Editorial Comment

Treatment of Combined Dislipidemia: Statins or Fibrates?

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Physiological lipid processing is a dynamic and extremely effective process. The mean daily fat intake ranges from 100 to 140 g. This quantity is totally absorbed by the gut and introduced to the circulation, since stools contain almost no fat. The mechanisms that determine lipid metabolism are sensitive to genetic changes in the proteins involved in the creation and transportation of lipoproteins. In consequence, small genetic deviations can have a significant effect on lipid levels in the blood.[1]

The paper by Tsimihodimos et al in this issue[2] reports on the effect of atorvastatin and fenofibrate on apolipoprotein B-containing lipoprotein subfractions in patients with combined hyperlipidemia. Combined hyperlipidemia is characterized by elevated levels of serum cholesterol and triglycerides; its incidence is on the increase and it accompanies obesity and increased insulin resistance.[3,4] Familial hyperlipidemia is the most frequent familial lipid disorder and is responsible for more than 10% of cases of early coronary artery disease.[5] The increase in cholesterol and triglycerides is due to an increase in apolipoprotein B-containing lipoproteins, that is, very low density (VLDL) and low density lipoproteins (LDL). LDL particles are heterogeneous and vary according to the size, the density and the composition of the fat they contain. Recently, the small and dense LDL particles and the oxidative alteration of LDL have been connected causatively with the creation of atherosclerosis. The small, dense LDL particles cross very easily to the arterial endothelium and form complexes with the proteoglycans of the media, which undergo oxidation in their turn, thus increasing their atherogenic properties. It is believed that the creation of small, dense LDL is facilitated by an increase in triglycerides. There are several prospective studies showing that the existence of small, dense LDL particles is accompanied by an increased risk for the development of coronary artery disease.[7] On the other hand, there are no large, randomized, epidemiological studies concerning the incidence of cardiovascular events in relation to altered LDL subfractions. The Familial Atherosclerosis Treatment Study found a high correlation between a reduction in small, dense LDL and an improvement in angiographic coronary stenoses, but the patients were under medication with nicotinic acid and cholesteramine, or lovastatin and cholesteramine.[8]

The treatment of combined hyperlipidemia employs hypolipidemic drugs of the statin and fibrate groups. The hypertriglyceridemia that is related to this disorder is affected by drugs that inhibit the production of VLDL in the liver, such as nicotinic acid and fibrates. On the other hand, it is likely that effective doses of statins would have a similar action.

Of the 44 patients participating in the Tsimihodimos study, 21 were taking 20 mg atorvastatin and 23 200 mg fenofibrate daily, in order that the effect of the two drugs on concentrations and qualitative distribution of LDL subfractions could be compared. The determination of LDL subfractions requires special methods of analysis in specialized laboratories. As expected, atorvastatin administration significantly reduced total and LDL cholesterol by 30% and 36%, respectively, while LDL cholesterol also reduced significantly (by 19%) under fenofibrate treatment. The most important finding of the study was that the administration of atorvastatin in a daily dose of 20 mg caused a reduction in the concentration of all LDL subfractions, including small, dense LDL, to the same degree as did 200 mg fenofibrate.

The effect of fenofibrate on small, dense LDL has already been demonstrated by previous studies.[9-11] It should, however, be noted that the high dose of atorvastatin (20 mg daily) in the Tsimihodimos study,[2] compared with the 10 mg used in previous studies, resulted in a greater reduction in triglycerides, equal to that seen under fenofibrate administration. Therefore, the equal reduction in small, dense LDL with both drugs can be explained by the equal reduction in triglycerides.

How may these findings be translated into clinical practice? The primary aim of hypolipidemic medication is the reduction of LDL, since this is considered to be the most atherogenic lipoprotein and in all prospective, randomized studies it was LDL reduction that gave the best results in terms of a reduction of cardiovascular events.[12] Hypolipidemic medication means the administration of statins in 90% of cases in Greece and in other European countries.[13] The guidelines of the relevant bodies concerned with hypolipidemic medication set goals for LDL cholesterol lowering: a) to below 100 mg% in patients with coronary artery disease or equivalent, such as peripheral vascular disease or abdominal aortic aneurysm, symptomatic carotid artery disease and diabetes mellitus; b) to below 130 mg% in asymptomatic patients with more than 2 risk factors and a risk of 10%-20% of experiencing a cardiovascular event during the next decade; c) to below 160 mg% in individuals at low risk, with one or no risk factors and probability of a cardiovascular event below 10% during the next decade.

The primary aim of LDL cholesterol reduction also applies to combined hyperlipidemia, where the increase in total and LDL cholesterol coexists with elevated triglycerides. The administration of drugs such as fibrates, which have an excellent effect on triglycerides, can also achieve a lowering of the small, dense form of LDL. However, the disadvantage of fibrates is the unsatisfactory reduction of LDL cholesterol. From the findings of the Tsimihodimos study[2] it appears that statins can also provide anti-atherogenic protection together with an improvement in the qualitative composition of LDL subfractions, while also reducing the small, dense forms in the LDL spectrum. It is clear that statins, with their very powerful LDL lowering combined with a simultaneous, significant reduction in triglycerides, especially when given in strong doses, are the treatment of choice in patients with combined hyperlipidemia.

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