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Original Article

Elevated lipoprotein(a) and low-density lipoprotein cholesterol as predictors of the severity and complexity of angiographic lesions in patients with premature coronary artery disease

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BACKGROUND: Elevated lipoprotein(a) (Lp[a]) and low-density lipoprotein (LDL) cholesterol are important inheritable risk factors for premature coronary artery disease (CAD). Lp(a) mediates cardiovascular risk through prothrombotic, proinflammatory, and proatherogenic properties. The association of Lp(a) and LDL cholesterol with angiographic disease severity and complexity in patients with premature CAD has yet to be established.

OBJECTIVE: To investigate the relationship of Lp(a) and LDL cholesterol with the severity and complexity of coronary artery lesions using the SYNergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery (SYNTAX) and Gensini scores, in patients with premature CAD.

METHODS: Plasma Lp(a) levels were consecutively measured by an automated latex-enhanced immunoassay in 147 patients with premature coronary events (aged <60 years). Elevated Lp(a) was defined as >0.5 g/L, and elevated LDL cholesterol as an untreated LDL cholesterol of >5.0 mmol/L (>193 mg/dL). Demographical, biochemical, and clinical data were retrospectively collected from medical records. SYNTAX and Gensini scores were independently assessed by 2 investigators.

RESULTS: Patients were subdivided into tertiles using SYNTAX scores. The proportion of patients with elevated Lp(a) and elevated LDL cholesterol were significantly higher in patients with higher SYNTAX and Gensini scores ($P < .05$). In multivariate analysis (adjusting for age, diabetes, hypertension, and previous coronary event), elevated Lp(a) and elevated LDL cholesterol remained significant, independent predictors of higher SYNTAX and Gensini scores ($P < .05$). Patients with both elevated Lp(a) and elevated LDL cholesterol constituted most of the patients in the highest SYNTAX tertile,

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while patients with nonelevated Lp(a) and nonelevated LDL cholesterol were predominantly in the lowest SYNTAX tertile ($P < .05$).

CONCLUSION: In patients with premature CAD, elevated Lp(a) and LDL cholesterol (in a range consistent with familial hypercholesterolemia) were significant, independent predictors of the severity of CAD. Both lipid disorders should be routinely screened for in younger patients presenting to the coronary care unit.

Introduction

Elevated lipoprotein(a) (Lp[a]) and low-density lipoprotein (LDL) cholesterol are inherited disorders associated with increased risk of atherosclerotic cardiovascular disease (CVD).[1,2] Lp(a) is an LDL-like particle covalently bound to the glycoprotein apolipoprotein(a) (apo[a])[3] and has atherothrombotic and proinflammatory properties, with little influence from dietary or environmental factors.[3–7] There is an evolving body of evidence supporting the role for Lp(a) in the risk of coronary artery disease (CAD), in epidemiological studies,[8,9] Mendelian randomization,[10] and genome-wide association studies.[11] Elevated Lp(a) is also relatively common in patients with premature CAD.[12–14] A recent study demonstrated that LDL cholesterol ≥190 mg/dL (≥4.91 mmol/L) is associated with an accelerated risk of CAD,[15] and the coexistence of both elevated LDL cholesterol and Lp(a) may exacerbate this risk.[16,17]

Beyond the onset of a CAD event, the extent/severity of CAD itself is also predictive of subsequent coronary events and long-term prognosis.[18,19] Various angiographic scoring classification systems exist to provide an objective quantification of CAD, including the Gensini score[20] and SYNTAX score (SYNergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery).[21] The SYNTAX score is a relatively new but well-validated scoring system, which has been shown to predict outcomes in patients undergoing multivessel and left main percutaneous coronary intervention.[22,23]

Limited studies have previously demonstrated an association between the complexity of angiographic disease and, separately, a diagnosis of elevated Lp(a) and/or LDL cholesterol levels.[24–28] Much less is known about the relationship between Lp(a) and LDL cholesterol and angiographic disease severity and complexity in the specific cohort of patients with premature CAD, which has important implications for the management of these vulnerable patients. Therefore, the main aim of this study was to determine if elevated Lp(a) and/or LDL cholesterol are associated with more advanced atherosclerosis, as quantified using both the SYNTAX and Gensini scores, in patients with premature CAD.

Methods

Patient cohort

Between January and August 2016, we measured plasma Lp(a) concentration in 147 consecutive patients admitted with an acute coronary syndrome to the coronary care unit of Royal Perth Hospital who met the following inclusion criteria: (1) aged <60 years[29] and (2) underwent coronary angiography during the same admission. Patients with a previous history of coronary artery bypass grafting were excluded. Demographics, medical history (type 2 diabetes, hypertension, smoking, depression/anxiety), medications at admission and discharge, and biochemical data were retrospectively collected from the medical records. Secondary causes of LDL cholesterol >5.0 mmol/L, including uncontrolled hypothyroidism, diabetes, and macroproteinuria were excluded. Clinical audit approval was granted by Royal Perth Hospital (Governance Evidence Knowldege Outcome Quality Activity 10431).

Laboratory analyses

All biochemical measurements were performed using routine assays in an accredited laboratory during the admission. Total cholesterol, triglyceride, high-density lipoprotein cholesterol and glucose concentration were determined by standard enzymatic methods (Architect c16000 Analyzer; Abbott Diagnostics, IL) and LDL cholesterol by Friedewald calculation.[30] A direct measure of LDL cholesterol was used where triglyceride concentrations exceeded 4 mmol/L. Haemoglobin A1c was measured by a turbidometric inhibition immunoassay (Tina-quant Hemoglobin A1c Gen.2; Roche Diagnostics, Basel, Switzerland). Lp(a) was measured by an automated latex-enhanced immunoassay[31] (Quantia Lp(a) assay and standard), also on the Abbott Architect c16000 platform (Abbott Laboratories, Abbott Park, IL).

Definitions: elevated Lp(a) and elevated LDL-cholesterol

Elevated Lp(a) was defined as >0.5 g/L as previous studies have demonstrated that Lp(a) concentration exceeding this threshold significantly increased CAD risk.[1,32] Elevated LDL cholesterol was defined as an untreated LDL cholesterol >5.0 mmol/L.[15,33] As this definition relies on an untreated LDL cholesterol level and given that 30.6% of the patients were admitted on lipid-lowering therapy, we estimated the untreated concentrations using published correction factors.[34] We also adjusted the LDL cholesterol concentration for the estimated cholesterol content of Lp(a) particles[35] before applying the 5.0 mmol/L cutoff. The adjustment was applied by subtracting 30%