Genetic variability of lipoprotein(a) controls vascular inflammation/redox signalling and predicts adverse cardiovascular outcomes in coronary artery disease

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Introduction: Lipoprotein(a) [Lp(a)] has an established link with cardiovascular disease, however the underlying mechanisms are incompletely understood.

Objective: We investigate the prognostic value of LPA genetic variants that determine Lp(a) levels, in patients with coronary artery disease.

Methods: We determined the plasma Lp(a) levels of 1472 cardiac surgery patients and performed genotyping to identify 7 SNPs in LPA that are associated with increased Lp(a) levels. We compared subjects with alternative LPA alleles from ≥3 SNPs (alternative group) to those without (reference group). The arterial redox state of internal mammary artery (IMA) samples was quantified using lucigenin chemiluminescence and nicotinamide adenine dinucleotide phosphate (NADPH). Coronary inflammation was measured using coronary CT angiography (CCTA) by applying Perivascular Fat Attenuation Indexing (FAI) in the proximal left anterior descending (LAD) coronary artery. To best describe cytokine-driven vascular inflammation, a radiotranscriptomic signature (C19RS) derived from the perivascular space around the aorta and the IMA was used. Patients were followed up for a median of 7.8 years.

Results: Patients with high plasma Lp(a) levels, those in the top third of the population, had significantly increased arterial NADPH-stimulated O2.- (A) compared to those with medium or low plasma Lp(a) levels. Amongst patients with high plasma Lp(a); those with Lp(a) levels ≥75th percentile (compared to those below) had a significantly increased perivascular FAI (B), and those with Lp(a) levels ≥95th percentile (compared to those below) had a significantly increased C19RS (C). Images of CCTA FAI mapping of LADs from alternative and reference LPA variant group patients are shown (D). Amongst insulin-sensitive patients with high plasma Lp(a), those in the alternative LPA variant group (vs the reference group) had significantly increased plasma Lp(a) levels (p<0.001), plasma apolipoprotein-B (ApoB) levels (p=0.025), resting arterial O2.- levels (E), and C19RS (F). There was a significantly increased observed risk of major adverse cardiovascular events, independent of plasma ApoB, for patients with high plasma Lp(a) levels (adj. HR=2.664, p=0.022) as well as for those in the alternative LPA variant group (adj. HR=2.018, p=0.049). IMA RNAseq pathway enrichment analyses revealed that, in patients with plasma Lp(a) levels ≥95th percentile, there was a significant upregulation of genes involved in the mitochondrial electron transport chain, reactive oxygen species response and positive regulation of lymphocyte chemotaxis.

Conclusions: We demonstrate for the first time that Lp(a) leads to increased coronary inflammation in humans, which could mediate the increased risk of major adverse cardiovascular events associated with high Lp(a) levels.
(A) IMA NADPH-stim. ΔO₂⁻ (RLUs/mg tissue)  
Plasma Lp(a)  Low/Med.  High  

(B) Perivascular FAI (HU)  
Lp(a) Centile  <75  ≥75  

(C) C19RS  
Lp(a) Centile  <95  ≥95  

(D) LAD-1st group - Low FAI  LAD-2nd group - High FAI  

(E) IMA Resting ΔO₂⁻ (RLUs/mg tissue)  
LPA variant group  Ref.  Alt.  

(F) C19RS  
LPA variant group  Ref.  Alt.  

*p<0.05; ****p<0.0001