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Highly Electronegative LDL Is Elevated in Patients With Acute Myocardial Infarction and Triggers Platelet Activation and Aggregation

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Abstract:
Background: Human LDL can be chromatographically resolved into 5 subfractions. L5, the 5th and most negatively charged subfraction, is capable of inducing atherogenic responses in vitro and in vivo. Platelet activation and aggregation are major events underlying acute thrombosis in myocardial infarction (MI). We examined the relationship between L5 and acute MI and the role of L5 in platelet activation and aggregation.
Methods and Results: Plasma L5 concentration ([L5]) was measured and compared between subjects with (1) no risk factors (healthy controls), (2) STEMI, (3) stable coronary artery disease (CAD), and (4) hyperlipidemia (HLP) without CAD. In STEMI subjects, LDL cholesterol (LDL-C) levels were similar to those in CAD and control subjects and lower than those in HLP subjects, but L5/LDL% and [L5] (L5/LDL% × LDL-C) were significantly elevated (Table). L5 from STEMI subjects but not L1 (least electronegative LDL subfraction) induced tissue factor and P-selectin expression in human coronary arterial endothelial cells (ECs) in a concentration-dependent manner; in platelets, L5 increased glycoprotein (GP)IIb/IIIa and P-selectin expression and decreased cAMP production (for all, n=8, *P*<.01 vs PBS). L5 also increased ADP-stimulated platelet aggregation twofold higher than L1 and induced massive platelet–EC adhesion. Experiments with pharmacologic inhibitors indicated that L5 signals through platelet-activating factor receptor and lectin-like oxidized LDL receptor-1 to reduce cAMP production via Akt and trigger granule release and GPIIb/IIIa activation via PKC-α. Injection of human L5 (5 mg/kg) in C57BL/6 mice twice a week for 6 weeks shortened tail-bleeding time by 43% when compared to L1 (n=3; *P*<.01) and increased expression of P-selectin and GPIIb/IIIa in mouse platelets.
Conclusions: L5 triggers platelet activation and aggregation, as well as adhesion to ECs. The significant elevation of L5 in STEMI strongly suggests L5's involvement in acute MI.

Table. L5 LDL distribution in different groups of subjects.

	Control n=6	STEMI n=30	CAD n=28	HLP n=35	*P*-value*
LDL-C (mg/dL)	112.8 ± 29.6	112.8 ± 30.6	118.0 ± 40.0	146.0 ± 34.9	*P*=.001
L5/LDL%	0.6 ± 0.4	16.4 ± 21.2	3.7 ± 3.1	2.3 ± 1.3	*P*<.001
[L5] (mg/dL)	0.71 ± 0.13	18.6 ± 25.7	4.16 ± 3.08	3.24 ± 2.00	*P*<.001

STEMI, ST-elevation myocardial infarction; CAD, (stable) coronary artery disease; HLP, hyperlipidemia without CAD; LDL-C, LDL cholesterol; [L5], concentration of L5 (L5/LDL% × LDL-C).
*ANOVA was used for statistical analysis.

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