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Understanding Lp(a): Clinical Implications of an Underrecognized Genetic Dyslipidemia

Announcer:
Welcome to ReachMD.

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Host:
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Hello, and welcome to this video, where we will be discussing lipoprotein(a) and its clinical relevance in atherosclerosis and cardiovascular events. We will be speaking with Dr Santica Marcovina, a clinical scientist who is renowned for her research on lipoprotein(a) and is the senior director of Clinical Laboratories Sciences at Medpace Reference Laboratories.

Welcome, Dr Marcovina. Could you start out by giving us a basic idea of what is lipoprotein(a) and what we should know about it?

Dr. Marcovina:
Of course, I will be glad to. Before discussing Lp(a), let’s start by giving a brief look to an LDL particle as depicted here.

We all know LDL particles are formed by a lipid core surrounded by a molecule of apoB-100. LDL varies in size, depending on the apoB-to- cholesterol ratio, and its atherogenicity varies with the ratio, with small dense LDL being more atherogenic than the large buoyant.[1]

Let’s now give a look to lipoprotein(a), commonly referred to as Lp(a). Lp(a) is a particle with a structural composition similar to LDL, which is lipid core surrounded by a molecule of apoB. However, Lp(a) is characterized by additionally containing one molecule of apo(a), a very peculiar carbohydrate-rich protein covalently bound to a molecule of apoB. Due to the presence of apoB, Lp(a) is part of the apoB-containing lipoprotein particles, together with the VLDL, IDL, and LDL, all demonstrated to have a causal link with increased coronary vascular disease risk.[2]

Let’s now focus our attention on apo(a), the distinguished protein of Lp(a), which separates all the Lp(a) from all the other apoB-containing lipoprotein particles.

Apo(a) is formed by a series of basic motifs called kringles, with a high amino acid sequence homology with the coagulation protein plasminogen, by a plasminogen-like but inactive protease domain.[3] One of the kringles, the kringle IV type 2 is present in individuals in a variable, genetically determined number of identical repeats, resulting in over 40 different apo(a) isoforms, which are primarily responsible for the large-size heterogeneity of Lp(a) particles.[4] Lp(a) levels are inversely correlated to the size of apo(a), which, I remind you, is genetically determined, thus rendering Lp(a) the most common inherited form of dyslipidemia.[5]

In a future presentation we will be discussing in more detail how the size heterogeneity of apo(a), as well as the binding of Lp(a) to oxidized phospholipids, affects the atherogenicity of Lp(a) particles.[6]

Host:
What is clinically significant about an elevated Lp(a) that we should know?

Dr. Marcovina:

An elevated Lp(a) is associated with increased risk of developing severe events. As you can see here in a study performed on over 460,000 individuals, Lp(a) was associated with coronary vascular disease, both in individuals with and without cardiovascular disease at study entry.[7]

Multiple studies have also demonstrated that elevated Lp(a) levels are a causal and independent risk factor for atherosclerotic cardiovascular disease.[8,9] You can see here the increased risk between the highest and the lowest levels of Lp(a) for a variety of cardiovascular events, with the major risk increase being observed for coronary artery stenosis, a five-fold increase; myocardial infarction, a three-to-four-fold increase; and valvular aortic stenosis, with a three-fold increase.[9]

An Lp(a), an elevated Lp(a), has been reported in about 15% to 20% of a population of white ancestry.[10]

The pronounced differences in distribution of Lp(a) levels observed across different racial ethnic populations will be discussed in a future presentation.[10]

Host:
You said that Lp(a) is an inherited dyslipidemia. Are there gender or age differences in Lp(a) levels? Also, are there any dietary or lifestyle measures that can reduce Lp(a) in affected individuals?

Dr. Marcovina:
Lp(a) levels, in general, are fairly consistent over a person's lifetime.[9]

The Lp(a) gene is fully expressed by 1 to 2 years of age. Lp(a) expression reaches adult levels by 5 years of age.[9] This means that in individuals with high Lp(a) level, its atherogenic and inflammatory actions start at a very young age. In general, no significant differences have been observed between men and women, even though Lp(a) levels tend to increase in postmenopausal women with decrease of hormones.[11]

Regarding your question about the potential dietary or lifestyle intervention to lower Lp(a), the answer, unfortunately, is no.[6,10]

Host:
You talked about risk, but, precisely, what is known about how Lp(a) levels actually impact vessel wall biology?

Dr. Marcovina:
We know that Lp(a) has multiple pathologic actions in and on the vessel wall. Its unique proatherosclerotic, proinflammatory, prothrombotic properties are also due in part to the apoB and the oxidized phospholipid components of Lp(a).[6]

We also know that elevated Lp(a)s are associated with carotid plaque progression and are an independent predictor of atherosclerotic burden, even after adjustment for all the other lipids.[8,12]

As seen in this graph from a recent study of patients with elevated Lp(a) who were receiving intensive lipid-lowering therapy, carotid artery atherosclerosis progressed despite LDL levels being maintained at less than 70 mg/dL in all study participants.[12]

Host:
You are quite persuasive that an elevated Lp(a) is associated with multiple cardiovascular risks, but how would I know if I have an elevated Lp(a)?

Dr. Marcovina:
That's easy; plasma concentration of Lp(a) can be measured in most laboratories by using automated instruments, even though there are important methodological issues that need to be taken into consideration, and this topic will be discussed in more details in the future presentation.[13]

At the present, it is recommended that Lp(a) be measured, preferably early in life, as part of the initial lipid screening to assess the cardiovascular risk.[14] Lp(a) levels being fairly stable, the majority of individuals will only need to be tested once.

Host:
Dr Marcovina, thank you for your insights and information about Lp(a), and I look forward to continuing discussing this fascinating topic with you.

Dr. Marcovina:
Thank you. I would be delighted to be there.

Announcer:

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