Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 449 - 464
Received 16 February 2021; Accepted 08 March 2021.

Dynamics of Innate Immunity Parameters in Acute Kidney Injury after Coronary Bypass Grafting

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ABSTRACT

The problem of acute kidney injury (AKI) after cardiac surgery is still unsolved, despite the high level of surgical technique development, protection of organs and tissues in conditions of artificial circulation. According to different authors, complications occur in up to 42%, and the necessity for renal replacement therapy in up to 1-8%.The purpose of the research was to assess the diagnostic and prognostic value of innate immunity parameters - interleukins (IL) 6, 8, 10, 17 and tumor necrosis factor alpha (TNF-α), growth factors TGF-β1 and matrix metalloproteinases 8 (MMP 8) and its tissue inhibitor 1 (TIMP 1) in patients with acute kidney injury before and after CABG. Blood serum of 120 patients of both sexes with coronary heart disease (CHD) was studied before and after CABG. An increase in the concentration of cytokinins IL 6, 8, 10, 17, TNF-α, TGF-β 1 in all groups after surgery on the first and second days was recorded, changes in MMP 8 and TIMP 1 serum concentrations in patients with acute kidney injury were assessed. The problem of immune disorders in cardiac surgery patients with AKIwas studied. Possible additional predictors of AKIwere identified.

KEYWORDS

Acute Kidney Injury, Coronary Bypass Grafting, Cytokines, Metalloproteinases, Renal Injury.

Introduction

Acute renal injury (AKI) is one of the most common complications in patients undergoing cardiac surgery [6,11,12]. More than 2 million heart operations are performed worldwide annually, and AKI associated with cardiovascular surgery ranges from 5% to 42%, and due to their occurrence occupy the second place after sepsis. They are associated with high mortality, prolonged stay in the intensive care unit and intensive care unit, and with high cost of treatment due to the use of renal replacement therapy in 1-5% of cases [5, 25]. The transition of AKI to chronic kidney disease (CKD) often worsens the quality of patient's life and a ten-year prognosis of survival, and, in the case of terminal kidney disease, requires chronic hemodialysis. AKI

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pathogenesis in cardiosurgical patients is still not clear. The main factors in kidney injury development are: hypoperfusion, neurohumoral activation, oxidative stress, nephrotoxins, mechanical factors that induce a cascade of protective and adaptive reactions in the patient's body [10,14, 25]. Common criteria (AKI - KDIGO) for the AKI syndrome after heart surgery are a sharp decrease in kidney function, which is manifested by the increased serum creatinine level ≥ 0.3 mg / dl (26 μmol / L) within 48 hours or the increased serum creatinine more than 1.5 times of the known or expected level within the last 7 days of the original value, or the decreased rate of urine output less than 0.5 ml / kg / hour for 6 hours [4]. Routine determination of serum creatinine in the postoperative period is an available, but uninformative method, since many factors such as: initial creatine clearance, drugs that block tubular secretion, and background chronic diseases (diabetes mellitus, liver diseases), race may influence the result [6.9]. Therefore, much attention has recently been paid to the search for the so-called biomarkers of acute renal injury, which allow early detection of pathological changes in kidneys and determine their nature, differentiate the lesion of different parts of the nephron, accurately establish the stage of the process, evaluate the severity of inflammation and the intensity of fibrogenesis [8]. Previously discovered biomarkers: NGAL, KIM1, Cystatin C, IL18 are uninformative and do not have sufficient sensitivity and specificity [7,10,16]. In recent years, the search for immunological markers of acute kidney injury has become very important, as it allows to identify early pathological changes in the kidneys, determine their nature, differentiate the lesion of different parts of the nephron, and evaluate the intensity of fibrogenesis [13, 17]. The release of a large number of cytokines is associated with subclinical kidney injury, primarily with blocking filtration in the renal glomeruli. Determining the concentration of inflammatory markers in the blood serum, which could reflect the activity of the inflammatory process, is important for predicting and correcting treatment, and for identifying predictors of severeinjury with the possibility to begin early RRT after hospitalization. However, there is still no consensus on the direction, degree of changes in pro- and anti-inflammatory cytokines at the systemic level in patients with coronary heart disease with AKI before and after heart operations, their prognostic value and the problem is still controversial. Data on the correlation of changes in the level of factors regulating the state of the intercellular matrix with renal dysfunction and their prognostic significance in patients with acute kidneyinjury who underwent coronary bypass grafting are of interest. Possible changes in the system of matrix metalloproteinases and their inhibitors may be useful for predicting the risk of renal complications, which may allow to use them as AKIbiomarkers of [15].

The Aim of the Research

The aim of the researchwas to identify immunological predictors of development and an unfavorable prognosis of acute kidney injury in patients with coronary artery injury who underwent coronary artery bypass grafting.

Materials and Methods

Patients (n = 120) aged from 44 to 75 years of both sexes with coronary heart disease who were planned for coronary artery bypass grafting in conditions of artificial circulation were examined. The control group consisted of practically healthy persons (n = 30) comparable in age and sex. Determination ofinterleukins - IL 6, 8, 10, 17 and tumor necrosis factor alpha - TNF-α, and growth factors TGF-β 1, and matrix metalloproteinases 8 - MMP 8 and its tissue inhibitor - TIMP

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1, as well as markers of acute NGAL and Cystatin C levels was performed in serum by enzyme-linked immunosorbent assay using diagnostic kits R & D Systems, USA, in 120 patients with coronary heart disease of both sexes from 45 to 74 years before and after cardiac surgery at the University Hospital of the Far Eastern Federal University the city of Vladivostok. The research protocol was approved by the local ethics committee of the Pacific State Medical University of the Russian Ministry of Health in accordance with the Declaration of Helsinki Ethics adopted by the World Medical Association, in the Ethical Principles of Medical Research with People and the Principles of Good Clinical Practice in the Russian Federation. Written informed consent was obtained from all the patients prior to inclusion in the research (protocol No. 4 of 12/26/2016). The right to perform the research was confirmed by the informed consent of the patient. The criteria for inclusion in the researchconsisted of:

- Patients with coronary heart disease 44-75 years of both sexes (n = 40) before and after coronary artery bypass grafting with complications in the early postoperative period associated with acute kidney injury (group I);
- Patients with ischemic heart disease 44-75 years of both sexes with concomitant pathology (diabetes mellitus) (n = 40) before and after coronary artery bypass grafting with complications in the early postoperative period associated with acute kidney injury (group II);
- Patients with ischemic heart disease 44-75 years of both sexes (n = 40) before and after coronary artery bypassgrafting without pathology in the postoperative period (group III);
- Group of healthy volunteers of comparable gender and age (n = 30).

The Criteria for Exclusion in the Research Consisted of:

- Patients of both sexes with concomitant oncopathology, mental illness, concomitant autoimmune diseases, acute infectious diseases;
- Pregnant and lactating women;
- Patients under the age of 44 years and older than 75 years;
- Refusal to participate in the research.

In patients of the main groups, a four-fold sampling was made: before the operation, on the 1st day, 2nd day and the 7th day after the operation and were retrospectively distributed depending on the clinical condition after CABG; in persons of the control group - a single blood sampling. The control figures of the parameters show the limits for a healthy population in table 1 and are presented in pg / ml for cytokines and in ng / ml for growth factor and metalloproinases.

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Table 1. Contentofmediatorsinfluencingthestateofintracellularmatrixintheblood ofpatientswithIHDafterCABG

Marker	**Me; Q25;Q75**
Cytokine	pg/ml
IL-6	2.17 (1.07;2.64)
IL-8	19.34 (8.01;28.34)
IL-10	1.52(0.36; 2.17)
IL-17	5.12 (2.03;9.14)
TNFa	4.44 (3.62;5.13)
Growth factors	ng/ml
TGF-b1	18.8 (17.44;24.06)
Matrix metalloproteinases	ng/ml
MMP-8	8.1 (5.7;19)
Matrix metalloproteinase inhibitors	ng/ml
MMPI-1	263 (220;319)

Clinical intraoperative data: the mean aortic clamping time was 94 ± 18 min., the meanartificial circulation(AC) time was 85 ± 29 min., the meanartificial circulation time after removing the aortic clamp was 52 ± 18 min.; spontaneous restoration of sinus rhythm was observed in 89% of cases; the use of intraoperative electric defibrillation was required in 9.5% of patients (in 80% of cases, defibrillation was required with aortic clamping duration of more than 100 minutes). Clinical postoperative data: the mean duration of inotropic / vasopressor stay in ICU was 10–8 hours; temporary need for artificial imposition of heart rhythm was observed in 17% of cases; new episodes of atrial fibrillation were registered in 8.6% of patients; there were no postoperative myocardial infarctions; the mean stay in ICU was 50 ± 18 hours; there were no cases of hospital mortality. Laboratory data: determination of creatinine and markers of acute kidney injury NGAL and Cystatin C are shown in table 2.

Table 2. CreatinineandAKImarkersintheserumofpatientswithIHDafterCABG

Bio marker	Control group (n= 30)	Group with acute kidney Injury (n=80)		Group without renal complications (n=40)	
		before the operation	first day	before the operation	first day
NGAL, ng/ml	52.42 (37.79;60.27)	16.36 (11.33;28.55)	53.62 (37.86;76.59)	21.41 (15.97;38.63)	32.71 (23.45;48.51)
Cystatin	561.42 (489.1;610.9	706.61 (482.84;789.2	732.92 (694.94;906.4	1067.36 (894.33;1362.6	764.21 (577.29;962.3

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C, ng/ml	5)	7)	3)	9)	9)
Creatinine, mcmol/l	66.4 (50.3;79.8)	72.8 (60.4;80.1)	105.3 (90.1;120.7)	70.9 (59.7;79.3)	78.4 (84.5;90.4)

Statistical processing of the obtained data was carried out by nonparametric methods. The results were presented as median, upper and lower quartiles (Me, Q25, Q75). The confidence level was set to 95%, i.e. null hypotheses were rejected when the achieved significance level P of the used statistical criterion was less than 5%. Statistical processing was performed using the SPSS Statistics v.16 program. Within and between-group differences were evaluated using the Mann-Whitney test as part of an application program. To check the relationship or independence between the proposed parameters an assessment of $\chi 2$ was done. The quality and specificity of the method of the proposed model was confirmed by the ROC analysis method.

Results

Cytokines and chemokines are important mediators of inflammatory reactions that can be easily measured in serum. The work showed that cytokines both in low and high concentrations are associated with risk profiles of cardiovascular diseases, the accompanying background in the form of diabetes mellitus, and also depending on postoperative renal complications. However, their levels can vary greatly due to various pathophysiological processes initiated by various factors.

The performed research revealed that TNF-α concentration in group II with renal complications before surgery significantly exceeded that in group IV, 2.8 (0.8; 10.9) pg / ml vs 8.63 (6.75; 10.51) pg / ml, $p < 0.001$. On the first day, TNF-α concentration in the serum of patients with complications increased and was significantly higher compared to the level before the intervention: in group I – 4.95 (3.96; 5.94), $p < 0.05$ and in group II – 9.12 (5.75; 17.3) pg / ml, $p < 0.001$, which was also significantly higher than in the control group, $p < 0.001$. On the second day after surgery, TNF-α content remained at high values only in group II - 8.73 (1.71; 10.14) pg / ml, $p < 0.001$ in comparison with other groups. A decrease in TNF-α level was observed on the 7th day after the operation in all groups, but still was high in group II – 6.07 (3.35; 10.6) pg / ml, ($p < 0.001$).Analysis of IL-6 content before surgery in group II revealed its increased content in comparison with group I, III and IV - 4.2 (3.1; 6.4) pg / ml versus 2.66 (2.63; 2.74), 2 (1.67; 2.2) 4.2 (3.1; 6.4), 3.03 (2.95; 13.3), pg / ml, respectively, $p < 0.05$. On the 1st day after the operation in groups I, III and II the level was more than 10 times higher than in the control group - 23.02 (20.67; 34.07), 22.43 (10.24; 43, 55), 32.9 (21.8; 44.32) pg / ml and 3.03 (2.95; 13.3, $p < 0.001$, and the values remained elevated on the 2nd day after the operation. One week after the intervention, in all the compared groups these figures decreased significantly compared with the previous values, but also exceeded the reference interval ($p < 0.001$). On the first day after the operation IL-8 level in groups I and II with complications was more than twice higher than that in group IV - 19.47 (8.41; 29.32) pg / ml and in group III - 23.51 (17.96; 46.08) pg / ml, vs 48.4 (35.36; 128.33) and 46.8 (43.3; 48.9) pg / ml, respectively, $p < 0.001$. On the 2nd day, the indicator in groups II and III significantly decreased – 14.8 (10.87; 15.42) and 12.3 (10.27; 13.4) pg / ml, $p < 0.01$, but the values did not exceed the value in the control group 19.47 (8.41; 29.32) pg / ml, $p < 0.001$. A week after the operation, the serum level of the indicator approached the

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control values in all compared groups. IL-17 level in groups I, II, III at all stages of the research was significantly lower than in group IV - 4.09 (4.03; 4.15), 3.065 (3.03; 3.09), 4.07 (3.92; 5.24) pg / ml vs 5.57 (1.89; 9.45) pg / ml, p <0.05. No significant differences in dynamics at all stages of blood sampling were found.

Analysis of the anti-inflammatory cytokines content in patients with complications in groups I and II showed an increase of IL-10 by more than 4 times compared with the value in groups III andIV - 407.015 (346.22; 431.21), 421, 57 (354.64; 517.04), vs 90.63 (69.12; 402.5) and 18.5 (7.12; 36.69) pg / ml, respectively, p <0.001. However, the serum cytokine level in group II on the 2nd day was more than 2 times higher than the values in I and III groups - 34.17 (28.61; 51.05) pg / ml vs 9.93 (7.91; 20.44) pg / ml and 13.66 (11.21; 18.44) pg / ml, respectively, p <0.001. On the seventh day, the cytokine level in all compared groups approached reference values, p <0.05. Analysis of transforming growth factor TGFβ-1 concentrations in the serum of patients before CABG showed significantly higher levels in groups I and II compared to group III - 15.41 (13.44; 17.32), 10.01 (9.4; 12.89) ng / ml, but did not exceed the level in the control group - 19.02 (17.50; 23.54) ng / ml, p <0.05. On the following days, group I showed higher values in comparison with groups II and III - 19.99 (15.3; 23.01), 21 (18.15; 21.8) and 18.9 (15.2; 19) ng / ml vs 14.9 (13; 20), 10.56 (9.5; 12), 9.49 (9.01; 12.1) ng / ml and 7.81 (6.02; 9.01), 11 (10.51; 11), 7.94 (6.43; 8.41), 6.59 (6.54; 7.92) ng / ml, p <0.05. The results are presented in tables 3, 4, 5.

Table 3. Cytokine and growth factors content in the serum of patients with AKI after CBG

Biomarker	**IV control group (n=30)**	**I group AKI (n=40)**			
		beforethe operation	**1-st day**	**2-nd day**	**7-th day**
IL 6	3.03 (2.95;13.3)	2.66 (2.63;2.74) ***	23.02 (20.67;34.07) *	34.8 (24.72; 46.11) *	9.94 (5.41;16.68) *
IL 8	19.47 (8.41; 29.32)	6.1 (5.78;11.98) **	48.4 (35.36;128.23) *	14,8 (10.87;15.42) **	16,1 (14.35;19.6) ***
IL 10	18.5 (7.12; 36.69)	5.8 (5.61;5.98) ***	407.015 (346.22;431.21) *	9.93 (7.91;20.44) ***	8.4 (7.4;16.58) ***
IL 17	5.57 (1.89; 9.45)	4.095 (4.03;4.15) ***	4.3 (4.04;4.6) ***	4.17 (3.54;4.21) ***	3.99 (3.92;4.05) **
TGF β1	19,02 (17.50;23.54)	15.41 (13.44;17.32) ***	19.99 (15.3;23.01) ***	21 (18.15;21.8) ***	18.9 (15.2;19) ***
TNF α	2.8 (0.8; 10.9)	2.17 (1.88;2.19) ***	4.95 (3.96;5.94) ***	1.87 (1.71;2.07) ***	2.3 (2.06;2.54) ***

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 449 - 464
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* p<0.001 – incomparisonwiththecontrolgroup; ** p<0.01 – incomparisonwiththecontrol group;
*** p<0.05 – in comparison with the control group

Table 4. Serum cytokine and growth factors content in patients with AKI and DM 2type after CBG

Biomarker	**IV control group (n=30)**	**II group with AKI and DM 2 type (n=40)**			
		Before the operation	**1-st day**	**2-nd day**	**7-th day**
IL 6	3.03 (2.95;13.3)	4.2 (3.1;6.4) ***	32.9 (21.8;44.32) *	32 (20.44;43.1) *	7.53 (4.21;10.55) *
IL 8	19.47 (8.41; 29.32)	16.1 (14.35;19.6) ***	46.8 (43.3;48.9) *	12.3 (10.27;13.4) **	14.64 (13.38;15.4) ***
IL 10	18.5 (7.12; 36.69)	13.14 (12.61;13.67) **	421.57 (354.64;517.04) *	34.17 (28.61;51.05) *	11.575 (10.37;13.62) ***
IL 17	5.57 (1.89; 9.45)	3.065 (3.0375;3.09) ***	3.33 (3.1;3.41) ***	3.61 (2.98;4.19) ***	3.29 (3.01;3.57) **
TGF β1	19,02 (17.50;23.54)	10.01 (9.4;12.89) ***	14.9 (13;20) ***	10.56 (9.5;12) ***	9.49 (9.01;12.1) ***
TNF α	2,8 (0.8; 10.9)	8.635 (6.75;10.51) *	9.12 (5.75;17.3) *	8.73 (1.71;10.4) ***	6.07 (3.335;10.6) *
* p<0.001 - incomparisonwiththecontrolgroup ; ** p<0.01 - incomparisonwiththecontrolgroup; *** p<0.05 - incomparisonwiththecontrolgroup					

Table 5. Serum cytokine and growth factors content in patients without AKI after CBG

Biomarker	**IV control group (n=30)**	**III group without AKI (n=40)**			
		Before the operation	**1-st day**	**2-nd day**	**7-th day**
IL 6	3.03 (2.95;13.3)	2 (1.67;2.2) ***	22.43 (10.24;43.55) *	21.46 (13.21;32.71) *	5.11 (3.14; 9.52) ***
IL 8	19.47 (8.41; 29.32)	5.15 (4.56;5.5) **	23.51 (17.96;46.08) **	7.3 (6.95;9.3) *	4.8 (2.5;5.02) **
IL 10	18.5 (7.12; 36.69)	5.26 (5.24;6.33) ***	90.63 (69.12;402.5) *	13.66 (11.21;18.44) ***	13.78 (13.01;15.01) ***
IL 17	5.57 (1.89; 9.45)	4.07 (3.92;5.24) ***	3.93 (3.9;5.1) ***	3.79 (3.32;5.37) ***	4.21 (3.74;5.34) ***

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 449 - 464
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TGF β1	19.02 (17.50;23.54)	7.81 (6.02;9.01) ***	11 (10.51;11) ***	7.94 (6.43;8.41) ***	6.59 (6.54;7.92) ***
TNF α	2.8 (0.8; 10.9)	1.19 (1.06;1.93) ***	4.34 (4.12;5.02) ***	0.76 (0.65;0.99) ***	0.87 (0.65;0.95) **
* p<0.001 - incomparisonwiththecontrolgroup; ** p<0.01 - incomparisonwiththecontrolgroup; *** p<0.05 - incomparisonwiththecontrolgroup					

The data obtained on changes in the state of the intercellular matrix are interesting. Initially higher serum MMP-8 levels were noted in patients from group I before surgery - 2.46 (1.38; 7.91) ng / ml, p <0.001, compared with group II – 1.39 (0, 30; 3.23) ng / ml, p <0.001 and without in group III - 1.07 (0.64; 1.41) ng / ml, p <0.001. In the main group I, on the 2nd day after CABG, a significant increase in serum MMP-8 up to 20.76 (10.45; 29.31) ng / ml; p <0.001, was obtained which differs significantly from group II - 9.07 (1.21; 21.61) ng / ml, p <0.001, as well as from group III without AKI 2.76 (0.18; 5.21) ng / ml, p <0.001. Analyzing the data obtained, the use of MMP-8, as an early predictor and biomarker of acute kidney injury, is possible. A reliable relationship was established between MMP-8 level and the risk of renal complications ($\chi 2 = 3.86$; df = 1, p <0.001**)** (Fig. 1).

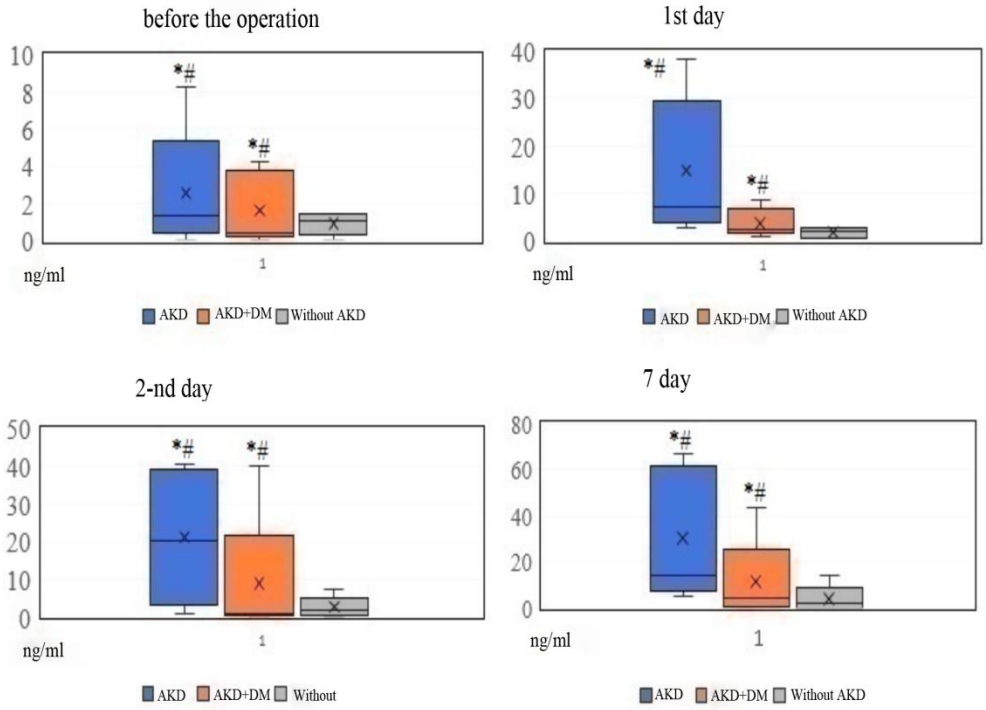

Fig.1. Serum matrix metalloproteinase 8 level (ng/ml)
Statistical significance of differences with the control group (p <0.001) - *; with a group without AKI (p <0.001) - #

A ROC analysis confirmed that the initially elevated MMP-8 serum level before and on the 1st day of cardiac surgery (AUC = 0.8 and AUC = 0.85) in patients with coronary heart disease has a high probability of the proposed diagnostic sign - the risk of acute renal injury (Fig 2).

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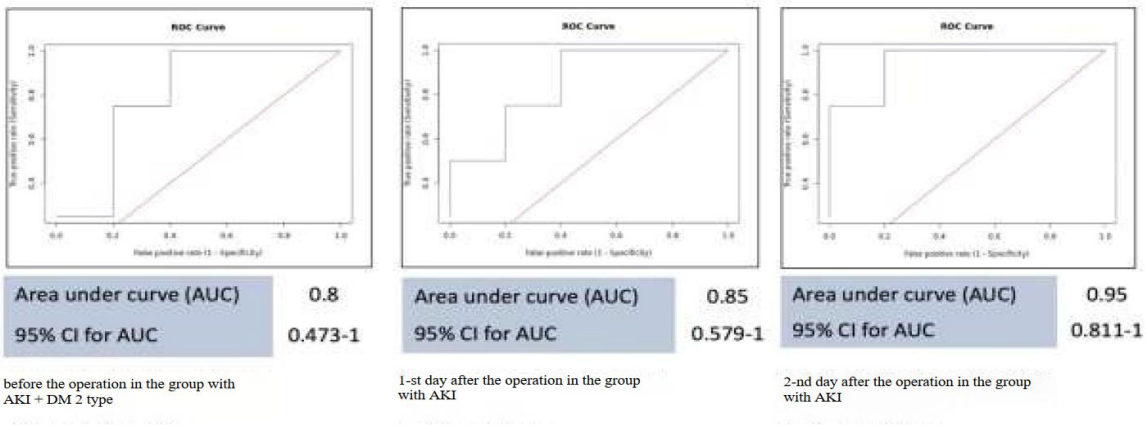

Fig.2. Graphs of ROC analysis of MMP-8

Analysis MPMI 1content in the serum of patients showed certain differences in the three groups. It was found that in the dynamics on the 1st and 2nd day after the operation MPMI 1 level in group I patients was significantly lower than 197.18 (186.44; 210.62) ng / ml, p <0.001, than in the other groups of patients. Whereas in group II patients, MPMI 1serum level was increased even before the surgery 259.30 (240.42; 270.28), p <0.001, remaining above the control data and data of group I patients up to 7 days after the surgery, p <0.001. In the group III of patients with a smooth course of the postoperative period, serum MPMI 1 increased one day after CABG, p <0.001 and remained at a high level throughout the monitoring period. On the seventh day after the operation, no significant differences between the groups of patients were registered, p <0.005. MPMI1 level was above the reference values in all patients. The results are presented in table 6.

Table 6. Reference cytokine and growth factors levels in the serum

№ n/n	Biomarker	IV control goup (n=30)	Patients with AKI after CABG depending on etiology (Me; Q25;Q75), ng/ml		
			I group AKI (n=40)	II group with IKI and DM 2 type (n=40)	Without AKI (n=40)
1	MMP -8 (before the operation)	9.3 (8.06;12.9)	2.45 (1.37;7.91) *	1.39 (0.30;3.23) *	1.07 (0.64;1.41) *
2	MMP-8 (1st lay)		4.92 (2.87;7.49) *	3.73 (1.59; 6.62) *	0.91 (0.32;1.01) *
3	MMP-8 (2nd day)		20.76 (10.45;29.31) *	9.07 (1.21;21.61) *	2.76 (0.18;5.21) *
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	MPP-8 (7 day)		30.41 (14.11; 61;81) *	11.50 (4.19;25.91) *	4.09 (1.91;9.73) *
5	MMP-1(before the operation)	200.04 (194.1;203.5)	197.18 (186.44; 210.62) *	259.30 (240.42; 270.28) *	233.57 (221.06;233.19) *
6	MMP-1(1st day)		190.67 (178.56;215 .15) *	257.68 (221,.9;265.51) *	256.21 (230.31;278.41) *
7	MMP-1(2-nd day)		254.3 (224.09;271 .45) *	301.72 (269.76;321.24) *	325.42 (268.15;370.56) *
8	MMP-1(7 day)		238.92 (231.82; 291.22) *	267.67 (244.75; 290.62) *	300.81 (256.17;327.14) *
* p<0,001 – incomparison with the control group; ** p<0,01 -in comparison with the control group; *** p<0,05 - in comparison with the control group					

Discussion

AKI is characterized by the development of an acute inflammatory reaction on the background of a sluggish inflammatory process (the presence of a concomitant age-related pathology). Acute tissue inflammation is a response to injury of the kidney parenchyma depending on the duration of ischemia (in this case, mechanical aortic clamping and duration of cardiopulmonary bypass), while the previous chronic inflammation depends on the presence of risk factors and concomitant diseases such as coronary heart disease, carbohydrate metabolism disorders [22]. During surgical interventions, renal blood flow and oxygenation of the renal parenchyma decrease, which is accompanied by a sharp activation of the pro-inflammatory cytokines secretion: TNFα, IL-6, IL-8 [28]. This is accompanied by aggravation of organ ischemia and the development of inflammation in it, initiated by oxidative stress, aseptic inflammation, which leads to serious injury of the structure of the kidney parenchyma, even to acute tubular necrosis. In addition to cytokines, the pathological process is aggravated by migration into the organ of cellular elements and plasma components - neutrophils, which respond to own cell changesby developing an inflammatory reaction involving innate immunity mechanisms, where the fragments serve as initiating agents [3]. They activate adhesion molecules and interact with the endothelium via the rolling adherence mechanism. Endothelial dysfunction develops, vascular permeability increases, which leads to the release of blood cells into the interstitial fluid. Activated leukocytes from blood synthesize pro-inflammatory cytokines, chemokines, matrix metalloproteinases, nitric oxide and reactive oxygen [2]. Chemokines are extremely important for the development of tissue inflammation, as they regulate the release from the vascular bed and the infiltration of the inflammation focus by almost all types of leukocytes, monocytes, lymphocytes and their functional activation [1]. Tumor necrosis factor is a powerful pro-inflammatory cytokine and

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 449 - 464
Received 16 February 2021; Accepted 08 March 2021.

plays a decisive role in the process of inflammation, in particular, causing dysfunction of the microvasculature of the organ, participates in lipid metabolism, in blood coagulation, in the formation of insulin resistance, being an active participant in the immune response and apoptosis reactions. Its activation in kidneys ischemic-reperfused lesions leads to an increase in the formation of chemokines and neutrophils activity. Renal parenchyma inflammation develops [32]. It stimulates the expression of a large number of inflammatory mediators: IL-6, chemotaxis IL-8 cytokines [23]. Although the imbalance and increase in the level of proinflammatory cytokine TNF do not fully reflect the development of pathological changes and prognosis. Prolonged ischemia is accompanied by an increase in the levels of other pro-inflammatory mediators in the blood serum, especially IL-6, the concentration of which increases significantly in the first hours after open heart surgery and correlates with the development of AKI and high mortality. According to some authors IL-6 and IL-8plasma levels are associated with mortality in patients with AKI. It is now recognized that chronic inflammation and activation of the immune system are actively involved in the pathogenesis of diabetes mellitus and in the development and progression of diabetic nephropathy. Inflammatory parameters are known to include inflammatory cytokines; they are strict predictors of diabetes and diabetic nephropathy development. At the same time, inflammation can play the main role in the occurrence of disorders such as insulin resistance, hyperglycemia, oxidative stress and endothelial dysfunction with secondary effects that play an important role in the development of kidney injury and the progression of the disease. In this case, cytokines regulate the inflammatory immune response involving cytokine-associated signaling pathways and have a pleiotropic effect in case of tissue injury [29]. Main cytokines involved in diabetes mellitus are TNF-α,IL-6. Besides, recent studies have shown that inflammation, and in particular inflammatory cytokines, are crucial in the development of microvascular complications of diabetes, including neuropathy, retinopathy, and nephropathy [33].Based on these data, the authors of the work suggested that TNF-α biological activity plays a significant role in the development of kidney injury in diabetes mellitus [31].We were able to confirm a sufficiently high expression of TNF-α in patients with type 2 diabetes. TNF-α also induces apoptosis and cell necrosis, can contribute to the development of microvascular complications in diabetes, changes the intraglomerular blood flow and glomerular filtration rate (GFR) due to hemodynamic imbalance between vasoconstricting and vasodilating mediators, and also changes epithelium permeability. TNF-α disturbs the distribution of adhesion receptors involved in intercellular adhesion and inhibits the formation of F-actin stress fibres [27].As a result, rearrangement of intercellular connections occurs leading to a loss of endothelial permeability. Significantly higher IL-17 serum concentration in patients with hypertension is believed to be a sign of immuno-inflammatory activation with an autoimmune component, which was registered in our research. This cytokine stimulates the development of inflammation by activating synthesis of the known pro-inflammatory cytokines. Previously, in experimental studies, it was shown that in animals with no gene responsible for IL-17 production, there is no chronization of the hypertensive reaction and disturbances in endothelium-dependent vasodilation, in contrast to animals with induced hypertension. It was found that IL-17 stimulates chemotaxis of inflammatory cells, especially neutrophils. The accumulation of lymphocytes in the vascular wall was significantly less in mice with no IL-17. All this indicates the important pathogenetic role of IL-17 in the initiation and prolongation of kidney injury after CABG[30]. The anti-inflammatory effect of IL-10 is known to be associated with a suppression of pro-inflammatory cytokines synthesis and an increase in the functional activity of T-lymphocytes. One of the main mechanisms for the realization of IL-10 immunoregulatory role in terms of suppressing the development of the immune response is its participation in the generation and

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 449 - 464
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realization of the effective functions of T-lymphocytes. Apparently, the biological role of this cytokine is to limit the development of congenital and acquired immunity reactions that can cause injuryof the kidney parenchyma [34].For example, the experimental administration of IL-10, a potent anti-inflammatory cytokine, provided nephroprotection by inhibiting cytokines synthesis by Th1 cells. TGF-β1, multifunctional cytokine, first isolated from white blood cells and platelets, is able to stimulate cell growth and cause their transformation in vitro. TGF-β1 is a powerful pro-fibrotic factor, and is also normally an important regulator of cell proliferation, differentiation, apoptosis, immune response, remodelling of extracellular matrix. TGF-β1 is believed to play a role in the progression of glomerulosclerosis and interstitial fibrosis. In patients with impaired carbohydrate metabolism with and without kidney injury, an increased level of TGF-β1 is observed, correlating with biochemical parameters: creatinine and urea increase, glomerular filtration rate decrease, reflecting this cytokine participation as the main factor in the development of AKI due to the activation of the fibrosis process.Hyperglycaemia and complete glycosylation products increase TGF-β1 production and can affect the thickness of the basement membrane, changing filtration and significantly reducing glomerular function. It is worth noting that TGF-β1 deficiency can play a protective role in the development of renal complications, as is seen in the group without postoperative renal complications.

Matrix metalloproteinases (MMPs) is a large family of proteinases. Besides fundamental role in extracellular matrix remodelling (ECM), they also break down cell surface proteins, activate cytokines, and are involved in multiple cellular processes [20]. The activity of MMPs is regulated by numerous mechanisms, including inhibition by endogenous tissue inhibitors of metalloproteinases (TIMP). MMPs perform several functions in kidneys. They are involved in maintaining the protein framework of the extracellular matrix, but with their excessive accumulation they can induce the development of kidney tissue fibrosis in diabetic nephropathy [18,24]. Cytokines and chemokines that respond to ischemia probably participate both in injury of the tubular epithelium and in the regeneration of the tubular epithelium, but the mechanism is still unclear. The effects of MMPs are opposed by their inhibitors (TIMP), therefore, the imbalance in this system can be considered as an indicator of the intensity of the formation and degradation of the intracellular matrix components. MMPs and TIMP imbalance is likely to modulate ECM proteins accumulation in blood vessels and promotes rearrangement of the vascular wall cytoskeleton [21]. These changes help to adapt to stress factors, but can also have adverse consequences in the form of impaired blood supply to the kidney tissue [19]. The development of renal complications was accompanied by an increase in the MMP-8 serum concentration level. MMP-8 is involved in remodelling of the extracellular matrix, which is necessary to maintain the structural and functional integrity of the kidney tissue: glomeruli and interstitium. Background pathology – arterial hypertension, severity and duration of carbohydrate metabolism disorders can affect the profile of matrix metalloproteinases. Low MMP 8 activity in the group with early renal complications and impaired carbohydrate metabolism may be associated with a suppression of ECM components catabolism under conditions of hyperglycaemia. Compensatory increase inTIMP 1 level after surgery in both studied groups with postoperative complications was insufficient, which could lead to an imbalance of proteolytic activity with impaired filtration function, where the basis is progressive sclerosis of blood vessels and glomeruli, which is subsequently accompanied by a decrease in the number of functioning nephrons and an increase hemodynamic load on the structural units of the kidney. This process activates the processes of fibrotic transformation in them, depletes reserve capabilities and closes the vicious circle. Also, a tissue inhibitor (TIMP1) can be inactivated by a proteolytic enzyme - neutrophil elastase (MMP-

8), which significantly increases the activity of various metalloproteinases. Changes in the level of parameters in groups I and II in comparison with the control group and the smooth course of the postoperative period confirm the participation of MMPs and their inhibitors in the mechanisms of renal complications through activation of proteolysis, which leads to the increased vascular and tubular permeability, and can affect glomerular death and tubular cells.

Conclusion

Thus, the immunological aspects of acute renal injury are quite multiple, but it is necessary to consider them when developing renal dysfunction in patients undergoing cardiac surgery. The obtained data on changes in the system of matrix metalloproteinases and their inhibitor allowed to regard them as an additional diagnostic sign, which increased the accuracy and efficiency of the diagnosis of acute kidney injury in the early stages of the disease.

Authors notify of the absence of any conflicts of interest.

Acknowledgments

We would like to thank all patients for participating in the research. This research is dedicated to them.

Conflict of interests: No conflict of interests.

Funding: The work is not funded.

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