

Lipoprotein (A) as a cause of statin-resistance: how to treat it? – Case report

Carolina Négrier Lourenço, Marta Rebelo, Elsa Gaspar, Diniz Vieira, José Manuel Silva, J. J. Alves de Moura

Abstract

Lipoprotein (Lp(a)) is considered a cardiovascular risk factor, and nicotinic acid is the only available drug for reducing its levels.

The authors present the case of a 44-year-old male patient with hypercholesterolemia that responded poorly to statin therapy. After identifying high Lp(a) levels, combined therapy with nicotinic

acid was initiated, resulting in normalization of LDL-cholesterol levels. The authors also carried out a theoretical review of Lp(a) and nicotinic acid.

Key words: Lipoprotein (a); LDL-cholesterol; cardiovascular risk; nicotinic acid.

Introduction

Lp(a) is a functional lipoprotein which is structurally unique, and is considered, based on numerous epidemiological studies, as an independent risk factor for coronary disease,¹⁻⁴ cerebrovascular disease, peripheral vascular disease⁴ and venous thromboembolism¹. Given its particular structure, characterized by a high degree of homology with plasminogen, and given the fact that it is considered a variant of LDLs, it has been attributed a double pathogenic role, namely, as a contributor to the processes of atherogenesis and thrombosis.^{1,2,4} Its levels are not influenced by statins, fibrates and resins.

With the discovery, in 1955, that nicotinic acid lowers cholesterol level, it became the first agent used to modify the lipid profile and to prove effective in preventing cardiovascular disease and death.^{5,6} Following initial studies that demonstrated poor tolerance and even contraindication in diabetic patients, its use was consequently restricted, but today it is reappe-

aring in modified release formulas. Recent studies have shown that nicotinic acid is relatively safe and effective in the above-mentioned group of patients. Besides its beneficial effect on the lipid profile, which includes the reduction of cholesterol LDL values, triglycerides (TG) and Lp(a) and increase of cholesterol HDL values, nicotinic acid also has anti-oxidant and anti-inflammatory effects which are unrelated to lipid reduction.^{5,6}

Clinical case

Male patient, aged 44, Caucasian, civil servant, born and residing in Amarante, who was referred to the Lipidology/Dyslipidemia Clinic at our Service in May 2005 for mixed dyslipidemia which was resistant to statin treatment.

Personal antecedents included a diagnosis of type 2 Diabetes, and 3 vessel coronary disease (episode of unstable angina), for which patient underwent myocardial revascularization surgery in September 2003. In the first consultation, the patient was medicated with transdermal nitroglycerin 5 mg id, carvedilol 12.5 mg 2 id, rosuvastatin 20 mg id, perindopril 4 mg id, acetylsalicylic acid 100 mg id, glybenclamide 5 mg 2id, metformin 1000 mg 2id, ranitidine 150 mg 2id and diazepam 5 mg 2 id. The patient denied alcoholism or smoking habits. In the physical examination, the patient presented a Body Mass Index of 28.6 kg/m² (weight 75.0 kg [\pm 12 stones], height 1.62 m [5ft5in]) and absence of carotid murmurs or other alterations.

Of the laboratory exams carried out, alterations in lipid profile were highlighted, with total cholesterol

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of 278 mg/dl, LDL cholesterol of 186 mg/dl, HDL cholesterol of 57 mg/dl, TG of 123 mg/dl, and Lp(a) of 105 mg/dl. The study also revealed glycemia of 123 mg/dl and HbA1c of 5.6%. The other indicators studied namely, renal, hepatic and thyroid functions, hemogram and proteinuria, were normal.

In the Carotid Echo-Doppler, the presence of thickening of both carotid axes was detected, without formations of atheromatous plates or any hemodynamic repercussions.

In the attempt to improve therapeutic efficiency, the patient was medicated with association of simvastatin and ezetimibe 20/10 mg id, suspending the rosuvastatin and maintaining the remaining drugs. In the reevaluation carried out after three months of treatment, together with a hypolipid diet, no significant alterations were observed in the lipid profile: total cholesterol of 304 mg/dl, LDL cholesterol of 187 mg/dl, HDL cholesterol of 75 mg/dl and TG of 211 mg/dl. Treatment with nicotinic acid was then added, increasing the dose progressively up to 2g per day and increasing the simvastatin + ezetimibe association to 40/10 mg id.

A new evaluation of lipid profile, carried out after two months, revealed total cholesterol values of 186 mg/dl, LDL of 106 mg/dl, Lp(a) of 85 mg/dl, HDL cholesterol of 59 mg/dl and TG of 105 mg/dl. Reevaluation on subsequent visits to the clinic revealed values of the various lipid subclasses within the limits proposed by the international guidelines.⁷

Discussion

The clinical case described is another example of how very high Lp(a) values constitute one of the factors which, in clinical practice, can result in a poor response to statins, and is of interest for the dosage of this lipoprotein in these situations, particularly considering that a drug is available which is relatively effective in decreasing Lp(a) levels.

Lp(a) was described by Berg, in 1963, as a modified form of LDL, due to a covalent bond created by a disulphide bridge between an apolipoprotein molecule (a) and the apo B100 fraction of the LDL.⁴ Subsequently, a high degree of homology has been demonstrated between the apo domain and the plasminogen.⁴ Due to this structural similarity, Lp(a) competes with the plasminogen, preventing its activation and the consequent generation of plasmin, and affecting fibrinolysis. There is evidence that Lp(a) also promotes

the formation of foam cells through the bond with the macrophages and the deposition of cholesterol on the atherosclerotic plates. Thus, there is speculation as to the doubly harmful effect of Lp(a), and its contribution to both atherosclerosis and thrombosis.^{1,2,4}

Although some studies do not show a significant association, the majority are consistent in demonstrating a relation between high Lp(a) levels and coronary disease, notably in the presence of hypercholesterolemia and/or hypoalphalipoproteinemia^{1-4,8}. The Prime study showed an association between Lp(a) and the risk of myocardial infarction and angina, which was more evident in patients with high LDL levels.⁸ A possible role has been suggested in the rupture of the plate, given its frequent association with unstable angina and the presence of complex coronary lesions,² as well as its role in restenosis following angioplasty and the insertion of coronary stents, and also in the physiopathology of acute myocardial infarctions due to vasospasm.²

Lp(a) is also considered to be a risk factor for cerebrovascular disease, aneurism of the abdominal aorta and thrombotic disturbances such as venous thromboembolism.⁴ High concentrations of lipoprotein also appear to exacerbate the risk associated with other prothrombotic risk factors, such as Factor V Leiden.¹

Various mechanisms have been proposed by which Lp(a) may contribute to the process of atherogenesis: 1) Bonding with atherosclerotic lesion macrophages, with subsequent endocytosis and accumulation of lipids; 2) Endothelial dysfunction; 3) Increase in expression of intracellular adhesion molecule-1 (ICAM-1), with a consequent recruitment of monocytes and promotion of the formation of foam cells; 4) Increase in susceptibility of the LDL to oxidative modification; 5) Proliferation of smooth muscle through the inhibition of Transforming Growth Factor (TGF- β); and 6) Interference with fibrinolysis by competition with the plasminogen.^{1,2} It was recently suggested that the atherogenicity of Lp(a) maybe be mediated, in part, by proinflammatory oxidized phospholipids present in the apo-B100.³

Lp(a) is structurally heterogeneous (by variations in the lipoprotein component) and its serum levels are genetically determined. The high individual variability is due to the high degree of genetic polymorphism of the apo(a), with many isoforms in the plasma. Blacks tend to present higher levels than Caucasians.

According to the Framingham Heart Study, the 90 percentile of Lp(a) is 39 mg/dl (1.01 mmol/L) among males, and 39.5 mg/dl (1.01 mmol/L) among females.² It is also known that the plasma concentrations of this lipoprotein are inversely related to the molecular weight of the apo(a) isoforms, while those of low molecular weight are more consistently related to early coronary disease.²

The physiological role of Lp(a) is unknown, although various authors have suggested a potential intervention in the bonding and detoxification of proinflammatory oxidized phospholipids. Besides being involved in the transport of cholesterol, Lp(a) may also play a role in inflammation, since it was associated with acute phase proteins and monocyte chemotaxis in the vascular endothelial cells.³

The determination of Lp(a) involves some technical difficulties and currently, it is not routinely recommended, research and treatment of high levels of this lipoprotein being indicated only in patients with coronary disease or a strong family history of coronary disease, and without any other identified dyslipidemia, in patients with arterial hypertension and early lesion of the target organ, and in patients with hypercholesterolemia which is resistant to treatment with statins and biliar acid chelates.^{2,8}

It is worth nothing that high Lp(a), given that this lipoprotein has an LDL particle in its constitution, may contribute to the increase in total LDL levels calculated by the Friedewald formula. This observation, together with the observation that standard hypolipidemia therapies do not significantly decrease Lp(a) levels, justifies the latter indication. The aim of therapy to reduce Lp(a) levels would be to achieve an appropriate LDL value for each patient, according to the individual risk. Some data suggest that a reduction in LDL levels to values lower than 80 mg/dl could reduce the risk of coronary disease associated with excess Lp(a).²

Nicotinic Acid (Niacin)

Nicotinic acid, a precursor vitamin of coenzymes that participate in cellular oxidation-reduction reactions which are essential for the formation of ATP, is currently the only agent available that is effective in reducing Lp(a) levels.^{5,6,9} The daily requirements for this vitamin are approximately 20mg, while the hypolipemiant effects occur at doses of over 500mg per day.

Niacin has been used for around 50 years in the treatment of a wide variety of dyslipidemias. However, due to its secondary effects, the opinion created based on initial studies, that niacin would be poorly tolerated in diabetic patients, and due to the appearance of more potent drugs, a certain reluctance emerged towards its use. New galenic forms and new studies have proven its safety and contributed to its reemergence in the therapeutic panorama.^{5,6,8-11}

Niacin is effective for all classes of lipids: it decreases the levels of total cholesterol, LDL, particularly the small, dense LDL, and TG; increases the HDL by 25-35% and is, as mentioned earlier, the only drug available for reducing Lp(a) levels.^{5,6,9} These effects are proportional to the dose used. Its effect in decreasing TG occurs through the inhibition of the TG synthesis limiting enzyme involved in the formation of VLDL, leading, as a direct consequence, to a decrease in the formation of LDL.⁶ On the other hand, the reduction in cholesterol transfer of HDL to LDL, and the decrease in ApoA1 catabolism, are responsible for the increase in HDL levels.⁶

It was also demonstrated that the decrease in free plasma fatty acids (FA) caused by the nicotinic acid is mediated by the inhibition of lipase in the adipose tissue, and consequently, the lipolysis, which limits the synthesis of hepatic TGs due to the lack of substrate. It was suggested that a consequence of this lipolysis inhibition is a rebound response in a subacute phase of the administration, with an increase in levels of free AG, which could explain the insulin-resistance that occurs in the chronic administration of niacin.⁶ It has also been pointed out that niacin increases the expression of the PPAR- γ (Peroxisome Proliferator-Activated Receptor γ).⁶ Finally, other favorable effects of niacin include the reduction in fibrinogen plasma levels⁶ and its antioxidant and anti-inflammatory action.⁶

Despite all this beneficial effect in the lipid profile, the use of nicotinic acid has been limited by its secondary effects. The most significant effect, which has contributed to abandonment of the treatment by many patients, is flushing, a cutaneous vasomotor reaction involving the D2 and E2 prostaglandins, among other factors, and which occurs in 80% of patients who take the rapid release form, and which can be attenuated by acetylsalicylic acid. Another important secondary effect is the increase in insulin resistance, which can occur in poorly controlled diabetes patients, notably at high doses (> 4g/day).^{5,6} A third important secon-

dary effect inherent to very slow release formulas is hepatotoxicity,⁵ which can range from an asymptomatic increase in aminotransferases to fulminant hepatitis, with monitoring of hepatic function being advisable. Another secondary effect is an increase in uricemia.

With the aim of minimizing flushing and hepatotoxicity, prolonged release formulas – Niaspan® - have been developed, which enable the drug to be taken in a single daily dose. The daily dose should be 375 mg in the first month, which is progressively increased to 1 to 2g, with monitoring of the lipid effects and safety parameters. In this regard, the NAUTILUS study showed that this new form was, in general, well tolerated,⁹ while the Coronary Drug Project demonstrated its capacity to reduce cardiovascular and overall mortality (the latter in the long term), apparently independently of the glycemic status.¹¹

Particular attention has been paid to the association of niacin with statins, as a greater effect has been demonstrated in relation to monotherapy with statin.^{6,10} The HATS trial, in association with simvastatin, demonstrated excellent hypolipemiant effectiveness and reduction of evolution of coronary stenoses and clinical events.¹² The results of the AIM-HIGH trial, a multicentre trial which compares simvastatin in monotherapy with the association of simvastatina+niacin, are eagerly awaited.⁹

Conclusion

We can conclude, therefore, that high levels of Lp(a) contribute to one of the mechanisms of statin resistance. In this context, the use of nicotinic acid in prolonged release formula may be a particularly powerful weapon. ■

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