Impact of Metabolic Syndrome on Subclinical Atherosclerosis in Asymptomatic Individuals

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Background: Little is known about subclinical atherosclerosis on coronary computed tomographic angiography (CCTA) in asymptomatic individuals with metabolic syndrome (MetS).

Methods and Results: We analyzed 5,213 asymptomatic individuals who underwent CCTA. A cardiac event was defined as a composite of all-cause death, myocardial infarction, unstable angina, or coronary revascularization. Of the study participants, 2,042 (39.2%) had MetS. MetS was an independent predictor of significant coronary artery disease (CAD) in at least 1 coronary artery (odds ratio [OR]=1.992, 95% confidence interval [CI]=1.623–2.445, $P<0.001$) and significant CAD in the left main (LM) or proximal left anterior descending (LAD) artery (OR=2.151, 95% CI=1.523–3.037, $P<0.001$). During the follow-up period (median 28.1 [interquartile range, 19.2–36.5] months), 111 individuals had 114 cardiac events. Individuals with MetS were significantly associated with more cardiac events than those without (RR [rate ratio]=1.67, 95% CI=1.15–2.43, $P=0.007$). In the MetS group, individuals with significant CAD had the majority of cardiac events (RR=64.33, 95% CI=29.17–141.88, $P<0.001$). Furthermore, in the MetS with significant CAD group, those with significant CAD in the LM or proximal LAD had more cardiac events (RR=2.63, 95% CI=1.51–4.59, $P=0.001$).

Conclusions: MetS was associated with subclinical atherosclerosis on CCTA with subsequent high risk for cardiac events. These findings suggest the importance of reducing unfavorable metabolic conditions in asymptomatic individuals. (*Circ J* 2015; **79**: 1799–1806)

Key Words: Atherosclerosis; Coronary artery disease; Metabolic syndrome

Over the past decades, the prevalence of metabolic syndrome (MetS), characterized by a cluster of conditions including abdominal obesity, glucose intolerance, hypertension, and dyslipidemia, has rapidly increased in most countries of the world.^{1,2} MetS is a strong risk factor for cardiovascular mortality and morbidity.^{3–5} Furthermore, even in asymptomatic individuals, MetS is associated with a more than 50% increase in the risk of sudden death, independent of coronary artery disease (CAD) risk factors.⁶ Therefore, MetS has become a major public health concern.⁷

Recently, with the advent of multidetector row computed tomography, coronary computed tomography angiography (CCTA) has proven effective in providing comprehensive information on CAD, including lesion location, severity, and characteristics of atherosclerotic plaque.⁸ In previous studies of asymptomatic individuals undergoing CCTA, the effect of MetS on the risk of subclinical atherosclerosis was studied. However, those studies focused on the prevalence of subclinical atherosclerosis and plaque characteristics, so the clinical implications of these findings were lacking.^{7,9} Therefore, through

Received October 31, 2014; revised manuscript received March 18, 2015; accepted March 26, 2015; released online May 8, 2015 Time for primary review: 26 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-1197

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a large cohort of asymptomatic individuals undergoing CCTA, we sought to investigate the effect of MetS on the risk of sub-clinical atherosclerosis and clinical outcome.

Methods

Study Population

From January 2007 to June 2011, 7,478 consecutive South Korean individuals aged 18 years and older, who had undergone self-referral CCTA evaluation as part of a general health examination in the Health Screening and Promotion Center at the Asan Medical Center, were enrolled. All subjects were made aware of the possible risks associated with CCTA and provided informed consent. Of these, 5,732 (76.7%) consented to participate this study. Subjects with (1) previous history of angina or myocardial infarction (MI), (2) abnormal rest ECG results (ie, pathological Q waves, ischemic ST segment or T wave changes, or left bundle-branch block), (3) structural heart disease, (4) prior history of open heart surgery, (5) past history of percutaneous coronary intervention (PCI), (6) previous cardiac procedure, and (7) renal insufficiency (creatinine >1.5 mg/dl) were excluded. Thus, 5,213 subjects were finally enrolled and analyzed (Figure 1). This study was approved by the local Institutional Review Board at the Asan Medical Center, Seoul, Korea. All patients provided written informed consent.

The basic demographic data of the subjects were acquired from a database maintained by the Health Screening and Promotion Center at the Asan Medical Center. Any medical history of angina, MI, stroke, structural heart disease, open heart

surgery, PCI, previous cardiac procedure, diabetes mellitus, hypertension, or hyperlipidemia; family history of CAD and smoking status were collected from a systemized questionnaire administered prior to the general health examination. In the general health examination, height, body weight, body mass index, waist circumference, and blood pressure were measured, and an ECG was performed. Moreover, fasting plasma glucose, glycated hemoglobin, uric acid, blood urea nitrogen, creatinine, total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein concentrations were measured on the day of the examination after a fasting period of ≥12 h. CAD risk was calculated using the Framingham risk model.¹⁰

Definition of MetS

MetS was defined according to the 2005 revision of the criteria from the National Cholesterol Education Program Adult Treatment Panel III.¹¹ Abdominal obesity was redefined on the basis of an Asian-specific cut-off point, as recommended in the National Cholesterol Education Program Adult Treatment Panel III criteria. Subjects were considered to have MetS if they had 3 or more of the following abnormalities: abdominal obesity (waist circumference ≥90 cm in men and ≥80 cm in women), hypertriglyceridemia ≥150 mg/dl, low high-density lipoprotein cholesterol (<40 mg/dl in men and <50 mg/dl in women), high blood pressure (≥130/85 mmHg) or use of anti-hypertensive medication, and high fasting glucose (≥100 mg/dl) or use of antidiabetic medication.

CCTA Image Acquisition and Analysis

CCTA was conducted using either a single-source 64-slice CT (LightSpeed VCT, GE, Milwaukee, WI, USA) or dual-source CT (Somatom Definition, Siemens, Erlangen, Germany). Patients with no contraindication to β -adrenergic blocking agents and with initial heart rates greater than 65 beats/min received an oral dose of 2.5 mg bisoprolol (Concor, Merck, Darmstadt, Germany) 1 h before the CT examination. CT scanning was performed in the prospective ECG-triggering mode or the retrospective ECG-gating mode with ECG-based tube current modulation. Two puffs (2.5 mg) of isosorbidedinitrate (Isoket spray, Schwarz Pharma, Monheim, Germany) were sprayed into the patient's mouth before contrast injection. During CCTA acquisition, 60–80 ml of iodinated contrast (Iomeron 400, Bracco, Milan, Italy) was injected at 4 ml/s, followed by a 40-ml saline flush. A region of interest was placed on the ascending aorta, and image acquisition was automatically initiated once a selected threshold (100 Hounsfield units [HU]) had been reached using bolus tracking. A standard scanning protocol was used, and the tube voltage and tube current-time product were adjusted according to the patient's body size as follows: 100 kVp or 120 kVp tube voltage; 240–400 mAs per rotation (dual-source CT); and 400–800 mA (64-slice CT) tube current.

All CCTA scans were analyzed using a dedicated workstation (Advantage Workstation, GE; or Volume Wizard, Siemens) by experienced cardiovascular radiologists (D.H.Y., T.-H.L. and J.-W.K.) blinded to the clinical information. Final decisions regarding the findings were reached by consensus. According to the guidelines of the Society of Cardiovascular Computed Tomography, a 16-segment coronary artery tree model was used.¹² A coronary artery calcium score (CACS) was measured as described,¹³ with categorization by scores of 0, 1–10, 11–100, 101–400, and >400.¹⁴ Plaques were defined as structures >1 mm² within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques containing calcified tissue involving more than 50% of the plaque area (density >130 HU) were classified as calcified, plaques with <50% calcium were classified as mixed, and plaques without calcium were classified as non-calcified lesions.¹⁵ The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the site of maximal stenosis and compared with the mean value of the proximal and distal reference sites.¹⁶ Stenosis $\geq 50\%$ was defined as significant. In addition, overall plaque burden was determined from coronary artery plaque scores, calculated from modified Duke prognostic scores, segment stenosis scores, and segment involvement scores, as described.¹⁷

Clinical Outcomes

Follow-up clinical data were obtained by a review of medical records at the end of August 2012. Cardiac events were defined as a composite of all-cause death, non-fatal MI, unstable angina requiring hospitalization, or coronary revascularization. Death was identified by identification numbers, which were assigned to the subjects on their birth certificates, in the National Statistical Office.¹⁸ The diagnosis of MI was based on the presence of new Q waves in at least 2 contiguous leads or an elevation of creatine kinase or its MB isoenzyme to at least 3-fold the upper limit of the normal range at follow-up. Revascularization was performed if there were stenosis of at least 50% of the diameter on invasive coronary angiography with a positive stress test or if there was a stenosis of at least 70% on invasive coronary angiography.¹⁹

Statistical Analysis

Categorical data were compared with chi-square statistics or Fisher's exact test and presented as frequencies. Continuous variables were analyzed using unpaired Student's *t* test and presented as mean $\pm$ standard deviation. Multivariate logistic regression analyses were performed to identify clinical predictors of significant CAD in at least 1 coronary artery and significant CAD in the left main (LM) or left anterior descending (LAD) artery on CCTA. A backward elimination process was used to develop the final multivariable model, and an adjusted odds ratio (OR) with 95% confidence intervals (CI) was calculated. For clinical outcomes, we calculated the incidence rate per 1,000 person-years as the number of cases divided by the 1,000 person-years. That is, the incidence rate = number of cases/the summation of time spent in the study across all participants $\times 1,000$. CIs of the incidence rates were also estimated according to the assumption that the number of cases followed a Poisson distribution. All reported *P*-values are 2-sided, and *P* < 0.05 was considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® Version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline Characteristics of the Patients

The baseline characteristics of the study population according to MetS are listed in [Table 1](#). The mean age of the study population was 53.9 ± 8.3 years and 3,810 (73.1%) participants were male. The average Framingham risk score was $7.9 \pm 5.4\%$. Of the study population, 2,042 (39.2%) individuals had MetS. Individuals with MetS had more comorbid conditions than those without MetS.

CCTA Findings

[Table 2](#) shows the CCTA findings of individuals with and without MetS. Individuals with MetS had a higher CACS than those without (*P* < 0.001). The incidence of any coronary atherosclerotic, calcified, non-calcified, or mixed plaque was significantly higher in individuals with MetS (*P* < 0.001 for all). Individuals with MetS also had higher plaque burden scores including the modified Duke prognostic score, segment stenosis score, and segment involvement score (*P* < 0.001 for all). Individuals with MetS had more significant CAD, multivessel disease, and significant CAD in the LM or proximal LAD on CCTA than those without (*P* < 0.001 for all).

After adjustment for clinical risk factors, multivariate logistic regression analysis revealed that MetS was an independent predictor for significant CAD in at least 1 coronary artery (OR = 1.992, 95% CI = 1.623–2.445, *P* < 0.001) and significant CAD in the LM or proximal LAD on CCTA (OR = 2.151, 95% CI = 1.523–3.037, *P* < 0.001) ([Table 3](#)).

Clinical Outcomes

During the follow-up period (median 28.1 [interquartile range, 19.2–36.5] months), a total of 114 cardiac events occurred in 111 individuals: 19 deaths, 2 non-fatal MIs, 2 unstable angina requiring hospitalization, and 91 coronary revascularizations ([Table 4](#)). Individuals with MetS was significantly associated with more cardiac events than those without (RR [rate ratio] = 1.67, 95% CI = 1.15–2.43, *P* = 0.007). However, there was no significant difference in the hard events such as death, MI and unstable angina between individuals with and without MetS (RR = 1.01, 95% CI = 0.44–2.33, *P* = 0.984). In the MetS group, those with significant CAD had more cardiac events than those without (RR = 64.33, 95% CI = 29.17–141.88,

Table 1. Baseline Characteristics of Asymptomatic Individuals With and Without MetS

	Overall (n=5,213)	MetS (n=2,042)	Non-MetS (n=3,171)	P value
Age, years	53.9±8.3	55.1±8.3	53.1±8.2	<0.001
Male, n (%)	3,810 (73.1)	1,571 (76.9)	2,289 (70.6)	<0.001
Body mass index, kg/m ²	24.7±2.9	26.2±2.8	23.7±2.6	<0.001
Waist circumference, cm	86.1±8.4	90.7±7.6	83.2±7.5	<0.001
Systolic BP, mmHg	119.6±12.9	123.9±12.9	116.8±12.1	<0.001
Diastolic BP, mmHg	76.3±10.3	79.4±10.1	74.3±10.0	<0.001
Diabetes mellitus, n (%)	843 (16.2)	544 (26.6)	299 (9.4)	<0.001
Hypertension, n (%)	1,920 (36.8)	1,239 (60.7)	681 (21.5)	<0.001
Hyperlipidemia, n (%)	1,646 (31.6)	1,049 (51.4)	597 (18.8)	<0.001
Current smoker, n (%)	1,250 (24.0)	553 (27.1)	697 (22.0)	<0.001
Family history of CAD,* n (%)	807 (15.5)	330 (16.2)	477 (15.0)	0.276
Total cholesterol, mg/dl	195.2±34.4	192.7±37.0	196.8±32.4	<0.001
LDL-cholesterol, mg/dl	121.3±30.1	119.4±32.6	122.4±28.3	<0.001
HDL-cholesterol, mg/dl	53.0±13.5	47.7±11.7	56.4±13.4	<0.001
Triglyceride, mg/dl	134.3±83.6	173.6±96.7	108.9±61.8	<0.001
Fasting blood glucose, mg/dl	105.3±21.4	113.4±24.9	100.1±16.9	<0.001
Glycated hemoglobin, %	5.7±0.8	6.0±0.9	5.5±0.7	<0.001
Creatinine, mg/dl	0.9±0.2	0.9±0.2	0.9±0.2	<0.001
Uric acid, mg/dl	5.6±1.4	5.9±1.5	5.4±1.3	<0.001
hsCRP ≥2 mg/dl, %	52 (1.0)	16 (0.8)	36 (1.1)	0.212
Framingham risk score	7.9±5.4	10.1±5.7	6.5±4.7	<0.001

Values are given as mean±standard deviation or number (%). *CAD in a first-degree relative of any age. BP, blood pressure; CAD, coronary artery disease; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MetS, metabolic syndrome.

Table 2. Coronary Computed Tomographic Angiographic Findings in Asymptomatic Individuals With and Without MetS

CCTA characteristics	Overall (n=5,213)	MetS (n=2,042)	Non-MetS (n=3,171)	P value
Mean CACS	44.0±154.7	67.1±200.6	29.1±113.6	<0.001
CACS score classification, n (%)				<0.001
0	3,352 (64.4)	1,099 (53.9)	2,253 (71.1)	
1–10	482 (9.3)	220 (10.8)	262 (8.3)	
11–100	831 (16.0)	398 (19.5)	433 (13.7)	
101–400	406 (7.8)	238 (11.7)	168 (5.3)	
>400	134 (2.6)	83 (4.1)	51 (1.6)	
Any plaque, n (%)	2,244 (43.0)	1,101 (53.9)	1,143 (36.0)	<0.001
Plaque characteristics, n (%)				
Calcified plaque	1,596 (30.6)	815 (39.9)	781 (24.6)	<0.001
Non-calcified plaque	956 (18.3)	474 (23.2)	482 (15.2)	<0.001
Mixed plaque	479 (9.2)	256 (12.5)	223 (7.0)	<0.001
Modified Duke prognostic index	1.2±0.7	1.3±0.8	1.1±0.6	<0.001
Segment stenosis score	0.7±2.0	1.0±2.6	0.5±1.6	<0.001
Segment involvement score	1.1±1.8	1.5±2.1	0.9±1.6	<0.001
Stenosed vessels, n (%)				
Significant CAD	440 (8.4)	251 (12.3)	189 (6.0)	<0.001
1-vessel disease	320 (6.1)	180 (8.8)	140 (4.1)	<0.001
Multivessel disease	120 (2.3)	71 (3.5)	49 (1.5)	<0.001
Significant CAD in the LM or proximal LAD	144 (2.8)	87 (4.3)	57 (1.8)	<0.001

Values are given as mean±standard deviation or number (%). CACS, coronary artery calcium score; CCTA, coronary computed tomographic angiography; LAD, left anterior descending artery; LM, left main. Other abbreviations as in Table 1.

Table 3. Independent Clinical Predictors of Significant CAD (1) and Significant CAD in the LM or Proximal LAD Artery (2) as Detected by CCTA in Asymptomatic Individuals With and Without MetS

	Univariate analysis (1)			Multivariate analysis (1)*			Univariate analysis (2)			Multivariate analysis (2)**		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age, years	1.089	1.077–1.102	<0.001	1.097	1.084–1.111	<0.001	1.097	1.077–1.117	<0.001	1.104	1.083–1.126	<0.001
Male	2.291	1.744–3.008	<0.001	2.785	2.096–3.702	<0.001	1.968	1.255–3.087	0.003	2.404	1.515–3.815	<0.001
Body mass index, kg/m ²	1.063	1.029–1.098	<0.001				1.097	1.041–1.157	0.001			
Waist circumference, cm	1.032	1.020–1.044	<0.001				1.046	1.026–1.066	<0.001			
Systolic BP, mmHg	1.026	1.019–1.033	<0.001				1.027	1.015–1.039	<0.001			
Diastolic BP, mmHg	1.021	1.011–1.030	<0.001				1.022	1.006–1.038	0.007			
Diabetes mellitus	2.479	1.993–3.085	<0.001				2.433	1.697–3.488	<0.001			
Hypertension	2.653	2.175–3.237	<0.001				2.950	2.095–4.154	<0.001			
Hyperlipidemia	1.785	1.464–2.177	<0.001				1.979	1.419–2.760	<0.001			
Current smoker	1.105	0.883–1.383	0.383				1.107	0.743–1.648	0.617			
Family history of CAD†	1.216	0.941–1.571	0.134	1.534	1.172–2.008	0.002	1.391	0.919–2.105	0.119	1.781	1.160–2.734	0.008
Total cholesterol, mg/dl	1.001	0.999–1.004	0.565				1.001	0.996–1.006	0.682			
LDL-cholesterol, mg/dl	1.003	0.999–1.006	0.112	1.006	1.003–1.009	<0.001	1.004	0.999–1.009	0.147	1.007	1.002–1.013	0.007
HDL-cholesterol, mg/dl	0.974	0.966–0.982	<0.001				0.970	0.956–0.984	<0.001			
Triglycerides, mg/dl	1.002	1.001–1.003	<0.001				1.002	1.000–1.003	0.037			
Fasting glucose, mg/dl	1.015	1.012–1.019	<0.001				1.011	1.006–1.016	<0.001			
Glycated hemoglobin, %	1.634	1.496–1.785	<0.001				1.474	1.306–1.665	<0.001			
Creatinine, mg/dl	4.535	2.476–8.306	<0.001				5.038	1.813–14.000	0.002			
Uric acid, mg/dl	1.127	1.053–1.207	0.001				1.088	0.969–1.222	0.154			
hsCRP ≥2 mg/dl	1.420	0.603–3.344	0.422				2.179	0.671–7.076	0.195			
Framingham risk score	1.132	1.113–1.150	<0.001				1.117	1.090–1.146	<0.001			
MetS	2.211	1.815–2.694	<0.001	1.992	1.623–2.445	<0.001	2.431	1.733–3.411	<0.001	2.151	1.523–3.037	<0.001

*Multiple logistic regression analysis (1) adjusting for age, male sex, family history of CAD, LDL-cholesterol, creatinine, uric acid, and MetS.

**Multiple logistic regression analysis (2) adjusting for age, male sex, family history of CAD, LDL-cholesterol, creatinine, uric acid, hsCRP ≥2 mg/dl, and MetS. †CAD in a first-degree relative of any age. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

$P<0.001$). Furthermore, in the MetS with significant CAD group, those with significant CAD in the LM or proximal LAD had more cardiac events than those without ($RR=2.63$, 95% $CI=1.51$ – 4.59 , $P=0.001$).

We present a representative case. A 67-year-old man with MetS underwent a regular medical check-up including CCTA on July 9, 2008. On CCTA, significant stenosis was detected at the proximal LAD and first diagonal (D1) bifurcation lesion with dense calcified plaque (Figures 2A–C) and a non-calcified plaque portion was revealed in the distal segment. At that time, we recommended further coronary evaluation, but he refused. Approximately 1 month later (August 11, 2008), he presented to the emergency room with resting chest pain.

Coronary angiography showed diffuse significant stenosis at the proximal to mid-LAD and D1 (Figure 2D). Therefore, we treated the patient by deploying 2 stents from the proximal to mid-LAD lesion and ballooning the D1 lesion (Figure 2E).

Discussion

The main findings of this study were as follows: (1) individuals with MetS had a higher prevalence of subclinical coronary atherosclerosis despite the absence of symptoms; (2) after adjustment for clinical risk factors, MetS was an independent predictor for significant CAD in at least 1 coronary artery and significant CAD in the LM or proximal LAD; (3) individuals

Table 4. Clinical Outcomes of Asymptomatic Individuals With and Without MetS									
Overall population	MetS						Rate ratio	95% CI	P value
	Yes (n=2,042)			No (n=3,171)					
	n	Rate*	95% CI	n	Rate*	95% CI			
Clinical outcome									
Death	6	1.26	0.25–2.27	13	1.75	0.80–2.70	0.72	0.27–1.90	0.510
Non-fatal MI	1	0.21	0–0.62	1	0.13	0–0.40	1.57	0.10–25.05	0.751
Unstable angina	2	0.42	0–1.01	0	0	–	–	–	–
Coronary revascularization	50	10.78	7.79–13.77	41	5.58	3.87–7.29	1.93	1.28–2.92	0.002
Death/MI/UA	9	1.90	0.66–3.14	14	1.88	0.90–2.87	1.01	0.44–2.33	0.984
Death/MI/UA/revascularization	57	12.30	9.11–15.50	54	7.35	5.39–9.31	1.67	1.15–2.43	0.007
Significant CAD on CCTA									
MetS group	Yes (n=251)			No (n=1,791)			Rate ratio	95% CI	P value
	n	Rate*	95% CI	n	Rate*	95% CI			
Clinical outcome									
Death/MI/UA/revascularization	50	107.98	78.05–137.91	7	1.68	0.44–2.92	64.33	29.17–141.88	<0.001
Significant CAD in the LM or proximal LAD on CCTA									
MetS with significant CAD group	Yes (n=87)			No (n=164)			Rate ratio	95% CI	P value
	n	Rate*	95% CI	n	Rate*	95% CI			
Clinical outcome									
Death/MI/UA/revascularization	27	189.09	117.77–260.42	23	71.82	42.47–101.17	2.63	1.51–4.59	0.001

*Crude incidence rate per 1,000 person-years. MI, myocardial infarction; UA, unstable angina. Other abbreviations as in Tables 1–3.

with MetS had more cardiac events during the follow-up period than those without; and (4) in the MetS group, individuals with significant CAD, and especially those with significant CAD involving the LM or proximal LAD, had the majority of cardiac events.

The association between MetS and cardiovascular risk has been investigated in earlier studies, using carotid intima-media thickness, coronary artery calcification, and myocardial perfusion imaging.^{20–22} Recently, CCTA has been widely used in the comprehensive evaluation of CAD, including lesion location, severity, and plaque characteristics. However, less is known about subclinical atherosclerosis assessed by CCTA in asymptomatic individuals with MetS. Previous observational studies using CCTA in this population showed that atherosclerotic plaque was observed in 30–52% and significant CAD occurred in 10% of individuals.^{7,9} Consistent with those studies, in our study, atherosclerotic plaques were identified in 1,101 (53.9%) individuals, and of those, 251 (12.3%) had significant stenosis on CCTA. In addition, after adjustment for clinical risk factors, MetS was associated with significant CAD in at least 1 coronary artery on CCTA. It is difficult to directly compare the findings of this study with those of previous studies because the age, sex, and associated comorbid conditions of the study groups were different. Nevertheless, in this and previous studies, individuals with MetS were associated with an approximately 2-fold increase in significant CAD on CCTA compared with those without.⁷ These findings imply that subclinical atherosclerosis in asymptomatic individuals with MetS is a problem that should not be ignored.

In this cohort, individuals with MetS had more multivessel disease and significant lesions in the LM or proximal LAD, which are known to be associated with a worse prognosis, compared with those without.^{17,23} Even after adjustment for other clinical risk factors, MetS was associated with significant CAD in the LM or proximal LAD on CCTA. Our findings are in agreement with a previous study in which asymptomatic individuals with MetS had more multivessel disease than those without.⁷ These findings indicate that MetS causes qualitatively as well as quantitatively worse subclinical atherosclerosis.

The mechanisms by which MetS increases cardiovascular risk are unclear.³ Our study provides some insights into the mechanisms. In this study, during the follow-up period, individuals with MetS had more cardiac events than those without. In the MetS group, the majority of cardiac events occurred in individuals with significant CAD, especially in those with significant lesions in the LM or proximal LAD. These findings imply that the severity of subclinical coronary atherosclerosis determines subsequent cardiac events in asymptomatic individuals with MetS.

Cardiac events occur after long periods of subclinical disease. Early identification of individuals with subclinical atherosclerosis and aggressive lifestyle modification may prevent cardiac events in high-risk subjects.²⁴ It is well known that MetS promotes or increases the risk of developing diabetes mellitus and subsequent cardiovascular disease.²⁵ This and previous studies showed that subclinical atherosclerosis as assessed by CCTA was not negligible in asymptomatic individuals with MetS.^{7,9} The relationship between MetS and subclinical atherosclerosis is important from a prevention perspective.²⁰ Furthermore, this study revealed that the severity of subclinical atherosclerosis determines future cardiac events in this population. Therefore, to prevent future cardiac events in asymptomatic individuals, efforts should be made to reduce the unfavorable metabolic conditions.

Study Limitations

First, the present study was performed in a single center, so there was potential for selection bias. Second, the study population was exclusively Korean, which limits the applicability of our findings to other ethnic groups. Third, calcified plaques and higher CACS may lead to overestimation of significant CAD.²⁶ Fourth, most of cardiac events were coronary revascularizations, which is partly attributable to the fact that all individuals went to hospital for their general health examination and were asymptomatic. Therefore, in asymptomatic individuals with MetS, future studies to evaluate the association between hard clinical events and subclinical atherosclerosis are needed. Fifth, the napkin-ring sign, positive vessel remodeling, and low-attenuation plaque are known as high-risk plaque features.^{27,28} In our cohort, the number of individuals with acute coronary syndrome (MI and unstable angina) was only 4 (0.08%) and analysis of these characteristics was not performed. Other large studies are required to elucidate the clinical effect of these high-risk plaque characteristics in asymptomatic individuals. Finally, CCTA itself has potential limitations, including radiation hazard, use of contrast, and higher cost.²⁹ Although our study enrolled only volunteers, the use of CCTA in asymptomatic individuals with MetS has not yet been justified.

Conclusions

This large observational study of asymptomatic individuals with MetS showed that the prevalence of subclinical atherosclerosis was not negligible. Individuals with significant CAD, and particularly those with significant CAD in the LM or proximal LAD, had a subsequent risk of cardiac events. For the prevention of cardiac events in asymptomatic individuals, our results suggest the importance of reducing unfavorable metabolic conditions.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065, H12C0630, and H10C2020).

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