EPIDEMIOLOGY AND GENETIC STUDIES SHOWING AN ASSOCIATION OF LP(A) WITH ELEVATED CARDIOVASCULAR RISK AND AORTIC VALVE DISEASE

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Abstract

Lipoprotein(a) [Lp(a)] has been demonstrated to be an independent risk factor for cardiovascular disease (CVD) in observational, genetic and large Mendelian randomization studies and it is likely to be a causal risk factor. It is also one of the determinants of residual risk in patients on statin therapy. In fact, statin therapy appears to increase levels of Lp(a), despite reducing overall levels of low-density lipoprotein-cholesterol (LDL-C), which include the cholesterol carried in Lp(a) particles. Plasma levels of Lp(a) are about 80%–90% genetically determined with the main genetic determinant being the LPA gene. Lp(a) levels are inversely associated with smaller isoforms of apolipoprotein(a) which can be synthesized more rapidly by hepatocytes. The distribution of Lp(a) levels varies in different ethnic groups and Lp(a) levels may also increase with inflammation.

Valvular aortic stenosis (VAS) has several risk factors in common with atherosclerotic CVD and oxidized phospholipids carried by Lp(a) may provide a mechanistic link in the pathological processes. This is supported by genetic studies. Prospective population-based studies show that individuals with Lp(a) in the top 5th percentile (≥120 mg/dL) compared with those in the lower 20th percentile (<5 mg/dL) have 3- to 4-fold increased risk of myocardial infarction and 3-fold increased risk of VAS. Genomewide association studies in large case-control consortia have generally found that genetic variation in the human genome related to high Lp(a) levels confers the highest risk of atherosclerotic CVD and VAS of all the variants tested. Measurement of Lp(a) levels may be particularly useful to refine risk assessment for atherosclerotic CVD in selected subjects and to identify those at risk for progressive VAS. Currently available therapies have limited effects on Lp(a) levels and it remains to be seen whether newer treatments that can lower Lp(a) levels more substantially can reduce the risk of atherosclerotic CVD and VAS in those with higher levels.

Keywords

Cardiovascular disease, lipoprotein(a), valvular aortic stenosis