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Lipoprotein (a), metabolic syndrome and coronary calcium score in a large occupational cohort

K.-C. Sung [a,*], S.H. Wild [b], C.D. Byrne [c,**]

[a] Division of Cardiology, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, #108, Pyung Dong, Jongro-Ku, 110-746 Seoul, Republic of Korea
[b] Centre for Population Health Sciences, University of Edinburgh, UK
[c] Nutrition and Metabolism Unit, IDS Building, Southampton General Hospital, University of Southampton, and Southampton National Institute for Health Research Biomedical Research Centre, MP 887, Southampton, UK

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Abstract *Background and aims:* Whether lipoprotein (a) [Lp(a)] concentration is associated with metabolic syndrome (MetS) and pre-clinical atherosclerosis in different ethnic groups is uncertain. The association between Lp(a), MetS and a measure of pre-clinical atherosclerosis was studied in a large Asian cohort.
Methods and results: Data were analyzed from a South Korean occupational cohort who underwent a cardiac computed tomography (CT) estimation of CAC score and measurements of cardiovascular risk factors ($n = 14{,}583$ people). The key exposure was an Lp(a) concentration in the top quartile (>38.64 mg/dL)) with a CAC score >0 as the outcome variable and measure of pre-clinical atherosclerosis. Logistic regression was used to describe the associations. 1462 participants had a CAC score >0. In the lowest Lp(a) quartile (<11.29 mg/dL), 25.8% had MetS, compared with 16.1% in the highest Lp(a) quartile (>38.64 mg/dL ($p < 0.001$). MetS, and component features, were inversely related to Lp(a) concentration (all $p < 0.0001$). In the highest Lp(a) quartile group, there was an association between Lp(a) and CAC score >0 in men (OR 1.21[1.05, 1.40], $p = 0.008$), and women (OR 1.62[1.03, 2.55], $p = 0.038$), after adjustment for age, sex, lipid lowering therapy, and multiple cardiovascular risk factors. There was no evidence of an interaction between highest quartile Lp(a) and either high LDLc

Abbreviations: MetS, metabolic syndrome; HDLc, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; BMI, body mass index; CAC, coronary artery calcium score; CVD, cardiovascular disease; FRS, Framingham Risk Score.

* Corresponding author.
** Corresponding author. Endocrinology and Metabolism Unit, IDS Building, Southampton General Hospital, University of Southampton, MP 887, Tremona Road, SO166YD Southampton, UK.
E-mail addresses: kcmd.sung@samsung.com (K.-C. Sung), sarah.wild@ed.ac.uk (S.H. Wild), c.d.byrne@soton.ac.uk (C.D. Byrne).

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(>147 mg/dL) ($p = 0.99$), or MetS ($p = 0.84$) on the association with CAC score >0.
Conclusion: Lp(a) levels are inversely related to MetS and its components. There was a robust association between Lp(a) concentration >38.6 mg/dL and marker of early atherosclerosis in both men and women, regardless of LDLc, level MetS or other cardiovascular risk factors.

Introduction

Lipoprotein(a) [Lp(a)], is a low-density lipoprotein (LDL) – like particle with a specific apolipoprotein, apolipoprotein (a) [apo (a)], bound to apolipoprotein B 100 by a disulfide bridge [1]. Since the original sequencing of the apo(a) cDNA showing high homology with plasminogen [2], and the characterization of the apo(a)/plasminogen gene cluster on chromosome 6 [3], there has been a considerable interest in this enigmatic apolipoprotein that potentially links altered fibrinolysis, a procoagulant phenotype and atherosclerosis [4].

Recent evidence shows that measurement of Lp(a) concentration in people without known cardiovascular disease (CVD) leads to a small improvement in CVD risk prediction compared with the use of total cholesterol and HDLc concentrations [5]. Genetic studies show that apo(a) variants are strongly associated with both an increased level of Lp(a) and an increased risk of coronary disease [6,7]; and analyses of large scale prospective studies [8,9] and meta-analysis data [10], show that increased Lp(a) concentrations are a risk factor for CVD.

Most of the evidence to date, suggesting that increased Lp(a) concentration is an important cardiovascular risk factor, has been obtained in populations of European ancestry, and whether Lp(a) is an equally important cardiovascular risk in other ethnic groups is less certain. For example, in ethnic Chinese, in a prospective cohort study of 3884 participants, baseline Lp(a) concentration was not significantly associated with stroke, all-cause death, and CHD in multivariate analyses [11]. In contrast to these findings, it has been suggested that high Lp(a) may be more strongly associated with IHD in Asian Indians [12,13]. In blacks, it has also been shown that Lp(a) concentration is a risk factor for cardiovascular outcomes (coronary heart disease and ischemic strokes) [14]. However, blacks tend to have higher Lp(a) concentrations than whites, suggesting that Lp(a) might be a more influential risk factor for IHD in blacks than whites. A recent large gene-centric analysis of genetic variants in genes responsible for recognized cardiovascular risk factors in South Asians and Europeans did not find clear evidence of major variation in genetic risk factors for coronary artery disease [15], suggesting that genetic variation in regulation of Lp(a) concentrations is unlikely to explain the higher CVD prevalence in South Asians compared to Europeans [16]. Thus these data suggest that the relationship between Lp(a) levels and CVD may be different between ethnic groups but the explanation for this is uncertain. MetS prevalence differs between ethnic groups and it is accepted that insulin resistance, features of the metabolic syndrome (MetS) and diabetes are cardiovascular risk factors, but to date the relationship between Lp(a) concentrations and insulin resistance, metabolic syndrome and diabetes remains controversial [17].

Coronary artery calcium (CAC) scoring with cardiac computed tomography (CT) is a sensitive method to demonstrate the presence of pre-clinical atherosclerosis and the use of CAC scores may be also be useful in identifying individuals at increased risk of cardiovascular disease (CVD) [18]. Therefore the aim of our study was to investigate the association between Lp(a), insulin resistance, features of the MetS and a CAC score >0 (as a marker of early or pre-clinical atherosclerosis).

Methods

The study population consisted of individuals who had a comprehensive health check examination in 2010 at Kangbuk Samsung Hospital, College of Medicine, Sungkyunkwan University in South Korea. Initially 14,912 participants underwent coronary CT scanning to establish a CAC score and individuals were excluded from the current analyses if data were missing for the following variables: alcohol consumption ($n = 116$), smoking ($n = 143$), exercise ($n = 111$), BMI ($n = 12$), waist circumference ($n = 12$), and high sensitivity C reactive protein (hs-CRP) ($n = 168$), Lp(a) ($n = 157$). Data from 14,583 participants were analyzed. In South Korea, employees are required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. The Institutional review board at Kangbuk Samsung Hospital has ruled that because our study is an analysis of routine data, they consider that there is no need for specific informed personal consent to be given.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Questionnaires were used to ascertain information regarding alcohol consumption (glass/day), smoking (never, ex, current), and frequency of moderate activity each week. Moderate activity was defined as more than 30 min activity per day that induced slight breathlessness. Framingham Risk Score (FRS) was calculated. Metabolic syndrome (MetS was defined by the 2009 joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention criteria), with waist circumference thresholds of ≥90 cm for men and ≥80 cm for women that are specific for Asian populations [19].

Blood samples for laboratory tests were collected after an overnight fast. Fasting plasma glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDLc) and high density lipoprotein cholesterol (HDLc) concentrations were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Concentrations of serum ferritin were measured by an electrochemiluminescence