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Letter to the Editors-in-Chief

Coagulation factor XIII-A subunit and activation peptide levels in individuals with established symptomatic acute deep vein thrombosis

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Dear Editors,

Plasma factor XIII (FXIII) is a hetero-tetramer of two protransglutaminase A- and two carrier B-subunits (FXIII-A_2B_2). Activation of FXIII-A_2B_2 into the active transglutaminase FXIIIa is initiated by thrombin cleavage of the activation peptide (AP-FXIII) from FXIII-A followed by dissociation of the A- and B-subunits. FXIIIa stabilises fibrin clots by cross-linking fibrin strands and incorporating anti-fibrinolytic proteins into the clots [1]. We have shown earlier that AP-FXIII is released into plasma upon FXIII activation and can be measured by ELISA [2,3]. In a pilot study we have shown that AP-FXIII was not detectable in healthy volunteers but could be quantified in 34 out of 66 patients with acute ischaemic stroke. Higher AP-FXIII levels were associated with more severe stroke and worse prognosis [4]. Contrary to arterial thrombosis, FXIII levels have rarely been studied in venous thromboembolism (VTE). A small study demonstrated a significant decrease in FXIII-A subunit antigen levels in 19 patients with acute deep vein thrombosis (DVT) compared with 12 controls [5]. We found significantly lower FXIII-A subunit levels in 71 patients with acute pulmonary embolism (PE) compared with 49 controls [6]. In the non-acute phase, FXIII levels did not differ between patients with a history of DVT and controls [7], and in a prospective study, FXIII levels were not altered in individuals who later developed VTE compared with individuals who remained free of VTE [8].

The aim of the present study was to measure FXIII-A subunit antigen levels in a larger patient population with acute symptomatic DVT and to investigate for the first time whether free AP-FXIII can be detected in plasma samples from patients with acute DVT.

Plasma samples were obtained from consecutive patients referred for suspected acute symptomatic DVT of the leg to the Academic Medical Center in Amsterdam, The Netherlands, between September 1999 and May 2006. DVT was diagnosed when a proximal leg vein was not compressible on ultrasound or by the presence of an intraluminal-filling defect on venography. If compression ultrasound showed no venous thrombosis and the D-dimer plasma level was ≥ 0.5 mg/L, compression ultrasound was repeated after 7 days. DVT was ruled out in case of a Wells score ≤ 1 in combination with a low plasma D-dimer level (< 0.5 mg/L), normal venography, or negative compression ultrasound in combination with a low D-dimer level (< 0.5 mg/L) or after a repeated negative ultrasound. On the basis of plasma availability, we selected 134 plasma samples of patients with a first DVT (cases) and 171 plasma samples of patients with a clinical suspicion of DVT but in whom DVT was objectively excluded (controls). Controls had no history of previous VTE and were individually matched to the cases for sex and age. Patients with DVT were selected irrespective of the presence of thrombophilia or comorbidities. Patient characteristics were assessed using a structured questionnaire in all patients before objective testing for DVT. The study was approved by the institutional medical ethics board and all patients provided written informed consent.

FXIII-A subunit antigen levels were measured by ELISA [9] and expressed in percent relative to a normal reference plasma (CRYOcheck™ Normal Reference Plasma, Precision BioLogic, Dartmouth NS, USA). AP-FXIII antigen levels were measured by an in-house ELISA with two monoclonal antibodies [3,4].

Statistical analyses were performed with SPSS (version 22.0) software (SPSS, Chicago, IL). Patient characteristics and FXIII variables were tested for normality (Shapiro-Wilk test, skewness, kurtosis, visual inspection of histograms). Differences between FXIII-A subunit levels were analysed using unpaired *t*-tests unless stated otherwise. Differences between AP-FXIII were analysed using Mann Whitney *U* tests. Associations between FXIII-A subunit levels and the diagnosis of DVT were evaluated by logistic regression and expressed as Odds Ratios (OR) and 95% confidence intervals (95% CI). The highest (fifth) quintile of FXIII-A subunit levels of controls served as reference category. The potential confounding influence of malignancy, recent immobilisation, and hospitalisation < 6 months before presentation, were evaluated using multivariate logistic regression models. Statistical significance in all analyses was set at $p < 0.05$.

The demographic characteristics did not differ between the 134 cases and 171 controls. The mean age was 59 years (± SD 16) in cases and 58 years (± SD 16) in controls. Among the cases, 46% were male and 47% among the controls. There was concomitant malignancy in 17% of cases and 12% of controls. As expected, known risk factors of DVT such as immobilisation, hospitalisation and oral contraceptive use were more prevalent among cases.

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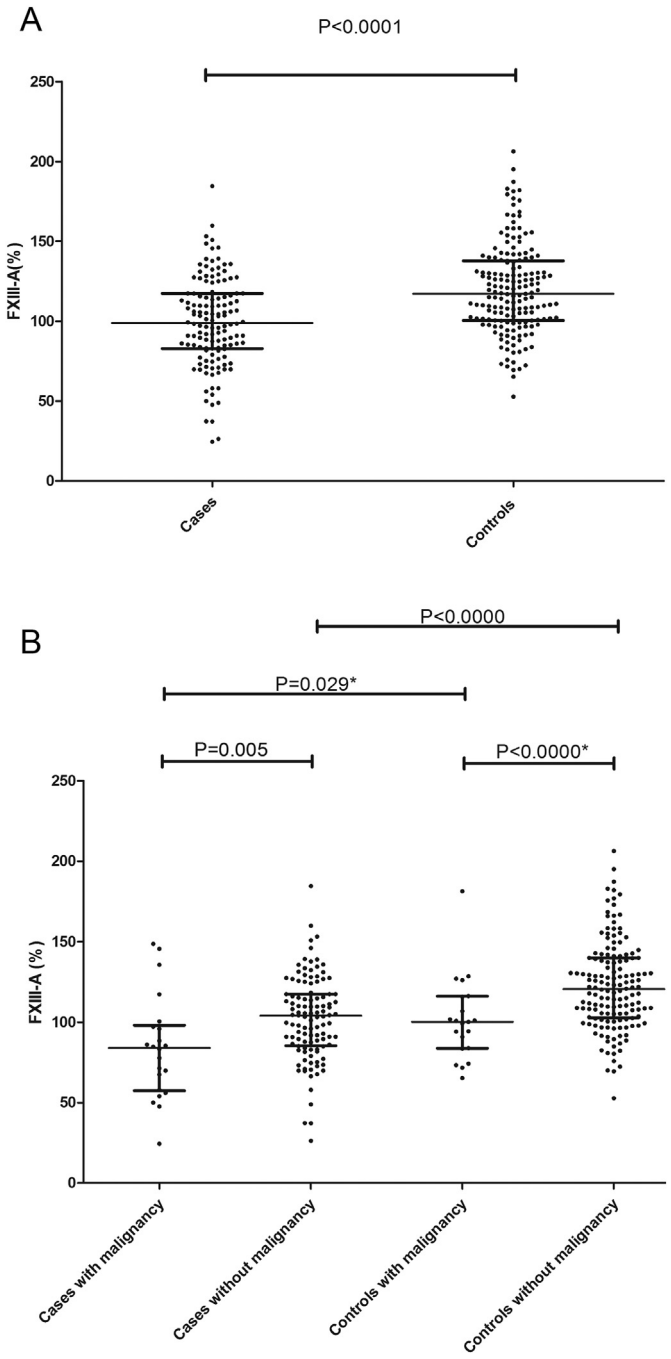

Fig. 1. Levels of FXIII-A subunit in DVT cases and controls. Levels of FXIII-A subunit in 134 cases and 171 controls (A) and levels of FXIII-A subunit stratified into groups with and without malignancy (B). Medians and interquartile ranges are depicted. * Groups were compared by means of Mann Whitney *U* test instead of *t*-test.

Table 1
Association between plasma FXIII-A subunit level and presence of DVT comparison to the highest quintile of controls (reference category).

Quintiles of FXIII-A (%) in controls	Cases (n = 134)	Controls (n = 171)	Odds ratio (95% CI)	Odds ratio (95% CI) (adjusted)[a]
Quintile 5 (> 141.9)	7	34	1 (ref.)[b]	1 (ref.)[b]
Quintile 4 (141.9–125.8)	19	34	2.71(1.01–7.29)	2.86 (1.04–7.86)
Quintile 3 (125.8–109.7)	23	35	3.19 (1.21–8.41)	3.18 (1.16–8.71)
Quintile 2 (109.7–97.8)	21	34	3.00 (1.13–7.98)	2.61 (0.95–7.19)
Quintile 1 (< 97.8)	64	34	9.14 (3.67–22.80)	7.74 (3.04–19.74)

[a] Odds Ratios were adjusted for malignancy, recent immobilisation and hospitalisation by means of logistic regression.
[b] Fifth quintile of controls; reference category.