The Heart Surgery Forum #2015-1400
19 (3), 2016 [Epub June 2016]
doi: 10.1532/hsf.1400

Online address: http://journal.hsforum.com

The Influence of Metabolic Syndrome on Acute Kidney Injury Occurrence after Coronary Artery Bypass Grafting

Atike Tekeli Kunt, MD, PhD [1] Hakan Parlar, MD,[1] Orhan Findik, MD,[1] Cagri Duzyol, MD,[1] Ozgur Baris, MD,[1] Canan Balci, MD[2]

Departments of [1]Cardiovascular Surgery and [2]Anesthesiology, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey

ABSTRACT

Background: Metabolic syndrome (MetS) is defined as a cluster of systemic abnormalities: hyperglycemia, dyslipidemia, abdominal obesity, and hypertension. Acute kidney injury (AKI) is one of the devastating complications after cardiac surgery. Age, DM, preexisting renal dysfunction, hypertension, impaired left ventricular function, and severe arteriosclerosis of the aorta are the major risk factors for the development of AKI. The purpose of the current study was to analyze the influence of MetS on AKI occurring after coronary artery bypass grafting (CABG).

Methods: We retrospectively reviewed the prospectively collected data of 500 adult patients who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value <1.4 mg/dL) from January 2011 to January 2015. The patients were divided into two groups either having the diagnosis of MetS (Group I) or not (Group II). MetS was diagnosed based on International Diabetes Federation definition. Kidney injury was interpreted according to RIFLE classification. The effect of MetS on AKI after CABG was determined using logistic regression analysis and the results were expressed as odds ratio (OR) with a 95% confidence interval (CI). A *P* value <.05 was considered statistically significant.

Results: Metabolic syndrome was diagnosed in 16.4% of all patients. Postoperative AKI occurred in 26 patients (31.7%) in Group I whereas there were 53 patients (12.7%) in Group II. On logistic regression analysis, the presence of MetS was shown to be associated with increased incidence of postoperative AKI (OR, 3.197; 95% CI, 1.850-5.526; *P* = .000).

Conclusion: The presence of MetS seems to be associated with increased incidence of AKI after cardiac surgery. MetS is a modifiable issue; if its components are well controlled its dreadful effects after cardiac surgery might be controlled as well.

Received September 11, 2015; accepted October 21, 2015.

Correspondence: Atike Tekeli Kunt, MD, PhD, Associate Professor of Cardiovascular Surgery, Kocaeli Derince Education and Research Hospital, Department of Cardiovascular Surgery, Kocaeli, Turkey; +905327467869 (e-mail: atikemd@gmail.com).

INTRODUCTION

Metabolic syndrome (MetS) is defined as a cluster of systemic abnormalities: hyperglycemia, dyslipidemia, abdominal obesity, and hypertension [Alberti 2005]. International Diabetes Federation (IDF) defined MetS as the presence of any of two of the factors listed in Table 1 in addition to central obesity. If body mass index (BMI) is >30kg/m^2, central obesity is assumed and waist circumference does not need to be measured according to this definition of IDF [Alberti 2005]. Diabetes mellitus (DM) and obesity are individually known risk factors for morbidity and mortality after cardiac surgery [Carson 2002; Pan 2006]. It is clear that their combination, namely MetS, should add on to their negative effects after cardiac surgery. Acute kidney injury (AKI) is one of the devastating complications after cardiac surgery. Age, DM, preexisting renal dysfunction, hypertension, impaired left ventricular function, and severe arteriosclerosis of the aorta are the major risk factors for the development of AKI [Doddakula 2007;

Table 1. The International Diabetes Federation (IDF) Definition of Metabolic Syndrome (adapted from Alberti 2005)

Central obesity (defined as waist circumference with ethnicity specific values) plus any 2 of the following 4 factors:	
Raised triglycerides	≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure (BP)	systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose (FPG)	FPG ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

OGTT indicates oral glucose tolerance test.

Table 2. RIFLE Classification (adapted from Bellomo 2004)

	GFR Criteria	Urine Output Criteria
Risk	Increased plasma creatinine ×1.5	<0.5 mL/kg^{-1}/h^{-1} × 6 hours
Injury	Increased plasma creatinine ×2	<0.5 mL/kg^{-1}/h^{-1} × 12 hours
Failure	Increased plasma creatinine ×3 or acute plasma creatinine ≥350 μmol/L or acute rise ≥44 μmol/L	<0.3 mL/kg^{-1}/h^{-1} × 24 hours or anuria × 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function >4 weeks	
ESKD	End-stage kidney disease (>3 months)	

ESKD indicates end-stage kidney disease; GFR, glomerular filtration rate.

Weerasinghe 2001; Chertow 1997]. Intraoperatively, inflammatory response syndrome due to cardiopulmonary bypass (CPB), nonpulsatile flow, and renal hypoperfusion are also important causes of AKI [Suen 1998; Hall 1997].

The purpose of the current study was to analyze the influence of MetS on AKI occurring after coronary artery bypass grafting (CABG).

METHODS

Patients

After we received institutional review board approval (approval date: 05.05.2015; number: KOU KAEK 2015/145), we retrospectively reviewed the prospectively collected data of 500 adult patients who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value <1.4 mg/dL) from January 2011 to January 2015. All patients had previously granted permission for use of their medical records for research purposes. The patients were divided into two groups either having the diagnosis of MetS (Group I) or not (Group II). MetS was diagnosed if patients had 2 or more of the criteria listed in Table 1 based on IDF definition [Alberti 2005] in addition to central obesity. When the patients had BMI >30kg/ m^2 central obesity was assumed and waist circumference was not measured. Hypertension was defined as a systolic blood pressure ≥130mmHg and a diastolic blood pressure ≥85mmHg and also a requirement for antihypertensive drug treatment. DM was defined as fasting glucose levels of plasma ≥100mg/dL or previously diagnosed type 2 diabetes. Dyslipidemia was defined as triglyceride levels ≥150mg/dL or specific treatment for this lipid abnormality and HDL cholesterol levels <40mg/dL in males and <50mg/dL in females or specific treatment for this lipid abnormality [Alberti 2005].

Kidney injury was interpreted according to RIFLE classification [Bellomo 2004], explained as R: risk; I: injury; F: failure; L: loss; and E: end-stage kidney disease (Table 2). Patients who were on either hemodialysis or peritoneal dialysis, patients with peripheral vascular disease, recent myocardial infarction, emergent surgery, and patients undergoing operations other than or in conjunction with CABG were excluded from the study.

CABG Procedure

All operations were performed in a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Dideco Compactflo Evo, USA). Mild to moderate (28-32°C) hypothermia and pulsatile flow of 2.2-2.4 L/m^2. Myocardial protection was achieved with tepid antegrade blood cardioplegia and a "hot shot" (250-500 mL) was delivered just prior to the removal of the aortic cross-clamp. The perfusion pressure was kept over 70mmHg at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized in all patients (phentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all of the operations.

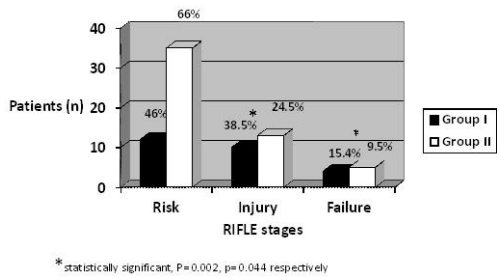
Postoperative Management

Postoperatively patients were followed in the intensive care unit (ICU) according to protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, chest tube output, and hourly urine output were monitored. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances were corrected immediately with appropriate management. Hematocrit values <25% were corrected with erythrocyte suspension administration.

Daily blood urea nitrogen (BUN), serum and urea creatinine, and serum electrolytes were measured uniformly in all patients until discharge from the hospital. Preoperative and postoperative creatinine clearances and peak creatinine clearance were calculated according to the formulations reported in the literature [Lassnigg 2000; Cockcroft 1976].

The indication criteria for RRT were determined by our staff nephrologists and they were the same for both of the study groups. These criteria included hyperkalemia (>6 mmol/L), anuria or oliguria <0.5ml/kg/h for 12 hours, and metabolic acidosis.

Vascular access was with a dual lumen catheter via a central venous vein. Patients were heparinized to achieve activated clotting time of 200 seconds. A fresenius polysulfone filter



Comparison of Group I and Group II according to RIFLE classification.

Table 3. Baseline and Perioperative Characteristics of Patients

	Group 1* (n = 82)	Group 1† (n = 412)	*P*‡
Age, years	62.8 ± 10.5	60.5 ± 10.3	.065
Female, %	38	20	.001
Body mass index, kg/m^2	31.2 ± 4.9	27.4 ± 3.9	.000
Hypertension, n	52	255	.390
Diabetes mellitus, n	79	100	.000
Hyperlipidemia, n	63	228	.000
Smoking, n	55	250	.133
CPB time, min	109.2 ± 38.9	104.1 ± 40.3	.290
Cross-clamp time, min	63.5 ± 24.4	60.2 ± 23.8	.256
LV function, %	55.8 ± 8.0	54.6 ± 9.9	.304
Serum creatinine, mg/dL	0.9 ± 0.24	0.9 ± 0.20	.139
Creatinine clearance, mL/min	79.5 ± 31.5	87.1 ± 34.1	.061
Blood urea nitrogen, mg/dL	17.8 ± 7.4	18.7 ± 7.0	.314

Data are presented as mean ± SD where indicated. CPB indicates cardiopulmonary bypass; LV, left ventricle.

*Group I: Patients diagnosed with metabolic syndrome.

†Group II: Patients without the diagnosis of metabolic syndrome.

‡Chi-square and unpaired Student t tests. Values in bold are statistically significant.

(Fresenius Medical Care, Bad Homburg, Germany) was used for filtration.

Statistical Analysis

All statistics were performed using SPSS version 17.0 for Windows (IBM, New York, USA). Continuous variables were expressed as mean ± SD and were compared by unpaired Student test or the Pearson chi-square test. The effect of MetS on AKI after CABG was determined using logistic regression analysis and the results were expressed as odds ratio (OR) with a 95% confidence interval (CI). A *P* value <.05 was considered statistically significant.

RESULTS

Patient demographics and perioperative data are shown in Table 3. Among the patient characteristics and perioperative data, female sex, body mass index, DM, and hyperlipidemia were significantly higher in Group I. Other data did not assure statistically significant differences between groups. Metabolic syndrome was diagnosed in 16.4% of all patients. Postoperative AKI occurred in 26 patients (31.7%) in Group I whereas it occurred in 53 patients (12.7%) in Group II. On logistic regression analysis, the presence of MetS was shown to be associated with increased incidence of postoperative AKI (OR, 3.197; 95% CI, 1.850-5.526; *P* = .000). Multivariate logistic regression analysis revealed that hyperglycemia (OR, 2.835; 95% CI, 1.736-4.629; *P* = .000) and obesity (BMI >30kg/m2) (OR, 2.553; 95% CI, 1.553-4.199; *P* = .000) were other independent risk factors for AKI after isolated CABG.

The preoperative mean serum creatinine was 0.96 ± 0.24 mg/dL in Group I and 0.92 ± 0.21 mg/dL in Group II (*P* = .139). Postoperative peak serum creatinine levels were higher in Group I patients than Group II (1.29 ± 0.51 mg/dL and 1.08 ± 0.41 mg/dL respectively; *P* = .000).

When results were compared according to the RIFLE stage, the 26 patients in Group I included 12 patients (46.1%) in RIFLE R, 10 patients (38.5%) in RIFLE I, and 4 patients (15.4%) in RIFLE F stage. Whereas 53 patients in Group II included 35 patients (66%) in RIFLE R, 13 patients (24.5%) in RIFLE I, and 5 patients (9.5%) in RIFLE F stage (RIFLE R *P* = .095; RIFLE I P = .002; RIFLE F *P* = .044 respectively) (Figure).

Renal replacement therapy was used in 3.4% (n = 17) of patients (14 patients were in Group I, and 3 patients were in Group II, *P* = .000). The creatinine value before commencement of RRT was 3.95 ± 0.93 mg/dL. RRT was started 36-50 hours after surgery and used for 5 days. The mean creatinine level was 1.39 ± 0.81 mg/dL prior to hospital discharge and none of the patients became hemodialysis dependent.

The mean ICU time was 76.05 ± 27.94 hours in Group I and 59.82 ± 28.17 hours in Group II (*P* = .000); in-hospital stay time was 8.11 ± 3.25 days in Group I and 6.85 ± 2.44 days in Group II (*P* = .001). The intraaortic balloon pump (IABP) support was required in 3.6% of patients (7 patients in Group I and 11 patients in Group II, *P* = .017). Prolonged ventilatory support was necessary in 4% of patients and the mean ventilatory support time was 9.85 ± 7.71 in Group I and 7.25 ± 2.18 in Group II, *P* = .003) and one of these patients required tracheotomy. The 30-day mortality was 3.4% (n = 17, 6 patients in Group I and 11 patients in Group II, *P* = .044). Thirteen patients died due to low cardiac output and multiorgan failure and these patients required RRT. Two patients died due to cerebrovascular accident, 1 patient died due to massive pulmonary embolism, and 1 patient died due to mesentery artery ischemia.

DISCUSSION

Society of Thoracic Surgeons (STS) reported in 2006 that the incidence of AKI was 3.6% in patients who underwent isolated CABG and 7.5-12.9% after CABG combined with valvular procedures [Mirmuhammad-Sadeghi 2013]. AKI was observed in about 15.8% of the patients in our study. Our results suggested that MetS was shown to be associated with increased incidence of postoperative AKI. The exact mechanism of postoperative AKI is still unclear. Hypertension, DM, age, severe arteriosclerosis, and impaired left ventricular function are the known major preoperative risk factors for postoperative AKI [Doddakula 2007; Weerasinghe 2001; Chertow 1997]. We hypothesized that these individual risk factors, when collected under the name of MetS as a cluster, should further increase the risk. It is reported that the prevalence of MetS is high in patients undergoing CABG [Echahidi 2007]. In our study MetS was diagnosed in 16.4%

of all patients. This prevalence of MetS seems to be lower according to the literature. This could be due to our inclusion criteria, as we did not include patients with creatinine levels above 1.4 mg/dL. If we did so, the prevalence of MetS was expected to be 38%. In the literature, it is suggested that MetS in the general population increases the risk of renal dysfunction [Kurella 2005]. It is also reported that MetS is associated with postoperative AKI after both on-pump and off-pump CABG [Kajimoto 2009; Hong 2010] as well as non-cardiac surgery [Glance 2010]. A decrease in cardiac output, nonpulsatile flow, and intraoperative hypotension are the known causes of AKI after on-pump CABG [Mirmuhammad-Sadeghi 2013]. Inflammatory response, hypoperfusion, and transient circulatory failure are the suggested causes of AKI during off-pump CABG [Hong 2010]. Lastly, obesity was identified as being an important cause of AKI after non-cardiac surgery since it resulted in a 3-7 fold higher risk for postoperative AKI [Glance 2010].

The important question to be answered should be: why is MetS a risk factor for AKI? The most suitable answer to this question lies in the definition and components of MetS, predominantly hyperglycemia and central obesity. Both hyperglycemia and obesity are important risk factors for kidney disease. Hyperglycemia results in tubulointerstitial lesions in kidney and obesity results in glomerulopathy [Uendo 1997; Kambham 2001]. These results might explain why patients with MetS developed AKI more than the non-MetS patients in our study. Multivariate logistic regression analysis revealed that both hyperglycemia and obesity (BMI >30kg/m^2) were independent risk factors for AKI in the present study.

We compared the patients according to the severity of AKI and reported that the MetS group had a higher number of patients in RIFLE I and RIFLE F stages. Renal hemodynamics are demonstrated to be affected by insulin resistance and hyperinsulinemia, which are the main pathogenic factors of MetS [Kajimoto 2009]. This could explain the association of MetS and AKI.

Postoperative AKI that requires RRT has an independent effect on early mortality and morbidity. It is suggested that postoperative AKI requiring RRT has an overall mortality of 40-80% [Lassnigg 2000]. The present study demonstrates that RRT was required in 3.4% of patients. Fourteen patients were in Group I, and 3 patients were in Group II, and this result was statistically significant. None of the patients became hemodialysis dependent. The higher rates of RRT use in the MetS group might be due to microvascular renal disease in this group [Mariam 2009].

The mean ICU time, the length of hospital stay, and mean ventilatory support times were statistically longer in Group I. This could be due to the increased use of RRT in MetS patients. Our results are similar to the other studies in the literature. However, Swart et al [Swart 2012] reported that although the length of hospital stay is longer in MetS patients, they could not demonstrate a difference between MetS and non-MetS groups regarding renal dysfunction.

The effect of the presence of MetS on mortality is well documented in the literature [Sprecher 2000; Kajimato 2008]. In the present study we detected an increased IABP use and 30-day mortality in the MetS group. Most of the patients died due to low cardiac output and required RRT. Hemodynamic instability in MetS patients due to altered vasoactive response as a result of increased circulating levels of cytokines [Despres 2003] might explain this result.

There are some limitations of the study. First, the study design is retrospective. Second, in the present study, we might have had patients with some components of MetS but who did not fulfill the MetS criteria. Thus our control group suggested as non-metabolic syndrome group could have risk factors for poor outcome after CABG. Lastly, our prevalence of MetS was lower than the literature, which could be due to a lower number of patients and also due to the inclusion criteria of our study, which did not include patients with serum creatinine levels above 1.4mg/dL.

Conclusions

AKI after CABG results in various postoperative complications and leads to prolonged hospitalization, and eventually increased costs as well as increased rate of mortality. MetS is a common risk factor that showed a significant predictive effect for morbidity and mortality after CABG. MetS is a modifiable issue; if its components are well controlled, even with small lifestyle modifications and postoperative management protocols, its dreadful effects after cardiac surgery might be controlled as well.

REFERENCES

Alberti KG, Zimmet P, Shaw J. 2005. The Metabolic Syndrome: a new worldwide definition. Lancet 366:1059-62.

Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. 2004. Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204-12.

Carson JL, Scholz PM, Chen AY, et al. 2002. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 40:418-23.

Chertow GM, Lazarus JM, Christiansen CL, et al. 1997. Preoperative renal risk stratification. Circulation 95:878-84.

Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41.

Despres JP. 2003. Inflammation and cardiovascular disease: is abdominal obesity the missing link? Int J Obes Metab Disord 27suppl:S22-24.

Doddakula K, Al-Sarraf N, Gately K, et al. 2007. Predictors of acute renal failure requiring renal replacement therapy post cardiac surgery in patients with preoperatively normal renal function. Interact Cardiovasc and Thorac Surg 6:314-18.

Echahidi N, Pibarot P, Despres JP, et al. 2007. Metabolic syndrome increases operative mortality in patients undergoing coronary artery bypass grafting surgery. J Am Coll Cardiol 50:843-51.

Glance LG, Wissler R, Mukamel DB, et al. 2010. Perioperative outcomes among patients with the modified metabolic syndrome who are undergoing noncardiac surgery. Anesthesiology 113:859-72.

Hall RI, Smith MS, Rocker G. 1997. The systemic inflammatory

response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. Anesth Analg 85:766-82.

Hong S, Youn YN, Yoo KJ. 2010. Metabolic syndrome as a risk factor for postoperative kidney injury after off-pump coronary artery bypass surgery. Circ J 74:1121-6.

Kajimato K, Kasai T, Miyauchi K, et al. 2008. Metabolic syndrome predicts 10-year mortality in non-diabetic patients following coronary artery bypass surgery. Circ J 72:1481-6.

Kajimoto K, Miyauchi K, Kasai T, et al. 2009. Metabolic syndrome is an independent risk factor for stroke and acuterenal failure after coronary artery bypass grafting. J Thorac Cardiovasc Surg 137:658-63.

Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. 2001. Obesity-related glomerulopathy: An emerging epidemic. Kidney Int 59:1498-1509.

Kurella M, Lo JC, Chertow GM. 2005. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 16:2134-40.

Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. 2000. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 11:97-104.

Mariam PA, Tejas VP, Youssef MK, Adriana F, Helmut GR, Ajay KS. 2009. Kidney pathological changes in metabolic syndrome: A crosssectional study. Am J Kidney Dis 53:751-9.

Mirmuhammad-Sadeghi M, Naghiloo A, Najarzadegan MR. 2013. Evaluating the relative frequency and predictors of acute renal failure following coronary artery bypass grafting. ARYA Atheroscler 9:287-92.

Pan W, Hindler K, Lee VV, Vaughn WK, Collard CD. 2006. Obesity in diabetic patients undergoing coronary artery bypass graft surgery is associated with increased postoperative morbidity. Anesthesiology 104:441-7.

Sprecher DL, Pearce GL. 2000. How deadly is the "deadly quertet?" A post-CABG evaluation. J Am Coll Cardiol 36:1159-65.

Suen WS, Mok CK, Chiu SW, et al. 1998. Risk factors for development of acute renal failure (ARF) requiring dialysis in patients undergoing cardiac surgery. Angiology 49:789-90.

Swart MJ, De Jager WH, Kemp JT, Nel PJ, Van Staden SL, Joubert G. 2012. The effect of the metabolic syndrome on the risk and outcome of coronary artery bypass graft surgery. Cardiovasc J Africa 23:400-4.

Uendo M, Kawashima S, Nishi S, et al. 1997. Tubulointerstitial lesions in non-insulin dependent diabetes mellitus. Kidney Int Suppl 63:S191-4.

Weerasinghe A, Hornick P, Smith P, Taylor K, Ratnatunga C. 2001. Coronary artery bypass grafting in non-dialysis-dependent mild-to-moderate renal dysfunction J Thorac Cardiovasc Surg 121:1083-9.