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Lipid lowering in liver and chronic kidney disease

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Lipid lowering, particularly with HMG CoA reductase inhibitors ("statins"), reduces the risk of cardiovascular disease. Patients with chronic liver and kidney disease present challenges to the use of lipid medications. In the case of most liver disorders, the concern has been one of safety. There is evidence that most lipid-lowering medications can be used safely in many situations, although large outcomes trials are not available. In contrast, in chronic kidney disease, dosing of lipid medications may require substantial modification depending on creatinine clearance. There are significant alterations in lipid metabolism in chronic kidney disease with concomitant increases in cardiovascular risk. Some data are available on cardiovascular outcomes with dyslipidemia treatment in renal patients. This review will examine lipid physiology and cardiovascular risk in specific liver and kidney diseases and review the evidence for lipid lowering and the use of statin and non-statin therapies in chronic liver and kidney disease.

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Lipid lowering in chronic liver disease

Many medications approved for treating hyperlipidemia have historically been contraindicated in patients with abnormal liver enzymes. The obesity epidemic and the rise in prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have increased the number of hyperlipidemic patients with abnormal liver tests who are candidates for lipid lowering therapy for cardiovascular risk reduction. However, data suggest that lipid-lowering medications can be used safely in chronic liver disease. We will: 1) summarize the evidence on the use of statins in chronic liver disease; 2) assess the evidence on the use of non-statin lipid lowering agents in chronic liver disease; and 3) discuss lipid physiology in specific liver conditions.

Statins and the liver: mechanisms and guiding principles

Lipid metabolism is one of the liver's primary functions. Statins interrupt cholesterol synthesis in the liver by blocking the conversion of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) to mevalonic acid, which is the rate-limiting step of cholesterol biosynthesis. A recent meta-analysis from the Cholesterol Treatment Trialists, using patient level data from 27 randomized trials, demonstrates that reducing LDL-C by 1 mmol/L (39 mg/dl) with a statin decreases the risk of major vascular events by ~20% (RR 0.79, 95% CI 0.77–0.81) [1].

Seven statins are marketed in the United States: lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin. Lovastatin, simvastatin and atorvastatin are metabolized by CYP3A4. Fluvastatin is metabolized by CYP2C9, and pravastatin, rosuvastatin and pitavastatin are not extensively metabolized through the cytochrome p450 system and are less likely to have drug interactions [2]. While statin steady state and peak concentrations may be higher in patients with advanced liver disease, there does not appear to be a difference in statin pharmacokinetics in mild liver disease. Patients with advanced liver disease are less likely to need lipid-lowering therapy because of impaired cholesterol synthesis and poor prognosis [3,4].

As a class, statins raise transaminase levels, ALT > AST, usually transiently during the first three months of therapy. Across many statin clinical trials, a sustained elevation >3× the upper limit of normal (ULN) has been seen in <1% of the population as a whole, but up to 2–3% for atorvastatin 80 mg/day and in combination with ezetemibe [4,5]. However, it is unclear that this transaminase elevation actually reflects liver damage in the absence of other signs of synthetic dysfunction [4]. In fact, Hy's Law states that drug liver toxicity is unlikely in the absence of bilirubin elevation (>2× ULN), and transaminase elevations alone have not been associated with histopathologic change [6]. Transaminases often return to baseline without adjustment of the statin dose, and restarting the same statin after stopping may not result in recurrent elevation of ALT [7]. The Merck Worldwide Adverse Event Database found the rate of fulminant liver failure from lovastatin to be 2 per 1 million patients, and only 3 of 51,741 liver transplants performed between 1990 and 2002 were attributed to statins, of which 2 were from cerivastatin, which is no longer marketed [5]. Both the Liver Expert Panel of the National Lipid Association's Safety Task Force and the FDA now recommend against routine monitoring of liver function tests in patients on long term statin therapy. Irreversible liver damage is very rare with statins, and routine monitoring will frequently miss uncommon idiosyncratic hepatotoxicity [4,8].

Value of statins in chronic liver disease

There is little prospective long-term data from randomized controlled trials using statins in chronic liver disease. Details of the available studies are presented in Table 1. The best evidence comes from a multicenter, randomized, double blind, placebo controlled trial comparing pravastatin 80 mg and placebo in patients with hypercholesterolemia and well compensated chronic liver disease [9]. This study is unique in that it included patients with much higher transaminases than any other. Notably, pravastatin significantly reduced LDL-C in comparison to placebo, and there was no significant difference between groups in the rate of ALT doubling. There was actually a trend toward lower ALT in the pravastatin group; however, the study was not powered to examine ALT differences.