Introduction

The markedly elevated cardiovascular risk observed in renal patients is increasingly recognized as an important treatment target [1]. Among the renal populations, proteinuric patients are at particularly high risk, as apparent from the observation of an almost 6-fold increased incidence of myocardial infarction in such patients [2]. Moreover, proteinuria has been shown to be an independent risk factor for cardiovascular morbidity and mortality [3,4]. Most likely, proteinuria-associated lipid abnormalities play a main role in the high cardiovascular risk in proteinuric patients, and thus provide an important treatment target.

Several studies have underlined the efficacy of statins, not only to improve the lipid profile, but also to reduce cardiovascular morbidity and mortality in hyperlipidaemic and hypertensive populations [5,6], and recent post-hoc data from the CARE study showed that statin treatment reduces cardiovascular morbidity in subjects with chronic renal insufficiency [7]. Therefore, statins will most likely be a cornerstone in cardiovascular prevention for years to come in non-renal and renal populations.

For overtly proteinuric patients, however, solid data on cardiovascular risk management are still lacking, in spite of the obvious need for aggressive risk management in this high-risk population. Rational principles for cardiovascular risk management in this population can nevertheless be formulated, based on the available evidence. In this respect, lipid management is an important target. Importantly, proteinuria reduction exerts a clear-cut lipid lowering effect, irrespective of the way (class of drug, dietary intervention, or both) it is achieved. Here, we will briefly

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Lipid management in the proteinuric patient: do not overlook the importance of proteinuria reduction

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review the distinct effects of proteinuria reduction and antihyperlipidaemic treatment on lipid status in proteinuric patients, and discuss their implications for lipid management and overall risk management in proteinuric patients.

Plasma lipoproteins in proteinuria

Lipid abnormalities are among the hallmarks of the nephrotic syndrome. Experimental data have causally linked hyperlipidaemia to urinary protein loss [8]. The typical abnormalities include elevated concentrations of plasma total cholesterol, due to an increase in low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol, and of plasma triglycerides [9]. Consequently, the plasma level of apolipoprotein (Apo) B, the major apolipoprotein of LDL and VLDL, is elevated. High density lipoprotein (HDL) cholesterol and Apo A-I, the quantitatively most abundant apolipoprotein associated with this lipoprotein, is found to be decreased in many studies, albeit not uniformly so [9,10]. As a result, proteinuria is associated with an unfavourable high total cholesterol/HDL cholesterol ratio. Moreover, the highly atherogenic lipoprotein(a) (Lp[a]) is elevated in proteinuric patients [11]. In many patients, proteinuria as such is not the only factor that exerts an unfavourable effect on lipid profile. Other factors, such as renal function impairment, insulin resistance and diabetes frequently coincide with proteinuria, and may therefore also contribute to dyslipidaemia. A recent study of 150 non-diabetic patients showed that the lipid profile, i.e. plasma total cholesterol, total cholesterol/HDL cholesterol ratio, is not only correlated with proteinuria but also with the severity of renal function impairment [12].

Effects of symptomatic antiproteinuric treatment on plasma lipoproteins

In patients and experimental animals, reduction of proteinuria results in a proportional decrease in plasma total cholesterol and triglycerides [13,14], irrespective of the type of intervention. The quantitative relationship between proteinuria reduction and decrease in total cholesterol is illustrated in Figure 1, summarizing mean proteinuria and total cholesterol before and after different antiproteinuric regimens in clinical studies [15]. Apparently, the reduction in total cholesterol and triglycerides does not depend on class of drug, but is related to the efficacy of proteinuria reduction: as it is obtained with angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists (AIIA), non-steroidal inflammatory drugs (NSAID) or a combination of these drugs [16–18]. Moreover, further reduction of proteinuria by supportive measures such as protein restriction, sodium restriction, or co-treatment with diuretic also results in a further decrease of cholesterol. Accordingly, for a single drug regimen, the dose–response for lipid reduction closely follows the dose–response for antiproteinuric efficacy, as shown in experimental animals and in humans [13,14]. Also, when the top of the dose–response for proteinuria is shifted towards greater maximal efficacy by sodium restriction, lipid reduction is more effective [13]. Roughly, for a proteinuria reduction of 2–3 g/day a decrease in total cholesterol of ~1 mmol/l may be expected.

The reduction in total cholesterol is largely explained by a drop in LDL cholesterol, and accompanied by a fall in triglycerides [14]. Moreover, proteinuria reduction leads to a decrease in Lp[a] [17,19]. Thus, the lipoprotein profile appears to be altered favourably by reduction of proteinuria. However, antiproteinuric treatment has also been reported to be associated with a reduction in HDL cholesterol in several independent studies [14,17]. The mechanism and clinical significance of this unexpected finding are still uncertain. Theoretically, effects on reverse cholesterol transport could lead to a drop in HDL. However, data on cholesterol metabolism during antiproteinuric treatment are scarce. Our group has shown that the drop in HDL cholesterol during RAS blockade was possibly associated with a decrease in lecithin: cholesterol acyltransferase activity [19]: the enzyme responsible for cholesterol esterification in HDL and one of the first steps in the reverse cholesterol transport pathway. The effects of antiproteinuric treatment on other aspects of reverse cholesterol transport, and/or oxidative properties of HDL, are currently unknown, and deserve further exploration.
Effects of lipid lowering drugs in proteinuric patients

As in other populations, in proteinuric patients different classes of lipid-lowering agents reduce elevated plasma lipid levels [20]. Statins are particularly effective, as illustrated by double-blind data in 56 non-diabetic proteinuric patients, showing a reduction of 47% in LDL cholesterol after 9 months simvastatin therapy [21]. However, it should be noted that statins do not modify Lp[a] levels, be it in non-proteinuric or in proteinuric subjects [21,22].

For appropriate risk management, target levels of plasma lipoproteins have been defined. Guidelines from the National Kidney Foundation and the American Diabetes Association recommend strict control of LDL cholesterol (<100 mg/dl or <2.58 mmol/l) in patients with end-stage renal disease and diabetes [23,24]. No target lipid levels have been recommended for proteinuric subjects specifically. However, given their high overall risk it is highly desirable that strict lipid control should be pursued in this population.

Achievement of target lipid levels with monotherapy, however, can be problematic. A large-scale analysis in general practices reported that with statins the recommended target level was reached in only 40% of the patients [25]. The same appears to apply to proteinuric patients [21,26], indicating that despite statin treatment, lipid control in these patients is often suboptimal.

Renoprotective effects of statins in proteinuric conditions

Interestingly, long-term therapy with statins may exert renoprotection that may partly be independent of the lipid-lowering effects. Animal studies support such a renoprotective effect. Moreover, statin treatment was shown to restore the response to ACE inhibition in renal conditions resistant to intervention with RAS blockade [27]. In humans, long-term treatment with statins was reported to reduce proteinuria in renal patients [20] and in hypertension [28], although not uniformly so. The renoprotective potential of statins is furthermore supported by post-hoc data from the CARE study, showing a reduction in the rate of renal function loss with statins in subjects with chronic renal insufficiency [29]. Statins added to ACEi or AIIA can result in further proteinuria reduction, as recently shown in humans [28,30]. As RAS blockade is an established first-choice therapy in proteinuric conditions, this added efficacy is relevant for the clinical application of statins in proteinuric patients. Although the renoprotective properties of statins in man still await prospective confirmation, the odds seem to be in its favour.

Conclusion

Proteinuric patients are at high risk of progressive renal function loss as well as cardiovascular morbidity and mortality. Overall risk management in these patients requires appropriate control of blood pressure, proteinuria, lipid profile, and intervention in other cardiovascular and renal risk factors, such as smoking and obesity. Obviously, these risk factors are closely linked and require an integrated approach.

RAS blockade, as first-choice treatment in proteinuric patients, together with statins for specific lipid control provides a rational combined approach for overall risk reduction, with added efficacy and with complementary properties regarding the specific effects on HDL cholesterol and Lp[a]. Achievement of the intermediate targets, i.e. optimal blood pressure control, maximal proteinuria reduction and lipids within target levels, should be actively pursued by appropriate dosing and supportive measures. Future studies should address optimal dosing schedules for this setting and evaluate the eventual benefit in terms of cardiovascular and renal risk.

Conflict of interest statement. None declared.

References

The changing profile of acute tubulointerstitial nephritis

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‘Cellular and fluid exudation in the interstitial tissue...’ was described by Councilman in 1898 when he examined the kidneys of patients dying of scarlet fever and diptheria [1]. In particular he noted that the organs were sterile thus raising the possibility of an allergic-type phenomenon. This entity was termed acute tubulointerstitial nephritis (ATIN). The widespread introduction of percutaneous renal biopsy led to the discovery of similar findings in association with drug-related renal failure, in particular related to the use of penicillins and sulphonamides. Histological examination in ATIN reveals an infiltrate, which is largely composed of T cells, together with some macrophages and plasma cells. As there is some evidence for cutaneous delayed-type hypersensitivity and positive in vitro lymphocyte stimulation tests in response to suspected drugs, the aetiology is presumed to be immune-mediated [2]. This is illustrated by the rapid recrudescence of disease upon inadvertent rechallenge in drug-related ATIN, a clear manifestation of an immunological memory response [3–5].