CHAPTER 16

EFFECT OF LIPID LOWERING MEDICATIONS ON PON1

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Abstract: Lipid abnormalities are among the most important risk factors of the development of atherosclerosis. Inhibitors of 3-hydroxy-methylglutaryl-coenzyme A reductase (statins) and peroxisome proliferator-activated receptor (PPAR) alpha ligand (fibrates) are widely used as lipid lowering drugs in patients with disturbed lipid metabolism. Apart from reducing plasma lipid levels, these agents have additional beneficial effects on other processes involved in the atherosclerotic process. In the last few years the favourable effect of these drugs on human paraoxonase-1 activity was extensively investigated both in vitro and in vivo studies. This chapter summarizes the results of in vivo and in vitro studies, and the putative mechanisms of altered PON1 activity caused by statin and fibrate administration. The possible causes of discrepancies in currently available data will be also discussed

Keywords: statin, fibrate, lipid lowering

1. LIPID LOWERING MEDICATION – NEW GUIDELINES: AGGRESSIVE MANAGEMENT

Cardiovascular disease (CVD) is currently the leading cause of morbidity and mortality worldwide and its incidence is likely to increase. Multiple risk factors contribute to CVD. Elevated LDL-cholesterol (LDL-C) and triglyceride levels, and low HDL-cholesterol (HDL-C) levels are key modifiable risk factors (Ballantyne et al., 2005). In the last decades various therapeutic strategies that target lowering of LDL-C or augmentation of HDL-C have been employed to prevent atherogenesis (Saini et al., 2005). Of among these strategies fibrates and statins are the clinically most important and widely used agents. Primary and secondary prevention trials with lipid lowering agents in a wide variety of populations have demonstrated that lowering plasma LDL-C levels retards the progression of atherogenesis and reduces the risk of coronary events.

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It must be noted that none of these trials have achieved the optimal reduction in LDL-cholesterol concentration for high-risk patients as recommended by the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. The recent update of the NCEP is the most aggressive approach to date for reducing LDL-cholesterol. A basic element of the update is the modification of LDL-cholesterol goal in very high risk patients to 70 mg/dl (Grundy et al., 2004). Overall, the trend continues towards a more aggressive management of patients with atherogenic lipid profile, particularly if they fall within the high risk or very high risk categories. These studies have been carried out using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). It has been proved that high doses of statins are needed for aggressive lipid lowering but these were found to have a greater risk of causing adverse effects (Grundy et al., 2004; Saini et al., 2005).

On the other hand, previous experimental and clinical evidence demonstrates that the antiatherogenicity of statins also includes cholesterol-independent pleiotropic effects. Such effects include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, antiinflammatory properties, stabilization of atherosclerotic plaques, the ability to recruit endothelial progenitor cells, immunosuppressive activity, and inhibition of cardiac hypertrophy. Many of these pleiotropic effects operate independently of LDL-cholesterol reduction, correlate poorly or not at all with LDL-cholesterol changes (Davidson, 2005).

The dyslipidemia associated with obesity, metabolic syndrome, insulin resistance, and type 2 diabetes consists of increased triglyceride, reduced high-density lipoprotein (HDL) cholesterol, and increased numbers of small, dense low-density lipoprotein (LDL) particles (Krauss and Siri, 2004). The inverse relationship between plasma levels of HDL and coronary heart disease has been demonstrated in a number of observational epidemiological studies, as well as in several interventional studies, which showed that increased HDL concentrations independently predicted lowered risk of coronary artery disease (Ballantyne et al., 2005). Fibrates have been shown to activate peroxisome proliferator-activated receptor alpha (PPARα)/ retinoid X receptor (RXR) signal transduction pathway and cause a significant decrease in serum triglyceride and increase in HDL-cholesterol levels. Results of several clinical trials showed that fibrates attenuate atherosclerosis and reduce the incidence of cardiovascular death, myocardial infarction and stroke in patients with coronary artery disease (CAD). In addition it has been demonstrated that fibrates prevent progression of CAD in diabetic patients (Israelian-Konaraki and Reaven, 2005).

In the last few years, because of the limited effectivity and the risk of adverse effects, targets other than LDL-cholesterol and triglyceride lowering ones have been suggested to increase HDL-cholesterol levels, including the cholesterol absorption inhibitor ezetimibe, acyl-cholesterol acyl transferase (ACAT) inhibitors and cholesterol ester transfer protein (CETP) inhibitors. Furthermore, the multicausal nature of atherosclerotic diseases including oxidative processes, inflammation, endothelial dysfunction, immune processes and other cellular events indicates new therapeutical