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THE ROLE OF DYSLIPIDEMIA IN THE PATHOGENESIS OF DIABETIC ANGIOPATHIES AND ITS CORRECTION BY CRATAEGUS PENTAGYNA

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Diabetes mellitus is one of the important medical and social problems facing the healthcare systems of all countries of the world. Dyslipidemia plays a significant role in the pathogenesis of vascular complications of the disease. In this regard, correction of blood lipid composition is inevitable. To contribute to the solution of the problem, we conducted an experimental study on 21 rabbits. Blood lipid parameters were studied against the background of the combined effect of atorvastatin and hawthorn during experimental diabetes. It was found that when atorvastatin is used together with phytotherapy, the amount of atherogenic lipoproteins decreases sharply, and the level of anti-atherogenic lipoproteins increases. It can be concluded that it is recommended to add phytotherapy with statins to the dyslipidemia correction protocol.

Key words: diabetes mellitus, total cholesterol, triglycerides, lipoproteins, five-toothed hawthorn.

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РОЛЬ ДИСЛІПІДЕМІЇ У ПАТОГЕНЕЗІ ДІАБЕТИЧНИХ АНГІОПАТІЙ ТА ЇЇ КОРЕКЦІЯ З CRATAEGUS PENTAGYNA

Цукровий діабет є однією з важливих медико-соціальних проблем, які постають перед системами охорони здоров'я всіх країн світу. Дисліпідемія відіграє істотну роль у патогенезі судинних ускладнень захворювання. У зв'язку з цим корекція ліпідного складу крові неминуча. Для вирішення цієї проблеми нами було проведено експериментальне дослідження на 21 кролику. Вивчалися показники ліпідів крові на тлі поєднаної дії аторвастатину та глоду при експериментальному діабеті. Встановлено, що при сумісному застосуванні аторвастатину з фітотерапією різко знижується кількість атерогенних ліпопротеїдів та підвищується рівень антиатерогенних ліпопротеїдів. Можна зробити висновок, що фітотерапію статинами рекомендовано включити до протоколу корекції дисліпідемії .

Ключові слова: цукровий діабет, загальний холестерин, тригліцериди, ліпопротеїни, глід п'ятистовпчиковий.

Diabetes is widely recognized as an emerging epidemic that has a cumulative impact on almost every country, age group, and economy across the world [9]. Diabetes mellitus (DM) is a pandemic with numbers anticipated to increase from 463 million in adults aged 20–79 years in 2019 to 700 million by 2045 [10]. Chronic hyperglycemia in DM is accompanied by damage, dysfunction, and failure of various organs and tissues, development of micro- (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disorders) complications [3, 4, 7].

Oxidative stress, dyslipidemia, endothelial dysfunction and impaired hemostasis, which develop against the background of chronic hyperglycemia, play an important role in the development of vascular complications in diabetes mellitus [2].

Diabetic dyslipidemia is highly prevalent in patients with T2DM (> 75 %). It is usually a mixed (atherogenic) hyperlipidemia and comprises a major CV risk factor. It is commonly related to insulin resistance and is characterized by moderate increases of low-density lipoproteins cholesterol, elevations of triglycerides, low high-density lipoprotein cholesterol, and small-dense (atherogenic) low-density lipoprotein cholesterol particles [1].

Lipid profile changes significantly as diabetic kidney disease (DKD) progresses [6]. Albuminuria increases plasma free fatty acid levels that stimulate hepatic triglycerides synthesis and very-low-density lipoprotein production. The increased levels of triglyceride-rich lipoproteins enhance cholesteryl ester transfer and decrease high-density lipoproteins. DKD is an independent causative factor for dyslipidaemia and it exacerbates lipid disorders in diabetics.

Diabetes mellitus frequently results in hyperlipidemias that increase the risk of arteriosclerotic vascular disease. The most common associated phenotypes involve elevated levels of plasma triglycerides. Whereas the role of triglycerides in atherosclerotic vascular disease was initially not widely accepted, triglycerides are now recognized to be of major importance [5]. Metabolic derangements that increase the production of triglycerides can lead to hepatic steatosis and to elevated triglycerides in very-low-density lipoproteins in plasma. These lipoproteins are ultimately converted by lipolysis to intermediate density (IDL), then to low-density lipoproteins. Both are also atherogenic. Elevated triglycerides can alter the particle diameters and triglyceride content of low-density lipoproteins, an effect associated with increased atherogenicity [8].

The above proves that dyslipidemia plays a significant role in diabetic vascular complications and requires research in this direction. Considering that chemical drugs used for this purpose have a more toxic effect on the body, all this is considered an indication for adding phytotherapy to the treatment complex in diabetes mellitus in order to reduce intoxication and make the results obtained more long-lasting.

The purpose of the study was to investigate the principles of correction of changes in lipid metabolism during experimental diabetes.

Material and methods. The studies were carried out on 21 heads of rabbits of the genus Chinchilla, weighing 2.5–3.0 kg. Experiments on rabbits were performed in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals and Directive 86/609/EEC. Animals were divided into intact and experimental groups. The diabetes model was created using a 100 % solution of alloxan monohydrate with a score of 5 ml per kg of weight. In accordance with the duration of the experiment (5th, 15th, 30th, 60th and 90th days of the study) in the blood taken from the heart cavity of animals, total cholesterol (TC), cholesterol in the composition of high-density lipoproteins (HDL-C), low density lipoproteins containing cholesterol (LDL-C), cholesterol contained in very low density lipoproteins (VLDL-C) and the amount of triglycerides were determined. Animals included in the experimental group were injected with atorvastatin and five-pointed Hawthorn (Crataegus pentagyna) from the flora of Azerbaijan. During the study, an extract made from the plant was injected into the stomach of animals through a probe. In our studies, we determined the lipid metabolism indices in the blood using the BioScreen MS-2000 biochemical analyzer (Germany) using ready-made reagent kits. All digital data obtained during the experiments were statistically processed taking into account modern requirements. Group indices were arranged in a variation series. The arithmetic mean (M) and its standard error (m) were determined for each group. The nonparametric Wilcoxon (Mann-Whitney U-test) test was used to compare and determine the reliability of differences in quantitative values in groups and subgroups. All calculations were performed using the EXCEL spreadsheet and the results were summarized in tables and diagrams.

Results of the study and their discussion. The results of the study of lipid metabolism indices in the blood are presented in Table 1. As can be seen from it, modeling of alloxan diabetes mellitus in rabbits leads to dyslipidemia. This was expressed in an increase in the content of TC, LDL-C, VLDL-C and TG in the blood against the background of a very pronounced decrease in the concentration of HDL-C, which indicates an increase in the atherogenicity of lipids in experimental diabetes.

Table 1

Blood lipid metabolism indices in alloxan diabetes mellitus (M±m; n=21)

Indices	Intact condition	After administration of alloxan (24 hours)				
		5	15	30	60	90
N	4	3	4	4	3	3
TC mmol/l	2.14±0.04	2.19±0.03	2.43±0.05 *	2.57±0.04 **	2.6±0.03 **	2.73±0.03 **
HDL-C mmol/l	0.71±0.03	0.67±0.04	0.37±0.02 ***	0.33±0.03 ***	0.40±0.02 ***	0.57±0.03 **
LDL-C mmol/l	0.63±0.02	0.72±0.05 *	1.1±0.04 ***	1.5±0.05 ***	1.3±0.03 ***	1.4±0.5 ***
VLDL-C mmol/l	0.44±0.02	0.55±0.03	0.74±0.04 *	0.68±0.03 **	0.72±0.04	0.60±0.05
TG mmol/l	0.92±0.03	1.2±0.3 **	1.29±0.05 **	1.32±0.06 ***	1.45±0.05 ***	1.33±0.04 ***

Note: Statistical significance between measures: As compared to intact measures: * – $p < 0.05$; ** – $p< 0.01$; *** – $p< 0.001$.

Thus, an increase in the TC content in the blood was observed starting from the 15th day of the study. During the specified period of the study, its content increased by 13.5 % compared to the initial value ($p<0.05$). This dynamic persisted until the end of the study. That is, as the TC content gradually increased as the duration of the study increased and reached its maximum value until the end of the study (after 90 days of the study it exceeded the norm by 27.5 %, $p<0.01$). At the same time, the HDL-C content in the blood decreased markedly. Such shifts in blood also appeared starting from the 15th day of the study. During the specified period of the study, the HDL - H content decreased to 52.1 % of the baseline

($p<0.001$). Such dynamics persisted in the subsequent period (after 30 days of the study), the study – the content of which decreased to 46.5 % of the initial one ($p<0.001$). However, from the 60th day of the study, the reverse wave of the shift was observed – the HDL-H content gradually began to increase, first to 56.3 %, and after 90 days of follow-up to 80.3 % of the initial ($p<0.001$). It should be noted that against this background, the TG, LDL-C and VLDL-C content increased markedly. Thus, modeling of alloxan diabetes mellitus also contributed to an increase in the TG content in the blood – first to 130.4 % of the initial ($p<0.01$), and then within 60 days – to 157.6 % of the initial ($p<0.001$). The TG content in the blood subsequently decreased slightly (after 90 days of the study – up to 144.5 %) ($p<0.001$). The TG, LDL-C and VLDL-C content, as well as the TG content in the blood, increased markedly starting from the 5th day of the study, exceeding the initial values by 14.3 % and 25.0 %, respectively ($p<0.05$–0.01). Such a LDL-C dynamics persisted for 30 days of follow-up. At the same time, the LDL-C content in the blood exceeded the initial value by more than 2.3 times ($p<0.001$), and the VLDL-C content during 15 days and exceeded the initial level by only 68.2 % ($p<0.001$). Subsequently, the blood content of both types of lipids gradually decreased – LDL cholesterol to 206.3 %, VLDL cholesterol to 136.3 % of the corresponding initial value ($p<0.001$).

Thus, the results of our research have shown that modeling of alloxan diabetes mellitus leads to dyslipidemia in rabbits. This was expressed in a decrease in the blood content of atherogenic lipids (HDL-C) against the background of an increase in the blood content of atherogenic lipids (LDL-C and VLDL-C).

The combined use of atorvastatin and Five-toothed hawthorn (Crataegus pentagyna) in the treatment of experimental diabetes contributed to noticeable changes in blood lipid metabolism. This was expressed in a significant decrease in the TC level of in the blood during the entire observation period, both in comparison with the baseline level (the maximum decrease was recorded after 15 days of the study – decreased to 75.3 % of the control, $p<0.05$), and in comparison, with the corresponding control indicators (the maximum decrease was recorded after 30 days of the study – decreased up to 64.2 % of the control, $p<0.01$). Despite the fact that the HDL-C content at the beginning of the experiment (during the 30 days of the study) was within the baseline level, and then (starting from the 30 days of the study) it decreased and was lower until the end of the study (after a maximum of 60 days of the study, it decreased to 71.4 % of the initial level) ($p<0.01$). At the same time, the content of atherogenic lipids in the blood increased markedly. This was most pronounced in the study of LDL-C, which, starting from the 15th day of the study, exceeded the initial value – a maximum (by 54.8 %) after 30 days of the study ($p<0.001$). However, when comparing these data with the corresponding control indicators, it was found that the combined use of atorvastatin and Five-toothed hawthorn (Crataegus pentagyna) contributes to a significant decrease in the LDL-C level – a maximum (up to 54.0 % of the control) after 90 days of the study ($p<0.001$). The same dynamics were revealed in the study of the VLDL-C content (Table 2).

Table 2

Dynamics of lipid metabolism parameters in the blood with the combined use of atorvastatin and five-toothed hawthorn in the complex treatment of experimental diabetes mellitus (M±m; n=21)

Indices	Intact condition	After administration of alloxan (24 hours)				
		5	15	30	60	90
n	4	3	3	4	3	4
TC mmol/l	2.11±0.06	2.27±0.08	1.59±0.08	1.65±0.06 ⋆⋆⋆**	1.70±0.07 ⋆⋆⋆**	2.84±0.08 ⋆⋆*
HDL-C mmol/l	0.77±0.03	0.81±0.04 ⋆⋆	0.71±0.02 ⋆⋆⋆	0.63±0.04 ⋆⋆⋆**	0.55±0.03 ⋆⋆**	0.64±0.04 ⋆*
LDL-C mmol/l	0.62±0.04	0.66±0.03	0.83±0.04 ⋆⋆**	0.96±0.03 ⋆⋆⋆***	0.85±0.04 ⋆⋆⋆**	0.76±0.03 ⋆⋆⋆**
VLDL-C mmol/l	0.47±0.03	0.53±0.04 *	0.50±0.03 ⋆⋆	0.45±0.04 ⋆⋆	0.46±0.03 ⋆⋆⋆	0.57±0.04 *
TG mmol/l	0.91±0.04	1.2±0.07 **	0.90±0.07 ⋆⋆	0.75±0.06 ⋆⋆⋆**	0.80±0.04 ⋆⋆⋆	0.85±0.06 ⋆⋆

Note: Statistical reliability between indices: indices of intact state (*) and II-control group (⋆):*⋆–$p<0.05$; **⋆⋆–$p<0.01$; ***⋆⋆⋆–$p<0.001$.

Upon comparing this indicator with the baseline level, it was revealed that it exceeds the baseline level after 5 (by 12.7 %) and 90 days (by 21.3 %) of the study ($p<0.05$–0.01). For the rest of the study periods, it was within the initial range. However, in relation to the corresponding control values, it was less (after 15 days of the study to 67.7 %, after 30 days of the study to 66.2 % and after 60 days of the study to 62.5 % of the corresponding control level, $p<0.001$). The dynamics of the TG content in the blood was different. So, at first, compared with the baseline level, the TG content in the blood increased, exceeding it by 31.9 %, and then it decreased, first to the baseline level (after 15 days of the study), after 30 days of the study to 82.4 % of the baseline ($p<0.05$). Subsequently, it increased again, reaching the initial level after 60 and 90 days of the study. The TG level of in the blood decreased starting from the 15th day of the study and was lower than the corresponding control value until the end of the study – after a maximum of 60 days of the study (it was 44.8 % less, $p<0.001$).

Evidence of this is the fact that modeling alloxan diabetes leads to very pronounced lipid metabolism disorders, which negatively affected the lipid composition in the blood [4]. At the same time, the level of atherogenic lipids increased, against the background of a very pronounced decrease in antiatherogenic lipids, which creates a favorable condition for atherosclerotic changes. From the literature data [1, 4, 5, 6, 8] it follows that lipid metabolism disorders play an important role in the occurrence and aggravation of diabetic angiopathies in diabetes mellitus.

Conclusion

Thus, summarizing the above, it can be concluded that the combined use of atorvastatin and Five-toothed hawthorn (Crataegus pentagyna) in the treatment of experimental diabetes has a beneficial effect on the lipid composition of the blood. This is due to the fact that the combined use of atorvastatin and Five-toothed hawthorn (Crataegus pentagyna) most significantly reduces the content of atherogenic lipids (low and very low-density lipoproteins) in the blood against the background of an increase in the content of non-atherogenic lipids (high-density lipoproteins) in the blood. The applied pathogenetic correction can be of great importance in the treatment and prevention of diabetic angiopathies developing against the background of dyslipidemia. Also, the addition of phyto preparations to the treatment complex not only enhances the effect of statins, but also allows for high therapeutic results. It should be noted that the correct selection of doses for their combined use is considered one of the main conditions for significantly increasing the therapeutic effect of treatment.

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