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Prognostic Usefulness of Metabolic Syndrome Compared with Diabetes in Korean Patients with Critical Lower Limb Ischemia Treated with Percutaneous Transluminal Angioplasty

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Purpose: Metabolic syndrome (MS) is a clinical condition that shares many common characteristics with diabetes. However, unlike diabetes, the usefulness of MS as a prognostic entity in peripheral arterial disease is uncertain. This study evaluated the prognostic usefulness of MS in critical lower limb ischemia (CLI) patients. **Materials and Methods:** We compared the 2-year clinical outcomes in 101 consecutive CLI patients (66±14 years; 78% men) with 118 affected limbs treated with percutaneous transluminal angioplasty (PTA) according to the presence of MS and diabetes. **Results:** The number of MS patients was 53 (52%), of which 45 (85%) had diabetes. During a 2-year follow-up, the incidence of clinical outcomes, including reintervention, major amputation, minor amputation, and survival, was not significantly different between MS and non-MS patients; however, the incidence of minor amputation was significantly higher in diabetic than in non-diabetic patients (42% vs. 17%; p=0.011). Cox regression analysis for the 2-year primary patency demonstrated no association between MS and 2-year primary patency [hazard ratio (HR), 1.02; 95% confidence interval (CI), 0.45-2.30; p=0.961], whereas there was a significant association between diabetes and 2-year primary patency (HR, 2.81; 95% CI, 1.02-7.72; p=0.046). Kaplan-Meier analysis revealed no significant difference in the 2-year primary patency between MS and non-MS patients; however, the 2-year primary patency was lower in diabetic than in non-diabetic patients (p=0.038). **Conclusion:** As a prognostic concept, MS might conceal the adverse impact of diabetes on the prognosis of CLI patients treated with PTA.

Key Words: Metabolic syndrome, diabetes, critical limb ischemia, angioplasty

INTRODUCTION

Metabolic syndrome (MS) is a cluster of several cardiovascular risk factors, with insulin resistance as a major characteristic.[1,2] Although MS may be a useful clinical entity for the prevention of type 2 diabetes and cardiovascular disease (CVD) in

the general population,[3,4] the prognostic usefulness of MS in established CVD, particularly peripheral arterial disease, is uncertain. A recent study has strongly recommended the exclusion of condition of established diabetes or CVD from the definition of MS;[5] however, data justifying this recommendation are scarce.

Peripheral arterial disease with critical lower limb ischemia (CLI) is a major atherosclerotic complication that is associated with high morbidity and mortality.[6] Percutaneous transluminal angioplasty (PTA) is a useful therapeutic procedure to save limbs from amputation.[7] Previous studies have reported that diabetes is associated significantly with the development and prognosis of CLI.[8,9] However, data on the prognostic usefulness of MS, which shares many common characteristics with diabetes,[10-12] in patients with CLI are scarce. The purpose of this study is to investigate the prognostic usefulness of MS compared with diabetes in patients with CLI who underwent PTA. We compared the 2-year clinical outcomes of CLI patients treated with PTA according to the presence of MS and diabetes, and evaluated the clinical risk factors for the 2-year primary patency in CLI patients after a successful PTA.

MATERIALS AND METHODS

Subjects and study design

We retrospectively analyzed the clinical data on 118 affected limbs from 101 consecutive patients with CLI (defined by Rutherford-Becker grades 4, 5, or 6),[13] who had undergone PTA between April 2002 and May 2008. All blood samples were obtained after 8 h of fasting and were analyzed for glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol. Body mass index (BMI) was calculated as weight (kg)/height (m^2). All patients were divided into 2 groups according to the presence of MS or diabetes. MS was defined as the presence of 3 or more following: 1) BMI ≥25 kg/m^2; 2) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; 3) fasting triglycerides ≥150 mg/dL; 4) blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic, or on treatment; 5) impaired fasting glucose, defined as fasting glucose ≥100 mg/dL, a referral diagnosis of diabetes, or diabetes treatment according to the National Cholesterol Education Program-Adult Treatment Panel III definition.[1] Diabetes was defined as either symptoms of diabetes, including polyuria, polydipsia, and unexplained weight loss with a casual plasma glucose ≥200 mg/dL, fasting glucose ≥126 mg/dL, a referral diagnosis of diabetes, or antidiabetic treatment. Kidney function was assessed by the estimated glomerular filtration rate (eGFR) calculated with the formula validated in the Modification of Diet in Renal Disease study, and end-stage renal disease was defined as an eGFR of ≤15 mL/min/1.73 m^2 or the need for dialysis.[14] The study protocol was approved by the local ethics committee of our institution, and informed consent for the procedure was obtained from each patient. Follow-up included clinical examination during the hospital stay and at 1 month after PTA to document hemodynamic improvement. Subsequent follow-up was performed when patients' clinical status worsened, measured by using peripheral angiography, computed tomography angiogram, or the ankle-brachial index. The causes and date of death were examined by chart review, telephone contact or checking with the national statistics office.

Procedure of PTA

All patients were medicated with 100 mg of aspirin daily before PTA, and then indefinitely in the absence of contraindication. Blood samples, including those for complete blood count, blood urea nitrogen, and creatinine, were routinely evaluated 1 day or immediately before and after the index procedure. Vascular access for PTA was performed by ipsilateral or contralateral puncture of the common femoral artery under local anesthesia. After placement of the 6-7 Fr sheath, a bolus of 5000 IU heparin was injected through the femoral sheath. Additional heparin was administered to maintain an activated clotting time between 250 and 300 s, if needed. Infrapopliteal lesions were passed with a 0.36-0.89 mm hydrophilic guidewire. Lesions with failed transluminal recanalization or total occlusion were recanalized through the subintimal dissection plane with re-entrance into the true lumen. PTA was performed with balloons of adequate size (2.25-4.0 mm) at 6-10 atm. In case of a flow-limiting dissection or elastic recoil after balloon dilatation, stents were implanted for bailout purposes. Concomitant procedures were performed if other proximal lesions were present in arteries such as the ipsilateral iliac, femoral, or popliteal arteries.

Definition of technical and clinical outcomes

Technical success was defined as PTA resulting in <30% residual stenosis with good antegrade flow, and a suboptimal result was defined as PTA resulting in 30-50% residual stenosis or sluggish flow. Primary clinical success was defined

as improvement in at least 1 clinical category in the Rutherford-Becker classification. Major amputation was defined as the loss of limbs below or above the knee, and minor amputation was defined as a transmetatarsal, or a more distal, amputation of the lower extremity. Primary patency was defined as persistent patency without any reintervention or amputation performed on or at the margins of the treated lesions after a technically successful PTA.

Statistical analysis

Values are expressed as mean±SD for continuous variables and as numbers and percentages, n (%), for categorical variables. Continuous variables were compared using Student's t-test, and categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate Cox regression analysis was performed to identify the individual risk factors for the 2-year primary patency. Kaplan-Meier survival analysis was performed for primary patency according to the presence of MS and diabetes, and comparisons between groups were performed using the log-rank test. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Values of $p<0.05$ were considered statistically significant.

RESULTS

Baseline characteristics of patients

The baseline characteristics of the 101 CLI patients (66±14 years; 78% men) in this study are presented in Table 1. This study included 53 patients with MS (52%) and 48 patients without MS (48%). The incidences of male gender, hypertension, and diabetes were significantly higher in patients with MS than in those without MS. Patients with MS had significantly higher BMI and triglyceride levels, and had significantly lower eGFR and HDL levels than patients without MS.

Clinical characteristics of affected limbs

The clinical characteristics of the 118 affected limbs in this study are shown in Table 2. The incidence of diabetic limbs was significantly higher in the MS group than in the non-MS group (86% vs. 54%; $p<0.001$). There were no significant differences between the 2 groups with respect to the lesion

Table 1. Baseline Characteristics of the Study Subjects

	All (n=101)	Non-MS (n=48)	MS (n=53)	*p* value
Age (yrs)	66±14	64±18	67±9	0.212
Male sex, n (%)	79 (78)	43 (90)	36 (68)	0.015
Body mass index (kg/m^2)	23.2±3.5	22.3±2.4	24.2±4.1	0.009
Smoking, n (%)	41 (41)	23 (48)	18 (34)	0.163
Comorbid disease, n (%)				
Hypertension	69 (69)	21 (44)	48 (91)	<0.001
Diabetes mellitus	70 (70)	25 (52)	45 (85)	<0.001
Cerebrovascular accident	11 (11)	4 (8)	7 (13)	0.531
Coronary artery disease	54 (54)	23 (48)	31 (59)	0.322
ESRD	22 (22)	9 (19)	13 (25)	0.630
Laboratory data				
Hemoglobin (g/dL)	11.4±1.9	11.5±1.9	11.3±1.9	0.553
Sodium (mmol/L)	138±4	138±4	139±4	0.334
Potassium (mmol/L)	4.4±0.6	4.4±0.5	4.4±0.6	0.999
Fasting glucose (mg/dL)	151±98	134±81	167±111	0.093
Total cholesterol (mg/dL)	170±62	165±46	174±73	0.512
Triglyceride (mg/dL)	141±93	113±85	167±94	0.003
HDL (mg/dL)	40±15	47±14	34±13	<0.001
LDL (mg/dL)	101±47	96±36	106±55	0.357
C-reactive protein (mg/dL)	4.6±8.9	4.6±7.1	4.6±10.2	0.998
Creatinine (mg/dL)	2.6±2.9	2.4±2.8	2.8±3.0	0.556
eGFR (mL/min/1.73 m^2)	54±33	61±35	47±30	0.029

ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MS, metabolic syndrome.
Data are expressed as n (%) or mean±SD.

location, incidence of total occlusion, and revascularization methods.

Clinical outcomes with respect to the presence of MS and diabetes

The initial and 2-year clinical outcomes are shown in Table 3. The incidences of initial clinical outcomes, including technical success, primary clinical success, and complications after PTA, were not significantly different with respect to the presence of MS or diabetes. During the 2-year follow-up period, the incidences of clinical outcomes, including re-intervention, major amputation, minor amputation, and sur-

Table 2. Clinical Characteristics of the Studied Limbs

	All (n=118)	Non-MS (n=59)	MS (n=59)	*p* value
Claudication, n (%)	28 (24)	13 (22)	15 (25)	0.829
Resting pain, n (%)	72 (61)	37 (63)	35 (59)	0.850
Gangrenous change, n(%)	58 (49)	26 (44)	32 (54)	0.357
Clinical category, n (%)				
Rutherford-Becker 4	52 (44)	28 (48)	24 (41)	0.578
Rutherford-Becker 5 or 6	66 (56)	31 (53)	35 (59)	0.578
Diabetic limb, n (%)	83 (70)	32 (54)	51 (86)	<0.001
Left limb, n (%)	63 (53)	33 (56)	30 (51)	0.712
Location, n (%)				
Anterior tibial artery	86 (73)	45 (76)	41 (70)	0.535
Posterior tibial artery	42 (36)	20 (34)	22 (37)	0.848
Peroneal artery	30 (25)	15 (25)	15 (25)	0.999
Dorsalis pedis artery	3 (3)	1 (2)	2 (3)	0.999
Total occlusion, n (%)	60 (51)	34 (58)	26 (44)	0.197
Combined procedure, n (%)				
Iliac artery	7 (6)	5 (9)	2 (3)	0.439
Femoral artery	42 (36)	24 (41)	18 (31)	0.336
Popliteal artery	16 (14)	8 (14)	8 (14)	0.999
Antegrade approach, n (%)	58 (49)	27 (46)	31 (53)	0.581
Subintimal approach, n (%)	11 (9)	7 (13)	4 (7)	0.528
Stent implantation, n (%)	10 (9)	8 (14)	2 (4)	0.094

MS, metabolic syndrome.
Data are expressed as n (%) or mean±SD.

Table 3. Initial and 2-Year Clinical Outcomes According to the Presence of MS and Diabetes

	All (n=118)	Non-MS (n=59)	MS (n=59)	*p* value	Non-diabetes (n=35)	Diabetes (n=83)	*p* value
Initial clinical outcomes, n (%)							
Technical success	82 (70)	39 (66)	43 (73)	0.549	27 (77)	55 (66)	0.280
Suboptimal results	26 (22)	16 (27)	10 (17)	0.267	6 (17)	20 (24)	0.474
Primary clinical success	98 (83)	50 (85)	48 (81)	0.807	31 (89)	67 (81)	0.422
Complication							
Dissection	25 (21)	9 (15)	16 (27)	0.176	5 (14)	20 (24)	0.325
Rupture	6 (5)	1 (2)	5 (9)	0.207	0 (0)	6 (7)	0.177
Embolism	1 (1)	1 (2)	0 (0)	0.999	1 (3)	0 (0)	0.297
Two-yr clinical outcomes, n (%)							
Reintervention	7 (6)	5 (9)	2 (3)	0.439	2 (6)	5 (6)	0.999
Major amputation	6 (5)	2 (3)	4 (7)	0.679	2 (6)	4 (5)	0.999
Minor amputation	41 (35)	20 (34)	21 (36)	0.999	6 (17)	35 (42)	0.011
Survival*	72 (61)	33 (72)	39 (77)	0.647	24 (83)	48 (71)	0.311

MS, metabolic syndrome.
Data are expressed as n (%) or mean±SD.
*A total of 101 patients (48 non-MS patients vs. 53 MS patients, 31 non-diabetic patients vs. 70 diabetic patients).

vival were not different between patients with MS and those without MS. However, the incidence of minor amputation was significantly higher in patients with diabetes than in those without diabetes (42% vs. 17%, p=0.011).

Risk factors related to 2-year primary patency

Univariate Cox regression analysis for identifying individual risk factors related to 2-year primary patency showed a significant association between primary patency and the Rutherford-Becker grades [hazard ratio (HR), 3.43; 95% confidence interval (CI), 1.64-7.19; p=0.001], C-reactive protein level (HR, 1.06; 95% CI, 1.01-1.12; p=0.032), or diabetes (HR, 2.81; 95% CI, 1.02-7.72; p=0.046), but no significant association between primary patency and MS (HR, 1.41; 95% CI, 0.60-3.30; p=0.478) (Table 4).

Kaplan-Meier analysis for 2-year primary patency according to the presence of MS and diabetes

Kaplan-Meier analysis for 2-year primary patency revealed that there was no significant difference in primary patency between patients with MS and those without MS (p=0.961), but that patients with diabetes had a lower primary patency than those without diabetes (p=0.038) (Fig. 1).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the usefulness of MS as a prognostic concept compared with diabetes in Korean patients with CLI treated with PTA. The results showed that MS had no association with clinical outcomes, but that diabetes was significantly associated with minor amputation and with the 2-year primary patency in patients with CLI treated with PTA. These results imply that MS may not be an appropriate prognostic concept in CLI patients and that the inclusion of diabetes in the domain of MS as a component of impaired fasting glucose may not be reasonable.

MS is a common condition affecting approximately 31% of adults in Korea.[15] Previous studies reported that MS is a

Table 4. Univariate Cox Proportional Hazard Regression for Identifying the Individual Risk Factors of 2-Year Primary Patency

	Two-yr primary patency	
	HR (95% CI)	p value
Age ≥65 (yrs)	0.74 (0.33-1.65)	0.458
Male sex	1.95 (0.58-6.56)	0.279
Smoking	0.63 (0.28-1.43)	0.268
LDL	1.00 (0.99-1.01)	0.325
Rutherford-Becker grades	3.43 (1.64-7.19)	0.001
C-reactive protein	1.06 (1.01-1.12)	0.032
Diabetes	2.81 (1.02-7.72)	0.046
MS	1.02 (0.45-2.30)	0.961
ESRD	2.15 (0.91-5.05)	0.080

CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; LDL, low-density lipoprotein; MS, metabolic syndrome.

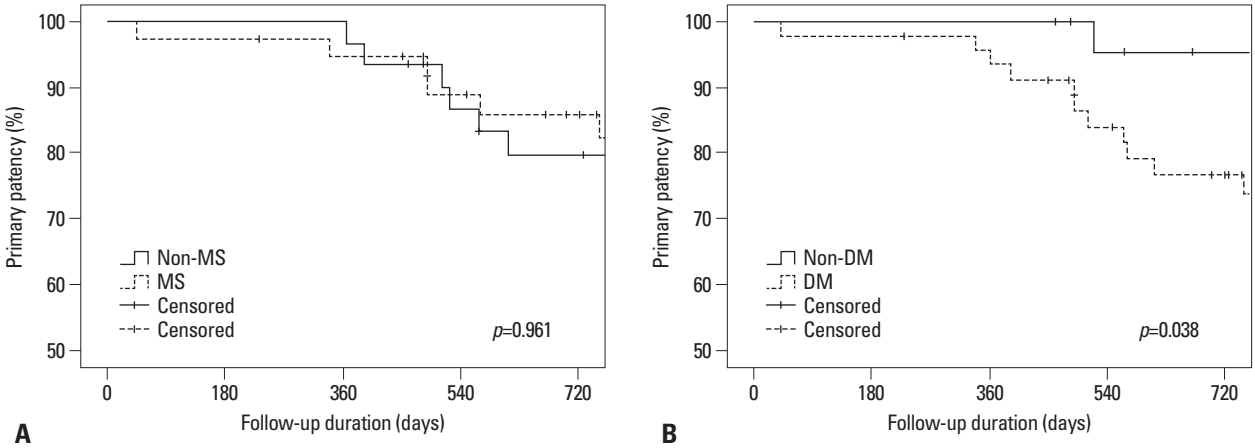

Fig. 1. Kaplan-Meier analysis for the 2-year primary patency. Outcomes were analyzed according to the presence of (A) metabolic syndrome (MS) and (B) diabetes mellitus (DM).

useful educational concept for the development of CVD.[3,4] However, the prognostic usefulness of MS in patients with established CVD, particularly peripheral arterial disease, was unknown. Recently, the World Health Organization (WHO) strongly recommended that an established diagnosis of diabetes or CVD should be excluded from the definition of MS because MS is a pre-morbid condition rather than a clinical diagnosis.[5] It may be a substantive issue whether to include diabetes as a criterion of MS with respect to impaired fasting glucose and to apply MS as a prognostic indicator in subjects with established CVD. MS has been proposed as a means for identifying the risk of diabetes;[16,17] however, most definitions of MS have simultaneously included diabetes in the diagnostic criterion, as a component of impaired fasting glucose. In addition, the impact of MS on atherosclerosis may be explicitly different from that of the diabetic status. Won, et al.[18] recently reported that MS and its individual components had a significant impact on subclinical atherosclerosis in conditions without diabetes, and a concurrent diagnosis of MS in subjects with established diabetes might be of little value for the risk stratification of CVD. Previous studies also suggested that the progression of atherosclerosis may be independently associated with long-term hyperglycemia in patients with established diabetes.[19,20] The present study evaluated the usefulness of MS compared with diabetes as a prognostic concept in patients with CLI treated with PTA, which is an effective therapeutic method for salvaging limbs from both major and minor amputation.[21,22] The results showed that MS was not associated with adverse clinical outcomes, but that diabetes had an incremental impact on minor amputations and primary patency in CLI patients treated with PTA during the 2-year follow-up. The clinical significance of MS for preventing CVD in the general population has been definitely identified; however, the prognostic usefulness of MS in patients with established CVD remains uncertain. The present study revealed that diabetes is significantly associated with poor prognosis in CLI patients treated with PTA but that the prognostic significance of MS can be influenced by the inclusion of degree of diabetic conditions. Concerning the application of MS in established diabetes, the diabetic condition is divided into different groups depending on the presence of MS because MS is a cluster of conditions defined by the individual criteria of its components. The present study suggests that MS may not be a useful concept compared with diabetes for predicting adverse clinical outcomes in patients with CLI. The application of MS as a prognostic concept could conceal the adverse impact of diabetes in CLI patients treated with PTA. Furthermore, the exclusion of the diabetic condition from the definition of MS might be considered, as in the previous WHO recommendation. This study may provide proper evidence to argue against the inclusion of patients with established diabetes in the domain of MS and the application of MS in subjects with established CVD.

The present study has some limitations. First, we used BMI instead of waist circumference to define MS. Therefore, there may be some degree of MS misclassification. However, an earlier study noted that BMI was significantly associated with abdominal fat and waist circumference.[23] Second, the criterion of MS may be dependent on race and ethnicity.[24] However, the present study was performed only in Korean patients with CLI. Third, we did not perform angiography or any other imaging modality in asymptomatic patients after PTA during the follow-up period. Finally, the application of the present results to most patients with CVD has limited validity because of the small sample size of this study. Further prospective studies with larger sample sizes are necessary to address these issues.

In conclusion, MS may not be a useful concept for predicting prognosis in patients with CLI treated with PTA. As a prognostic concept, MS may conceal the adverse impact of diabetes on the prognosis of CLI patients.

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