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

Introduction: In this study, we aimed to compare the early postoperative period results of type 2 diabetes patients taking oral antidiabetics or insulin medications, with microalbuminuria and normal creatinine levels after coronary artery bypass. Materials and methods: Eighty patients with type 2 diabetes and taking oral antidiabetics 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 oral antidiabetics type 2 diabetes and insulin medication patient groups with microalbuminuria. When the two groups were compared with each other, increase in creatinine levels of the patients using insulin was higher than the patients taking oral antidiabetics, and 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. Keywords: Type 2 diabetes mellitus, insulin, microalbuminuria, coronary artery bypass.

Introduction

It is known that coronary artery bypass surgery is the most effective treatment method for angina pectoris seen in coronary artery diseases and increases long-term survival(1). Although it is widely used for this purpose worldwide, it causes end organ damages, multiple organ ischemia, necrosis, and consequently mortality and morbidity(2). 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 occur(3). Neurological, pulmonary and renal dysfunctions, superficial and deep tissue infections can be seen as a result of cardio pulmonary bypass(4, 5, 6, 7).

Classically, microalbuminuria is known as a parameter indicating renal damage. Barriers in the glomeruli prevent macromolecules such as albumin 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(8).

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 (9). 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(10).

Diabetes is known as an independent risk factor for cardiovascular diseases(11). In addition, every 1% increase in Hemoglobin A1c (HbA1c) level in diabetic diseases causes an increase of about 11% in coronary artery diseases(12). Especially in patients with insulin-dependent diabetes microalbuminuria is considered as a sign of nephropathy and a marker of the prevalence of atherosclerosis(13).

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

Materials and Methods

This prospectively planned study was conducted by including 80 patients with microalbuminuria who underwent coronary artery bypass surgery in our clinic between February 2019 and December 2020. 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 (NPH) or mixed insulin. Those taking oral antidiabetics 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(14). The patients were divided into two groups, namely as having insulin medication and taking oral antidiabetics. 42 patients were in the insulin medication group and 38 patients were in the oral antidiabetics medication group.

All operations were performed by the same surgical team, on-pump. Stockert S5 Roller Pump (Sorin Group) and Terumo FX oxygenators 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 anestomoses 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 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(15), 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). Statistical significance level was accepted as $p<0.05$.

Findings and Statistics

A total of 80 patients were included in this study, whose demographic data are given in Table 1. 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.

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***** Mann-Whitney U test

Table 1. Demographic characteristics of the groups (BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction)

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).

As mediastinitis presented in one patient in the diabetic patient group, antibiotic treatment was started according to the culture result and VAC treatment was applied. While VAC of the patient was changed every 3 days, the wound culture was taken and followed up at the same time. After reaching negative culture results twice the sternotomy incision was closed primarily.

No hospital mortality was detected in our study.

	Insulin Group	**Insulin Group**	**OAD group**	**OAD group**	
	Mean±SD	**Median(IQR)**	**Mean±SD**	**Median(IQR)**	**p***
Cross Clamp Time	62,10±11,07	62,00(17.25)	59,67±11,29	58,00(14,50)	0,38
Total Pump Time	114,71±13,99	115,00±(22,75)	113,90±14,36	11350(20,25)	0,82
Bypass Numbers	4,04±0,58	4,00(0,00)	4,10±0,7	4,00(1,00)	0,92

*Mann-Whitney U test

Table 2. Perioperative data

	Insulin Group	**Insulin Group**	**OAD group**	**OAD group**	
	Mean±SD	**Median(IQR)**	**Mean±SD**	**Median(IQR)**	**p***
Microalbumin	34,60,10±10,15	31,00(16.00)	37,00±20,75	30,50(16,75)	0,78
Preoperative Creatinine	0,88±0,16	0,85(0,19)	0,93±0,21	0,88(0,21)	0,26**
Post-Op 3rd Day Creatinine Level	1,01±0,18	0,95(0,27)	1,33±0,46	1,21(0,35)	**<0,001**
Duration of Stay on the Ventilator	7,67±1,67	7,50(3,00)	8,21±2,44	8,00(3,00)	0,57
Drainage Amount	567,85±196,36	575,00(287,5)	515,47±154,00	500,00(212,50)	0,27
Length of Stay in ICU	2,17±0,72	2,00(1,00)	2,64±1,30	2,00(1,25	0,18

	Insulin Group	Insulin Group	OAD group	OAD group	
Length of Hospital Stay	7,92±1,38	7,00(2,00)	9,07±3,13	8,00(3,00)	0,11

* Mann-Whitney U test, ** Student t test

Table 3. Preoperative and postoperative data.

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Table 4. Within-group creatinine elevation levels.

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 to the patients having oral antidiabetic 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 to other surgical disciplines (16). Diabetes mellitus is accepted as an independent risk factor especially for coronary atherosclerosis, which concerns a wide age group(17). It is known that diabetes alone increases mortality and morbidity in coronary artery disease, both at younger ages and with more widespread involvement(18), and in coronary artery bypass operations(19). The following can be considered as 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, arrhythminogenic, and increased fatty acids that decrease myocardial oxygen demand(20,21). Since the effect of diabetes on coronary bypass surgery is known to increase mortality and morbidity, in our study, we aimed to investigate on type 2 diabetic patients using insulin and taking oral antidiabetics in terms of kidney functions and morbidity.

Today, most of the coronary artery bypass surgeries are performed on-pump. We have done all the operations we have performed 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(22). Loss of renal functions causes cardiac dysfunction, lung function impairment, wound healing problems, and prolongation of stay intensive care and hospital stays(23).

While microalbuminuria is seen as a marker of complications that develop in diabetic patients, it is considered a sign of diabetic nephropathy(24) and it is also known to increase early mortality in these patients(25). It is accepted as a marker of atherosclerosis, which is the cause of ischemic heart diseases in patients without diabetes(26).

While clinical studies investigating the effects of microalbuminuria on mortality and heart failure in cardiovascular diseases were previously conducted we aimed to investigate diabetic patients using insulin and taking oral antidiabetics(27). Studies on patients who had undergone coronary artery bypass surgery were generally compared on patient groups with and without microalbuminuria(28). In a study conducted by Kristina S. and al. in 2015, patients with microalbuminuria who have type 2 diabetes were compared with non-diabetic patients(29). In our searches we did not find a previous study comparing type 2 diabetes patients receiving insulin medication and taking oral antidiabetics.

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 oral antidiabetics 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 difference 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 durations of stay on the ventilator 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 length of stay in intensive care unit and hospital stays were compared, there was no statistically significant difference, although the average of the diabetic group receiving insulin treatment was high.

No postoperative early mortality observed in both patient groups.

Mediastinitis developed in one patient who was in the diabetic group receiving insulin treatment. Mediastinitis is generally 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 (30). 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 on renal functions. The mean preoperative creatine level of diabetic group taking oral antidiabetics was 0.88 $\pm$ 0.16, and the mean creatine level was 1.01 $\pm$ 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 diabetic group receiving insulin treatment were 0.93 $\pm$ 0.21, the mean postoperative day 3 creatine levels were found to be 1.33 $\pm$ 0.46, and the increase in creatine levels was also 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 oral antidiabetics, 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 to the diabetic group taking oral antidiabetics, 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 oral antidiabetics, and these patients even have the risk of acute renal failure.

As the conclusion of this study, we think 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. In addition, we think that the surgery of patients with microalbuminuria can be performed safely, since there is no difference between the durations of stay on the ventilator, the length of stay in intensive care unit and hospital stay, and the impairment of kidney functions can be treated with an effective intensive care treatment without the need for dialysis.

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.

Disclosure statement

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References

1. Eagle KA, Guyton RA, Davidoff R, Ewy GA, Fonger J, Gardner TJ, et al. ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999; 34(4): 1262-347.
2. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998; 128(3): 194-203.
3. Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 2003; 75(2): S715-S720.
4. Almassi GH, Sommers T, Moritz TE, Shroyer AL, London MJ, Henderson WG, et al. Stroke in cardiac surgical patients: determinants and outcome. Ann Thorac Surg 1999; 68(2): 391-7.
5. Asimakopoulos G, Smith PL, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68(3): 1107-15.
6. Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: evaluation of renal function. Ann Thorac Surg 1999; 68(2): 493-8.
7. Jensen RH, Storgaard M, Vedelsdal R, Obel N. Impaired neutrophil chemotaxis after cardiac surgery. Scand J Thorac Cardiovasc Surg 1995; 29(3): 115-8.
8. Remuzzi G, Bertani T: Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? Kidney Int 38: 384 –394, 1990
9. Amann K, Wanner C, Ritz E: Cross-talk between the kidney and the cardiovascular system. J Am Soc Nephrol 17: 2112–2119, 2006
10. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 32: 219 –226, 1989
11. Turner R, Millins H, Neil H et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23) the United Kingdom Prospective Diabetes Study Group. BMJ 316, 823–828 (1998)
12. Vazquez-Benitez G, Desai JR, Xu S et al. Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes Care 38(5), 905–912 (2015).
13. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warran JH, Krolewsk AS: Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol. 2007, 18: 1353-1361. 10.1681/ASN.2006080872.
14. Jarraya F, Lakhdar R, Kammoun K, Mahfoudh H, Drissa H, Kammoun S, et al. Microalbuminuria A Useful Marker of Cardiovascular Disease. Iranıan J Kidney Dis. 2013; 7(3): 178-86.
15. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker for acute renal injury following cardiac surgery. Lancet 2005;365:1231-8.
16. Gültekin Y,Bolat A.Bir üniversite hastanesi kliniğinde yapılan ilk 200 açık kalp ameliyatı sonuçları:Kırıkkale Üniversitesi,Tıp Fakültesi,Kalp-Damar Cerrahisi,KÜ Tıp Fak Derg 2020;22(3):348-356.
17. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. J Am Coll Cardiol 1988;12:114–120
18. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T. Coronary heart disease in young type I (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 1987;30:144–148.
19. Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg 1999;67:1045-52.
20. Carson J, Scholz PM, Chen AY, Peterson FD, Gold J, Schneider SH. Diabetes mellitus increases short-

term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418-23.

21. Cohen Y, Raz I, Merin G, Mozes B. Comparison of factors associated with 30 -day mortality after coronary artery bypass grafting in patients with versus without diabetes mellitus. Am J Cardiol 1998;81:7-11.
22. Mazzarella V, Gallucci MT, Tozzo C, Elli M, Chiavarelli R, Marino B, et al. Renal function in patients undergoing cardiopulmonary bypass operations. *J Thorac Cardiovasc Surg.* 1992;104(6):1625–7.
23. Yavuz S, Ayabakan N, Goncu MT, Ozdemir IA. Effect of combined dopamine and diltiazem on renal function after cardiac surgery. *Med Sci Monit.* 2002;8(5):145–150.
24. Viberti GC, Hill RD, Jarrett RJ, et al. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1(8287):1430–2
25. Mogensen CE (1984) Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 6:356-60
26. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington Diabetes Survey. Lancet 1988;2(8610):530–3.
27. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6.
28. Mirmohammad-Sadeghi M, Naghiloo A, Najarzadegan MR. Evaluating the relative frequency and predicting factors of acute renal failure following coronary artery bypass grafting. ARYA Atheroscler 2013;9: 287–92.
29. Kristina S Shafranskaya,Vasiliy V Kashtalap,Anton G Kutikhin,Olga L Barbarash,Leonid S Barbarash.Microalbuminuria and prediction of cardiovascular complications in patients with coronary artery disease and type 2 diabetes mellitus after CABG surgery. Heart Lung Circ. 2015 Oct;24(10):951-9.
30. Francel TJ, Kouchoukos NT. A rational approach to wound difficulties after sternotomy: the problem. Ann Thorac Surg 2001;72:1411-8.