all aspects of their influence have been definitively clarified [6]. According to some studies, the level of magnesium in the blood plasma is directly proportional to the sensitivity to insulin, and its deficiency can lead to violations of the tyrosine kinase activity of the insulin receptor and an increase in the content of intracellular calcium, which causes the development of insulin resistance [7, 8]. It was also shown that chromium deficiency leads to impaired glucose tolerance [9].

However, today, there is insufficient experimental evidence for the use of Cr and Mg in the prevention and easing of DM symptoms, so the results of long-term trials are needed to evaluate the possible beneficial role of these chemical elements.

Material and methods

The study was carried out on white laboratory male Wistar rats, held in a vivarium under a constant temperature regime (20–25°C), humidity (40–45%) and lighting in compliance with the general ethical principles of conducting experiments on animals in accordance with the "General principles of work on animals" approved by 1st National Congress on Bioethics (Kyiv, Ukraine, 2001) and agreed with the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, France, 1985). Rats had free access to compound feed; meanwhile, drinking water was strictly supplemented (20 mL daily). All experiments were also approved by the local institutional ethical commission.

Four groups of animals (control and three experimental) with five same-age rats per group, weighing 130–150 g, have been formed.

Animals of the control group (CG) and the first experimental group (EG1) have been fed drinking water without additives. Animals of the second (EG2) and the third (EG3) experimental groups were given magnesium citrate ($C_6H_6O_7Mg$) and chromium citrate ($C_6H_5CrO_7$) to their drinking water during 30 days of the experiment, respectively. EG2 group rats received 250 mg Mg^{2+}/kg body weight and 25 μg Cr^{3+}/kg body weight; EG3 group rats received 250 mg of Mg^{2+}/kg body weight and 10 μg of Cr^{3+}/kg body weight daily.

In order to induce experimental diabetes mellitus in animals of three experimental groups (EG1, EG2, EG3), a solution of alloxan monohydrate (Synbias, Ukraine) was administered (150 mg/kg body weight, in 0.85% physiological solution) after 24-hour fasting by a single intraperitoneal injection on the 21st day from the moment of dietary supplementation start. The rats were humanly sacrificed under ether anesthesia after 24-h fasting by decapitation on the 30th day from the start of the experiment.

Statistical data were analyzed using Microsoft Excel (Microsoft, USA) and Statistica ver. 10.0 (StatSoft, USA). Average values with standard deviations were calculated for each group for each analyzed blood lipid parameter.

One-way ANOVA was used to analyze the statistical influence of treatment (namely, the animal group – CG, EG1, EG2, EG3) on each blood lipid parameter. If the influence of the treatment was significant ($p<0.05$), means were separated using Fisher's LSD procedure.

Results

Analysis of the concentrations of various groups of blood lipids and their percentage ratios allows us to estimate the degree of destruction of cell membranes and shifts in overall metabolism during DM.

One-way ANOVA revealed that the animal group (CG, EG1, EG2, EG3) had a significant influence on all investigated classes of lipid percentages from total ($p<0.05$), except phospholipids ($p>0.05$)

While analyzing blood plasma lipids of EG1 rats with DM, an increase has been found in the content of total lipids by 1.5% (Figure 1). As for relative content of different groups of lipids, namely, phospholipids, cholesterol, diacylglycerols and fatty acids increased by 8.8%, 6.4%, 18.5% and by 33.4%, respectively. The content of triacylglycerols and esterified cholesterol decreased by 0.9% and 15.2%, respectively, while comparing DM EG1 group animals with the control CG group rats (Figure 1).

Interestingly, the combined use of magnesium and chromium citrates has partially normalized lipid content indicators. Thus, in EG2 group animals, we have observed a trend towards a decrease in the content of total lipids (by 1.9%), phospholipids (by 14.3%), a significant decrease in the content of cholesterol (by 52.8%), diacylglycerols (by 37.1%) and free fatty acids (by 19.9%),

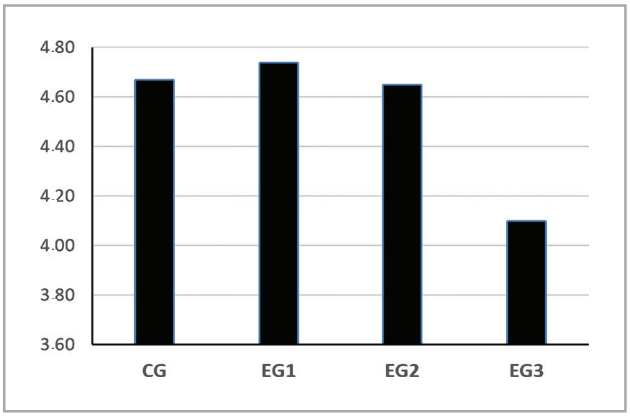

Figure 1: Absolute content of total lipids (g/L) in the blood plasma of rats with DM (EG1 group) and under the combined effect of magnesium and chromium citrates (groups EG2 and EG3), compared to the unaffected control group (CG).

as well as an increase in the content of esterified cholesterol (by 16.2%) compared to their level in DM group EG1 rats (Table 1).

When analyzing blood plasma lipid content of EG3 group animals, a decrease has been found in the content of total lipids (by 13.5%), phospholipids (by 3.9%), triacylglycerols (by 32.9%), cholesterol (by 26.5%), diacylglycerols (by 33.9%) and free fatty acids (by 28.4%), as well as an increase in the content of esterified cholesterol (by 14.3%), compared to EG1 group rats (Table 1).

Discussion

Lipids play an important role in metabolism, as well as in the formation of the structure of body cells, in particular, they are the main building material of cell membranes, thereby acting as a barrier to the penetration of substances into or out of the cell. In particular, phospholipids (sphingolipids, glycolipids) provide plastic properties and fluidity of membranes. In contrast, cholesterol provides stiffness and stability, and changes in their ratio mainly determine the fluidity/stiffness of the cell membrane, as well as the degree of cholesterol solubility and its atherogenic properties [10–12]. The number of lipids and their percentage ratio indicates the degree of destruction of cell membranes. Thus, under various pathological processes in the body, caused in particular by DM, the percentage ratio of lipid fractions, which are more easily oxidized, increases [11]. Additionally, after the establishment of type one DM, which is modeled by alloxan treatment in our case, the catabolism of the body shifts from the use of glucose and other carbohydrates to free fatty acids and ketone bodies as an energy source. Therefore, DM affects total blood lipid contents and specific blood lipid fractions as the rat organism tries to adjust to new pathophysiological conditions [13, 14].

These changes are confirmed by our research results, as the content of both total lipids and their certain classes increased in the blood plasma of animals with DM. In particular, the increase in the amount of cholesterol under the DM conditions is due to the fact that during the oxidative stress caused by pancreatitis, intensive oxidation of lipids takes place, particularly monoacylglycerols and diacylglycerols. This is due to the fact that these classes of lipids, forming the basis of the lipid bilayer of cell membranes, are more easily oxidized compared to triacylglycerols, which are more saturated fatty acids. Thus, the body tries to restore those areas of cell membranes that are damaged due to lipid oxidation at the expense of cholesterol molecules, increasing its percentage ratio.

It is known that magnesium acts as an essential cofactor for more than 30 magnesium-dependent enzymes of lipid metabolism (acyl-CoA synthetase of medium-chain fatty acids, lecithin-cholesterol acyltransferase, ligase of long-chain fatty acids), which are involved in the signaling pathways for the insulin receptor and fat metabolism [5, 8]. Previously, it was shown that magnesium supplementation in an alloxan-induced DM model may have a possible protective effect on the pancreas against the negative influence of alloxan on pancreatic β cells [15]. Chromium, in turn, participates in the regulation of lipid metabolism, as well as affecting the secretion of insulin and its activity. It was shown that low chromium concentrations in the blood cause hyperinsulinemia, which is one

Table 1: Relative content of blood plasma lipid classes of rats with DM (group EG1) and DM under the combined effect of magnesium and chromium citrates (group EG1 and EG2), compared to intact CG control group. (Ave ± st. dev., n=5).

Class of lipids (% ± st. dev.)	Group of animals			
	CG Control	EG1 Disease	EG2 Disease + Supplementation	EG3 Disease + Supplementation
Phospholipids	24.25±0.59 [a]	26.39±0.83 [a]	22.62±2.54 [a]	25.37±0.28 [a]
Cholesterol	9.59±0.79 [a]	10.20±0.26 [a]	4.81±0.57 [c]	7.50±0.21 [b]
Cholesterol esters	19.45±0.52 [a]	16.50±0.39 [b]	19.17±0.98 [a]	18.86±1.19 [a]
Diacyl glycerols	12.52±1.13 [b]	14.84±0.03 [a]	9.33±0.52 [c]	9.80±0.28 [c]
Triacyl-glycerols	18.08±1.32 [a]	17.91±1.48 [a]	17.95±0.15 [a]	12.01±0.58 [b]
Free fatty acids	15.12±0.06 [c]	20.17±0.04 [a]	16.14±0.65 [b]	14.45±0.39 [d]

Note: [a, b, c, d] – Values with the same letters within the same row (same class of lipids) are not significantly different ($p>0.05$).

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of the factors of hyperlipidemia and hypercholesterolemia [16, 17].

Therefore, it can be assumed that changes in the percentages of different classes of lipids in the blood plasma of EG2 and EG3 animals compared to EG1 animals are caused by the inclusion of blood glucose in anabolic processes in the liver, as a result of which the formation of other substances from glucose, in particular diacylglycerols and monoacylglycerols, increases. It is possible that the additional intake of magnesium and chromium in the body ensures the maintenance of the activity of certain enzymes of lipid metabolism.

In general, our research data revealed that the prophylactic complex use of magnesium and chromium citrates might contribute to the normalization of lipid content and lipid metabolism in the blood of rats under conditions of hyperglycemia caused by alloxan-induced DM.

Conclusion

Under the conditions of alloxan-induced experimental DM, the content of total lipids, phospholipids, cholesterol, diacylglycerol and free fatty acids in the blood plasma of experimental animals has increased. As a result of data analysis, it has been established that the prophylactic combined use of magnesium and chromium citrates contributed to a decrease in the content of total lipids, as well as the percentage content of phospholipids, cholesterol, diacylglycerol and free fatty acids in the blood plasma of rats under conditions of hyperglycemia caused by DM.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The study was approved as a part of the research projects of the Laboratory of Biochemistry of Animal Adaptation and Ontogenesis of the Institute of Animal Biology of the National Academy of Sciences of Ukraine according to the projects "To investigate the effect of magnesium citrate on the carbohydrate metabolism and antioxidant system of rats under conditions of hyperglycemia" (task 31.00.01.01 F, project approval No. 0111U006159) and "To investigate complex influence of chromium and magnesium citrates on metabolic processes in the body of rats under conditions of hyperglycemia" (task 35.00.01.02 F, project approval No. 0116U001407)

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