UvA-DARE (Digital Academic Repository)

Thrombin-activatable fibrinolysis inhibitor and its relation with inflammation in rheumatoid arthritis

Peters, M.J.L.; Nurmohamed, M.T.; van Eijk, I.C.; Verkleij, C.J.N.; Marx, P.F.

DOI

[10.1136/ard.2008.097485](https://doi.org/10.1136/ard.2008.097485)

Publication date

2009

Document Version

Final published version

Published in

Annals of the Rheumatic Diseases

[Link to publication](#)

Citation for published version (APA):

Peters, M. J. L., Nurmohamed, M. T., van Eijk, I. C., Verkleij, C. J. N., & Marx, P. F. (2009). Thrombin-activatable fibrinolysis inhibitor and its relation with inflammation in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 68(7), 1232-1233.
<https://doi.org/10.1136/ard.2008.097485>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)

Thrombin-activatable fibrinolysis inhibitor and its relation with inflammation in rheumatoid arthritis

M J L Peters, M T Nurmohamed, I C van Eijk, et al.

Ann Rheum Dis 2009 68: 1232-1233

doi: 10.1136/ard.2008.097485

Updated information and services can be found at:

<http://ard.bmj.com/content/68/7/1232.full.html>

These include:

References

This article cites 8 articles, 2 of which can be accessed free at:

<http://ard.bmj.com/content/68/7/1232.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:

<http://ard.bmj.com/cgi/reprintform>

To subscribe to *Annals of the Rheumatic Diseases* go to:

<http://ard.bmj.com/subscriptions>

Thrombin-activatable fibrinolysis inhibitor and its relation with inflammation in rheumatoid arthritis

Rheumatoid arthritis (RA) is associated with an excessive risk of cardiovascular morbidity and mortality, and inflammation appears to be the missing link explaining this markedly elevated risk.¹ Inflammation is a potent inducer of coagulation and

fibrinolysis and may contribute to atherosclerotic and thrombotic components of cardiovascular events.² Thrombin-activatable fibrinolysis inhibitor (TAFI), a procarboxypeptidase in plasma, is a regulatory protein of the coagulation/fibrinolysis balance as well as inflammation. TAFIa, the activated form of TAFI, acts by removing C-terminal arginine and lysine residues from substrates such as fibrin degradation products, bradykinin and the anaphylatoxins C3a and C5a. Elevated TAFI levels may reflect an enhanced risk of developing cardiovascular disease, although evidence for this is somewhat contradictory since the

Table 1 Characteristics from patients with rheumatoid arthritis (RA) in high versus low inflammatory state

	CRP > 10 mg/litre	CRP < 10 mg/litre	p Value
Demographic:			
Age (years)	63 (9)	63 (8)	0.74
Men, %	33	33	0.97
Disease activity:			
CRP (mg/litre)	59 (51 to 72)	1 (1)	<0.01
ESR (mm/h)	61 (47 to 71)	10 (5 to 11)	<0.01
DAS28 (0–10)	5.5 (1.0)	3.0 (1.1)	<0.01
Disease duration (years)	7 (4 to 10)	8 (5 to 10)	0.97
Disease severity:			
Erosions, %	62	95	0.01
RF positive, %	80	76	0.77
Drug therapy:			
NSAIDs, %	76	67	0.50
Methotrexate, %	52	67	0.37
Prednisone, %	33	24	0.50
Calcium supplementation, %	33	24	0.50
Aspirin, %	14	19	0.68
Statin, %	5	33	0.02
TAFI polymorphisms:			
Thr147Ala			
Thr/Thr, %	5	0	0.44
Thr/Ala, %	52	52	
Ala/Ala, %	43	48	
Thr325Ile			
Thr/Thr, %	48	29	0.59
Thr/Ile, %	43	57	
Ile/Ile, %	9	14	
TAFI levels (%)	147 (129 to 163)	114 (102 to 127)	<0.01

Data are expressed as mean (SD), median (interquartile ranges (IQR)), or as percentages of the total (%). Differences in baseline characteristics between both groups were evaluated by using independent t tests for normally distributed variables, Mann-Whitney U tests for skewed variables and Pearson χ^2 tests for dichotomous variables. Significant results are in bold.

CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; TAFI, thrombin-activatable fibrinolysis inhibitor.

use of genotype-sensitive assays complicates interpretation of the data.³⁻⁵ Furthermore, TAFI levels associate with acute phase reactants in patients with cardiovascular disease and are elevated in patients with RA, as compared with non-RA controls.^{6,7} TAFI's dual function in regulating haemostatic and inflammatory processes makes it an interesting protein to study in relation to RA. The objective of this study was to determine TAFI levels and its relation with inflammation in patients with RA.

In this study, the serum C-reactive protein (CRP) concentration was used to express the level of inflammation. A total of 21 patients with RA with normal CRP levels (low inflammatory state; <10 mg/litre) and 21 age-matched and sex-matched patients with RA with elevated CRP levels (high inflammatory state) were selected for evaluation of TAFI levels. All patients with RA attended the outpatient clinic at the Jan van Breemen Institute (Amsterdam, The Netherlands) where they were seen by a research doctor, and completed a questionnaire recording demographic data, medical and medication history (table 1). The local ethics committees approved the study protocol and all participants signed a written informed consent. TAFI levels were determined with a genotype-insensitive kinetic activity assay in which the zymogen is first quantitatively converted to TAFIa, as described previously.⁸ TAFI levels were expressed as the percentage of a plasma pool of 20 healthy volunteers.

TAFI levels were significantly higher in patients with RA with elevated CRP levels. These differences disappeared after adjustment for inflammation by means of erythrocyte sedimentation rate (ESR) or 28-joint Disease Activity Score (DAS28). Separate adjustments for potential other confounders (ie, age, gender, disease duration, IgM-rheumatoid factor (RF), the use of statins, aspirin, calcium supplementation, non-steroidal anti-inflammatory drugs (NSAIDs), prednisone or methotrexate) did not change these results. No differences in TAFI levels in this small population were found between patients with RA stratified for the TAFI polymorphisms 147 and 325.

In conclusion, we report that TAFI levels are significantly higher in the plasma of patients with RA with a high inflammatory state. This finding supports the need for prospective studies investigating the association between TAFI levels and cardiovascular disease as, on the one hand, high TAFI levels may facilitate the development of cardiovascular comorbidity by

shifting the haemostatic balance to a more hypofibrinolytic state and, on the other hand, TAFI levels may relate to the body's mechanisms dampening the excessive inflammatory reaction found in patients with RA.

M J L Peters,¹ M T Nurmohamed,^{1,2} I C van Eijk,² C J N Verkleij,³ P F Marx³

¹ Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands; ² Department of Rheumatology, Jan van Breemen Institute, Amsterdam, The Netherlands; ³ Department of Experimental Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to: P F Marx, Academic Medical Center, Department of Experimental Vascular Medicine, Meibergdreef 9, 1105 AZ (Room G1-145), Amsterdam, The Netherlands; p.f.marx@amc.uva.nl

Competing interests: None declared.

Ethics approval: The local ethics committees approved the study protocol and all participants provided written informed consent.

Accepted 29 September 2008

Ann Rheum Dis 2009;**68**:1232–1233. doi:10.1136/ard.2008.097485

REFERENCES

1. **Van Doornum S**, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;**46**:862–73.
2. **Sattar N**, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003;**108**:2957–63.
3. **Juhan-Vague I**, Morange PE, Aubert H, Henry M, Aillaud MF, Alessi MC, *et al*. Plasma thrombin-activatable fibrinolysis inhibitor antigen concentration and genotype in relation to myocardial infarction in the north and south of Europe. *Arterioscler Thromb Vasc Biol* 2002;**22**:867–73.
4. **Juhan-Vague I**, Morange PE. Very high TAFI antigen levels are associated with a lower risk of hard coronary events: the PRIME Study. *J Thromb Haemost* 2003;**1**:2243–4.
5. **Schroeder V**, Chatterjee T, Mehta H, Windecker S, Pham T, Devantay N, *et al*. Thrombin activatable fibrinolysis inhibitor (TAFI) levels in patients with coronary artery disease investigated by angiography. *Thromb Haemost* 2002;**88**:1020–5.
6. **Silveira A**, Schatteeman K, Goossens F, Moor E, Scharpe S, Stromqvist M, *et al*. Plasma procarboxypeptidase U in men with symptomatic coronary artery disease. *Thromb Haemost* 2000;**84**:364–8.
7. **So AK**, Varisco PA, Kemkes-Matthes B, Herkenne-Morard C, Chobaz-Peclat V, Gerster JC, *et al*. Arthritis is linked to local and systemic activation of coagulation and fibrinolysis pathways. *J Thromb Haemost* 2003;**1**:2510–15.
8. **Willemsse JL**, Leurs JR, Hendriks DF. Fast kinetic assay for the determination of procarboxypeptidase U (TAFI) in human plasma. *J Thromb Haemost* 2005;**3**:2353–5.