Published in final edited form as:

Am J Cardiol. 2008 April 15; 101(8): 1127–1130. doi:10.1016/j.amjcard.2007.12.012.

Relation of the Metabolic Syndrome to Quantity of Coronary Atherosclerotic Plaque

Javed Butler, MD, MPH^{a,b}, Eline AQ Mooyaart, MS^a, Nina Dannemann, BS^a, Fabian Moselewski, MD^{a,c}, Michael D. Shapiro, DO^a, Maros Ferencik, MD, PhD^a, Thomas J. Brady, MD^a, and Udo Hoffmann, MD, MPH^{a,c}

^a Cardiac MR PET CT Program, Massachusetts General Hospital, Harvard Medical School, Boston MA

^b Cardiology Division, Emory University, Atlanta GA

^c Harvard School of Public Health, Boston, MA

Abstract

Although metabolic syndrome (MS) is associated with adverse cardiovascular outcomes, its association with presence and extent of coronary atherosclerotic plaques is not well described. To assess this relationship, multi-detector computed tomography (MDCT) based pattern of coronary plaques were assessed in 77 patients enrolled in the ROMICAT study (age 54±12 years, 79% Caucasians and 36% females) and compared among those who did (n=35, 45%) and did not (n=42, 55%) have MS. The presence of any, calcified, and non-calcified plaque was significantly higher in patients with than without MS (91%, 74%, and 77% vs. 46%, 45%, and 40% segments with plaque respectively, all p<0.01). The overall number of segments with plaques was also higher in MS patients (5.8±3.7 vs. 2.1±3.3, p<0.001). Metabolic syndrome was independently associated with both presence and extent of overall plaques after adjusting for the Framingham risk score (OR 6.7, 95% CI 1.6–28.8, p<0.01 for presence, β coefficient 3.59, SE 0.88, p=0.009 for extent) and for individual risk factors including age, gender, smoking, body mass index, hypertension, diabetes, hyperlipidemia, and clinical coronary disease (OR 8.4, 95% CI 1.7–42.5, p=0.008 for presence, β coefficient 2.35, SE 0.86, p=0.007 for extent). Similarly, MS was independently associated with calcified and non-calcified plaques individually. In conclusion, MS is independently associated with the presence and extent of both calcified and non-calcified coronary atherosclerotic plaques as detected by MDCT. These data may explain the higher cardiovascular risk in these patients and may lay the foundation for studies to determine whether such information may improve risk stratification.

Keywords

Metabolic syndrome; coronary plaque; atherosclerosis; cardiac computed tomography

Address correspondence to: Udo Hoffmann, MD, MPH, Cardiac MR PET CT PET Program and Department of Radiology, Massachusetts General Hospital, 165 Cambridge Street, 4th floor, Suite 400, Boston MA 02114, Tel No. (617) 726-5954. Fax: (617) 724-4152. Email: uhoffman@partners.org.

Conflict of Interest: None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Metabolic syndrome (MS) is associated with an increased risk of adverse cardiovascular events and mortality. (1–3) It is highly prevalent in the United States adult population. (4) Recently the American Heart Association and the National Heart Lung and Blood Institute issued a joined statement on MS providing the revised diagnostic criteria. (5) The exact mechanism by which MS exerts excess risk is under active investigation. Accelerated coronary atherosclerosis may be related to the excess clinical risk associated with MS, as sub-clinical atherosclerosis is associated with increased adverse event rate. (6–7) Although some studies suggest increased coronary calcification in patients with MS, others did not find an association between MS and angiographic coronary disease. (8–10) The overall presence, type and extent of atherosclerotic plaque in patients with and without MS have not been reported previously. Coronary 64-slice multidetector computed tomography (MDCT) is a novel non-invasive imaging technology that now permits visualization of the coronary arteries and has been shown to detect both calcified and larger non-calcified coronary plaques in good agreement with intravascular ultrasound. (11–12) In this study we sought to assess whether MS is associated with the presence and extent of both calcified and non-calcified coronary atherosclerotic plaque as detected by MDCT and whether this association is maintained after adjustment for other cardiovascular risk factors.

Methods

This study represents a secondary analysis of Rule Out Myocardial Infarction by Computed tomography Angiography Trial data that were collected to assess the utility of cardiac MDCT in triaging patients who present to the emergency department with acute chest pain but without definitive evidence for a myocardial infarction. (13) Of the 103 patients who underwent MDCT scanning, adequate information was not present to designate MS diagnosis in 26 individuals restricting the final analysis to 77 patients. Subjects were classified into those who did (n=35, 45%) and did not (n=42, 55%) have MS using the modified Adult Treatment Panel III guidelines. (5) Participants taking anti-hyperglycemic medications were counted as meeting the glucose and those taking antihypertensive medication as meeting the blood pressure criterion. Abdominal waist measurements were not available. Instead, a body mass index of $> 30 \text{ kg/m}^2$ was used as a surrogate for waist circumference.

All MDCT imaging was performed with a “Sensation 64” scanner (Siemens Medical Solutions, Forchheim, Germany). Patients with a heart rate > 60 beats/minute received metoprolol in 5 mg intravenous boluses for a maximum of 25 mg, unless contraindications were present. Contrast-enhanced MDCT data were acquired with the use of a spiral scan with a $32 \times 0.6 \text{ mm}$ slice collimation, a gantry rotation time of 330 ms, tube voltage of 120 kV, and an effective tube current of 850–950 mAs depending on patient body size. Electrocardiographic correlated tube current modulation was used in order to restrict full tube current to the diastolic phase of the cardiac cycle, which reduces radiation exposure by up to 50%. (14) Contrast agent (Nycomed Amersham GE-Healthcare Vispaque 300 mg I/mL) was injected at a rate of 5 ml/second (mean volume $78 \pm 11 \text{ ml}$) with a delay calculated during the timing bolus scan followed by 40 ml of saline flush.

Overlapping transaxial images were reconstructed using a medium sharp convolution kernel (B25f) with an image matrix of 512×512 pixels, slice thickness and increment of 0.75/0.4 mm using an electrocardiogram gated half-scan algorithm with a resulting temporal resolution 165 msec. Image reconstruction was retrospectively gated to the electrocardiogram. The position of the reconstruction window within the cardiac cycle was optimized to minimize motion artifacts. Two study investigators (UH and MF) performed the readings independently using original axial source images, thin slice (5mm) maximal intensity projections and multi planer reconstructions parallel and perpendicular to the vessel centerline, and short axis cross-sectional reconstructions (1 mm thickness). Disagreement for the presence of plaque per segment was resolved by consensus. In case a consensus could not be reached, a third reader

adjudicated the finding. The coronary artery tree was assessed for the presence of calcified and non-calcified plaque in 17 segments using a modified American Heart Association classification. (15) Non-calcified plaque was defined as any discernible structure that could be assigned to the coronary wall that had the CT attenuation below the contrast-enhanced lumen but above the surrounding connective tissue/epicardial fat in at least two independent planes. (11–12) Any structure with a CT attenuation of >130 HU that could be visualized separately from the contrast-enhanced coronary lumen (either because it was “embedded” within non-calcified plaque or because its density was above the contrast-enhanced lumen) was defined as calcified atherosclerotic plaque. Inter observer agreement for the detection of any plaque per patient and per segment was excellent (Cohen’s $\kappa = 0.92$ and 0.81 , respectively).

Baseline demographic and clinical characteristics were compared between patients with and without MS using chi-square tests for categorical and *t*-test for continuous variables. The presence of plaques was assessed as a binary outcome (any plaque in any segments). The extent of plaque was defined as a continuous variable indicating the number of segments with any plaque. Stratified analyses were also performed according to plaque composition (all, calcified, and non-calcified). Multivariate logistic and linear regression analysis was performed to determine whether the relationship between MS and the presence and extent of plaques was independent of other risk factors. Separate models were used to examine the association between MS, plaque and the Framingham risk score; and MS, plaque and individual traditional risk factors. Logistic regression models for the presence of any plaque initially contained either the Framingham risk score (as a continuous or categorical variable) or traditional risk factors (age, gender, body mass index, and history of hypertension, dyslipidemia, smoking, coronary disease, and diabetes). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. In the next step we assessed the extent of plaques using linear regression following a similar analytic plan. Beta-estimates, 95%-confidence intervals, and adjusted *p*-values were assessed. A *p*-value of <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS for Windows Release 14.0, SPSS Inc., Chicago IL.

Results

Baseline differences between patients with and without MS are described in Table 1. Patients with MS were more likely to be males, smokers and with a past history of hypertension, hyperlipidemia, and history of coronary disease. Table 2 details the presence and characteristics of plaques among patients with and without MS. Patients with MS were more likely to have plaque and a greater extent of plaque distribution as compared to patients without MS. Similar results were found in analyses stratified for plaque composition for both calcified and non-calcified plaque.

Metabolic syndrome was independently associated with both the presence and extent of plaques after adjustment for the Framingham risk score used as a continuous variable (OR 6.7, 95% CI 1.6–28.8, *p*<0.01 for presence and β coefficient 3.59, SE 0.88, *p*=0.009 for extent). Results were similar when the Framingham risk score was used as a categorical variable (data not shown). The presence of MS remained significantly and independently associated with the presence and extent of any plaque (OR 8.4, 95% CI 1.7–42.5, *p*=0.008 for presence and β coefficient 2.35, SE 0.86, *p*=0.007 for extent) after adjustment for traditional risk factors (age, gender, smoking, body mass index, and a history of hypertension, diabetes, hyperlipidemia, or coronary artery disease). Similarly, in stratified analysis, MS was independently associated with the presence and extent of both calcified and non-calcified plaques (Table 3).

Discussion

In this study, we demonstrate that MS is significantly associated with the presence and extent of both calcified and non-calcified coronary atherosclerotic plaque as detected by MDCT. Furthermore, we demonstrate that this association is independent of the presence of individual traditional risk factors and after adjusting for the Framingham risk score. Our data show that MS is associated with both, a higher likelihood of having any coronary artery disease as detected by coronary MDCT and if present having more extensive disease as compared to patients without MS. This association remained positive even after adjusting for age, gender, smoking, body mass index, and history of hypertension, hyperlipidemia, coronary disease, diabetes, and the Framingham risk score.

These findings may contribute to our understanding of the increased cardiovascular event risk in patients with MS and may explain that this risk is increased above the sum of all individual risk factors. The interaction between the clinical components of MS and its biological phenotype e.g. insulin resistance and dyslipidaemia is known to contribute to the development of a vascular pro-inflammatory state including increased lipoprotein peroxidation, smooth muscle cell proliferation, accumulation of lipid laden material, extracellular matrix deposition, activation of platelets and thrombotic pathways; in summary all the aspects of atherosclerosis development and progression, and its culmination into adverse clinical events. (16–17) Although previous literature has suggested vascular abnormalities in patients with MS, these studies either did not control for the individual risk factors or were non-coronary vascular studies; coronary artery imaging per se in patients with MS have been reported to show varying results. (8–9,18–20) In this respect, our study shows a direct coronary imaging evidence of increased atherosclerosis among these patients controlling for the common risk factors. This may at least partially explain the excess risk among patients with MS

Our results may also have therapeutic implications. Optimally, information on the presence and extent of coronary artery disease may identify patients at low and high cardiovascular event risk among patients with MS. Considering the high prevalence of MS and the obesity epidemic, only targeted therapies to high-risk patients may be safe and cost-effective. (4,21)

Our study also has several limitations. Our patient population consisted of specifically patients presenting with acute chest pain in the emergency department without definitive evidence of acute infarction or ischemia and our results may not be generalized to the entire population with metabolic syndrome, who might have a lower prevalence of abnormalities. Study of long-term cardiovascular event risk in subjects with MS is important and MDCT may represent a target to improve risk stratification in such patients; however the costs and the risks (radiogenic and non-radiogenic) of MDCT will need to be assessed in light of the benefit magnitude. In addition, the retrospective nature of the study necessitated case ascertainment based on body mass index rather than waist circumference. Body mass index has been shown to correlate well with waist circumference and with impaired glucose tolerance. (22) The World Health Organization definition of MS also uses body mass index of $> 30 \text{ kg/m}^2$. (23) Finally, coronary artery calcium (CAC) scores were not assessed on these patients. We therefore cannot comment on the incremental value of contrast enhance MDCT over CAC score, which have been associated with sub-clinical coronary atherosclerosis in patients with MS. (24) However, MS is highly prevalent in younger to middle aged population who tend to have more non-calcified plaques than calcified as compared to older subject. This issue however needs further study.

Acknowledgments

ROMICAT Study is supported by the National Institute of Health (R01 HL080053), General Electric Healthcare, Siemens Medical Solutions, and the New York Cardiac Center.

References

1. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle aged men. *JAMA* 2002;288:2709–2716. [PubMed: 12460094]
2. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circ* 2004;110:124501250.
3. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497. [PubMed: 11368702]
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359. [PubMed: 11790215]
5. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. American Heart Association. National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circ* 2005;112:2735–2752.
6. Kuller L, Borhani N, Furberg C, Gardin J, Manolio T, O'Leary D, Psaty B, Robbins J. Prevalence of sub clinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol* 1994;139:1164–1179. [PubMed: 8209875]
7. Bigi R, Cortigiani L, Colombo P, Desideri A, Bax JJ, Parodi O. Prognostic and clinical correlates of angiographically diffuse non-obstructive coronary lesions. *Heart* 2003;89:1009–1013. [PubMed: 12923011]
8. Ellison RC, Zhang Y, Wagenknecht LE, Eckfeldt JH, Hopkins PN, Pankow JS, Djoussé L, Carr JJ. Relation of the metabolic syndrome to calcified atherosclerotic plaque in the coronary arteries and aorta. *Am J Cardiol* 2005;95:1180–1186. [PubMed: 15877990]
9. Kullo IJ, Cassidy AE, Peyser PA, Turner ST, Sheedy PF 2nd, Bielak LF. Association between metabolic syndrome and subclinical coronary atherosclerosis in asymptomatic adults. *Am J Cardiol* 2004;94:1554–1558. [PubMed: 15589016]
10. Mellen PB, Cefalu WT, Herrington DM. Diabetes, the metabolic syndrome, and angiographic progression of coronary arterial disease in postmenopausal women. *Arterioscler Throm Vasc Biol* 2006;26:189–193.
11. Moselewski F, Ropers D, Pohle K, Hoffmann U, Ferencik M, Chan RC, Cury RC, Abbasa S, Jang IK, Brady TJ, Daniel WG, Achenbach S. Comparison of measurement of cross-sectional coronary atherosclerotic plaque and vessel areas by 16-slice multidetector computed tomography versus intravascular ultrasound. *Am J Cardiol* 2004;94:1294–1297. [PubMed: 15541250]
12. Achenbach S, Moselewski F, Ropers D, Ferencik M, Hoffmann U, MacNeill B, Pohle K, Baum U, Anders K, Jang IK, Daniel WG, Brady TJ. Detection of calcified and non-calcified coronary atherosclerotic plaque by contrast-enhanced, sub-millimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. *Circ* 2004;109:14–17.
13. Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, Cury RC, Butler J, Abbasa S, Brown DF, Manini A, Nichols JH, Achenbach S, Brady TJ. Coronary Multidetector Computed Tomography in the Assessment of Patients with Acute Chest Pain. *Circ* 2006;114:2251–2260.
14. Hundt W, Rust F, Stabler A, Wolff H, Suess C, Reiser M. Dose reduction in multislice computed tomography. *J Comput Assist Tomogr* 2005;29:140–147. [PubMed: 15665702]
15. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the ad hoc committee for grading of coronary artery disease. American Heart Association. *Circ* 1975;51:5–40.
16. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J Am Coll Cardiol* 2005;46(46):1978–1985. [PubMed: 16325028]
17. Fortunato A, San Jose G, Moreno MU, Beloqui O, Diez J, Zalba G. NADPH oxidase overactivity underlies oxidative stress in metabolic syndrome. *Diabetes* 2006;55:209–215. [PubMed: 16380495]

18. Hassinen M, Komulainen P, Lakka TA, Vaisanen SB, Haapala I, Gylling H, Alen M, Schmidt-Trucksass A, Nissinen A, Rauramaa R. Metabolic syndrome and the progression of carotid intima-media thickness in elderly women. *Arch Int Med* 2006;166:444–449. [PubMed: 16505265]
19. Safar ME, Thomas F, Blacher J, Nzietchueng R, Bureau JM, Pannier B, Benetos A. Metabolic syndrome and age-related progression of aortic stiffness. *J Am Coll Cardiol* 2006;47:72–75. [PubMed: 16386667]
20. Iglseder B, Cip P, Malaimare L, Ladurner G, Paulweber B. The metabolic syndrome is a stronger risk factor for early carotid atherosclerosis in women than in men. *Stroke* 2005;36:1212–1217. [PubMed: 15890992]
21. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006;295(25):1549–1555. [PubMed: 16595758]
22. Farin HMF, Abbasi F, Reaven GM. Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in non diabetic adults. *Am J Clinical Nutrition* 2006;83:47–51. [PubMed: 16400048]
23. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP National Cholesterol Education Program Versus World Health Organization Metabolic Syndrome in Relation to All-Cause and Cardiovascular Mortality in the San Antonio Heart Study. *Circ* 2004;110:1251–1257.
24. Wong ND, Sciammarella MG, Polk D, Gallagher A, Miranda-Peats L, Whitcomb B, Hachamovitch R, Friedman JD, Hayes S, Berman DS. The metabolic syndrome, diabetes, and sub-clinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol* 2003;41(9):1547–53. [PubMed: 12742296]

Table 1

Baseline patient characteristics

Baseline Characteristic	Metabolic Syndrome		p
	Yes (n=35)	No (n=42)	
Age (years $\pm$ SD)	54 $\pm$ 12	53 $\pm$ 12	0.34
Men	74%	54%	0.08
White	86%	73%	0.55
Family history of premature coronary disease	64%	60%	0.81
Hyperlipidemia	69%	49%	0.10
Coronary disease	26%	9%	0.07
Smoker	66%	38%	0.02
Diabetes Mellitus	17%	9%	0.32
Hypertension	74%	36%	0.001
High density lipoprotein (mg/dl)	36 $\pm$ 8	54 $\pm$ 15	-
Triglycerides (mg/dl)	230 $\pm$ 181	139 $\pm$ 104	-
Body mass index (kg/m ²)	33 $\pm$ 7	28 $\pm$ 10	-
Glucose (mg/dl)	148 $\pm$ 179	104 $\pm$ 50	-
<i>Framingham Risk Score</i>			
Score (mean $\pm$ SD)	13.1 $\pm$ 7.4	7.4 $\pm$ 7.0	0.001
Low risk (%)	43%	80%	
Intermediate risk (%)	35%	15%	0.002
High risk (%)	22%	5%	

Table 2

Plaque characteristics among patients with and without metabolic syndrome

Plaque Characteristic	Metabolic Syndrome		P
	Yes (n=35)	No (n=42)	
Overall plaque presence	32 (91%)	20 (48%)	<0.001
Overall plaque extent (number of segments, mean $\pm$ SD)	5.8 $\pm$ 3.7	2.1 $\pm$ 3.2	<0.001
Calcified plaque presence	26 (74%)	19 (45%)	0.01
Calcified plaque extent (number of segments, mean $\pm$ SD)	4.7 $\pm$ 3.9	1.7 $\pm$ 3.0	0.001
Non-calcified plaque presence	27 (77%)	17 (41%)	0.001
Non-calcified plaque extent (number of segments, mean $\pm$ SD)	2.4 $\pm$ 2.3	0.9 $\pm$ 1.5	0.001

Table 3
Metabolic syndrome and presence of plaques: Univariate and multivariate risks

	OR	95% CI	p
Any plaque			
Unadjusted	11.7	3.1–44.3	<0.001
Adjusted for the Framingham risk score	6.7	1.6–28.8	<0.01
Adjusted for individual risk factors [*]	8.4	1.7–42.5	<0.001
Calcified plaque			
Unadjusted	3.5	1.3–9.2	0.01
Adjusted for the Framingham risk score	3.3	1.2–9.3	0.03
Adjusted for individual risk factors [*]	3.8	1.1–14.5	0.04
Non-calcified plaque			
Unadjusted	4.9	1.8–13.4	<0.01
Adjusted for the Framingham risk score	3.9	1.4–10.8	0.01
Adjusted for individual risk factors [*]	4.5	1.2–16.7	0.02

^{*} includes age, gender, smoking, body mass index, hypertension, diabetes, hyperlipidemia, and clinical coronary disease