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Evaluation of Early Postoperative Period Results of Patients With Type 2 Diabetes Taking Oral Anti-Diabetics Or Insulin Medications, With Microalbuminuria and Normal Creatinine Levels After Coronary Artery Bypass

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ABSTRACT

Background: Acute kidney injury (AKI) is one of the most important complications after cardiac surgery and is one of the main causes of morbidity and mortality. Diabetes mellitus also is one of the main risk factors for renal dysfunction in coronary artery bypass graft (CABG). In this study, we aimed to compare the early postoperative period results of type 2 diabetes patients taking oral antidiabetics (OAD) or insulin medications, with microalbuminuria and normal creatinine levels after CABG.

Methods: Eighty patients with type 2 diabetes and taking OAD or receiving insulin medication all with normal creatinine levels with microalbuminuria were included in this study. Preoperative creatinine values of the patients, albumin levels in spot urine, creatinine levels on the postoperative 3rd day, duration of ventilation, amount of drainage, length of stay in the intensive care unit, length of stay in the hospital, mediastinitis, and mortality rates were recorded.

Results: A statistically significant increase in creatinine was found in both taking OAD type 2 diabetes and insulin medication with microalbuminuria. When the two groups were compared with each other, the increase in creatinine levels of the patients using insulin was higher than the patients taking OAD. It also was statistically significant.

Conclusion: According to the result of our study, it can be suggested that postoperative creatinine elevation is observed in patients with type 2 diabetes mellitus with microalbuminuria and with normal creatinine levels, either having insulin medication or not. The elevation is higher in patients having insulin medication, while other results are similar, except for impaired renal function.

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INTRODUCTION

It is known that coronary artery bypass surgery is the most effective treatment method for angina pectoris seen in coronary artery diseases, and it increases long-term survival [Eagle 1999]. Although it is widely used for this purpose worldwide, it causes end-organ damage, multiple organ ischemia, necrosis, and consequently mortality and morbidity [Mangano 1998]. The vast majority of coronary artery bypass surgeries are performed on-pump and various proinflammatory effects, such as non-pulsatile blood flow, low mean blood pressure, and hypothermia, occurs [Levy 2003].

Neurological, pulmonary and renal dysfunctions, and superficial and deep tissue infections can be seen as a result of cardiopulmonary bypass [Almassi 1999; Asimakopoulos 1999; Gultekin Y 2021; Gulack 2017].

Classically, microalbuminuria is known as a parameter indicating renal damage. Barriers in the glomeruli prevent macromolecules, such as albumin from passing into the ultrafiltrate. Albumin, which passes to the ultrafiltrate in a small amount, is reabsorbed from the proximal tubules and some of it is metabolized and broken down into amino acids. Hence, there is a small amount of albumin in the urine. If the glomerular barrier and proximal tubule reabsorption is impaired, the amount of urine albumin increases. This shows us proximal tubule damage and indirectly interstitial inflammation and functional loss in the kidney [Remuzzi 1990].

Following the consensus that microalbuminuria indicates the loss of kidney function, new hypotheses developed on the idea that urinary albumin excretion is a parameter that increases the risk of cardiovascular disease. Among them, it has come to the fore that microalbuminuria is associated with the loss of general vascular functions and consequently it is an indicator of a high level of cardiovascular disease and kidney function loss [Amann 2006]. Based on this, it was thought that loss of vascular endothelial function might be a cause of vascular albumin leakage, and it was concluded that albumin leakage in renal vessels was related to general vascular permeability [Deckert 1989].

The prevalence of type 2 DM among patients with CAD who undergo coronary artery bypass graft (CABG) surgery varies from 19% to 30%. Diabetes is known as an independent risk factor for cardiovascular diseases [Turner 1998]. In addition, every 1% increase in Hemoglobin A1c (HbA1c)

level in diabetic diseases causes an increase of about 11% in coronary artery diseases [Vazquez-Benitez 2015]. Prevalence of renal dysfunction amongst patients with CAD and type 2 DM after CABG surgery may reach 20% in the early post-operative period [Kunt 2009]. Especially in patients with insulin-dependent diabetes microalbuminuria is considered a sign of nephropathy and a marker of the prevalence of atherosclerosis [Perkins 2007].

The aim of this study is to compare the mortality and morbidity results of type 2 diabetes patients receiving insulin medications or taking OAD, all with microalbuminuria and normal creatinine values after on-pump coronary artery bypass.

MATERIALS AND METHOD

This single-center study prospectively planned study was conducted by including 80 patients with microalbuminuria who underwent coronary artery bypass surgery in our clinic (Prof. Dr. Cemil Tascıoğlu City Hospital, Cardiovascular Surgery Clinic, Istanbul, Turkey) between February 2018 and December 2021. For this study, ethical approval was given by the local Ethics Committee and all research was conducted in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards. The aim of the study was clearly explained to all participants and their written informed consent was obtained.

In this study, the exclusion criteria were as follows: Preoperative chronic renal failure, preoperative dialysis, serum creatinine levels above 1.2mg/dl for males and 1.1mg/dl for females, underwent emergency surgery, active endocarditis, use of preoperative extracorporeal membrane oxygenator. Patients who had insulin medication more than one year were included in the group of having insulin medication, while those who had been receiving insulin for less than one year, were not included.

Patients having insulin medication were using short-acting (regular insulin) and/or long-acting or mixed insulin. Those taking OAD were receiving metformin and/or stagliptin. The mean of HbA1c was 7.1% in the group using insulin and 6.8% in the group receiving oral medication.

The records of the following risk factors were taken preoperatively: age, gender, body mass index (BMI), hypertension, chronic obstructive pulmonary disease (COPD), smoking, whether they had an infarction in the last 28 days, presence of peripheral artery disease (PAD), ejection fractions, serum creatine and microalbuminuria levels in spot urine.

Albumin levels of 20-200 mg/L in spot urine were accepted as microalbuminuria [Jarraya 2013]. The patients were divided into two groups, namely having insulin medication and taking OAD. Forty-two patients were in the insulin medication group, and 38 patients were in the OAD medication group.

All operations were performed by the same surgical team, on-pump. Stockert S5 Roller Pump (Sorin Group, Arvada, CO, USA) and membrane oxygenators (Inspire 8, LivaNova Sorin Group, Modena, Italy) were used. Arterial cannula and single venous cannulation were applied from the aorta after median sternotomy. Body temperature was reduced to 32 degrees. Cardiac arrest was achieved with the help of hyperpotassemic isothermal blood cardioplegia. After the distal bypasses were made, the cross-clamp was lifted, and the proximal anastomoses were side clamped. Pump outlet was inotrope, according to the need. In the diabetic patient group, blood glucose regulation was achieved with continuous crystallized insulin infusion.

Serum creatine levels on the postoperative 3rd day, duration of stay on the ventilator after surgery, amount of drainage, length of stay in the intensive care unit (ICU), length of hospital stay, mediastinitis, and mortality rates of the patients were recorded. It was found in previous publications that creatine levels increased 1-3 days after cardiac surgery [Mishra 2005], and we thought that we would obtain the most reliable results by recording creatine values on the 3rd day.

Statistical analysis: The research data were uploaded to the computer using the "SPSS (Statistical Package for Social Sciences) for Windows 26.0 (SPSS Inc, Chicago, IL)" and evaluated. Descriptive statistics are presented as mean and standard deviation. It was analyzed using quantitative analytical methods (Mann-Whitney U, Student T and Wilcoxan test). The statistical significance level was accepted as $P < 0.05$.

RESULTS

A total of 80 patients were included in this study, whose demographic data are given in Table 1. (Table 1) No difference was found between the groups.

There was no significant difference between the perioperative cross-clamp times of the patients, total pump times, and the number of bypasses performed. (Table 2)

Preoperative and postoperative data are shown in Table 3. (Table 3) There were no patients with chronic renal failure in either group. In one patient among the diabetic patient group, 24-hour urine output decreased to 800 cc, and creatine levels increased above 3.55 mg/dl on the postoperative 2nd day. The patient was given inotrope support, furosemide infusion therapy, and fluid restriction. The patient entered the polyuric phase on the 4th postoperative day without the need for hemodialysis and creatinine levels decreased to normal on the 7th postoperative day.

As mediastinitis presented in one patient in the diabetic patient group, antibiotic treatment was started according to the culture result and Vacuum-assisted closure treatment was applied. While Vacuum-assisted closure of the patient was changed every three days, the wound culture was taken and followed up at the same time. After reaching negative culture results twice, the sternotomy incision was closed.

The results of the within-group comparison of preoperative and postoperative creatinine levels are shown in Table 4. (Table 4) There was a statistically significant increase in creatinine levels in both groups.

No hospital mortality was detected in our study.

Table 1. Demographic characteristics of the groups

	Insulin group (*N* = 42)	OAD group (*N* = 38)	*P*
Age*	52.8±5.7	54.6±6.3	0.85
Gender**			
Female	20 (47.6%)	18 (47.3%)	0.97
Male	22 (52.3%)	20 (52.6%)	0.94
Hypertension**	12 (28.6%)	10 (26.3%)	0.82
BMI*	27.05±3.1	26.71±4.3	0.64
COPD**	11 (26.2%)	13 (34.2%)	0.43
MI (28 days)**	24 (57.1%)	20 (52.6%)	0.69
Smoking**	21 (50.0%)	23 (60.2%)	0.34
PAD**	7 (16.7%)	4 (10.5%)	0.43
Ejection fraction**	46.8±6.9	48.2±7.3	0.53
EuroSCORE (mean)	1.8±0.6	1.39±0.4	0.42

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral artery disease; OAD, oral antidiabetics. **Chi-square test, *Mann-Whitney U test

Table 2. Perioperative data

	Insulin group (*N* = 42)		OAD group (*N* = 38)		
	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	*P**
Cross-clamp time (minute)	62.10±11.07	62.00 (17.25)	59.67±11.29	58.00 (14.50)	0.38
Total pump time (minute)	114.71±13.99	11.00 (22.75)	113.90±14.36	113.50 (20.25)	0.82
Bypass numbers (n)	4.04±0.58	4.00 (0.00)	4.10±0.7	4.00 (1.00)	0.92

OAD, oral antidiabetics; SD, standard deviation. *Mann-Whitney U test

Table 3. Preoperative and postoperative data

	Insulin group (*N* = 42)		OAD group (*N* = 38)		
	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	*P**
Microalbumin (mg/l)	34.60±10.15	31.00 (16.00)	37.00±20.75	30.50 (16.75)	0.78
Preoperative creatinine (mg/dl)	0.88±0.16	0.85 (0.19)	0.93±0.21	0.88 (0.21)	0.26**
Postoperative 3rd day creatinine level (mg/dl)	1.01±0.18	0.95 (0.27)	1.33±0.46	1.21 (0.35)	<0.001
Duration of stay on the ventilator (hour)	7.67±1.67	7.50 (3.00)	8.21±2.44	8.00 (3.00)	0.57
Drainage amount (ml)	567.85±196.36	575.00 (287.50)	515.47±154.00	500.00 (212.50)	0.27
Length of stay in ICU (day)	2.17±0.72	2 (1)	2.64±1.30	2 (1.25)	0.18
Length of stay in hospital (day)	7.92±1.38	7.00 (2.00)	9.07±3.13	8.00 (3.00)	0.11

OAD, oral antidiabetics; SD, standard deviation; ICU, intensive care unit. *Mann-Whitney U test, **Student t test

Table 4. Within-group creatinine elevation levels

	Preoperative creatine (mg/dl)		Postoperative 3rd day creatine (mg/dl)		
	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	*P**
Insulin group (*N* = 42)	0.88±10.16	0.85 (0.19)	1.01±0.18	0.95 (0.27)	<0.001
OAD group (*N* = 38)	0.93±0.21	0.88 (0.28)	1.33±0.46	1.21 (0.35)	<0.001

OAD, oral antidiabetics; SD, standard deviation. *Mann-Whitney U test

DISCUSSION

At the end of this study, we determined that the creatinine levels of diabetic patients receiving insulin medication with normal creatinine and microalbuminuria increased significantly on the post-op 3rd day, when compared with the patients having OAD medication.

It is known that cardiac surgery, which has been performed for many years in the world, is a risky and difficult discipline in mortality and morbidity compared with other surgical disciplines [Gültekin 2020]. Diabetes mellitus is accepted as an independent risk factor, especially for coronary atherosclerosis, which concerns a wide age group [Zarich 1998]. It is known that diabetes alone increases mortality and morbidity in coronary artery disease, both at younger ages and with more widespread involvement [Jensen 1987], and in coronary artery bypass operations [Thourani 1999]. The following can be considered as the main reasons for poor prognosis during and after surgery due to diabetes: severe cardiac disease, subclinical insufficiency in renal functions in accompany, dehydration and electrolid disorders due to hyperglycemia, arrhythmogenic, and increased fatty acids that decrease myocardial oxygen demand [Carson 2002; Cohen 1998]. Since the effect of diabetes on coronary bypass surgery is known to increase mortality and morbidity, in our study, we aimed to investigate type 2 diabetic patients using insulin and taking OAD, in terms of kidney functions and morbidity.

Today, most coronary artery bypass surgeries are performed on-pump. We performed all the operations on-pump. It is known that on-pump coronary artery bypass operations alone cause an increase in renal functions and are an important cause of morbidity [Mazzarella 1992]. Loss of renal functions causes cardiac dysfunction, lung function impairment, wound healing problems, and prolongation of stay intensive care and hospital stays [Yavuz 2002].

Many cross-sectional studies in both diabetic and nondiabetic patients have shown that microalbuminuria is associated with coronary heart disease and peripheral vascular disease [Patrick 1990]. While microalbuminuria is seen as a marker of complications that develop in diabetic patients, it is considered a sign of diabetic nephropathy [Viberti 1982], and it is also known to increase early mortality in these patients [Mogensen 1984]. It is accepted as a marker of atherosclerosis, which is the cause of ischemic heart diseases in patients without diabetes [Yudkin 1988].

While clinical studies investigating the effects of microalbuminuria on mortality and heart failure in cardiovascular diseases previously were conducted, we aimed to investigate diabetic patients using insulin and taking OAD [Gerstein 2001]. Studies on patients who had undergone CABG generally were compared in patient groups with and without microalbuminuria [Mirmohammad-Sadeghi 2013]. In a study conducted by Kristina et al. in 2015, patients with microalbuminuria who had type 2 diabetes were compared with non-diabetic patients [Kristina 2015]. In our search, we did not find a previous study comparing type 2 diabetes patients receiving insulin medication and taking OAD.

In our study, we aimed to compare patients who underwent coronary artery bypass surgeries with type 2 diabetes patients receiving insulin treatments and patients taking OAD all with normal creatinine values of microalbuminuria, which is one of the poor prognostic factors.

According to the results we obtained, there were no statistically significant differences between the preoperative demographic data, preoperative microalbuminuria levels and perioperative cross-clamp times, total pump times, and bypass numbers of both groups.

When the postoperative duration of stay on the ventilator was compared, there was no statistically significant difference between the groups, although the durations were longer in the diabetic group receiving insulin treatment. There was no statistically significant difference between the amount of drainage. When the lengths of stay in the intensive care unit and hospital were compared, there was no statistically significant difference, although the average of the diabetic group receiving insulin treatment was high.

No postoperative early mortality was observed in both patient groups.

Mediastinitis developed in one patient, who was in the diabetic group receiving insulin treatment. Mediastinitis generally is seen with a rate of 1-4%, and it is known that rates of non-healing wounds and mediastinitis are higher in diabetic patients receiving insulin treatment [Francel 2001]. In our study, the rate of mediastinitis was calculated as 1.25%. When only the group receiving insulin treatment was considered, the rate was found as 2.38%. When we evaluated this result, we thought that diabetes treatment with insulin may have a facilitating role for mediastinitis rather than microalbuminuria.

When the postoperative data are examined, it is seen that the most important difference is in renal function. The mean

preoperative creatine level of a diabetic group taking OAD was 0.88 ± 0.16, and the mean creatine level was 1.01 ± 0.18 on the postoperative 3rd day. The increase in between was found to be statistically significant ($P < 0.001$). The mean preoperative creatine levels of a diabetic group receiving insulin treatment were 0.93 ± 0.21, the mean postoperative day 3 creatine levels were found to be 1.33 ± 0.46, and the increase in creatine levels also was statistically significant ($P < 0.001$). These two data showed that there was a significant increase in creatine levels after on-pump coronary artery bypass surgery of the type 2 diabetes patients using insulin and taking OAD, with microalbuminuria.

When the preoperative creatinine values of both groups were compared, there was no statistically significant difference. When the increases in creatinine levels on the postoperative 3rd day were compared between the groups, there was a much higher increase in the diabetic group using insulin compared with the diabetic group taking OAD, which was statistically significant ($P < 0.001$). Acute renal failure developed in only one patient in the diabetic group using insulin who returned to normal with the treatment, without any need for dialysis. This shows us that creatine levels of diabetic patients receiving insulin treatment with microalbuminuria have a significant increase when compared to ones taking OAD, and these patients even have the risk of acute renal failure.

The main strength of the study is that, to our knowledge, this is the first study. The number of patients included seems to be sufficient because only the patient group with microalbuminuria was determined as the target for our study, however, we think that a larger patient group should be studied and the results should be compared with another study including patients with low ejection fraction.

CONCLUSION

In conclusion, we detected that the presence of microalbuminuria in patients causes impairment in renal functions in the early postoperative period of on-pump coronary artery bypass operations, and this deterioration is much more severe in type 2 diabetes patients receiving insulin treatment. Preoperative microalbuminuria may be an independent predictor of kidney function after cardiac surgery in type 2 diabetes patients using insulin. So, we think that the surgery of patients with microalbuminuria can be performed safely, since there is no difference between the duration of stay on the ventilator, the length of stay in the intensive care unit and hospital, and the impairment of kidney functions can be treated with effective prevention and intensive care treatment without the need for dialysis.

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