The question of primary lipid nephrotoxicity

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Half a century ago, Bagdade [1] reported hypertriglyceridaemia in haemodialysis patients. Since then, the serum lipoprotein patterns of the various forms of kidney disease have been amply documented. In patients with reduced kidney function, this pattern is characterized by increases in triglycerides, apolipoprotein CIII and remnant particles as well as decreases in high-density lipoprotein (HDL) cholesterol and apolipoprotein A1. Low-density lipoprotein (LDL) cholesterol and apolipoprotein B are generally reported to be similar to those of healthy individuals. This pattern, largely explained by delayed removal of triglyceride-rich lipoproteins and disturbed synthesis of apolipoproteins in the liver, is full-blown in end-stage renal disease but changes can be detected early in chronic kidney disease [2, 3].

The focus of lipoprotein research in nephrology has changed. Small studies, documenting and searching for pathophysiological mechanisms of dyslipoproteinemia, have been replaced by large treatment trials and risk estimations with regard to cardiovascular disease and kidney function. This development is rational; the prevalence of lipid modifications with regard to cardiovascular disease and kidney function. This development is rational; the prevalence of dyslipoproteinemia in haemodialysis patients. Since then, the serum lipoprotein patterns of the various forms of kidney disease have been amply documented. In patients with reduced kidney function, this pattern is characterized by increases in triglycerides, apolipoprotein CIII and remnant particles as well as decreases in high-density lipoprotein (HDL) cholesterol and apolipoprotein A1. Low-density lipoprotein (LDL) cholesterol and apolipoprotein B are generally reported to be similar to those of healthy individuals. This pattern, largely explained by delayed removal of triglyceride-rich lipoproteins and disturbed synthesis of apolipoproteins in the liver, is full-blown in end-stage renal disease but changes can be detected early in chronic kidney disease [2, 3].

The part of the study that had statistically significant results was cross-sectional. Therefore, the associations found do not differentiate between cause and consequence. However, since the authors found very small differences in apolipoprotein A1 among the eGFR quartiles, the results support the notion that lipid nephrotoxicity may be a primary or at least an early-onset event in the process of kidney damage. The major strength of the study is the size of the two cohorts which are independent of each other. The use of the new CKD-EPI equation to estimate glomerular filtration rate (GFR) possibly increases the quality of the study. The equation is considered to give a more precise estimate of the higher levels of GFR, such as those of the majority of the study patients.
participants, and the authors noted tighter confidence intervals when comparing the equation with the Modification of Diet in Renal Disease equation [13]. Both cohorts are old, sampled during the periods 1988–91 and 1996–98, respectively. This may actually be an advantage since the use of statins was not as widespread at the time of sampling as it is today, which simplifies the interpretation of the study.

The notion of primary or early lipid nephrotoxicity is obviously of theoretical interest. The practical interest is closely associated with the potential renoprotective effects of lipid-modifying drugs. Two meta-analyses, including 13 and 27 studies, showed a lower rate of loss of kidney function in patients treated with statins compared with those who were not, whereas one meta-analysis of 11 trials showed that statin treatment did not improve GFR [14–16]. More importantly, the Study of Heart and Renal Protection (SHARP) trial, including 6247 patients with predialytic chronic kidney disease, randomized to treatment with simvastatin 20 mg plus ezetimibe 10 mg or placebo, showed no significant difference in any of the pre-specified measures of renal disease progression (end-stage renal disease defined as start of dialysis treatment or transplantation, end-stage renal disease or death and end-stage renal disease or doubling of the serum creatinine concentration) [17]. Thus, statin treatment cannot be recommended for renoprotective purposes at the present time. Moreover, the results of the SHARP are convincing and it is not likely that still larger clinical trials on the subject will be performed. This does not mean that there are no questions left to answer. Would higher statin doses be helpful [18]? Does lipid-modifying treatment prevent a potential primary nephrotoxicity? Would effective HDL cholesterol-raising therapy prevent early nephrotoxicity or halt the progression of kidney damage? The results of the study by Goek et al. underline these questions.

Conflict of interest statement. None declared.


References


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