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EDITORIAL COMMENT

Lipoprotein(a) as a novel therapeutic target for preventing cardiovascular disease: A whiter shade of pale?

Lp(a) como um novo alvo terapêutico na prevenção da doença cardiovascular: uma luz ao fundo do túnel?

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Research on the importance of lipoprotein(a) [Lp(a)] gained new momentum when it became a potential therapeutic target. Our understanding of this mysterious circulating lipoprotein particle has undergone advances and setbacks since its discovery in 1963 by Kåre Berg's group.[1]

Lp(a) is composed of liver-derived apolipoprotein A and apolipoprotein B-100, and has a similar structure to both low-density lipoprotein cholesterol (LDL-C) and plasminogen. Lp(a) thus has a proatherogenic and a prothrombotic component, and is associated with the pathogenesis of cardiovascular disease (CVD).

Findings from epidemiological, genetic and clinical studies[2–4] have provided compelling evidence establishing Lp(a) as a marker of increased CVD risk in both primary and secondary prevention, including myocardial infarction (MI), stroke, and calcific aortic valve disease (CAVD).

However, significant gaps in knowledge remain about the biology and pathophysiology of Lp(a). To address these gaps, a National Heart, Lung, and Blood Institute working group identified several challenges to fully understand the role of Lp(a) in CVD/CAVD.[5] These include its metabolism and pathophysiological mechanisms, how to measure it, current and emerging therapies for elevated Lp(a), and identification of patients at high Lp(a)-mediated risk.

Joaquim Menezes-Brandão carried out a single-center retrospective observational study, published in this issue of the *Journal*,[6] of 516 patients (224 male; 292 female; 98.6% Caucasian) with at least two cardiovascular risk factors who regularly attended outpatient consultations at a cardiovascular risk and metabolism clinic for primary prevention. The aim was to analyze the effect of combined standard pharmacological therapy along with lifestyle interventions for managing Lp(a) levels in patients at high cardiovascular risk but who had not suffered major adverse cardiovascular events. The patients were followed for a mean of 11.35±4.32 years.

The results show that, in this well-controlled population under different drug therapies (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, oral antidiabetics, antiplatelets, calcium channel blockers and allopurinol) there was a reduction in Lp(a) values during the follow-up period.

There was also a significant association between Lp(a) and cardiovascular risk scores in patients with high vascular risk. In a previous work in the same population,[7] the author reported that increased Lp(a) levels were also strongly associated with cardiovascular risk factors, such as

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carotid intima-media thickness, LDL-C and homocysteine, as well as with non-alcoholic hepatic steatosis.

This study points to the need to measure Lp(a) in routine assessment of at-risk patients, because as a marker of cardiovascular risk, Lp(a) should be recognized as a therapeutic target. It may be useful to initiate combined drug therapies and to promote healthy lifestyles in primary prevention, targeting various cardiovascular risk factors, in order to delay the atherosclerotic process.

These results may lead to better identification of target populations who will benefit most from Lp(a)-lowering therapies.

Several other studies have addressed this question. Among them, the BiomarCaRE project[8] confirmed Lp(a) as a marker of cardiovascular risk in the European population, demonstrating increased cardiovascular risk for Lp(a) >50 mg/dl, which is in line with the target level of <50 mg/dl recommended by the guidelines. Further, it showed a north-south gradient of Lp(a) levels across Europe, with lower levels in northern European cohorts.

Another study in different ethnic groups worldwide also showed that high Lp(a) concentrations (>50 mg/dl) were associated with significantly increased risk of MI in all populations except Arabs and Africans.[9]

Nevertheless, Lp(a) is not routinely tested in clinical practice, and there is a widespread lack of awareness of its role in accelerating atherosclerotic CVD.

Which patient groups should be screened for Lp(a)? The European Atherosclerosis Society Consensus Panel[10] recommends that Lp(a) should be measured in patients with intermediate or high risk for CVD or coronary heart disease (CHD). In particular, those patients presenting with (i) premature CVD, (ii) familial hypercholesterolemia, (iii) a family history of premature CVD and/or elevated Lp(a), (iv) recurrent CVD despite statin treatment, (v) 3% 10-year risk of fatal CVD according to the European guidelines[11] and (vi) 10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines. The measurement needs to be taken only once per patient life, and repeated measurements of Lp(a) are only indicated if a treatment for elevated Lp(a) levels is initiated in order to monitor therapeutic response.[12]

Screening for elevated Lp(a) will enable standard preventative measures to be introduced, including optimal control of blood pressure, diabetes and LDL-C levels and smoking cessation, and in the future the use of novel therapies that effectively lower Lp(a). Several agents are currently in development to lower Lp(a), such as proprotein convertase subtilisin/kexin type 9 inhibitors, antisense oligonucleotides targeting apolipoprotein B, and microsomal triglyceride transfer protein inhibitors.[13–15]

Early detection and intervention, preferably before the onset of atherosclerotic CVD, offers the best opportunity to reduce the time-dependent risk associated with this important cardiovascular risk factor. However, it should not be forgotten that there is to date no strong clinical evidence that lowering Lp(a) has any beneficial effects in preventing cardiovascular disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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