

# Response of plasma matrix metalloproteinases and tissue inhibitor of metalloproteinases to stent-graft surgery for descending thoracic aortic aneurysms

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**Objective:** The role of matrix metalloproteinases and their tissue endogenous inhibitors has been documented in abdominal aortic aneurysms, but few articles have investigated their role after thoracic aortic aneurysm treatment. Our report investigates matrix metalloproteinases and tissue endogenous inhibitor-1 plasmatic changes in patients who have undergone endovascular aneurysm repair for descending thoracic aortic aneurysms and assesses their clinical significance.

**Methods:** Thirty-two patients with thoracic aortic aneurysms who underwent endovascular aneurysm repair were compared with 25 healthy volunteers. Plasma matrix metalloproteinase-3/matrix metalloproteinase-9 and tissue endogenous inhibitor-1 values were determined by an enzyme-linked immunosorbent assay method at a predetermined time interval.

**Results:** The preoperative levels of matrix metalloproteinases in the endovascular aneurysm repair group were 3-fold and 2-fold higher than those in the control group ( $P < .001$  and  $.02$ , respectively). Matrix metalloproteinase values normalized after endovascular aneurysm repair, whereas patients experiencing endoleaks had higher matrix metalloproteinase values and matrix metalloproteinase-9/tissue endogenous inhibitor-1 ratio compared with the control group ( $P = .003$ ,  $< .001$ , and  $= .02$ , respectively, at 1-month follow-up). These values normalized with the resolution of the endoleak.

**Conclusions:** Plasma matrix metalloproteinase values are increased in patients with thoracic aortic aneurysms, along with reduced tissue endogenous inhibitor-1 expression. Successful endovascular aneurysm repair results in values normalization, whereas high levels persist in patients with endoleaks. The enzyme-linked immunosorbent assay test is a simple and reliable technique that is useful to assess the efficacy of endovascular aneurysm repair and to detect endoleaks.

**T**horacic aortic aneurysms (TAAs) are a serious and potentially lethal disease with high mortality and morbidity rates.<sup>1</sup> Even if atherosclerosis plays an important role in the genesis of TAAs, their formation and progression are a multifactorial process involving both cellular and extracellular processes that have not been extensively examined.<sup>2</sup>

Matrix metalloproteinases (MMPs) are a group of proteases that play an important role in the protein synthetic-lytic equilibrium of connective tissue. The extracellular matrix (ECM) degradation in aneurysm tissue is in part caused by MMPs. In addition, it has been demonstrated that the endogenous tissue inhibitor of metalloproteinases (TIMP) plays a role in the modulation of MMP activity.<sup>3</sup> MMP-3 and MMP-9 are the most important and widespread MMPs in abdominal aortic aneurysm (AAA) wall tissue, and although their role in the destructive rearrangement of the elastic aortic wall components has been well demonstrated in AAA models,<sup>4-8</sup> few reports have demonstrated their role in TAAs.<sup>9-12</sup> Moreover, although the role of MMPs and TIMPs as a marker of successful aneurysm exclusion after

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**Abbreviations and Acronyms**

|       |  |
|-------|--|
| AAA   | = abdominal aortic aneurysm              |
| CT    | = computed tomography                    |
| ECM   | = extracellular matrix                   |
| ELISA | = enzyme-linked immunosorbent assay      |
| EVAR  | = endovascular aneurysm repair           |
| MMP   | = matrix metalloproteinase               |
| TAA   | = thoracic aortic aneurysm               |
| TIMP  | = tissue inhibitor of metalloproteinases |

endovascular aneurysm repair (EVAR) of AAAs has been elucidated,<sup>5-7</sup> no study to date has determined their changes after EVAR of TAAs and their influence on the clinical outcome of patients.

The aim of our report is 2-fold: (1) to investigate the changes of MMP-3, MMP-9, and TIMP-1 in the blood plasma of patients who have undergone EVAR for descending TAAs and (2) to assess their clinical significance.

**Materials and Methods**

From June 2003 to June 2005, 32 patients (group A) who underwent EVAR for TAA were compared with 25 healthy volunteers

**TABLE 1. Clinical characteristics of control group and endovascular aneurysm repair group**

| Clinical variables                           | EVAR group<br>(n = 32) | Control group<br>(n = 25) | P     |
|--|------------------------|---------------------------|-------|
| Age, y                                       | 68.45 ± 5.78           | 66.07 ± 1.29              | .07   |
| Male   | 27 (84.4%)             | 19 (76.0%)                | .5    |
| Diabetes                                     | 9 (28.1%)              | 5 (20.0%)                 | .6    |
| Hypertension                                 | 21 (65.6%)             | 14 (56.0%)                | .5    |
| Ischemic heart disease                       | 4 (12.5%)              | —                         | .07   |
| Previous CABG                                | 3 (9.4%)               | —                         | .1    |
| Previous vascular surgery                    | 3 (9.4%)               | —                         | .1    |
| Renal insufficiency (creatinine > 1.5 mg/dL) | 6 (18.7%)              | —                         | .2    |
| Chronic obstructive pulmonary disease        | 13 (40.6%)             | 4 (16.0%)                 | .08   |
| ASA score                                    | 1.72 ± 0.5             | 1.21 ± 0.4                | .0005 |

EVAR, Endovascular aneurysm repair; CABG, coronary artery bypass graft; ASA, American Society of Anesthesiologists. Data are reported as mean ± standard deviation or n (%).

(group B). The 2 groups were matched for age and sex. Both EVAR and control groups were not on a regimen of statins, acetylsalicylic acid, or angiotensin-converting enzyme inhibitors, or any anti-inflammatory therapy that might affect MMP secretion.

**TABLE 2. Matrix metalloproteinase-3, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 plasma levels, and matrix metalloproteinase-9/tissue inhibitor of metalloproteinase-1 ratio at five different time points**

|                 | Control group<br>(20 patients) | EVAR group<br>(16 patients) | Endoleak group<br>(4 patients) | P value<br>EVAR vs control | P value<br>endoleak vs<br>control | P value<br>endoleak vs<br>EVAR |
|-----------------|--------------------------------|-----------------------------|--------------------------------|----------------------------|-----------------------------------|--------------------------------|
| <b>MMP-3</b>    |                                |                             |                                |                            |                                   |                                |
| Preoperative    | 136.0 ± 73.5                   | 392.2 ± 148.2               | 379.5 ± 14.4                   | <.001                      | <.001                             | NS                             |
| Discharge       | 134.4 ± 74.5                   | 154.6 ± 61.5                | 228.3 ± 15.5                   | NS                         | .001                              | .01                            |
| 1 mo            | 133.8 ± 73.6                   | 152.1 ± 61.6                | 326.0 ± 35.0                   | NS                         | .003                              | .002                           |
| 3 mo            | 135.7 ± 74.4                   | 145.2 ± 86.0                | 224.3 ± 34.4                   | NS                         | .04                               | NS                             |
| 6 mo            | 134.4 ± 73.2                   | 146.8 ± 87.9                | 188.0 ± 6.8                    | NS                         | NS                                | NS                             |
| <b>MMP-9</b>    |                                |                             |                                |                            |                                   |                                |
| Preoperative    | 63.1 ± 38.7                    | 124.1 ± 58.0                | 113.6 ± 29.4                   | .02                        | .02                               | NS                             |
| Discharge       | 64.8 ± 39.6                    | 97.3 ± 57.7                 | 126.0 ± 19.7                   | NS                         | .01                               | NS                             |
| 1 mo            | 64.4 ± 39.8                    | 92.3 ± 55.2                 | 150.0 ± 15.6                   | NS                         | <.001                             | .02                            |
| 3 mo            | 63.8 ± 40.0                    | 70.4 ± 46.2                 | 130.3 ± 32.2                   | NS                         | .02                               | .02                            |
| 6 mo            | 65.3 ± 40.8                    | 70.9 ± 50.8                 | 83.8 ± 27.2                    | NS                         | NS                                | .04                            |
| <b>TIMP</b>     |                                |                             |                                |                            |                                   |                                |
| Preoperative    | 11.1 ± 7.6                     | 5.4 ± 3.8                   | 5.9 ± 1.5                      | .04                        | NS                                | NS                             |
| Discharge       | 11.2 ± 8.0                     | 8.1 ± 4.8                   | 8.8 ± 2.5                      | NS                         | NS                                | NS                             |
| 1 mo            | 10.9 ± 7.5                     | 8.8 ± 5.4                   | 7.5 ± 2.6                      | NS                         | NS                                | NS                             |
| 3 mo            | 11.2 ± 7.8                     | 12.5 ± 7.9                  | 14.5 ± 6.1                     | NS                         | NS                                | NS                             |
| 6 mo            | 10.5 ± 7.3                     | 11.3 ± 8.8                  | 14.8 ± 3.8                     | NS                         | NS                                | NS                             |
| <b>MMP/TIMP</b> |                                |                             |                                |                            |                                   |                                |
| Preoperative    | 8.7 ± 7.0                      | 24.5 ± 9.7                  | 15.0 ± 3.6                     | .003                       | .005                              | NS                             |
| Discharge       | 8.8 ± 6.9                      | 14.4 ± 8.4                  | 22.1 ± 8.4                     | .01                        | .008                              | .01                            |
| 1 mo            | 8.3 ± 5.2                      | 13.9 ± 6.9                  | 22.2 ± 4.7                     | .01                        | .02                               | .01                            |
| 3 mo            | 8.1 ± 6.8                      | 6.3 ± 1.2                   | 9.7 ± 2.3                      | NS                         | NS                                | .006                           |
| 6 mo            | 9.0 ± 6.8                      | 7.2 ± 3.6                   | 8.7 ± 5.3                      | NS                         | NS                                | NS                             |

EVAR, endovascular aneurysm repair; TIMP, tissue inhibitor of metalloproteinases; NS, not significant.

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