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## John Hageman's factor and deep-vein thrombosis: Leiden Thrombophilia Study

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**Summary.** Because the relationship between factor XII deficiency and venous thrombosis is unclear and study results seem contradictory, we undertook a population-based case-control study.

Among 350 unselected patients younger than 70 years, with a first, objectively confirmed, episode of deep-vein thrombosis and without underlying malignant disease we detected a 6% frequency (21/350 patients) of factor XII deficiency (activity level <57%). Among 350 healthy control subjects, matched for age and sex, the frequency was 5% (18 subjects). Thus there is no increase in

prevalence of factor XII deficiency among thrombosis patients and no increase in thrombosis risk for subjects with low factor XII levels (matched odds ratio 1.2 (95% CI 0.6–2.4)). In addition, there was no relation between strata of factor XII levels and thrombosis risk. In conclusion, we do not consider factor XII to be a determinant of deep-vein thrombosis.

**Keywords:** clotting factor XII, Hageman factor, venous thrombosis, case-control study.

Clotting factor XII (Hageman's factor) is involved in the initiation of the intrinsic coagulation pathway and in fibrinolysis (Kaplan & Silverberg, 1987). Theoretically, deficiencies of factor XII may result in reduced coagulation (bleeding risk) or reduced fibrinolytic activity (thrombosis risk). There is a general consensus that factor XII deficiency usually does not result in a haemorrhagic diathesis and only exceptionally has a mild bleeding tendency been reported in subjects with severe factor XII deficiency (Haanen *et al*, 1960; Didisheim, 1962; Ikkala *et al*, 1971). Its relationship with overt venous thrombosis is still unclear. Some investigators have reported high prevalences of factor XII deficiency in patients with (recurrent) arterial and venous thrombosis (Mannhalter *et al*, 1987; Halbmayr *et al*, 1992). However, von Känel *et al* (1992) found no significant differences in factor XII levels between thrombophilic patients and control subjects, and subnormal factor XII values were found equally frequent in patients and control subjects.

To further elucidate these obviously contradictory results, we have investigated 350 unselected patients, aged less than 70, with a first, objectively confirmed, episode of deep-vein

thrombosis and without underlying malignant disease, and compared the plasma levels of factor XII with that of matched healthy control subjects. This work was performed as part of an ongoing population-based case-control study on hereditary venous thrombosis: the Leiden Thrombophilia Study (LETS).

### MATERIALS AND METHODS

Included were the first 350 patient-control pairs of the larger study. The selection procedures for patients and control subjects have been described in detail previously (Koster *et al*, 1993). Briefly, consecutive patients, younger than 70 years, who were referred for anticoagulant treatment after a first, objectively confirmed, episode of deep vein thrombosis that occurred between 1 January 1988 and 31 December 1992 were selected from the files of the anticoagulation clinics in Leiden, Amsterdam and Rotterdam. For each patient we had one healthy control who matched for age and sex.

The median time between the occurrence of the deep-vein thrombosis and venepuncture for this study was 18 (range 6–48) months. Factor XII coagulant activity (FXII:C) was measured by one-stage clotting assay using factor XII deficient plasma and Automated APTT (Organon Teknica,

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Durham, U.S.A.) on an Electra 1000c (MLA, Pleasantville, U.S.A.).

A reference range for factor XII was derived from the 350 healthy control subjects. After natural logarithmic transformation of the data and exclusion of two subjects with values below three standard deviations (SD) of the mean, the lower limit of the normal factor XII distribution was 57% (mean - 1.96 SD). We calculated crude matched odds ratios as estimates of the relative risk by simple cross tabulation. We used Miettinen's test-based 95% confidence limit. Since plasma factor XII has a continuum of values instead of binary outcomes, we calculated matched odds ratios, as estimates of the relative risk, over several factor XII strata, with 95% confidence limits.

## RESULTS

The male/female ratio among patients and controls was 1/1.5 and mean age was 46 years (range 17-70 patients, 17-73 controls).

Three patients had an initially prolonged APTT consistent with a lupus anticoagulant. Only one of them had a lower factor XII level (32%).

The mean (range) factor XII coagulant activity was 104% (19-186) for the patients and likewise for the controls (18-191).

Fig 1 shows that we found approximately the same number of individuals with low levels in patients and controls, regardless of the cut-off point used. If we apply our lower limit of normal (factor XII activity of 57%), 21 (6%) patients and 18 (5%) controls had low factor XII levels. There were 33 discordant patient-control pairs, in 18 of which the patients had low factor XII level and the control subjects did not, thus resulting in a matched odds ratio of 1.2 (95% CI 0.6-2.4), i.e. no increase in risk of thrombosis associated with low factor XII levels.

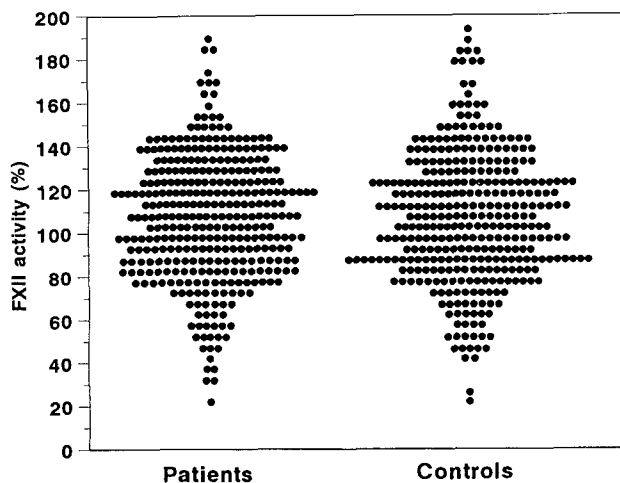


Fig 1. Factor XII activity levels of thrombosis patients and controls.

Table I. Thrombosis risk for strata of factor XII.

Factor XII activity (%)	Patients	Controls	Odds ratio (95% CI)
≥ 100	198	190	1*
60-100	129	138	0.9 (0.7-1.2)
30-60	21	20	1.0 (0.5-2.0)
<30	2	2	1.0 (0.1-7.0)

\* Reference category.

Table I gives the odds ratios for the strata of factor XII levels. It shows no relation between the risk of thrombosis and levels of factor XII, even for levels below 30% of normal.

## CONCLUSION

The finding of a similar 5-6% prevalence of reduced factor XII levels in 350 unselected patients, with a first, objectively diagnosed, episode of venous thrombosis, and in healthy age- and sex-matched controls, leads to the conclusion that reduced factor XII levels are fairly common and that these low levels do not represent an increased risk of deep-vein thrombosis.

We did not find a subject with a homozygous or double heterozygous factor XII deficiency (FXII < 1%). Therefore our results only apply to heterozygous subjects or to individuals with lowered levels. Since factor XII is only a weak plasminogen activator and because there is still no convincing evidence to support a causal relation between thromboembolism and abnormalities of the fibrinolytic system (Preston & Briët, 1993), one is tempted to theorize that homozygous factor XII deficiency will also prove not to be a predisposing cause of venous thrombosis. Therefore it might be that John Hageman's pulmonary embolism cannot be ascribed to his factor XII deficiency, but was more probably due to his fractured hemipelvis and subsequent bedrest (Ratnoff *et al*, 1968).

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