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MONITORING OF CYTOTOXIN – METHYLGLYOXAL AS A MARKER OF THE PATHOGENESIS OF ACUTE PYELONEPHRITIS IN DIABETES MELLITUS

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Introduction. Acute inflammatory diseases of the organs of the urinary system, complicated by concomitant diabetes given their increasing prevalence, severity of the course, and uncertainty of the prognosis, are urgent medical and social problems today. It was established that the development of a hyperglycemic state is accompanied by a significant increase in the content of the highly reactive dicarbonyl compound methylglyoxal, which plays an important role in the pathogenesis of vascular and kidney diseases.

The aim of the work is to study the correlation between the level of a marker of early protein glycolysis processes – methylglyoxal, the activity of pro-inflammatory factors, indicators of energy metabolism and pro-antioxidant status in the kidneys with pyelonephritis and accompanying diabetes under conditions of drug exposure in the experiment.

Conclusion. The obtained results indicate the presence of a pronounced positive correlation between methylglyoxal, a marker of the early processes of glycolysis of proteins, the level of eicosanoids prostaglandin E_2 and leukotriene B_4, of carbonyl protein groups and the activity of prooxidant enzymes xanthine oxidase and NADPH oxidase, which indicates their pathogenetic role in the development of acute inflammatory process in the kidneys of rats, especially with accompanying diabetes. A significant role in the progression of the inflammatory process in the kidneys with the hyperglycemic state, taking into account the presence of reliably significant correlations, is played by the depletion of thiol status and energy potential under conditions of oxidative/carbonyl stress development. The conducted correlation analysis showed the high efficiency of the use of etiotropic-pathogenetic medicinal effects in order to correct complex metabolic disorders in the kidneys of rats with acute pyelonephritis under hyperglycemic conditions and realize the nephroprotection effect.

Keywords: pyelonephritis, diabetes mellitus, eicosanoids, oxidative stress, energy metabolism, nephroprotection.

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МОНІТОРИНГ ЦИТОТОКСИНУ – МЕТИЛГЛІОКСАЛЮ ЯК МАРКЕРА ПАТОГЕНЕЗУ ГОСТРОГО ПІЄЛОНЕФРИТУ ПРИ ДІАБЕТІ

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Результати досліджень свідчать про позитивний взаємозв'язок між маркером ранніх процесів гліколізування білків метилгліоксалем, рівнем ейкозаноїдів простагландину E_2 і лейкотрієну B_4, карбонільних білкових груп та активністю прооксидантних ферментів ксантиноксидази і НАДФН-оксидази, що висвітлює їх патогенетичну роль у розвитку запального процесу в нирках щурів, особливо при цукровому діабеті. Значну роль у прогресуванні запального процесу в нирках в умовах гіперглікемічного стану відіграє виснаження тіолового статусу та енергетичного потенціалу за умов розвитку оксидативного/карбонільного стресу.

Кореляційний аналіз показав високу ефективність застосування етіотропно-патогенетичного медикаментозного впливу з метою корекції складних метаболічних порушень у нирках щурів з ГП в умовах гіперглікемічного стану та реалізації нефропротективного впливу.
Ключові слова: пієлонефрит, діабет, ейкозаноїди, оксидативний стрес, енергетичний обмін, нефропротекція.

Introduction. Acute inflammatory diseases of the urinary system complicated by concomitant diabetes mellitus (DM), given their increasing incidence, severity of the clinical course, and uncertainty of prognosis, are urgent medical and social problems now [1–3].

The concomitant acute pyelonephritis (AP) and diabetes mellitus, mosty of type 2, is characterised by high resistance of bacterial pathogens, complex metabolic changes, and impaired general body resistance, which leads to a high risk of complications and persistent renal dysfunction [4–7].

The development of hyperglycemic state is accompanied by a significant increase in the level of a highly reactive dicarbonyl compound – Methylglyoxal (MGL), which plays an important role in the pathogenesis of vascular and renal diseases [7–10]. MGL as well as previously Dipeptidyl peptidase IV could be a marker for kidney damage [11]. Also, the experimental hyperglycemia is associated with such renal changes as dilatation and blood fullness of glomerular capillary with their leukocyte infiltration [12].

Based on the mentioned above, further in-depth study of significant markers of the infectious inflammatory process and hyperglycemic state development, their role in the imbalance of the prooxidant state and energy metabolism in the kidneys, will contribute to the development of an effective treatment strategy to prevent irreversible complications of AP and concomitant diabetes mellitus [1; 3; 4; 7; 9; 13].

The aim of the work is to study the correlation between the level of methylglyoxal, a marker of early protein glycolysis, the activity of proinflammatory factors, indicators of energy metabolism and pro-antioxidant status in the kidneys with pyelonephritis and concomitant diabetes mellitus under conditions of drug treatment in the experiment.

Material and methods. The modelling of AP and hyperglycemic state was performed according to the protocol described [14; 15]. In Wistar rats aged 8–9 months, we modeled AP and AP complicated by hyperglycemic condition, reproduced by type 1 and type 2 diabetes mellitus.

Rats with AP on the background of type 2 diabetes mellitus received etiotropic drug treatment (EDT) and etiotropic-pathogenetic drug treatment (EPDT). With EDT, animals received the preparation "Hepatsef" – a cephalosporin family antibacterial drug (cefoperazone sodium salt) at a dose of 60 mg per kilogram of body weight per day intramuscularly for 14 days after AP modeling. With EPDT, the antibacterial drug "Hepatsef" was administered intramuscularly; and ribonucleic acid "Nuklex" – an immunomodu lator with metabolism-correcting, energotropic action was administered orally at a dose of 21 mg per kilogram of body weight per day; and the preparation "Armadin" – an antiplatelet agent, inhibitor of free radical processes, membrane protector (2-ethyl-6-methyl-3-hydroxypyridine succinate) was administered intramuscularly at a dose of 4.5 mg per kilogram of body weight per day for 14 days after AP modeling. In 28 days after the start of the modeling, the content of metabolic parameters in the kidneys of rats was studied: methylglyoxal, prostaglandin E_2, leukotriene B_4, carbonyl groups of proteins, xanthine oxidase, NADPH oxidase, ATP and glutathione.

For the correlation analysis, we used experimental data obtained during the determination of the above metabolic parameters in rats with AP complicated by hyperglycemic conditions under pharmacocorrection and published in the previous works [15–17].

Statistical analysis was performed using Statistica 7 for Windows (trial version) using Student's t-test. Correlation analysis of obtained data was performed, the significance of differences was at the level of $p<0.05$.

The experiment was carried out 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 authors complied with the Law of Ukraine "On Protection of Animals from Cruelty" No. 27, Art. 230, 2006, as amended by Law No. 1759-VI (1759-17) of 15.12.2009, information of the Supreme Council, 2010, No. 9, Art. 76, the general ethical principles of animal experimentation (First National Congress on Bioethics, 20.09.2001, Kyiv), the Ethical Principles of Animal Experimentation (I National Congress on Bioethics, 20.09.2001, Kyiv), the Ethical Code of Scientists of Ukraine (National Academy of Sciences of Ukraine, 2009), and the minutes of the meeting of the Bioethics Commission of Odesa National Medical University No. 118A of 09 June 2017.

The publication contains the results of interdepartmental research of the Department of General, Pediatric and Military Surgery with the Course in Urology and the Department of Propedeutics of Internal Diseases and Therapy of Odesa National Medical University.

Results. Considering that Methylglyoxal is a marker of early protein glycation in the kidney tissue under prolonged hyperglycemia, we studied the correlation between this indicator and the levels of proinflammatory factors of prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) in the kidneys of rats with acute pyelonephritis under conditions of concomitant diabetes mellitus in the experiment.

We found a positive correlation of medium strength between MGL and PGE_2 in normal rats with a correlation coefficient of $R = 0.64$, and between MGL and LTB_4 ($R = 0.59$) (Table 1).

With the development of AP in rats was found a significant increasing of correlation coefficient between MGL

Table 1

Correlation between the level of Methylglyoxal (MGL) and the content of renal proinflammatory factors (PGE_2, LTB_4) in acute pyelonephritis with concomitant diabetes mellitus in the experiment

Pairs of correlations	Norm		AP		AP +Type 1 DM		AP +Type 2 DM	
	R	p	R	p	R	p	R	p
MGL/PGE2	0.64	<0.05	0.75	<0.05	0.81	<0.05	0.79	<0.05
MGL/LTB4	0.59	<0.05	0.72	<0.05	0.77	<0.05	0.76	<0.05

Notes: R – correlation coefficient; p – level of correlation significance.

and the level of eicosanoids in the kidneys, between MGL and the level of prostaglandin E_2 (R = 0.75) and the level of leukotriene B_4 (R = 0.72), which is associated with the development of the acute inflammatory process.

Under conditions of AP and concomitant hyperglycemic state (type 1 and type 2 diabetes mellitus), the correlation between MGL and the level of eicosanoids in the kidneys of rats increased to a greater extent and was in type 1 diabetes mellitus between MGL and PGE_2 level – (R = 0.81) and LTB_4 – (R = 0.77), and in type 2 diabetes mellitus between MGL and PGE_2 level – (R = 0.79) and LTB_4 – (R = 0.76).

When assessing the correlation between the level of Methylglyoxal and indicators characterising oxidative and carbonyl stress: carbonyl groups of proteins, xanthine oxidase and NADPH oxidase in the kidney tissues of normal rats and those with AP with concomitant hyperglycemic state, we obtained a positive significant correlation (Table 2).

Thus, in the normal state, a significant positive correlation of "medium strength" between the levels of MGL and carbonyl protein groups in rats with a correlation coefficient (R = 0.58) was found.

An increase in the correlation coefficient to (R = 0.67) was noted during AP development, and under conditions of concomitant diabetes mellitus, the correlation coefficient was characterised by a "strong" correlation (R = 0.86) in type 1 diabetes mellitus and (R = 0.84) in type 2 diabetes mellitus.

These changes indicate the presence of significant "strong" positive correlation between the content of a marker of early protein glycation processes and the level of carbonyl stress intensity in the kidneys of rats with AP and the most pronounced with a concomitant hyperglycemic state.

When assessing the correlation between the level of Methylglyoxal and the activity of the prooxidant enzymes NADPH oxidase and xanthine oxidase, which produce reactive oxygen species (ROS) in the rat kidneys, we obtained the following results.

The correlation coefficient between the level of Methylglyoxal and the activity of xanthine oxidase and NADPH oxidase in the kidneys was the following: in the norm of "medium strength" – R = 0.52 and R = 0.56, in "medium strength" AP – (R = 0.64) and (R = 0.68), in AP and type 1 diabetes mellitus of "great strength" (R = 0.74) and (R = 0.79), in AP and type 2 diabetes mellitus of "great strength" – (R = 0.72) and (R = 0.76), respectively ($p<0.05$).

The findings indicate the presence of a significant positive relationship between the level of Methylglyoxal and the indicators that determine the generation of reactive oxygen species, causing an increase in oxidative stress in the inflammatory process in the kidneys under conditions of hyperglycemia.

We obtained a significant negative correlation of "medium strength" between the level of Methylglyoxal and the index of energy metabolism of ATP in the kidneys of normal rats – (R = -0.63), and between the level of Methylglyoxal and reduced glutathione – (R = -0.63) (Table 3).

With AP in the kidneys of rats, a significant "medium" negative correlation between the level of Methylglyoxal and ATP in normal conditions was found (R = -0.67), and between the level of Methylglyoxal and reduced glutathione it was "great" – (R = -0.75), which indicates a greater relationship between these indicators. The same trend was observed under conditions of AP with concomitant diabetes mellitus: in AP and type 1 diabetes mellitus – (R = -0.73) and (R = -0.86), in AP and type 2 diabetes mellitus – (R = -0.71) and (R = -0.84), respectively ($p<0.05$).

Threfore, the data obtained indicate the presence of a pronounced correlation between the level of Methylglyoxal, a marker of early processes of glycation of renal tissue proteins, under conditions of carbonyl and oxidative stress and indicators of energy metabolism (ATP) and thiol state (reduced glutathione) in the kidneys of rats with acute pyelonephritis under conditions of concomitant hyperglycemia.

Tables 4, 5, 6 show the correlation between the studied biochemical parameters of the kidney tissue of rats with

Table 2

Correlation between the level of Methylglyoxal (MGL) and indicators characterising oxidative and carbonyl stress in the kidney tissue in acute pyelonephritis with concomitant diabetes mellitus in the experiment

Pairs of correlations	Norm		AP		AP + Type 1 DM		AP + Type 2 DM	
	R	p	R	p	R	p	R	p
MGL/carbonyl protein groups	0.58	<0.05	0.67	<0.05	0.86	<0.05	0.84	<0.05
MGL/xanthine oxidase	0.52	<0.05	0.64	<0.05	0.74	<0.05	0.72	<0.05
MGL/NADPH oxidase	0.56	<0.05	0.68	<0.05	0.79	<0.05	0.76	<0.05

Notes: R – correlation coefficient; p – level of correlation significance.

Table 3

Correlation between the level of Methylglyoxal (MGL) and the index of energy metabolism (ATP) and antioxidant state (reduced glutathione GSH) of the kidneys in acute pyelonephritis with concomitant diabetes mellitus in the experiment

Pairs of correlations	Norm		AP		AP + Type 1 DM		AP + Type 2 DM	
	R	p	R	p	R	p	R	p
MGL/ATP	-0.63	<0.05	-0.67	<0.05	-0.73	<0.05	-0.71	<0.05
MGL/GSH	-0.65	<0.05	-0.75	<0.05	-0.86	<0.05	-0.84	<0.05

Notes: R – correlation coefficient; p – level of correlation significance.

Table 4

The effect of drug correction on the correlation between the level of Methylglyoxal and proinflammatory eicosanoids of kidney tissue in acute pyelonephritis with concomitant diabetes mellitus in the experiment

Pairs of correlations	AP + Type 2 DM		AP + Type 2 DM + EMT		AP + Type 2 DM + EPMT	
	R	p	R	p	R	p
MGL/PGE2	0.79	<0.05	0.76	<0.05	0.69	<0.05
MGL/LTB4	0.76	<0.05	0.74	<0.05	0.65	<0.05

Notes: R – correlation coefficient; p – level of correlation significance.

Table 5

The effect of drug correction on the correlation between the level of Methylglyoxal and indicators characterising oxidative and carbonyl stress in the kidney tissue in acute pyelonephritis with concomitant diabetes mellitus in the experiment

Pairs of correlations	AP + Type 2 DM		AP + Type 2 DM + EMT		AP + Type 2 DM + EPMT	
	R	p	R	p	R	p
MGL/carbonyl protein groups	0.84	<0.05	0.80	<0.05	0.72	<0.05
MGL/xanthine oxidase	0.72	<0.05	0.70	<0.05	0.59	<0.05
MGL/NADPH oxidase	0.76	<0.05	0.73	<0.05	0.63	<0.05

Notes: R – correlation coefficient; p – level of correlation significance.

Table 6

Effect of drug correction on the correlation between the level of Methylglyoxal (MGL) and the index of energy metabolism (ATP) and antioxidant status (GSH) in the kidney tissue in acute pyelonephritis with concomitant diabetes mellitus

Pairs of correlations	AP + Type 2 DM		AP + Type 2 DM + EMT		AP + Type 2 DM + EPMT	
	R	p	R	p	R	p
MGL/ATP	-0.71	<0.05	-0.69	<0.05	-0.66	<0.05
MGL/GSH	-0.84	<0.05	-0.81	<0.05	-0.68	<0.05

Notes: R – the correlation coefficient; p – the level of correlation significance.

acute pyelonephritis under conditions of concomitant diabetes mellitus and drug treatment.

With the use of etiotropic drug treatment (EMT), the correlation coefficient between the indicators was moderately reduced but had a pronounced significant positive relationship: between MGL and the level of PGE_2 – (R = 0.76), between MGL and the level of LTB_4 – (R = 0.74) (Table 4). The use of etiotropic and pathogenetic drug treatment (EPMT) in rats with AP and type 2 diabetes mellitus contributed to a decrease in the correlation coefficient between the indicators, which was significant and had a direct relationship: between MGL and PGE_2 level – (R = 0.69), between MGL and LTB_4 level – (R = 0.65).

In rats with AP under conditions of concomitant type 2 diabetes mellitus and EMT, the correlation between the level of MGL and carbonyl protein groups (CPG), the activity of prooxidant enzymes was: between MGL and CPG – R = 0.80, between MGL and xanthine oxidase activity – R = 0.70, between MGL and NADPH oxidase activity – R = 0.73 (Table 5).

The use of EPMT in rats with AP and type 2 diabetes contributed to a decrease in the correlation coefficient between the level of MGL and CBG – R = 0.72, and between MGL and xanthine oxidase activity – R = 0.59, between MGL and NADPH oxidase activity – R = 0.63 ($p<0.05$).

When using EMT, the data obtained indicate the presence of a significant negative correlation between the level of methylglyoxal, ATP and reduced glutathione in kidney tissue in rats with AP with hyperglycemia, namely (R = -0.69) and (R = -0.81), respectively (Table 6).

The data on the effect of EPMT on the correlation between the level of methylglyoxal, ATP and GSH of kidney tissue in rats with AP with hyperglycemia were obtained (Table 6). The correlation coefficient between the level of MGL, ATP and GSH was moderately reduced, significant and "medium strength" (R = -0.66 and R = -0.68, respectively).

Conclusions

1. In the kidneys of animals, there is an increase in the level of the marker of early processes of glycation of Methylglyoxal proteins and the level of eicosanoids, a decrease in energy potential against the background of oxidative/carbonyl stress and depletion of the enzymatic antioxidant system and imbalance of thiol status, as evidenced by a significant level of correlation coefficient between Methylglyoxal and prostaglandin E_2 and leukotriene B_4, MHL and carbonyl groups of proteins, xanthine and NADPH oxidase, as well as MHL with ATP and reduced glutathione (GSH).

2. A pronounced positive correlation between methylglyoxal, a marker of early protein glycolysis, and the levels of eicosanoids prostaglandin E_2 and leukotriene B_4 was confirmed, carbonyl protein groups and the activity of prooxidant enzymes xanthine oxidase and NADPH oxidase, indicating their pathogenic role in the development of the inflammatory process of AP in the rat kidneys, especially in the case of concomitant diabetes mellitus.

3. A significant role in the progression of the inflammatory process in the kidneys under hyperglycemic conditions, given the presence of significant correlations, is played by the depletion of thiol status and energy potential in the development of oxidative/carbonyl stress.

4. Correlation analysis showed high efficiency of etiotropic and pathogenetic drug treatment for the correction of complex metabolic disorders in the kidneys of rats with acute pyelonephritis under hyperglycemic conditions and the implementation of nephroprotective effect.

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