

## Aminoterminal Propeptide of Type III Procollagen and Matrix Metalloproteinases-2 and -9 Failed to Serve as Serum Markers for Abdominal Aortic Aneurysm

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**Objectives.** Matrix-metalloproteinase (MMP)-2 and -9 and aminoterminal propeptide of type III collagen (NIIINP) have been reported to be elevated in patients with abdominal aortic aneurysm (AAA). The aim of our study was to test NIIINP, MMP-2 and -9 as potential serum markers for AAA in a large population group at risk for AAA.

**Methods.** Fifty-five to 70 year old men were screened for AAA by abdominal ultrasound. Simultaneously, blood samples were taken and the patients were interviewed for known risk factors for AAA. Patients with a dilatation of the infrarenal aorta of  $\geq 25$  mm (Group 1, n=76) were compared to randomly assigned patients with normal aortic diameters (Group 2, n=83). A third group consisted of patients scheduled for operation of AAA (n=19).

**Results.** A total of 987 men were investigated with ultrasound. Seventy-six (7.7%) had an aortic dilatation  $\geq 25$  mm. Aortic dilatation was correlated with age (P=0.0001). However, serum levels of NIIINP and MMP 2 were not different between the three groups of patients. For MMP-9 there was a weak inverse correlation with lower serum levels in patients with aortic dilatation (P=0.043).

**Conclusions.** Both MMP-2 and -9 and NIIINP failed to show relevance as serum markers for aortic dilatation. Our results are, therefore, in contradiction to previous published results. AAAs cannot be diagnosed with a simple blood test.

**Keywords:** Abdominal aortic aneurysm; Serum marker; Metalloproteinases.

### Introduction

Ruptured abdominal aortic aneurysm (AAA) is associated with a high rate of fatality and is an important cause of sudden death.<sup>1,2</sup> Early detection through screening has been the only available way of detecting the majority of AAA in the community.<sup>3-9</sup> Degradation of extracellular matrix proteins in the aortic wall is a key event in the formation of AAA, resulting in decreased elastin concentration and increased collagen turnover. Several studies have shown the presence and involvement of matrix metalloproteinases (MMP) and aminoterminal propeptide of type III procollagen (NIIINP) in AAA disease. Theoretically, highly expressed soluble MMP or NIIINP could be continuously released into the systemic circulation and be measurable in the blood of patients with AAA. Preliminary studies have

suggested this concept.<sup>10-15</sup> The purpose of our study was to determine the validity of MMP-2 and -9 and NIIINP as serum markers for AAA in a large cohort at risk for AAA.

### Patients and Methods

We were invited to join a large prospective study initiated by our colleagues from urology. The study invites all male inhabitants at the age of 55–70 years from our county (i.e. 45,000) to undergo a prospective control for prostatic cancer. During 1999–2001, 1300 men were randomly assigned by postal code and invited by letter to screen for AAA. One thousand and forty-one (80%) agreed. Thirty-two men (3%) had exclusion criteria (i.e. surgery during the last 6 months, liver disease, cancer or rheumatoid arthritis). Twenty-two did not show up for ultrasound despite repetitive invitation and were excluded. Finally, 987 men were enrolled in the study. All participants gave written informed consent. The study was approved by

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the local ethical committee and the procedures were in accordance with institutional guidelines.

The diameter of the infrarenal aorta was measured by ultrasound (Panther 2002 Advanced Diagnostic Imaging, B-K Medical, Germany) in an anterior-posterior direction by three investigators. The largest diameter was chosen. The first 20 examinations of each investigator were cross-checked by an experienced radiologist to control for accuracy. Twenty milliliter of blood was obtained from the cubital vein of each participant and stored at  $-25^{\circ}\text{C}$ . All participants were screened with a standardized questionnaire for smoking (current or past 5 years), hypertension, diabetes mellitus and first-degree relatives with known aneurysmal disease. Group 1 consisted of patients with aortic dilatation  $\geq 25$  mm. A control group of 83 men without aortic dilatation comprised Group 2. These men were chosen at random (frequent given name) from the remaining 911 men without aortic dilatation  $> 25$  mm. Group 3 ( $n=19$ ) consisted of patients with known AAA that were operated on during study recruitment.

Serum levels of MMP-2 and -9 and NIIINP were determined in all three groups. MMP-2 and -9 were batch-analyzed with use of a commercially available enzyme-linked immunosorbent assay (ELISA) kit specific for human MMP-2 and -9 (Amersham Biosciences Europe GmbH, Freiburg, Germany). All samples were analyzed in duplicate and averaged. If the MMP sample levels from a patient varied by  $> 10\%$ , the serum was retested in triplicate and the averaged value was taken. The within-assay precision ( $< 6\%$ ) and the between-assay precision ( $< 10\%$ ) were determined by the manufacturer. PIIINP values were determined with a standardized radioimmuno-assay test (Orion Diagnostica, Espoo, Finland) in the same fashion.

Data were analyzed by STATA (Stata Corporation, College Station, TX, USA). All data are presented as mean  $\pm$  SD. The Wilcoxon's rank test was used to compare two groups with measured values and the Kruskal-Wallis test was used to compare more than two groups. Rank correlation according to Spearman was used to assess dependent variables. Statistical significance was set at  $P < .05$ .

## Results

### Age and aortic diameter

Aortic dilatation  $\geq 25$  mm was present in 76 (7.7%) of the 987 men. A diameter of 5 cm or more was found in

**Table 1. Comparison of patients divided into age groups and dilatation of the aorta at 25 shows normal distribution between groups**

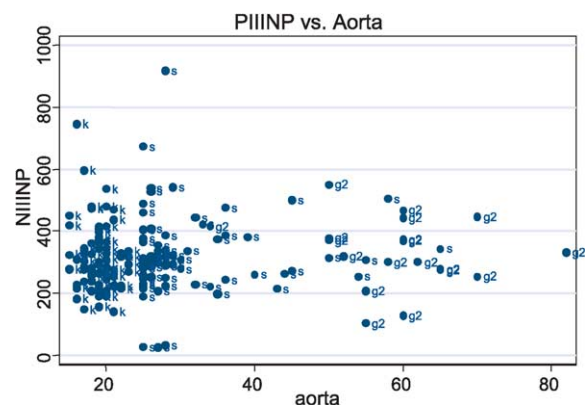
Age	Aorta $\geq 25$ mm	
55–59 years ( $n=332$ )	$n=16$ (4.8%)	
60–64 years ( $n=345$ )	$n=25$ (7.2%)	
65–70 years ( $n=310$ )	$n=35$ (11.3%)	
All ( $n=987$ )	$n=76$ (7.6%)	$P=.0001$

Expansion of aortic diameter with increasing age is significant ( $P=.0001$ ).

five (0.5%) patients. The mean age of all men was 62.1 ( $\pm 4.3$ ) years. The mean age of men with aortic dilatation  $\geq 25$  mm was 63.6 ( $\pm 4.1$ ) years. Age was distributed normally within age groups (55–59, 60–64 and 65–70 years). Aortic diameter was correlated to patients age ( $P=0.0001$ , Table 1).

### Serum values and aortic diameter

Mean values for NIIINP were  $322 \pm 130$   $\mu\text{g/l}$  (range 27–919),  $312 \pm 101$   $\mu\text{g/l}$  (range 143–748) and  $334 \pm 113$   $\mu\text{g/l}$  (range 104–552) in Groups 1, 2 and 3, respectively. Differences between groups were not statistically significant (Table 2, Fig. 1). MMP-2 mean values were  $1473 \pm 287$  (range 880–2320),  $1468 \pm 343$  (152–2640) and  $1432 \pm 328$  (980–2140) ng/ml in Groups 1, 2 and 3, respectively. There was no statistical difference between the three groups (Table 2, Fig. 2). For MMP-9 mean values were as follows: Group 1  $371 \pm 284$  (range 108–2044) ng/ml, Group 2  $455 \pm 499$  (102–4480) ng/ml and Group 3  $281 \pm 125$  (108–502) ng/ml. These differences showed a weak statistical significance between the three groups ( $P=0.043$ ,



**Fig. 1.** Distribution of serum values of NIIINP in relation to aortic diameter (mm).  $P=.378$  for comparison of all three groups (Kruskal-Wallis test). Aorta, aortic diameter; s, values of Group 1 (patients with aortic dilatation  $\geq 25$  mm,  $n=76$ ); k, values of Group 2 (randomized population without aortic dilatation,  $n=83$ ); g2, values of Group 3 (patients operated on for AAA,  $n=19$ ).

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