



The effect of time between angiography and coronary artery bypass grafting on postoperative acute kidney injury in patients with diabetes mellitus

Diabetes mellituslu hastalarda anjiyografi ve koroner arter baypas greftleme arasındaki zamanın ameliyat sonrası akut böbrek hasarı üzerine etkisi

Cem Doğan¹, Tanil Özer², Rezan Aksoy², Rezzan Deniz Acar¹, Zübeyde Bayram¹,
Taylan Adademir², Kaan Kırallı², Nihal Özdemir¹

¹Department of Cardiology, University of Health Sciences, Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkey

²Department of Cardiovascular Surgery, University of Health Sciences, Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Background: This study aims to investigate the effect of time interval between coronary angiography and coronary artery bypass grafting surgery on postoperative acute kidney injury in patients with diabetes mellitus.

Methods: Between December 2013 and November 2016, a total of 421 diabetic patients (274 males, 147 females; mean age 60±9.2 years; range, 31 to 84 years) who underwent coronary artery bypass grafting were included in the study. Data including demographic characteristics of the patients, comorbidities, medical, and surgical histories, previous coronary angiographies, and operative and laboratory results were retrospectively analyzed. The patients were divided into two groups as those with acute kidney injury (n=108) and those without acute kidney injury (n=313). The Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) criteria were used to define acute kidney injury. The patients were further classified into three subgroups according to the time interval: 0-3 days, 4-7 days, and >7 days.

Results: There was no statistically significant difference in the median time between coronary angiography and coronary artery bypass grafting between the patients with and without acute kidney injury (11.5 and 12.0 days; respectively p=0.871). There was no significant difference in the risk factors for acute kidney injury among the subgroups. Multivariate analysis revealed that previous myocardial infarction (odds ratio [OR]: 5.192, 95% confidence interval [CI]: 2.176-12.38; p<0.001) and the increase in the creatinine levels in the first postoperative day (OR: 4.102 and 95% CI: 1.278-13.17; p=0.018) were independent predictors of acute kidney injury.

Conclusion: Coronary artery bypass grafting can be performed without any delay after coronary angiography without an increase in the postoperative risk of acute kidney injury in patients with diabetes mellitus.

Keywords: Acute kidney injury; coronary angiography; coronary artery bypass grafting; diabetes mellitus.

ÖZ

Amaç: Bu çalışmada diabetes mellituslu hastalarda koroner anjiyografi ve koroner arter baypas greftleme arasında geçen zamanın ameliyat sonrası akut böbrek hasarı üzerindeki etkisi araştırıldı.

Çalışma planı: Aralık 2013 - Kasım 2016 tarihleri arasında koroner arter baypas greftleme yapılan toplam 421 hasta (274 erkek, 147 kadın; ort. yaş 60±9.2 yıl; dağılım 31-84 yıl) çalışmaya alındı. Hastaların demografik özellikleri, eşlik eden hastalıkları, tıbbi ve cerrahi öyküleri, daha önce yapılan koroner anjiyografileri ve cerrahi ve laboratuvar sonuçları dahil olmak üzere veriler retrospektif olarak incelendi. Hastalar akut böbrek hasarı olanlar (n=108) ve akut böbrek hasarı olmayanlar (n=313) olmak üzere iki gruba ayrıldı. Akut böbrek hasarı, Risk, Hasar, Yetmezlik, Kayıp, Son Dönem Böbrek Hastalığı (RIFLE) kriterlerine göre tanımlandı. Ayrıca hastalar zaman aralığına göre üç alt gruba ayrıldı: 0-3 gün, 4-7 gün ve >7 gün.

Bulgular: Koroner anjiyografi ve koroner arter baypas greftleme arasında geçen median süre açısından akut böbrek hasarı olan ve olmayan hastalar arasında istatistiksel olarak anlamlı bir fark yoktu (sırasıyla, 11.5 ve 12.0 gün; p=0.871). Akut böbrek hasarı risk faktörleri açısından alt gruplar arasında anlamlı bir fark yoktu. Çok değişkenli analizde geçirilmiş miyokard enfarktüsü (olasılık oranı [OR]: 5.192, %95 güven aralığı [GA]: 2.176-12.38; p<0.001) ve ameliyat sonrası birinci gün kreatinin düzeyilerindeki artışın [OR: 4.102, %95 GA: 1.278-13.17; p=0.018) akut böbrek hasarının bağımsız belirleyicileri olduğu bulundu.

Sonuç: Diabetes mellituslu hastalarda koroner anjiyografiden sonra, akut böbrek hasarı riskinde artış olmaksızın, herhangi bir gecikme olmadan koroner arter baypas greftleme yapılabilir.

Anahtar sözcükler: Akut böbrek hasarı; koroner anjiyografi; koroner arter baypas greftleme; diabetes mellitus.

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Correspondence: Tanil Özer, MD. SBÜ Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 34865 Kartal, İstanbul, Turkey.
Tel: +90 506 - 305 30 88 e-mail: drtanilozer@gmail.com

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Diabetes mellitus (DM) is known to be one of the most important risk factors for coronary artery disease (CAD). Coronary angiography (CA), which utilizes contrast agents, is the gold standard method in the diagnosis and estimation of the prevalence of CAD. One of the treatment methods for patients with CAD is coronary artery bypass grafting (CABG) and about 20 to 50% of DM patients undergo CABG.^[11-3]

Diabetes mellitus may also lead to acute kidney injury (AKI) either during the diagnosis of CAD with CA due to contrast-induced nephropathy (CIN) or during the treatment period for CAD with CABG. The frequency of AKI due to CIN is reported as 3% in the general population; however, it is claimed to be 20% in patients with severe cardiac pathologies and this figure may increase up to 50%.^[4] Diabetes mellitus and diabetic nephropathy are two major risk factors for CIN.^[5] The presence of DM has been estimated to double the risk of CIN, and multivariate analysis of a database has shown that having DM is an independent risk factor for CIN with an odds ratio (OR) of 1.9.^[6,7]

Acute kidney injury, which may occur after CABG, is a serious problem with an incidence of 7.6 to 48.5% in previous studies.^[8-10] It may lead to several complications including prolonged length of stay in hospital, an increased risk of hemodialysis and persistent kidney failure, and increased mortality rates.^[11] Review of the risk factors reveals that DM plays an important role in the development of AKI.

It is well-established that CA and CABG have an additive effect on AKI in patients with DM and several studies have been conducted to identify the optimal time between CA and CABG to inhibit this additive effect; however, the results have been inconclusive.^[12,13] In the present study, we aimed to investigate the effect of time between CA and CABG on postoperative AKI in patients with DM.

PATIENTS AND METHODS

Medical data of a total of 421 diabetic patients (274 males, 147 females; mean age 60±9.2 years; range, 31 to 84 years) who underwent CABG between December 2013 and November 2016 were retrospectively analyzed from the database of the University of Health Sciences, Kartal Kosuyolu Training and Research Hospital. Data including demographic characteristics of the patients, comorbidities, medical and surgical histories, CA findings, and operative and laboratory results were recorded. The patients were divided into two groups depending on creatinine levels as those with AKI

(n=108) and those without AKI (n=313) using the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) criteria.

Inclusion criteria were as follows: age between 18 and 80 years, DM, creatinine level <1.5 mg/dL on admission, and stable angina pectoris and unstable acute coronary syndrome which could not be treated percutaneously. The patients with CIN due to CA in which preoperative creatinine levels returned to pre-CABG levels were also included in the study. Exclusion criteria were as follows: creatinine level ≥1.5 mg/dL before CA and before CABG, previous treatment for renal insufficiency, history of previous cardiac surgery, history of nephrotoxic drugs other than renin angiotensin inhibitors, urgent or emergency CABG, ST-elevation myocardial infarction, cardiogenic shock, inotropic or mechanical circulatory device requirement before surgery, decompensated heart failure according to the New York Heart Association (NYHA) functional Class III-IV, multiple organ dysfunction, history of systemic disease affecting kidneys other than DM, and recent imaging study using a contrast agent. Patients with CIN due to CA in which preoperative creatinine levels were not regressed spontaneously or which regressed with renal replacement therapy, such as hemodialysis, were also excluded. Patients who required an additional intervention or treatment during CA or CABG, except for standard procedures, and those whose CA and other percutaneous interventions prior to CABG were performed in external centers were also excluded from the study.

A written informed consent was obtained from each patient. The study protocol was approved by the Kartal Kosuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Definitions of DM, AKI and CIN

Diabetes mellitus was defined as a fasting plasma glucose of >126 mg/dL or 2-h plasma glucose of >200 mg/dL during an oral glucose tolerance test; or in a patient with classical symptoms of hyperglycemia or hyperglycemic crisis. A random plasma glucose of >200 mg/dL and previously established diagnosis or treatment of DM were also accepted.

Creatinine levels in all patients before CA, for two consecutive days after CA, and for five consecutive days before and after CABG were recorded from our database. Acute kidney injury was defined according to the RIFLE consensus.^[14] The patients with AKI were further stratified into subgroups according to the increase in serum creatinine levels: those with a serum creatinine increase of 1.5 fold were classified

as Stage R, those with a two-fold increase as Stage I, a three-fold increase as Stage F, those with complete loss of function for four weeks were classified as Stage L, and end-stage kidney disease for longer than three months as Stage E. Since there was no data on the pre- or postoperative hourly urine output for the entire duration of the study, the urine output definitions in the RIFLE criteria were not employed. Primary definition

of AKI was the occurrence of RIFLE Class R or greater (a >50% increase in the creatinine levels from baseline) during the first five postoperative days.

In addition, CIN was defined according to the European Society of Urogenital Radiology as an increase in the serum creatinine concentration of 0.5 mg/dL or a 25% increase from the baseline within 48 h after contrast agent administration.

Table 1. Demographic and clinical characteristics of patients with and without AKI after CABG

	No AKI (n=313)				AKI (n=108)				<i>p</i>
	%	Mean±SD	Median	Min-Max	%	Mean±SD	Median	Min-Max	
Age (year)		60.1±9.1				61.9±9.5			0.198
Gender									
Male	69				53.7				0.004
Body Mass Index		29.3±5.1				30.7±6.3			0.034
Systolic BP (mmHg)		116.2±26.7				110.7±27.1			0.096
Diastolic BP (mmHg)		63.1±15.7				59.2±15.7			0.049
Peripheral AD	8.6				4.7				0.307
Hypertension	64.8				82.7				0.002
Previous MI	45.5				69.3				<0.001
Previous stroke	10.5				12.2				0.698
Blood glucose (mg/dL)		173.7±57.4				184.9±56.1			0.115
Urea (mg/dL)		22.1±10.1				23.3±9.9			0.315
Creatinine (mg/dL)		1.1±0.6				1.1±0.4			0.873
Hemoglobin (g/dL)		12.8±1.7				12.1±1.7			<0.001
RDW (%)		14.7±1.7				15.2±1.8			0.007
Albumin (g/dL)		4.1±0.5				3.9±0.5			0.073
Uric acid (mg/dL)		5.5±1.8				5.6±1.7			0.678
C-reactive protein (mg/dL)		1.7±3.0				1.6±2.4			0.729
Sedimentation (second)		32.9±24.8				41.3±25.7			0.006
CK-MB (U/L)									0.129
LDL (mg/dL)		110.6±42.2				110.4±55.0			0.369
HDL (mg/dL)		39.1±9.9				39.6±12.2			0.732
LV-EF (%)		53.2±12.1				52.4±12.7			0.574
PAPs (mmHg)		39.6±15.0				39.4±13.5			0.932
CA-CABG interval (day)			12	7-17			11.5	7-16	0.871
ICU stay (hours)			46	25-74.5			72	39-144	<0.001
Postoperative urea (mg/dL)		22.8±9.6				29.2±12.6			<0.001
Postop crea Day 1 (mg/dL)		1.1±0.5				1.6±1.0			<0.001
Postop crea Day 5 (mg/dL)		1.0±0.5				1.8±1.1			<0.001
Postoperative CK-MB (U/L)		40.7±30.4				68.1±90.4			<0.001
Postoperative albumine (g/dL)		3.24±0.48				3.10±0.43			0.024
Cross-clamp time		83.1±12.6				89±11.7			0.745
Postoperative blood product usage (unit)		2.1±0.2				1.6±0.4			0.126

AKI: Acute kidney injury; CABG: Coronary artery bypass grafting; SD: Standard deviation; BP: Blood pressure; AD: Artery disease; MI: Myocardial infarction; RDW: Red cell distribution width; CK-MB: Creatinine kinase-myocardial band; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LV-EF: Left ventricular ejection fraction; PAP: Systolic pulmonary artery pressure; CA: Coronary angiography; ICU: Intensive care unit; Postop crea Day 1: Postoperative first day creatinine level; Postop crea Day 5: Postoperative fifth day creatinine level.

Coronary angiography was performed after the cessation of nephrotoxic medications and following hydration with 0.9% saline infusion. During CA, six images for the left coronary artery system and two images for the right coronary artery system were obtained, and similar amounts of contrast agents were used. The time of surgery was decided depending-on the clinical status of the patient and the availability of the operating room. Coronary artery bypass grafting was typically performed with preoperative preparation and physical examination by an anesthesiologist, while the surgical method and postoperative follow-up were conducted according to the current guidelines. The patients were further classified into three subgroups according to the time interval: 0-3 days, 4-7 days, and >7 days.

Statistical analysis

Statistical analyses were performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were presented in mean ± standard deviation (SD), while non-homogeneous data were presented in median (interquartile range) and categorical variables were presented in percentage. Univariate comparisons between the groups of patients with or without AKI were performed using the chi-square test for categorical variables, while the Student's t-test or the Mann-Whitney rank-sum test were used for continuous variables, as appropriate. For the comparisons of patients with AKI of Stage R to E, analysis of variance (ANOVA) or the Kruskal-Wallis test was used for numerical variables, while the chi-square was used for categorical variables. Multiple logistic regression analysis was performed including variables for which $p < 0.05$ was found in the univariate analyses to predict the independent predictors of postoperative AKI development. The receiver operating characteristic (ROC) curves were plotted for the estimation of the optimal cut-off values for individual parameters to predict AKI and to establish the optimal cut-off points for use in clinical

decision making. A p value of < 0.05 was considered statistically significant.

RESULTS

Of all patients, 15% were in Stage R, 5.5% in Stage I, and 1% were in Stage F. Contrast-induced nephropathy was found in 7.2% of all patients. However, a total of 91 patients (21.6%) were not included in the study, as either they did not have spontaneous resolution and required hemodialysis or their preoperative creatinine levels did not return to normal. Demographic and clinical characteristics of the patients with and without AKI after CABG are shown in Table 1.

There were no significant differences in cardiopulmonary bypass (CPB) time and the amount of postoperative blood product used between the two groups. The median time interval between CA and CABG was not significantly different between the patients with and without AKI (11.5 [range, 7 to 16] days and 12 [range, 7 to 17] days, respectively; $p = 0.871$). Logistic regression analysis showed no significant differences in the risk factors for AKI such as age, gender, hypertension, left ventricular ejection fraction, baseline urea and creatinine, albumin, and hemoglobin levels, CPB time, and the amount of postoperative blood products among the three subgroups as stratified according to the time interval between CA and CABG. The risk for AKI after CABG was not statistically significant high among the three groups (Table 2).

According to the univariate analyses carried out to predict the risk factors for AKI, female gender, higher Body Mass Index, previous myocardial infarction, hypertension, elevated sedimentation rates, lower hemoglobin and red cell distribution width levels, higher postoperative creatinine and urea levels, lower albumin levels during the postoperative period, and increased creatinine kinase-myocardial band (MB) levels after the procedure were found to be associated with an increased risk (Table 2). However, our study

Table 2. Logistic regression analysis of risk for development of postoperative AKI as time interval between CA and CABG

Time intervals (day)	OR	95% CI	<i>p</i>	AKI (%)
0-3	0.509	0.171-1.511	0.224	15.4
4-7	1.278	0.782-2.088	0.328	29.2
>7	0.937	0.586-1.497	0.784	25.3

AKI: Acute kidney injury; CA: Coronary angiography; CABG: Coronary artery bypass grafting; OR: Odds ratio; CI: Confidence interval.

Table 3. Univariate and multivariate analysis of variables associated with development of postoperative AKI

	Univariate			Multivariate		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Male	0.521	0.333-0.815	0.004	0.479	0.186-1.235	0.128
Body Mass Index	1.045	1.003-1.089	0.034	1.037	0.968-1.112	0.300
Previous MI	2.709	1.560-4.703	<0.001	5.192	2.176-12.38	<0.001
Hypertension	2.600	1.382-4.890	0.002	2.119	0.812-5.529	0.125
Sedimentation	1.013	1.004-1.022	<0.001	0.991	0.971-1.011	0.381
Preoperative hemoglobin	0.781	0.685-0.891	0.006	1.002	0.737-1.362	0.988
Preoperative RDW	1.178	1.043-1.331	0.007	1.239	0.937-1.637	0.132
Postop crea day 1	4.346	2.723-6.936	<0.001	4.102	1.278-13.17	0.018
Postoperative urea	1.010	0.990-1.031	<0.001	1.006	0.943-1.73	0.861
Postoperative albumin	0.526	0.299-0.926	0.024	1.091	0.470-2.531	0.839
Postoperative CK-MB	1.011	1.005-1.017	<0.001	1.005	0.997-1.013	0.209

AKI: Acute kidney injury; OR: Odds ratio; CI: Confidence interval; MI: Myocardial infarction; RDW: Red cell distribution width; CK-MB: Creatinine kinase-myocardial band; Postop crea Day 1 postoperative first day creatinine level.

findings did not indicate that the time interval between CA and CABG was a risk factor for the development of AKI.

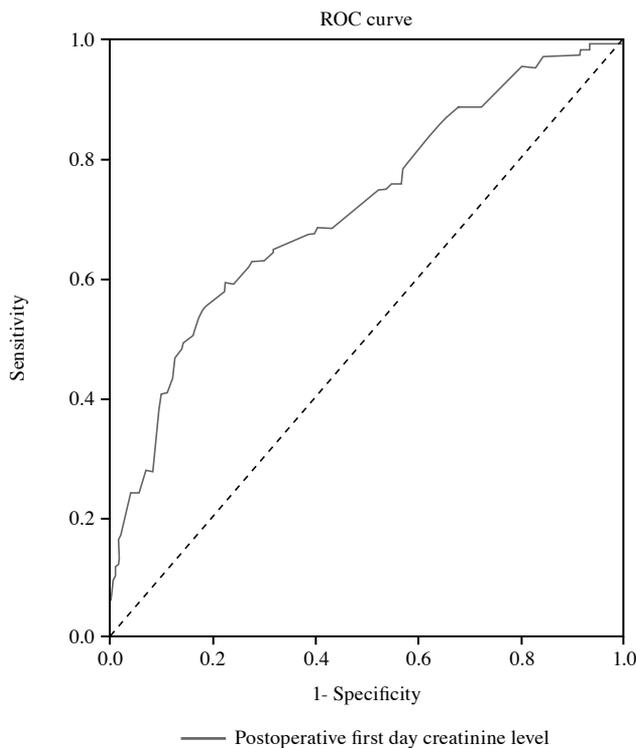


Figure 1. ROC curve analysis for postoperative first day creatinine level cut-off value in predicting development of postoperative AKI according to RIFLE criteria.

ROC: Receiver operating characteristics; AKI: Acute kidney injury; RIFLE: Risk, Injury, Failure, Loss, End-Stage Kidney Disease.

Multiple logistic regression analysis was performed to predict the independent risk factors for AKI after CABG. Previous myocardial infarction (OR: 5.192, 95% CI: 2.176-12.38; $p < 0.001$) and increased creatinine levels (OR: 4.102, 95% CI: 1.278-13.17; $p = 0.018$) on the first day of the postoperative period were found to be independent predictors of AKI development (Table 3).

In the ROC analysis, a creatinine level of 1.5 mg/dL as a cut-off value on the first day of the postoperative period showed 40% sensitivity and 90% specificity in predicting AKI (AUC: 0.718, 95% CI: 0.660-0.777; $p < 0.001$) (Figure 1).

DISCUSSION

In this study, we analyzed the data of diabetic patients who underwent isolated CABG and found no association between the time interval between CA and CABG and the risk of development of postoperative AKI defined according to the RIFLE criteria.

In several studies, it has been suggested that the development of postoperative AKI as an important risk factor for mortality and morbidity may be seen in 7.6 to 48.5% of cases.^[1,15-20] Risk factors for AKI include female gender, DM, hypertension, heart failure, low left ventricular ejection fraction, peripheral vascular disease, the need for intra-aortic balloon pump, urgent or emergency surgery, preoperative nephropathy, use of diuretics, prolonged cross-clamp time, use of aprotinin, blood transfusion, CPB time, preoperative anemia, increased blood albumin, elevated blood uric

acid levels, re-exploration, multiple grafts, mechanical ventilation time, preoperative angiography, and the use of contrast dye.^[15-20] In our study, the rate of the patients with postoperative AKI was 25%, consistent with previous reports.^[1-3,8,9]

As reported in previous studies, DM and the contrast agents used in CA are two well-known risk factors for the development of AKI.^[15-20] Although CIN is seen in up to 10% of patients with normal kidney function, this rate increases up to 25% in those with underlying renal dysfunction.^[21]

The mechanism of CIN involves the direct toxic effect of contrast agents as well as contrast-induced vasospasm leading to decreased renal medullary blood flow, resulting in medullary ischemia, enhanced reactive oxygen substrates formation, and oxidative stress.^[4,5] Patient-related risk factors for contrast-induced AKI include pre-existing chronic kidney disease, DM and diabetic nephropathy, advanced age, concomitant use of nephrotoxic drugs, multiple myeloma, and reduced kidney perfusion (i.e., dehydration, congestive heart failure, and hemodynamic instability). Contrast agent-related risk factors for CIN include a high volume of contrast agents, the use of hyperosmolar contrast agents, repeated exposure to contrast agents within a short period, and intra-arterial administration of contrast agents.^[20] The presence of DM also doubles the risk of developing CIN, and multivariate analysis of a database previously defined diabetes as an independent risk factor with an OR of 1.9.^[6,7]

Furthermore, the contrast agents used in CA and the stress of CABG (double-hit) may cause postoperative renal failure in these patients. Diabetes mellitus is a common risk factor for CAD and is also a risk factor for both CIN and AKI.^[1-3,5-7] Therefore, it has been suggested that it may be necessary to optimize the time interval between CA and CABG to reduce the additive effect of contrast agents and surgery in patients with DM. However, there are no data in the literature regarding the optimal time interval for isolated CABG in these patients. We, therefore, believe that this study would contribute to the body of knowledge in the literature by providing more data on the optimum time interval required for these patients.

In our study, we stratified the patients with AKI into three subgroups according to time interval to evaluate the effect of contrast agents used for CA on AKI development. Contrast-induced nephropathy usually occurs within 48 h; however, this time may take as long as seven days. Therefore, we specified the time intervals as 0-3 days, 4-7 days, and >7 days.

The rate of CIN was 7.2% in our study and there was no statistically significant difference in the logistic regression analysis among the three subgroups.

Studies by Del Duca et al.^[22] and Medalion et al.^[23] showed that surgery within the first five days after CA increased the risk of AKI development. Of note, the latter study included only patients with isolated CABG, while the Del Duca's study included those who underwent different types of surgeries, such as isolated heart valve surgery, CABG + heart valve surgery, other complex surgeries, and emergency surgeries. In another study, Ranucci et al.^[24] reported that surgery on the first day after CA increased the risk by three-fold in patients who underwent mixed type surgeries. Similarly, Hennessy et al.^[25] found an increased risk of valve surgery on the first day after CA.^[25] By contrast, Brown et al.^[26] concluded that it was safe to perform valve surgery on the same day as CA in selected patients. However, Mariscalco^[12] reported that CABG with valve surgery within the first five days increased the risk of AKI, although this increase was not observed in patients who underwent isolated CABG.

Altogether, we can conclude that there are conflicting results in the literature on the optimal time interval between CA and CABG. This may be due to the fact that the types of surgeries included in the studies are different (i.e., isolated CABG, CABG + valve surgery, and other complex surgeries) and, also, some of the studies were unable to differentiate between urgent and emergency surgeries. In the present study, we included a group of patients with normal baseline renal function, more limited and less frequent variables with DM, and elective isolated CABG. Based on our results, the time interval between CA and CABG did not show a correlation with the risk of AKI in these patients. Another important result of our study is that the increase in serum creatinine levels on the first postoperative day was found to be associated with the risk of AKI. Based on previous studies and literature data, the increase in creatinine levels within first five to seven days after surgery is accepted in diagnosing postoperative AKI. However, in our study, serum creatinine levels above 1.5 mg/dL on the first postoperative day could be used with 40% sensitivity and 90% specificity for the risk assessment for AKI. This result suggests that we should consider early postoperative increases in creatinine levels and take necessary precautions, accordingly.

Limitations of this study include the single-center, retrospective design with potential selection biases. In order to detect the effect of time interval to postoperative AKI incidence prospective randomized studies must be done. Our study population was small.

In conclusion, our study results show no correlation between time delay for coronary artery bypass grafting after coronary angiography and reduced risk of acute kidney injury development in patients with diabetes mellitus who have normal baseline renal functions. Therefore, coronary artery bypass grafting should be performed, when it is appropriate for the surgeon and the patient. In addition, it is of utmost importance to follow the creatinine level of patients on the first postoperative day, particularly in patients having previous myocardial infarction.

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