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Cardiovascular Surgery

Metabolic Syndrome as a Risk Factor for Postoperative Kidney Injury After Off-Pump Coronary Artery Bypass Surgery

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Background: Metabolic syndrome (MetS) is a clustering of risk factors, including dyslipidemia, hypertension, and increased plasma glucose levels, which increase the risk of cardiovascular disease and renal impairment. We retrospectively analyzed the relationship between MetS and acute kidney injury (AKI) after off-pump coronary artery bypass surgery (OPCAB).

Methods and Results: Patients who underwent isolated OPCAB between January 2006 and December 2008 were identified. Patients were grouped by using the National Cholesterol Education Program-Adult Treatment Panel III criteria with body mass index instead of waist circumference. From a total of 740 patients, 320 patients (43.2%) were in the MetS group, and 420 patients (56.8%) were in the non-MetS group. Postoperative AKI occurred in 84 patients (26.2%) in the MetS group and 44 patients (10.5%) in the non-MetS group (P<0.05). Multivariate logistic regression identified diabetes mellitus (odds ratio (OR), 1.83; 95% confidence interval (CI), 1.12–3.00; P=0.02), chronic kidney disease (OR, 4.79; 95%CI, 2.85–8.07; P<0.001), MetS (OR, 3.14; 95%CI, 1.79–5.49; P=0.001), and emergency surgery (OR, 5.08; 95%CI, 1.01–25.6; P=0.05) as independent risk factors for AKI after OPCAB.

Conclusions: MetS is a prevalent risk factor for postoperative AKI after OPCAB, and aggressive treatments of its components could have reduced operative morbidity. (*Circ J* 2010; **74:** 1121–1126)

Key Words: Acute kidney injury; Coronary artery bypass surgery; Metabolic syndrome; Off-pump

Metabolic syndrome (MetS) is a clustering of risk factors, including dyslipidemia, hypertension, and increased plasma glucose levels that increase the risk of cardiovascular disease. Diabetes mellitus (DM) and obesity are highly prevalent in patients undergoing coronary artery bypass grafting (CABG) and these are major factors in the development of MetS. These factors are related to renal impairment, and have a significant impact on morbidity after CABG.[1–7] However, few studies have investigated the relationship between MetS and postoperative renal dysfunction after CABG. The objective of this retrospective study was to determine the effect of MetS on acute kidney injury (AKI) after off-pump coronary artery bypass (OPCAB).

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Methods

Identification

The clinical identification of patients with MetS was defined using 3 or more of the following based on the National Cholesterol Education Program-Adult treatment Panel III criteria (except that obesity was defined as a body mass index (BMI) of ≥25 kg/m^2 according to the established Korean criterion for obesity, rather than waist circumference as per the American Heart Association/National Heart, Lung, and Blood Institute definition): triglycerides ≥150 mg/dl; high-density lipoprotein cholesterol <40 mg/dl for men, <50 mg/dl for women; blood pressure ≥130/85 mmHg or treatment with antihypertensive medication; and fasting blood glucose ≥100 mg/dl or treatment with oral hypoglycemic drugs or insulin injection.[8–10] Previously, the definition of AKI varied widely and was predominantly based on large changes in the level of serum creatinine; however, such definitions excluded milder stages of AKI. The classification of AKI was established by a consensus of critical care and nephrology societies worldwide.[11] This first globally developed classification incorporates the important findings that small increases in the level of serum creatinine negatively impact the outcome in AKI. AKI was diagnosed by an increase in the level of serum creatinine of ≥50% or ≥0.3 mg/dl, both from stable preoperative baseline values and within 48 h. The severity of AKI was classified into 3 stages, including stage 1 (level of serum

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Table 1. Preoperative and Operative Characteristics of 740 Patients

	Non-MetS group (n=420)	MetS group (n=320)	P value
Age (years)	64.9±8.49	64.3±8.05	0.71
EuroSCORE	3.61±2.58	3.81±2.51	0.35
Ejection fraction (preoperative, %)	56.3±13.7	55.6±13.8	0.46
Female sex	104 (24.8%)	116 (36.2%)	0.001
Diabetes mellitus	121 (28.8%)	182 (56.9%)	0.00
Obesity (BMI >25 kg/m^2)	90 (21.4%)	171 (53.4%)	0.00
Unstable angina	119 (28.3%)	109 (34.1%)	0.10
AMI (<30 days)	77 (18.3%)	57 (17.8%)	0.84
Emergency surgery	10 (2.4%)	4 (1.2%)	0.29
Hypertension	192 (45.7%)	254 (79.4%)	0.00
Smoking	135 (32.1%)	104 (32.5%)	0.59
Respiratory disease	14 (3.3%)	14 (4.4%)	0.57
CKD	21 (5.0%)	21 (6.6%)	0.33
Cerebral vascular disease	26 (6.2%)	38 (11.9%)	0.00
Peripheral artery obstructive disease	16 (3.8%)	14 (4.4%)	0.71
Bilateral internal thoracic artery use	92 (21.9%)	69 (21.6%)	0.92
Left main artery disease	116 (27.6%)	73 (22.8%)	0.14
Three vessel disease	309 (73.6%)	260 (81.2%)	0.03
Number of grafts	3.2±0.8	3.2±0.7	0.88
Complete revascularization	93.5%	90.5%	0.17

Values are presented as mean ± SD or number (%).
MetS, metabolic syndrome; EuroSCORE, European system for cardiac operatic risk evaluation; BMI, body mass index; AMI, acute myocardial infarction; CKD, chronic kidney disease; SD, standard deviation.

creatinine increased by 50–100% or ≥0.3 mg/dl), stage 2 (level of serum creatinine increased by 101–200%), and stage 3 (level of serum creatinine increased by >200% or there was a need for renal replacement therapy). Alternatively, stage 3 was defined by an increase in the level of serum creatinine ≥0.5 mg/dl when the baseline serum creatinine level was ≥4.0 mg/dl. The estimated glomerular filtration rate (eGFR) was calculated from a diet modification in a renal disease study.[12]

Patient Selection

We analyzed the data of 740 patients who underwent isolated OPCAB between January 2006 and December 2008. Preoperative and postoperative data were obtained using a retrospective review of the registry database, medical notes, and charts. The 320 patients (43.2%) who met the criteria for MetS were referred to as the MetS group, and the 420 patients (56.8%) who did not were referred to as the non-MetS group. The study was approved by the Institutional Review Board of the Medical College of Yonsei University.

Operative Techniques

All patients underwent a general endotracheal anesthesia with continuous Swan–Ganz catheter monitoring, transesophageal echocardiography, and arterial pressure monitoring. An OPCAB surgery was performed through a full sternotomy incision with harvesting of the left internal thoracic artery in a semi-skeletonized fashion. The radial artery was harvested from the non-dominant forearm by using a harmonic scalpel (Ethicon Endosurgery Inc, Cincinnati, OH, USA). If necessary, the great saphenous vein, right internal thoracic artery, or right gastroepiploic artery was harvested. Heparin was injected at a dose of 1 mg/kg to achieve the target activated clotting time at least 350 s before ligation of the distal internal thoracic artery.

A single 0-silk suture, which was passed through a tape (5×7 cm), was inserted into the posterior pericardium two-thirds of the way from the inferior vena cava to the left inferior pulmonary vein. This retraction stitch allowed anterior displacement of the cardiac apex and better visualization of the target coronary arteries. Stabilization of the target coronary arteries was accomplished using an Octopus tissue stabilizer (Medtronic, Minneapolis, MN, USA) during construction of the anastomosis. Generally, the anastomosis of the left internal thoracic artery to the left anterior descending artery was first constructed using an intracoronary shunt. An intracoronary shunt or proximal subcoronary silastic snare was used, if necessary, in other coronary artery anastomoses.

Statistical Analysis

In comparison of preoperative characteristics, continuous variables were expressed as mean ± standard deviation, and categorical data were tabulated as frequencies and percentages. For continuous variables, data were compared by using the chi-squared test or Student's t-test. The effect of MetS on early clinical outcomes after OPCAB was determined using logistic regression, and results are expressed as odds ratio (OR) with a 95% confidence interval (CI). Among risk factors, those with a P-value ≤0.10 were selected for the multivariate analyses. The multivariate model was constructed by using the enter method. A P-value <0.05 was considered statistically significant. All data were analyzed using SPSS software package for Windows (Statistical Product and Services Solutions, version 15.0, SPSS Inc, Chicago, IL, USA).

Results

The baseline characteristics of the 2 groups are shown in Table 1. Preoperatively, when compared with patients without MetS, those with MetS were more likely to be women and had a higher prevalence of DM, hypertension, obesity,

3-vessel coronary artery disease, and a history of cerebrovascular accident. The mean number of grafts was 3.2±0.84 grafts in the non-MetS group and 3.2±0.79 grafts in the MetS group (P=0.88). Complete revascularization was performed in 93.5% of the patients in the non-MetS group and in 90.5% of the patients in the MetS group (P=0.17). Preoperative levels of eGFR were significantly higher in the MetS group (P=0.01), but there was no difference between the 2 groups in terms of preoperative levels of serum creatinine (P=0.20; Table 2).

For postoperative outcomes such as atrial fibrillation, cerebral vascular disease, length of stay in the intensive care unit, and length of hospital stay, there were no differences between the 2 groups (Table 3). Postoperative AKI occurred in 84 patients (26.2%) in the MetS group and in 44 patients (11.0%) in the non-MetS group (P<0.05). When results were compared according to the stage of AKI, the 44 patients in the non-MetS group included 40 patients (10.0%) in stage 1, 2 patients (0.5%) in stage 2, and 2 patients (0.5%) in stage 3. However, the 84 patients in the MetS group included 64 patients (20.0%) in stage 1, 10 patients (3.1%) in stage 2, and 10 patients (3.1%) in stage 3 (Figure 1). In multivariate logistic regression analysis, MetS was found to be an independent risk factor for AKI after OPCAB (OR, 3.14; 95%CI, 1.79–5.49; P=0.001). Other independent risk factors for AKI after OPCAB were DM (OR, 1.83; 95%CI, 1.12–3.00; P=0.02), chronic kidney disease (OR, 4.79; 95%CI, 2.85–8.07; P<0.01), and emergency surgery (OR, 5.08; 95%CI, 1.01–25.6; P=0.05) (Table 4). When compared with patients without MetS and DM, the OR for AKI after OPCAB was 2.28 (95%CI, 1.14–4.55; P=0.02) in diabetic patients without MetS and 4.78 (95%CI, 2.52–9.03; P<0.001) in diabetic patients with MetS (Figure 2). Regarding a 30-day mortality, 2 patients (0.5%) died in the non-MetS group (1 patient each because of heart failure and aspiration pneumonia), and 2 patients (0.6%; P=0.75) died in the MetS group (both because of heart failure).

Table 2. Preoperative Renal Function in 740 Patients

	Non-MetS group (n=420)	MetS group (n=320)	P value
Creatinine level (mg/dl)	1.18	1.31	0.20
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	74.2	70.1	0.01
CKD (eGFR<60 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	21 (5.0%)	21 (6.6%)	0.33

eGFR, estimated glomerular filtration rate. Other abbreviations see in Table 1.

Table 3. Postoperative Outcomes

	Non-MetS group (n=420)	MetS group (n=320)	P value
30-day mortality	2 (0.5%)	2 (0.6%)	0.75
Atrial fibrillation	39 (9.3%)	27 (8.4%)	0.79
Acute kidney injury	44 (10.5%)	84 (26.2%)	<0.01
Cerebrovascular accident	1 (0.2%)	1 (0.3%)	1.00
Wound complication	5 (1.2%)	12 (3.8%)	0.02
ICU stay (days)	2.6±3.7	2.8±4.7	0.64
Hospital stay (days)	11.6±8.5	12.2±14.3	0.52

Values are presented as mean±SD or number (%).
ICU, intensive care unit. Other abbreviations see in Table 1.

Discussion

Many patients with coronary disease have one or more risk factors such as hypertension, DM, dyslipidemia, and obesity. Some studies report that MetS is related to morbidity and mortality after CABG, perhaps because of the considerable inflammatory reaction elicited by a cardiopulmonary bypass.[13,14]

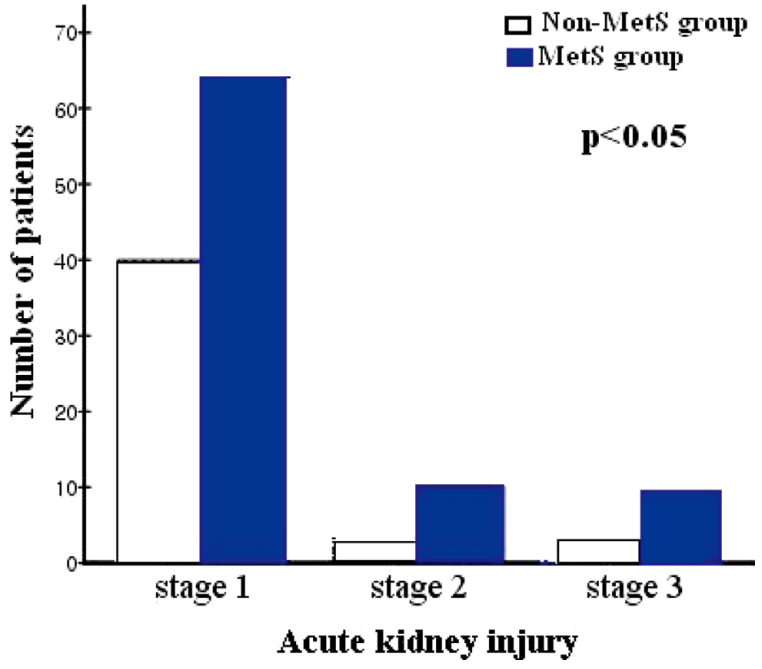

Figure 1. Comparison of the number of patients according to the stage of acute kidney injury between the MetS group and the non-MetS group. The P-value is the result of chi-square testing that analyzed the difference according to stage. MetS, metabolic syndrome.

Table 4. Potential Independent Risk Factors Associated With Acute Kidney Injury After OPCAB by Multivariate Logistic Regression

	OR	95%CI	P value
EuroSCORE	1.04	0.92–1.18	0.50
Female sex	0.69	0.38–1.26	0.23
Both ITA use	1.11	0.64–1.95	0.69
Age (years)	1.02	0.98–1.05	0.21
Preoperative eGFR	0.96	0.94–0.98	0.001
Preoperative creatinine level	1.01	0.84–1.13	0.76
Preoperative ejection fraction (%)	1.06	0.97–1.02	0.76
Diabetes mellitus	1.83	1.12–3.00	0.02
Obesity (BMI >25 kg/m^2)	0.73	0.43–1.25	0.26
Hypertension	1.65	0.98–2.84	0.06
AMI (<30 days)	1.14	0.61–2.12	0.68
CKD (eGFR<60 ml·min^{-1}·1.73 m^{-2})	4.79	2.85–8.07	<0.001
Respiratory disease	2.47	0.94–6.47	0.07
Cerebrovascular accident	1.31	0.66–2.61	0.42
Peripheral artery obstructive disease	1.31	0.47–3.65	0.60
Metabolic syndrome	3.14	1.79–5.49	0.001
Emergency surgery	5.08	1.01–25.6	0.05
Left main artery disease	0.58	0.32–1.04	0.17
Three vessel disease	0.62	0.33–1.16	0.14
Postoperative ejection fraction <35%	0.97	0.36–2.55	0.95
Severe sepsis/ shock	0.72	0.04–11.2	0.81
Nephrotoxic medication	1.29	0.41–4.09	0.65

OPCAB, off-pump coronary artery bypass; OR, odds ratio; CI, confidence interval; ITA, internal thoracic artery. Other abbreviations see in Tables 1,2.

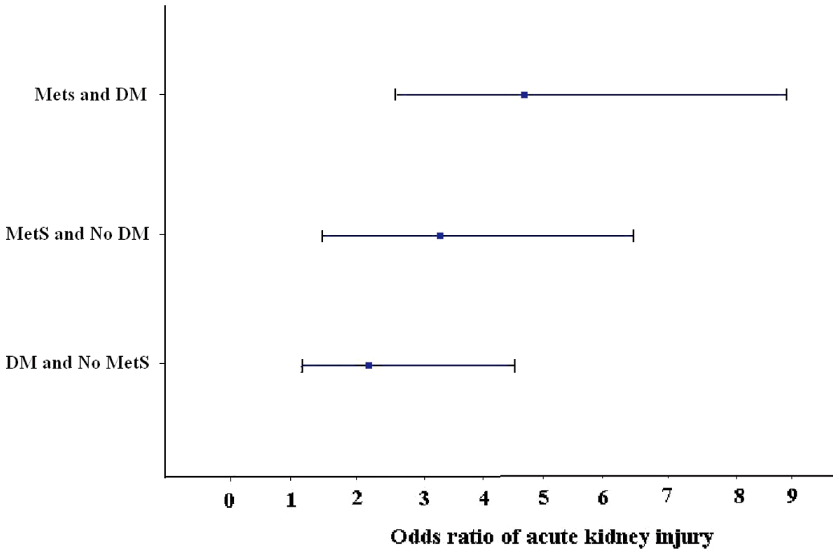

Figure 2. Comparison of the odds ratio according to MetS and DM. The group without MetS and without DM was used as the referent (odds ratio of 1). The error bars show the 95% confidence interval. DM, diabetes mellitus; MetS, metabolic syndrome.

Our initial hypothesis was that because hypertension, DM, dyslipidemia, and obesity could also be related to renal impairment, therefore, MetS as a cluster of these factors could be associated with increased creatinine or renal dysfunction after OPCAB. It was reported that the off-pump procedure eliminated the need for a cardiopulmonary bypass and was associated with a higher likelihood of AKI.[15] There were some reports comparing OPCAB and conventional CABG in AKI that developed in the early postoperative course. OPCAB patients presented a lower maximum serum creatinine level postoperatively and mild stage AKI, but a majority of AKI patients operated by using conventional CABG had severe forms. And there was also a trend towards a lesser requirement for renal replacement therapy after OPCAB.[16]

AKI is a complex disorder for which currently there is no accepted definition and is present in a variety of settings with clinical manifestations. In our study, AKI was defined according to the AKI network represented by the Acute Dialysis Quality Initiative group and 3 nephrology societies. They proposed the term "AKI" to reflect the entire spectrum

of acute renal failure, recognizing that an acute decline in kidney function is often secondary to an injury that causes functional or structural changes in the kidney. Serum creatinine level and changes in urine output are the most commonly applied measures of renal function. There are some reports that small increments in serum creatinine are associated with adverse outcomes. Current clinical practice does not focus much attention on small increases of serum creatinine. This diagnostic criteria for AKI is designed to facilitate the acquisition of a new concept in that small alterations in kidney function might contribute to adverse outcomes.

In our study, there were more women in the MetS group, and this result is in close agreement with previous studies. MetS is common in Korean adults, particularly in the elderly. The prevalence of MetS was 21.6% in 1998 and 21.4% in 2001 in Korean adults, and women had a higher prevalence than men, especially after the 6th decade.[17] In the National Health and Nutrition Examination Survey, the age-adjusted prevalence of MetS in a white population was 24.0% in men and 23.4% in women. However, after the age of 60 years, the prevalence of MetS was higher in women, and this reversal of MetS prevalence by sex after 60 years of age has also been reported in Korean adults.[18,19] The explanation for these results is not known, although this difference might reflect the effect of middle age or menopause on central obesity.

In postoperative outcomes, the occurrence of postoperative AKI and wound complications were different between the 2 groups. On multivariate analysis, MetS was not an independent risk factor for wound complications but was an independent risk factor for postoperative AKI. Hyperglycemia and obesity are related to pathologic changes in the kidneys. Hyperglycemia contributed to interstitial expansion and thickening of the tubular basement membrane without proteinuria,[20] and a review of the results of native renal biopsies over a 15-year period revealed that the incidence of obesity-related glomerulopathy, as indicated by glomerulomegaly and mild foot-process fusion, had increased 10-fold.[21] Obesity is also an important risk factor for kidney disease. A case-control study showed that obesity (BMI $\geq 30\,kg/m^2$) was associated with a significant 3-fold increased risk for chronic renal failure.[22] In addition, patients with MetS had a higher prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis, suggesting microvascular kidney disease on histological study.[23] These results shows that even in the absence of primary kidney disease, hyperglycemia or obesity might be related to glomerular function, and patients with these factors might be more vulnerable to AKI than patients without these factors. In our study, obesity was not an independent risk factor. This might be due to lower criteria of obesity (BMI $\geq 25\,kg/m^2$). However, preoperative eGFR was higher in the non-MetS group, although there was no difference in the preoperative prevalence of chronic kidney disease (defined as eGFR $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$). In addition, when comparing the severity of AKI according to what stage it is at, the MetS group had a higher number of patients in stage 2 or stage 3. These findings might be due to renal pathologic differences between the 2 groups. Drugs, such as antibiotics and NSAIDs, might affect renal function in the postoperative period. But in the present study, such drugs did not affect AKI. We used antibiotics, usually 2nd generation cephalosporin, until the 3rd postoperative day if there was no evidence of infection, and we used antibiotics in a dose reduction manner if preoperative eGFR was low. For the relief of postoperative pain, we used control analgesics mixed with fentanyl and ondansetron, which were less effective on renal function.

Why does off-pump surgery induce AKI? The inflammatory response during OPCAB might cause mild renal dysfunction.[24] Transient circulatory failure and global hypoperfusion occurring in exposure of the lateral vessels and atheroembolism as a result of aortic side clamping could be other possible explanations.[25,26] As a result of these circumstances that can take place during OPCAB, renal injury can occur, and this might be more harmful in patients with MetS than in patients without MetS.

The OR for postoperative AKI was higher in patients with both MetS and DM, compared with patients with MetS but without DM and patients without MetS but with DM. These results might indicate that the effect of MetS in AKI was not a single effect of DM, and the clustering of multiple factors, such as hypertension, hyperglycemia, and obesity, act as a combination risk factor for AKI after OPCAB.

MetS can be related to operative mortality, and MetS and acute coronary syndrome might jointly exacerbate poor long-term outcomes.[10,27] However, in our study, MetS was not associated with mortality. The reason is not clear, but it might be that OPCAB has better outcomes regarding morbidity and mortality in high-risk patients,[28] and our institution has a high level of experience with OPCAB.

Limitations of our study include its retrospective nature and that we did not consider some factors that could affect postoperative AKI, such as vasopressors. After CABG, vasopressors might be used to maintain graft flow, and these vasopressors might affect renal blood flow. However, it is difficult to determine this without specific study of this issue.

Conclusion

We found that MetS is associated with postoperative AKI after OPCAB. MetS is a potentially preventable and modifiable condition that often goes undiagnosed. The recognition of MetS could be useful to identify high-risk patients who would not otherwise be detected by the use of traditional risk factors. Hence, the addition of MetS into an operative risk algorithm might improve risk stratification, and aggressive treatment of its components, which, in large, are preventable conditions, and therefore could reduce operative morbidity.

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