Elevated factor XIII level and the risk of myocardial infarction in women

Factor XIII (FXIII) activity and antigen levels were determined in 955 patients investigated by coronary angiography. Patients were sub-grouped according to the presence or absence of coronary sclerosis (CS^+, CS^-) and a positive history of myocardial infarction (MI^+, MI^-). In females, but not in males, adjusted FXIII activity and antigen levels were significantly elevated in the CS^+MI^+ group compared to in the CS^+MI^- group. FXIII levels in the upper tertile were associated with significantly increased risk of MI in females, but not in males.

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Coronary artery disease (CAD) is a major health issue in both women and men, however the time of its onset, the course of the disease the presentation of clinical symptoms and the response to therapy show gender-specific features.[1,2] Fibrinogen and the fibrinolytic inhibitor PAI-1 are the most well-established hemostatic risk factors for CAD and gender-related differences could also be demonstrated concerning the effects of these risk factors.[3,4] Factor XIII (FXIII) is intimately related to fibrinogen and is a key factor in the regulation of fibrinolysis.[5] Its active form (FXIIIa) cross-links fibrin α- and γ-chains and covalently attaches α_2-plasmin inhibitor to fibrin. In this way, FXIIIa mechanically stabilizes fibrin and protects it from the fibrinolytic system.

In the present study FXIII activity and antigen levels were measured in a large number of patients with suspected CAD using REA-chrom FXIII and R-ELISA FXIII (Reanal) reagent kits, respectively.[6,7] Nine hundred and fifty-five consecutive patients admitted for coronary angiography were recruited for the study. Patients with ≥50% stenosis in a major coronary artery or in one of its branches were defined as having coronary sclerosis (CS^+). The diagnosis of myocardial infarction (MI^+) was established at the time of its onset according to WHO criteria. At least 3 months were allowed to elapse between the MI and the time of obtaining blood samples for analysis. Patients without significant coronary stenosis and with no history of MI were considered as the clinical control group (CS^-MI^-) to which subgroups of patients with CS and/or MI (CS^+MI^-, CS^-MI^+ and CS^+MI^+) were compared. Ethical approval was obtained from the University of Debrecen Ethics Committee, and the subjects gave informed consent.

Serum cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, apoAI, apoB, lipoprotein (a), homocysteine and fibrinogen were determined by routine laboratory methods. Age, current smoking, body mass index, and the presence of hypertension and diabetes mellitus were recorded. The median age of the women was 57.7 years; 91.7% were menopausal and they were not on hormonal replacement therapy.

Neither FXIII activity nor FXIII antigen levels of the clinical controls differed significantly from those measured in the healthy reference population. Multiple linear regression demonstrated that gender, smoking, cholesterol and fibrinogen levels were independently associated with FXIII activity and FXIII antigen levels, and mean FXIII levels adjusted for these parameters were used in the analysis.

CS and/or MI did not influence adjusted FXIII levels in either the overall population or in the male patients (Table 1). The relationship between CAD and plasma FXIII levels has been investigated in only a few studies including relatively low numbers of males or predominantly male patients.[8-10] The basically negative outcome of these studies agrees well with the results of the present study. The effect of CS or MI on FXIII levels in females has not been addressed previously. CS alone did not have an effect in females, either. However, when CS^+ females with and without a history of MI were compared, statistically significant elevations of both FXIII activity and antigen levels were observed in the MI^+ group. The comparison of CS^+MI^+ group to clinical controls also revealed a significant elevation of FXIII antigen. Given the small number of patients, the difference between the group with the highest FXIII levels (CS^-MI^+)

Table 1. Adjusted FXIII levels in different groups of male and female patients.*

Patient groups (female/male)	*CS^-MI^- (178/124)*	*CS^-MI^+ (11/23)*		*CS^+MI^- (112/200)*		*CS^+MI^+ (76/231)*	
	Mean (95% CI)	*Mean (95% CI)*	*p value**	*Mean (95% CI)*	*p value**	*Mean (95% CI)*	*p value**
FXIII activity (%)							
total	103 (100-106)	106 (98-114)	0.45	101 (98-104)	0.19	102 (99-105)	0.59
female	101 (96-107)	112 (97-126)	0.16	98 (92-105)	0.28	107 (100-115)°	0.09
male	103 (99-107)	103 (94-113)	0.88	101 (97-105)	0.55	101 (97-104)	0.39
FXIII antigen (mg/L)							
total	22.9 (22.2-23.6)	24.0 (22.2-25.8)	0.24	22.2 (21.5-23.0)	0.13	22.6 (21.9-23.3)	0.46
female	22.6 (21.4-23.7)	25.1(21.7-28.5)	0.13	22.1 (20.6-23.5)	0.46	24.1 (22.4-25.8)#	0.04
male	23.0 (22.0-24.0)	23.5 (21.3-25.7)	0.68	22.2 (21.4-23.1)	0.21	22.2 (21.4-23.0)	0.16

*Values represent adjusted mean plasma FXIII activity or antigen (95% confidence interval). FXIII activity is expressed as percentage of average normal. The median age of females and males was 57.7 years (range: 31-82), and 56.6 years (range: 30-88), respectively. The significance of differences in mean FXIII values between the clinical control and different patient groups was tested by analysis of variance (ANOVA). When one-way ANOVA indicated a significant difference, post-hoc pair-wise comparisons were made using the LSD (least significant difference) test. CS^+ and CS^-: patients with and without significant coronary sclerosis, respectively; MI^+ and MI^-: patients with and without a history of myocardial infarction, respectively. *Compared to the respective clinical control (CS^-MI^-) subgroup. °p=0.02 for comparison with females in the CS^-MI^- group. #p=0.02 for the comparison with females in the CS^-MI^- group. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 11.5).*

Table 2. The effect of FXIII levels in the upper tertile on the risk of coronary sclerosis or myocardial infarction in males and females.

Patient groups	CS^-MI^- *versus* CS^-MI^-		CS^-MI^+ *versus* CS^-MI^-		CS^+MI^+ *versus* CS^-MI^-		CS^+MI^+ *versus* CS^+MI^-	
	OR (95% CI)	*p value*	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*
FXIII activity								
female	1.553 (0.913-2.642)	0.10	2.437 (0.648-9.138)	0.19	3.091 (1.648-5.798)	<0.001	1.873 (1.015-3.458)	0.04
male	1.401 (0.842-2.332)	0.19	1.356 (0.528-3.482)	0.53	1.015 (0.608-1.694)	0.96	0.719 (0.476-1.086)	0.12
FXIII antigen								
female	1.286 (0.752-2.199)	0.36	2.287 (0.629-8.321)	0.21	2.346 (1.269-4.336)	0.007	1.999 (1.051-3.765)	0.03
male	0.757 (0.459-1.248)	0.28	1.196 (0.479-2.988)	0.70	0.753 (0.457-1.240)	0.27	0.918 (0.602-1.398)	0.69

CS^+ and CS^-: patients with and without significant coronary sclerosis, respectively; MI^+ and M^-: patients with and without a history of myocardial infarction, respectively. OR values represent adjusted odds ratios (95% confidence interval) which were computed from the corresponding regression coefficients in the logistic regression model that included parameters significantly associated with the presence of CS and/or MI. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 11.5).

and clinical controls did not reach the level of statistical significance.

FXIII levels in the upper tertile (FXIII activity > 110%, FXIII antigen > 24.1 mg/L) did not confer a significant risk of CS to either men or women without a history of MI (CS^+MI^- versus CS^-MI^-) (Table 2). In contrast to the respective male subgroup, when the female CS^+MI^+ subgroup was compared to female clinical controls high odds ratios with high statistical significance were calculated. To separate the effect of elevated FXIII level on the risk of CS and MI even more clearly, subgroups of patients with and without a history of MI, but with significant CS were compared (CS^+MI^+ versus CS^+MI^-). Elevated FXIII levels were associated with a significantly increased risk of MI in women, but not in men.

On the basis of these results, elevated FXIII can be regarded as a gender (female)-specific risk factor for MI, and FXIII determination could be a candidate for inclusion in the risk stratification for women. By preventing plasmin-induced degradation of fibrin, elevated FXIII levels could play a role in sustaining newly formed thrombus in coronary arteries. Although it remains to be seen why such a mechanism operates only in women, the results support the view that the clotting system plays a more prominent role in the development of MI in females than in males.

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