The question of primary lipid nephrotoxicity

Margret Arnadottir

Department of Nephrology, Landspitali University Hospital, Reykjavik, Iceland

Correspondence and offprint requests to: Margret Arnadottir; E-mail: margarn@landspitali.is

Keywords: apolipoprotein A1; apolipoprotein B; glomerular filtration rate; HDL cholesterol; kidney function

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 CII 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 Small studies, documenting and searching for pathophysiological mechanisms of dyslipoproteinaemia, have been replaced by large treatment trials and risk estimations with regard to cardiovascular disease and kidney function.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 chronic kidney disease is steadily increasing worldwide; there are many indications that dyslipoproteinaemia accelerates the progress of chronic kidney disease, and the cardiovascular risk is manifest in patients with reduced kidney function, increasing early in that process [4]. The entry of the statins has radically changed the treatment scene, even though the impact of lipid-modifying treatment in chronic kidney disease has not been fully elucidated.

In 1982, Moorhead et al. formulated the lipid nephrotoxicity hypothesis proposing that hyperlipoproteinaemia, secondary to proteinuria, could aggravate glomerular and tubulointerstitial disease, and in 2009, they published an eloquent update on their hypothesis [5, 6]. Several studies support the notion that established lipoprotein risk factors for atherosclerosis, i.e. increased LDL cholesterol, increased triglycerides and decreased HDL cholesterol, are also associated with progression of loss of kidney function [7–9]. There is experimental evidence that inflammatory stress, oxidative stress and endothelial dysfunction, generally associated with dyslipoproteinaemia and reported to be increased in chronic kidney disease, can contribute to renal pathophysiological changes [6]. In the context of this Editorial Comment, the effects of HDL are of particular importance. This lipoprotein particle does not only have a well-known role in reverse cholesterol transport but has been shown to possess important anti-inflammatory and antioxidant properties [10, 11].

Much evidence suggests that a precursor condition, such as intrarenal hypertension, hyperfiltration, decreased nephron mass or inflammation, is needed for the induction and progression of lipid-induced renal damage [6]. However, in two epidemiological studies, low HDL cholesterol was associated with inferior kidney function [7, 9].

The paper by Goek et al. [12], published in this issue of the Nephrology Dialysis Transplantation, describes the association of the apolipoproteins A1 and B and estimated glomerular filtration rate (eGFR) in two large cohorts derived from the general population: the third National Health and Nutrition Examination Survey (NHANES III, \( n = 7023 \)) and the Atherosclerosis Risk in Communities study (ARIC) \( ( n = 10292) \). The results were similar in both cohorts; higher apolipoprotein A1 and lower B/A1 quartiles were associated with significantly lower prevalence of chronic kidney disease Stages 3–5 and higher eGFR. After adjustment, the apolipoprotein B quartiles were not associated with any changes in kidney function. In a smaller cohort of the ARIC study, which was followed for 10 years \( ( n = 1659) \), the incidence rate ratio of chronic kidney disease was lower in the higher quartiles of apolipoprotein A1 but the overall trend of the association was not significant. Replacing the apolipoproteins with the corresponding lipids/lipoproteins did not have a major effect on the analyses, which allows further discussion about lipid nephrotoxicity to continue in lipid/lipoprotein terms.

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 population.
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


Received for publication: 19.1.2012; Accepted in revised form: 26.3.2012.