Published in final edited form as:
Vasc Med. 2011 October ; 16(5): 339–345. doi:10.1177/1358863X11422110.

Circulating levels of matrix metalloproteinase-9 and abdominal aortic pathology: From the Dallas Heart Study

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Abstract

Prior reports have associated increased circulating levels of matrix metalloproteinase-9 (MMP-9), an endopeptidase active in the extracellular matrix, with the formation and rupture of aortic aneurysms, raising the possibility that MMP-9 may be a useful diagnostic or therapeutic target for aortic pathology. However, associations between MMP-9 and pathological abdominal aortic phenotypes in the general population have not been reported. In the Dallas Heart Study, a population-based sample of Dallas County residents ($n = 2304$), we measured MMP-9 and performed magnetic resonance imaging (MRI) of the abdominal aorta, measuring aortic compliance, plaque, wall thickness and luminal diameter. After adjustment for traditional cardiac risk factors and body size, higher MMP-9 quartiles were independently associated with higher aortic wall thickness and larger luminal diameter ($p < 0.0001$ for each), but not abdominal aortic plaque ($p = 0.08$), coronary artery calcium ($p = 0.20$) or the aortic luminal diameter/aortic wall thickness ratio ($p = 0.37$), supporting the hypothesis that therapies targeting MMP-9 may affect the abdominal aortic wall and modify aortic pathology.

Keywords

aortic aneurysm; aortic luminal diameter; aortic wall thickness; matrix metalloproteinase-9

Introduction

Changes in the extracellular matrix play an essential role in a variety of pathologies across vascular beds. Matrix metalloproteinases (MMP) are a family of more than 20 proteases with a variety of physiologic functions.[1] MMPs affect extracellular matrix degradation and have been posited to promote the inflammatory pathogenesis of atherosclerotic plaque development and rupture.[2] Both MMP-9 expression and activity have been associated with

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Conflict of interests

Justin L Grodin, none declared; Tiffany M Powell-Wiley, none declared; Colby R Ayers, none declared; Darpan S Kumar, none declared; Anand Rohatgi, none declared; Amit Khera, none declared; Darren K McGuire, consulting income from Tethys Bioscience; James A de Lemos, Grant support from Alere, Inc. and Roche Diagnostics, consulting income from Johnson and Johnson and Tethys Bioscience; Sandeep R Das, none declared.

the pathogenesis of abdominal aortic aneurysms (AAA) and atherosclerotic vascular disease.[3,4] Previous cross-sectional studies in high-risk patient populations describe higher circulating MMP-9 levels in patients with acute coronary syndromes, stable coronary artery disease, cerebrovascular disease, peripheral vascular disease, and diabetes.[5–7] In contrast, much less is known about the association between circulating MMP-9 and subclinical aortic pathology in the general population. To address this issue, we utilized the Dallas Heart Study (DHS), a large multi-ethnic population-based cohort, to assess the cross-sectional associations between plasma levels of MMP-9 and multiple measures of abdominal aortic vascular disease.

Methods

Study population

The Dallas Heart Study is a multi-ethnic, probability-based population sample of 6101 Dallas County residents.[8] Subjects were invited to participate in three stages of data collection, the first involving a home visit interview for collection of demographic and anthropometric data, the second involving collection of blood and urine samples for laboratory testing, and the third visit involving detailed cardiac imaging including abdominal aortic magnetic resonance imaging (MRI) and electron beam computed tomography (EBCT) assessment of coronary artery calcium (CAC). The median time frame between phlebotomy and imaging was 28 days (IQR 9–60 days). The MMP-9 assays were measured once on each participant. The present study includes all DHS subjects who underwent measurement of plasma levels of MMP-9 and who completed all three phases of data collection, including aortic MRI and EBCT (n = 2304). The study protocol was approved by the University of Texas Southwestern Medical Center Institutional Review Board and all participants provided written informed consent.

Definition of variables

Hypertriglyceridemia was defined as a fasting triglyceride concentration ≥ 2.28 mmol/l. Low high-density lipoprotein cholesterol (HDL-C) was defined as < 1.03 mmol/l in men or < 1.29 mmol/l in women. Hypercholesterolemia was defined as fasting low-density lipoprotein cholesterol (LDL-C) ≥ 4.14 mmol/l; total cholesterol ≥ 6.21 mmol/l; or the use of a cholesterol-lowering medication. Hypertension was defined, based on an average of the last three of five measurements, as mean systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at the first study visit, or the use of an anti-hypertensive medication. Diabetes was defined as a fasting glucose ≥ 7.0 mmol/l; or the use of hypoglycemic medication. Height, weight, hip and waist circumference were measured at the same time as imaging was performed and body mass index (BMI) was calculated based on these measurements. Metabolic syndrome was defined as at least three of the following: abdominal obesity (waist circumference: men > 102 cm or BMI > 29 kg/m^2; women > 88 cm or BMI > 26 kg/m^2); fasting triglycerides ≥ 1.71 mmol/l or triglyceride lowering therapy; low HDL-C (< 1.03 mmol/l in men and < 1.29 mmol/l in women or HDL-C augmenting therapy); blood pressure ≥ 130/ ≥ 85 mmHg, or use of anti-hypertensive medication; fasting glucose ≥ 5.56 mmol/l, non-fasting glucose ≥ 7.78 mmol/l, or hypoglycemic therapy.

Imaging methods

All imaging studies were performed by investigators blinded to MMP-9 assay results. Magnetic resonance imaging of the infrarenal abdominal aorta was performed using a 1.5 Tesla whole-body MRI system (Intera; Philips Medical Systems, Best, The Netherlands). During free-breathing, six transverse slices of the infrarenal abdominal aorta were obtained using an ECG-gated, T2-weighted turbo spin-echo (black-blood) sequence. Slice thickness

was 5 mm and the interslice gap was 10 mm. Image acquisition used a commercial four-element abdominal phased-array receiver coil. Abdominal aortic plaque, aortic compliance, aortic wall thickness, and aortic luminal diameter were measured by trained observers using the Magnetic Resonance Analytical Software Systems (MASS) cardiac analysis software package (Version 4.2; Medis Medical Imaging Systems Inc., Leiden, The Netherlands). The maximum aortic diameter for this cohort was 30.6 mm. Criteria for aortic wall lesions have been previously reported.[9] Briefly, adventitial and luminal borders were drawn for each slice using a free-hand manual contour drawing tool. Atherosclerotic plaque was identified as an area of luminal protrusion, focal wall thickening, and increased MRI signal intensity.[9] Aortic luminal diameter was calculated as the average abdominal aortic luminal diameter (mm). Aortic wall thickness, measured in the infrarenal abdominal aorta, was calculated as vessel wall area divided by mean aortic circumference in each slice.[10] Areas for each were calculated as the difference between the areas described by the luminal and adventitial borders. These analyses excluded participants with AAA. As previously reported, the interclass correlation coefficient between luminal and cross-sectional area measurements for the two observers was 0.94 and the mean interobserver difference was 4.2 ± 6.6%.[10] The interstudy variability in aortic wall thickness measurements has also been previously described (0.03 ± 0.15 mm; $n = 32$).[11] To calculate aortic compliance, a high-resolution gradient-echo sequence with velocity-encoding gradient, at the level of the pulmonary bifurcation, was applied to obtain an 8-mm axial slice. QFLOW software (Version 4.1.6; Medis Medical Imaging Systems, Inc., Raleigh, NC, USA) was used to measure the aortic cross-sectional area on the axial images. The cross-sectional area was then multiplied by the aortic slice thickness to calculate aortic slice volume. In the MRI system, at the time of imaging, blood pressure measurements were obtained with an automated Welch-Allyn arm-cuff sphygmomanometer to calculate pulse pressure (PP = systolic blood pressure – diastolic blood pressure). Aortic compliance (μl/mmHg) was calculated using the following formula: aortic compliance = (maximum aortic slice volume – minimum aortic slice volume)/PP. EBCT measurement of CAC was performed in 2523 subjects with MMP-9 measured. Individuals with an average CAC score > 10 Agatston units over two measurements, a threshold selected to maximize reproducibility on paired scans, were classified as having prevalent CAC.[12]

Measurement of MMP-9 and other biomarkers

Venous blood samples were collected in EDTA tubes and maintained at 4°C for less than 4 hours, followed by centrifugation. Aliquots of plasma were frozen at −80°C and shipped to Biosite, Inc. (San Diego, CA, USA), where they were thawed for measurement. An immunoassay for MMP-9 was performed on Biosite's Luminex sandwich platform. For MMP-9, the minimal detection limit was 0.4 μg/l and average coefficient of variation across the assay range was 11%.

Statistical methods

SAS version 9.2 (SAS Corporation, Cary, NC, USA) was used. Two-sided p-values < 0.05 were considered statistically significant. For tests of trend across quartiles of MMP-9, the Jonckheere–Terpstra test was used for continuous variables, and the Cochran Armitage test was used for categorical variables. The associations between MMP-9 and the five imaging outcomes (abdominal aortic plaque, aortic compliance, aortic wall thickness, aortic luminal diameter, and CAC) were quantified both unadjusted, and with multivariable adjustment for age, sex, race/ethnicity, diabetes mellitus, hypertension, smoking status, body mass index (BMI), total cholesterol, HDL cholesterol, and triglycerides. Logistic regression was used for categorical variables (prevalent CAC and abdominal aortic plaque) and linear regression was used for continuous outcome variables (aortic wall thickness, aortic luminal diameter, aortic compliance). Sensitivity analysis was performed excluding patients taking statins.

Results

As shown in Table 1, the median age of this study population was 44 years (IQR 36–52) and median BMI was 30.3 kg/m^2 (IQR 25.4–34.6). The study sample was 56% women (36% post-menopausal), 52% black individuals and 30% white individuals, with a 34% prevalence of hypertension, 12% prevalence of diabetes mellitus, and 29% being current smokers. The overall median value of MMP-9 in this population was 9.7 μg/l (IQR 6.1–17.1). MMP-9 was higher in men than women: median (IQR) 10.2 μg/l (6.4–17.5) versus 9.4 (6.0–16.7), $p = 0.016$. Furthermore, there was no difference in post-menopausal status across quartiles of MMP-9, $p = 0.19$. There were no differences in subjects with statin or anti-hypertensive medication usage across quartiles of MMP-9. Increasing quartiles of MMP-9 were associated with higher prevalence of traditional cardiovascular disease risk factors, obesity and metabolic syndrome. For adjusted analyses the frequency of male sex was 1250 (45%), black race was 1401 (50%), Hispanic race was 468 (17%), white race was 878 (31%), diabetes mellitus was 334 (12%), hypertension was 964 (34%), hypercholesterolemia was 379 (14%), hypertriglyceridemia was 338 (12%), low HDL was 1144 (41%), and post-menopausal women 665 (24%). There was a difference in MMP-9 levels in non-smokers by race for MMP-9 in both unadjusted and adjusted analyses, but not for smokers – despite overall higher levels of MMP-9 in this group. There was no association between black versus white smokers with regards to MMP-9 ($p = 0.32$); however, in contrast to white race, black race was significantly associated with MMP-9 among non-smokers ($p < 0.0001$).

A significant association was observed between higher MMP-9 quartiles and higher aortic wall thickness ($p < 0.0001$), as shown in Table 2. This association remained significant after multivariable adjustment ($p < 0.0001$). No association was seen between MMP-9 quartiles and aortic compliance in either univariable or multivariable analyses. Although MMP-9 quartiles did not associate with aortic luminal diameter in univariable analyses, after adjustment, the association between higher MMP-9 levels and larger aortic luminal diameter became statistically significant ($p < 0.0001$); however MMP-9 levels remained unassociated with the aortic luminal diameter/aortic wall thickness ratio ($p = 0.37$). In addition, an analysis comparing 1st and 4th plasma MMP-9 quartiles confirmed the association between MMP-9 and higher aortic wall thickness in both unadjusted and adjusted analyses ($p < 0.0001$); a similar association was seen with aortic luminal diameter in adjusted analyses ($p < 0.0001$).

In unadjusted analyses, shown in Table 2, MMP-9 quartiles were not significantly associated with abdominal aortic plaque ($p = 0.07$) but did associate with prevalent CAC ($p = 0.005$). After multivariable adjustment, the association of MMP-9 with prevalent CAC was attenuated ($p = 0.20$). Results were similar when MMP-9 was modeled as a log-transformed continuous variable. An adjusted analysis showed no significant relationship between natural log-transformed CAC and log-transformed MMP-9 ($p = 0.69$). Adjusted analyses also yielded a positive correlation with log-transformed MMP-9 and left ventricular wall thickness ($p = 0.05$). A sensitivity analysis performed excluding subjects with histories of myocardial infarction, congestive heart failure, and diabetes mellitus yielded similar results ($n = 2356$), as did a sensitivity analysis excluding patients taking statins (data not shown).

Discussion

Higher plasma levels of MMP-9, which have previously been shown to correlate with increased MMP-9 activity,[13] have been associated with acute coronary syndromes, cerebrovascular disease, atherosclerosis and AAA formation and rupture in a number of small studies.[5–7,14,15] We measured plasma MMP-9 levels in a large, population-based cohort and correlated those levels with traditional risk factors for atherosclerosis and

multiple phenotypes of sub-clinical abdominal vascular pathology including aortic compliance, abdominal aortic plaque, aortic wall thickness, and aortic luminal diameter. We observed increasing plasma MMP-9 to be significantly associated with higher aortic wall thickness and larger aortic luminal diameter, but not a higher aortic luminal diameter/aortic wall thickness ratio. In addition, MMP-9 was not associated with prevalent abdominal aortic plaque or with CAC after multivariable adjustment.

One prior published report in the Framingham Offspring Study, a population free of heart failure or history of myocardial infarction that was older and less ethnically diverse than the DHS, suggested that the majority of healthy individuals do not have detectable levels of MMP-9.[16] In contrast, the majority of subjects in the present study had low but detectable levels of circulating MMP-9. This difference is most likely due to our use of a more sensitive assay with a minimal detection limit of 0.4 μg/l compared with the 4.0 μg/l threshold of the assay used in the prior study. In addition, it has been suggested that statins and anti-hypertensive medications may decrease MMP-9 levels.[17–20] Our observed rates of usage of these medications did not differ across MMP-9 quartiles, suggesting that the present analyses were likely not confounded by these medications. We found higher MMP-9 levels among black participants than those of other race/ethnicity groups, consistent with a previous finding that black individuals have increased expression of MMP-9,[21] which may also contribute to the higher MMP-9 levels seen in the present study cohort overall. Furthermore, we found an increasing prevalence of black race and decreasing prevalence of Hispanic race across quartiles of MMP-9. This finding suggests the possibility of other racial/ethnic determinants affecting expression of the MMP-9, and thus merits further investigation.

MMP-9 has been suggested to play a role in the pathogenesis of unstable atherosclerotic plaques.[5,22,23] However, less has been reported regarding levels of MMP-9 in stable atherosclerosis.[24,25] Our a priori hypothesis that MMP-9 levels would correlate with sub-clinical atherosclerotic disease was not supported as MMP-9 was not significantly associated with either detectable abdominal aortic plaque, CAC > 10 Agatston units, or log-transformed CAC. This finding may be attributable to the relatively young age of the DHS cohort and the overall low risk of CAD. Measurement of circulating MMP-9 levels may not have a role in detecting stable aortic or coronary atherosclerosis in young to middle-aged individuals from the general population.

Aortic wall thickness is an emerging marker of vascular pathology in the aorta. Greater aortic wall thickness has been associated with traditional cardiac risk factors and markers of inflammation, and with incident myocardial infarction.[26–28] In the present study, we demonstrate an independent association between MMP-9 and both aortic wall thickness and aortic luminal diameter. Furthermore, our finding that the first and fourth quartile MMP-9 levels were statistically different with regards to aortic wall thickness and aortic luminal diameter also supports an association between MMP-9 levels and differences in aortic morphology. MMP-9 activity has been shown to be increased in the aortas of individuals with AAA compared to non-diseased aortas, and areas of MMP-9 hyperactivity have been discovered in areas of aneurysm wall weakening and rupture.[4,15,29–31] Non-specific inhibitors of MMPs, such as doxycycline, are being studied as potential therapies in AAAs.[32,33] Newer, more specific therapies targeting MMP-9 expression are also being explored to slow the formation of AAAs.[34–37]

Although both aortic luminal diameter and aortic wall thickness increased with increasing MMP-9, we did not observe an association of MMP-9 with the ratio of aortic luminal diameter/aortic wall thickness. This finding suggests that MMP-9 may be a relatively non-specific marker of aortic remodeling and may not specifically detect early eccentric

remodeling that would be considered a precursor for non-fusiform AAA. The observation that black individuals have higher MMP-9 levels than white individuals, despite having a lower risk for AAA in the literature, questions the causality of MMP-9 in AAA formation.[38] However, our study was cross-sectional and we cannot exclude the association of elevated MMP-9 and aneurysm formation levels closer to the time of AAA development. Nevertheless, the potential role of MMP-9 in the development of aortic dilatation and aneurysm merits further investigation.

The present study has pertinent limitations that must be considered. Our study was cross-sectional and therefore we are unable to explore a temporal or causal relationship in the variables examined. We cannot exclude the possibility that unmeasured confounding may significantly modify the relationships we observed or that the non-significant association between MMP-9 and aortic luminal diameter and CAC may have been due to lack of sufficient statistical power. In addition, we did not assess thoracic aortic morphology, we used plasma levels of MMP-9 as a surrogate measure of MMP-9 activity, and we did not measure levels of other metalloproteinases or tissue inhibitors of metalloproteinases that may also play an important role in aortic biology. Furthermore, while the result of our sensitivity analysis excluding statins was reassuring, we did not have data on whether patients were taking other possible inhibitors of MMP-9.

Conclusion

In this large, ethnically diverse, population-based cohort with detailed aortic phenotyping by MRI, plasma levels of MMP-9 were independently associated with aortic wall thickness and aortic luminal diameter, but not with direct measures of atherosclerosis, suggesting that MMP-9 may not play a role in screening for subclinical atherosclerosis, but supporting the hypothesis that therapies targeting MMP-9 may affect aortic diameter or wall thickness.

Acknowledgments

Funding

Grant support for the Dallas Heart Study was provided by the Donald W Reynolds Foundation and by USPHS GCRC [grant #M01-RR00633 from NIH/NCRR-CR]. MMP-9 measurements were performed at Alere, Inc. (San Diego, CA, USA), who also provided limited administrative support for the study.

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Table 1

Clinical and biological variables by MMP-9 quartile

Variable	MMP-9 quartile (μg/l)				*p*-value (trend)
	Q1: < 6.1	**Q2: 6.1–9.7**	**Q3: 9.8–17.1**	**Q4: > 17.1**	
Age, years	45 [36, 53]	43 [36, 52]	43 [36, 51]	43 [37, 51]	0.057
Men	335 (41%)	361 (44%)	383 (46%)	377 (46%)	0.020
Race / ethnicity					
Black	384 (47%)	369 (45%)	420 (51%)	527 (64%)	< 0.0001
White	240 (29%)	270 (33%)	256 (31%)	209 (25%)	0.068
Hispanic	185 (22%)	159 (19%)	131 (16%)	80 (10%)	< 0.0001
Hypertension	269 (33%)	252 (31%)	271 (33%)	311 (38%)	0.013
Diabetes mellitus	93 (11%)	92 (11%)	87 (11%)	115 (14%)	0.142
Metabolic syndrome	258 (31%)	260 (32%)	278 (34%)	308 (37%)	0.006
Current smoker	155 (19%)	180 (22%)	258 (31%)	370 (45%)	< 0.0001
Hypercholesterolemia	89 (11%)	113 (14%)	112 (14%)	118 (14%)	0.047
Hypertriglyceridemia	75 (9%)	102 (12%)	109 (13%)	107 (13%)	0.013
Body mass index, kg/m^2	28.5 [24.8, 33.1]	29.3 [25.3, 34.3]	29.6 [25.7, 35.1]	30.5 [25.6, 35.8]	< 0.0001

Values shown are median [IQR], *p*-trend from Jonckheere–Terpstra test for continuous variables and prevalence data *n* (%), *p*-trend from Cochran Armitage test for categorical variables.

Table 2

Aortic compliance (AC), wall thickness (AWT), luminal diameter (AD), detectable plaque (AP), and coronary calcium (CAC) across quartiles of plasma MMP-9

Variable	MMP-9 quartile (µg/l)				*p*-value (trend)
	Q1: < 6.1	Q2: 6.1–9.7	Q3: 9.8–17.1	Q4: > 17.1	
AC, ml/mmHg					
Unadjusted	22.9 [15.9, 32.3]	24.1 [16.4, 33.2]	24.0 [16.9, 31.9]	22.9 [15.7, 30.5]	0.54
Adjusted[a]	25.3 [19.3, 30.8]	25.7 [19.9, 30.6]	26.0 [20.8, 30.5]	24.6 [19.0, 30.0]	0.38
AWT, mm					
Unadjusted	1.62 [1.43, 1.81]	1.65 [1.47, 1.81]	1.67 [1.5, 1.85]	1.70 [1.51, 1.89]	< 0.0001
Adjusted	1.68 [1.53, 1.82]	1.68 [1.55, 1.79]	1.69 [1.58, 1.82]	1.73 [1.60, 1.85]	< 0.0001
AD, mm					
Unadjusted	14.0 [12.8, 15.4]	14.0 [12.9, 15.4]	14.1 [12.7, 15.5]	14.1 [12.9, 15.3]	0.89
Adjusted	13.9 [13.1, 15.1]	14.1 [13.1, 15.1]	14.3 [13.2, 15.3]	14.4 [13.5, 15.2]	< 0.0001
AD / AWT ratio					
Unadjusted	8.81 [7.78, 9.74]	8.57 [7.63, 9.64]	8.53 [7.50, 9.46]	8.40 [7.31, 9.36]	< 0.0001
Adjusted	8.56 [8.14, 8.95]	8.61 [8.19, 9.00]	8.59 [8.15, 9.00]	8.55 [8.09, 8.92]	0.37
Detectable AP (%)					
Unadjusted	232 (38%)	211 (35%)	227 (40%)	237 (42%)	0.07
Adjusted	201 (31%)	181 (28%)	178 (28%)	221 (36%)	0.08
Detectable CAC (%)					
Unadjusted	125 (19%)	118 (19%)	148 (23%)	155 (25%)	0.005
Adjusted	74 (13%)	59 (10%)	75 (13%)	84 (15%)	0.20

Values shown are median [IQR], *p*-trend from Jonckheere–Terpstra test for continuous variables and *n* (%), *p*-trend from Cochran Armitage test for categorical variables.

[a]Adjusted for age, sex, race/ethnicity, diabetes mellitus, hypertension, smoking status, body mass index, high total cholesterol, low HDL cholesterol, and high triglycerides.