



## CLINICAL PRACTICE

## Lp(a) and coronary disease: Rules of engagement – when to measure and how to treat

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Lipoprotein (a) (Lp(a)) has been described as an important component of the lipid profile and a significant coronary risk factor when elevated. Controversy surrounds the importance of this lipoprotein variant, and its management is often challenging for clinicians. Important issues relate to the control and management of high Lp(a) levels, especially in patients at intermediate risk of cardiovascular disease. Clear guidelines are lacking on who needs Lp(a) measured, and when. We review practical points on investigating and managing Lp(a).

### Background

Lp(a) was first described in 1963 as a genetic variant of  $\beta$ -lipoproteins.<sup>1</sup> The physiological functions of Lp(a) remain a mystery. Most studies strongly suggest that it is an independent risk factor for cardiovascular disease.<sup>2</sup> A meta-analysis concluded that an increased plasma level of Lp(a) is an independent predictor of the presence of coronary artery disease (CAD), particularly in patients with hypercholesterolaemia.<sup>3</sup> The combination of high Lp(a) plasma concentrations and other cardiovascular risk factors, in particular low high-density lipoprotein (HDL), strongly increases the risk of CAD. In addition to containing significant amounts of cholesterol and being able to oxidise like low-density-lipoprotein (LDL), Lp(a) can exert antifibrinolytic actions, stimulate the proliferation of smooth-muscle cells, facilitate wound healing, act as an acute-phase reactant and generate bioactive derivatives that are retained in the vascular extracellular matrix. Lp(a) has been identified as the link between atherosclerosis and thrombosis. Stoichiometrically the

atherogenicity of Lp(a) is 10-fold that of LDL, though the latter dominates in the circulation. Lp(a) is also highly thrombogenic and bears structural resemblance to plasminogen, which explains its antifibrinolytic properties.<sup>4</sup>

### Coronary risk association

The plasma levels of oxidised phospholipids present in Lp(a) have been implicated in contributing to the atherogenicity of Lp(a),<sup>5</sup> which is a strong independent risk factor for CAD in various populations and ethnic groups.<sup>6</sup>

Lp(a) has a significant and well-described genetic heterogeneity. Its risk associations with vascular disease demonstrate racial and ethnic variations. Higher plasma concentrations are seen in blacks, postmenopausal women and people with hypercholesterolaemia. However, the strongest association with high Lp(a) levels and coronary disease is observed in middle-aged white men. High Lp(a) levels are associated with a high risk of stroke in blacks and in white women, but not in white men.<sup>7</sup>

Not all studies associate Lp(a) with increased coronary risk. The Physician's Health Study found no association between Lp(a) level and the risk of future ischaemic events,<sup>8</sup> but this observation could have been due to sampling and/or measurement errors. Some studies measured Lp(a) in long-term, frozen samples with insufficiently evaluated test kits. Moreover, owing to the wide range of plasma Lp(a) levels from less than 0.001 g/l to more than 3 g/l and the highly skewed distribution, studies that include small numbers of cases/controls are prone to random deviations.

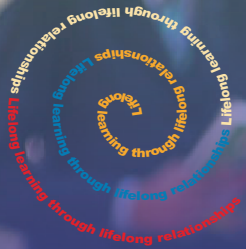
### Measurement

Studies are sometimes controversial, as it is difficult to standardise the measurement of Lp(a) due to its heterogeneity. Recognition of the biological importance of apolipoprotein (a) (apo(a)) is also reflected by the International Standardization Committee, which recommends that the previous practice of reporting Lp(a) as a total mass be superseded by the measurement of Lp(a) protein either in terms of apo(a) or as apo(a) linked to apoB100.<sup>9</sup> In this way the level of Lp(a) cholesterol can be estimated by comparing it with that of LDL, important information to the clinician.

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## ***“Clinical Training”***

### **Pediatric HIV/AIDS Management Course**

Children with HIV/AIDS are dying unnecessarily because of a lack of access to ARV treatment. The problems arise mainly from a lack of cheap feasible diagnostic tests for children under 18 months, lack of trained health personnel and the affordable child-friendly ARV drugs.

Simplified treatment guidelines coupled with a range of fixed-dose combinations of ARVs that require only one or two pills twice a day make it easier to treat HIV/AIDS in adults, but development of simplified drugs for children lags behind. Despite WHO simplified treatment guidelines that

specify which drugs to use in children, countries have difficulty in getting simple and affordable combinations of the drugs. Two generic fixed-dose combinations should enter clinical trials this year, and there are frighteningly few second-line ARV drugs available for children in countries with large numbers of infected children.

Date: 2 - 4 October 2009

Area: Pretoria

Price: R 3,200.00

### **HIV/AIDS Refresher Course**

HIV/AIDS is an ever-evolving discipline and with ARV drugs becoming more affordable, health professionals therefore need to stay abreast with the latest developments. The Foundation for Professional Development in association with the Southern African HIV Clinician Society developed this one-day refresher seminar which is targeted at alumni who successfully completed the 3-Day HIV/AIDS Management Course. We encourage all our alumni who completed the 3-day course to enrol on this refresher course so that they have access to the most recent evidence-based

Information on drugs and the management of HIV/AIDS patients.

Date: 12 September 2009

Area: Port Elizabeth

Price: R 1,300.00

Date: 7 November 2009

Area: Cape Town

Price: R 1,300.00

### **Clinical Management of Allergies**

The prevalence of allergy is increasing worldwide, particularly in urbanised communities. Asthma is thought to occur in at least 1 in 10 people, and allergic rhinitis may occur in 1 in 5, irrespective of race or socio-economic status. Therefore, all family practitioners, irrespective of which communities they serve, will probably see patients with hay fever every working day. In many instances the diagnosis is made easily, but sometimes the diagnosis is difficult to make and investigations will help to confirm the diagnosis of

allergy and the attendant inflammatory airway disease. The wide range of allergy tests available requires a logical approach to selecting the most cost-effective and appropriate test for each individual.

Date: 12 - 13 September 2009

Area: Pretoria

Price: R 3,249.00

### **Clinical Management of Dermatology**

Traditionally, dermatology is a subject that receives limited clinical and classroom attention at undergraduate level. A need therefore exists especially amongst general practitioners, frequently being the patient's first contact, to acquire skills in this field. A formal certificate course will further create an opportunity for these practitioners to differentiate their practice and respond to a growing consumer demand. There are only 138 dermatologists left in SA and classically dermatologists are located in major cities,

resulting in an urban bias. Geographically, the general practitioner therefore has the most initial and on-going contact with patients, which places them in the unique frontline position of identifying, managing and referring patients with dermatological conditions.

Date: 12 - 13 September 2009

Area: Johannesburg

Price: R 3,500.00

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# **FPD**



## Investigation

'In whom should we measure Lp(a)?' remains to be the main question to be answered.

Serum levels of Lp(a) are genetically determined, with environmental factors having a negligible impact.<sup>10</sup> Childhood levels of Lp(a) are a better predictor and marker than any other lipoproteins for future CAD in young adult life.<sup>11</sup> Most lipidologists recommend a once-off measurement of Lp(a) in patients with vascular disease, especially in patients with premature cardiovascular disease and premature stroke, where other risk factors fail to explain the causation. Lp(a) is also useful in patients in the intermediate-risk group, according to the Framingham, Australian and New Zealand or Procarn risk calculators. If Lp(a) is elevated above 0.3 g/l in these patients, it is very important to treat their other risk factors, especially LDL, aggressively.

## Management

HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins) have no demonstrable efficacy in modifying Lp(a) levels. There are few means whereby plasma Lp(a) can be reduced, the most efficient therapeutic modalities known to selectively reduce plasma Lp(a) being Lp(a)-apheresis and nicotinic acid (Table I).

**Table I. Influence of drugs and other substances on plasma Lp(a) concentrations**

Substance	% decrease
Omega-3 fatty acids	5 - 20
Palm oil	10 - 25
Vegetarian diet	10
Nicotinic acid and derivatives	15 - 35
Aspirin	15 - 20
L-carnitine	10 - 15
Lp(a)/LDL apheresis	60 - 80
ACE inhibitors	10 - 40

Nicotinic acid and its derivatives can reduce Lp(a) levels by up to 35%.<sup>2</sup> All angiotensin-converting enzyme (ACE) inhibitors in monotherapy lower elevated Lp(a) plasma concentrations in proteinuric patients by reversing proteinuria and in turn reducing Lp(a) production by the liver.<sup>12</sup> Fosinopril seems to be the only ACE inhibitor to reduce Lp(a) concentrations in non-proteinuric patients as well, probably by increasing apo(a) fragmentation and excretion into the urine (Kostner K *et al.*, unpublished data).

The most effective therapy for lowering Lp(a) is extracorporeal elimination of Lp(a) with apheresis. LDL-apheresis and selective Lp(a)-apheresis using antibody-coupled columns, precipitation and complex formation at low pH, double filtration and direct absorption have been demonstrated to lower plasma Lp(a) to the same extent as LDL cholesterol (up to 80%).<sup>13</sup> However, these treatments are expensive and accessible only to a small number of high-risk patients. Most lipidologists and clinicians recommend lowering LDL cholesterol more aggressively to levels below 1.8 mmol/l when the Lp(a) level is above 0.3 g/l, even though hard evidence to merit this practice is lacking.

## Conclusion

Measurement of Lp(a) provides useful additional information about cardiovascular risk in patients with premature vascular disease and intermediate risk profiles. Aggressive LDL reduction and global coronary risk factor modulation are recommended in patients with elevated Lp(a). Coronary disease is an emerging major health challenge in Africa, with CAD projected to be the leading cause of death in Africa by 2030.<sup>14</sup> However, information on the role of Lp(a) as a coronary risk factor among developing communities, especially in Africa, is seriously lacking and more studies are required.

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