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To the editor:

Increased coagulation factor VIII activity in patients with familial hypercholesterolemia

Coagulation factor VIII (FVIII) plays a crucial role in the coagulation cascade, but the factors, environmental or hereditary, determining its levels, are hitherto largely unknown. Murine in vivo data and genetic association studies have recently suggested a role for the low-density lipoprotein receptor (LDL-receptor) in the regulation of this coagulation factor.[1,2] Martinelli and colleagues have suggested to study patients with familial hypercholesterolemia (FH) to address the consequences of low expression levels of LDL-receptor in modulating FVIII levels.[1] In the current study, we did determine FVIII levels in individuals that underwent cascade screening for genetic FH, hypothesizing that patients who lack functional LDL-receptors would have higher FVIII levels than their unaffected relatives.

The study population derived from a cross-sectional study described in detail before.[3] In short, 421 individuals were invited within 18 months after genetic testing for FH and both non-affected relatives and FH patients were eligible. The study was approved by the local ethics committee and all participants gave written informed consent. For the current study, we had to exclude 156 individuals: 122 subjects were on lipid-lowering treatment at the time of study visit; 30 patients were identified with a pathogenic Apolipoprotein B mutation and of 13 individuals no plasma sample was left. Factor VIII activity (FVIII) and von Willebrand factor antigen (VWF) were measured as described previously.[4] Multivariate linear regression analysis was applied to compare FVIII between FH patients and unaffected relatives using the generalized estimating equations, as a method to account for correlations within families.

Demographic and baseline characteristics are shown in Table 1. The untreated participants with FH (N = 129) had, as expected, higher LDL-cholesterol and total cholesterol levels than unaffected relatives (N = 127). The unadjusted FVIII levels were also higher in FH patients than in unaffected relatives. This difference remained after adjustments for family ties ([mean ± SE] 102.8 ± 2.9 versus 95.4 ± 2.1, $P = .037$) and age (103.5 ± 2.9 versus 94.7 ± 2.2, $P = .019$). The association between LDLR-mutation and high FVIII levels remained statistically significant after additional adjustment for VWF, CRP and LDL-cholesterol (data not shown).

Table 1. Characteristics of the included study-subjects

	Heterozygous FH		
	Yes n = 129	No n = 127	Yes versus No *P*
Male sex, n (%)	50 (39)	55 (43)	.55
Age, y	35 ± 9.0	42 ± 8.7	< .001
Body mass index, kg/m^2	25.0 ± 5.5	25.6 ± 4.2	.37
Lipid profile, mmol/L			
TC	6.1 ± 1.4	5.3 ± 1.1	< .001
LDL-C	4.2 ± 1.4	3.4 ± 0.9	< .001
HDL-C	1.5 ± 0.4	1.5 ± 0.4	.90
Triglycerides (IQR)	0.78 (0.59-1.13)	0.86 (0.65-1.43)	.11
Factor VIII, %	103 ± 33	95 ± 24	.039
vWF, %	94 ± 35	99 ± 27	.23
hsCRP (IQR), mg/L	1.2 (0.4-3.2)	1.2 (0.4-2.5)	.64

hsCRP indicates high sensitivity C-reactive protein; IQR, borders of quartiles; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; TC, total cholesterol; and vWF, von Willebrand factor.

We demonstrated that patients with heterozygous FH had on average a significant 9% higher FVIII level than unaffected relatives. This finding confirms the hypothesis derived from previous findings, suggesting that the LDLR might have a suppressing role on FVIII levels.

Strength of the current study is that participants were recruited from families participating in genetic cascade screening, so in essence free from referral bias. A potential limitation is that a myriad of different LDLR mutations were present in our study population.[3,5] If LDLR activity is indeed a determinant of FVIII

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levels, than statin treatment would induce a (mild) anti-thrombotic effect, an effect supported by recent data from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),[6] potentially because up-regulating LDLR expression would result in a lower FVIII. Future studies that prospectively assess whether statin treatment can prevent the occurrence of venous thrombo-embolic events are eagerly awaited.

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