Features of the metabolic syndrome relating to cardiorenal outcomes

Commentary on

Decreased kidney function as a risk factor for cardiovascular events in subjects with metabolic syndrome – a pilot study

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Cardiovascular disease (CVD) is the single most common 'killer' in the industrialized world [1]. Also, chronic kidney disease (CKD) represents a major health problem since up to 11 million Americans exhibit various stages of renal function impairment [2]. The last decade has brought renewed interest in the relationship between CVD, CKD and factors that increase risk for both morbid situations [3]. Specifically, a large body of literature supports the view that CKD, manifested as low estimated glomerular filtration rates (eGFR), and albuminuria are strong and independent predictors of CVD [4]. Additionally, abnormalities known to be independently associated with increased CVD outcomes, such as diabetes mellitus, hypertension and dyslipidaemia, have a deleterious impact on renal function [5]. Therefore, treatment strategies for modification of traditional cardiovascular risk factors, including statin therapy, have been proved efficacious in improving renal functionality, particularly in patients with mild-to-moderate renal function impairment [6].

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities suggested to increase cardiovascular risk, such as hyperinsulinaemia, impaired fasting glucose, high blood pressure levels and atherogenic dyslipidaemia [7]. Other features of the MetS related to vascular disease include proinflammatory and hypercoagulability states, endothelial dysfunction, elevated uric acid levels and microalbuminuria [7]. It has also been suggested that the MetS as well as several individual components of this syndrome, including hypertension, dyslipidaemia, hyperuricaemia and impaired glucose homeostasis, are associated with increased risk for the development and progression of CKD [8].

The study by Barylski et al. provides further evidence with regard to renal function impairment in patients with the MetS [9]. Namely, the eGFR calculated by the MDRD (Modification of Diet in Renal Disease) formula was significantly lower in patients with the MetS compared with healthy controls (72±18 vs. 83±14 ml/min/1.73 m^2, respectively, $P<0.05$) [9]. Furthermore, the proportion of subjects exhibiting eGFR <60 ml/min/1.73 m^2 was higher

in the MetS group than in the control group (30 vs. 8%, respectively) [9]. These findings are in line with a previously published study by our team suggesting that among patients with coronary heart disease (CHD) those with the MetS had lower baseline eGFR compared with those without the MetS (69 vs. 82 ml/min/1.73 m^2, respectively, P<0.0001) [10]. Also, in this substudy of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study, we indicated that among non-statin treated patients with CHD those with the MetS exhibited greater eGFR decline as compared to those without the MetS during the 3-year follow-up of the study [10].

Atherogenic dyslipidaemia associated with the MetS is characterized by high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels along with a predominance of small, dense low-density lipoprotein particles [7]. This lipid pattern is frequently evident even in patients with CKD [11]. Barylski et al. [9] proposed an elevated triglyceride level as the component of the 'lipid triad' of the MetS that was related to the adverse impact of the syndrome on renal function. The literature has been replete with evidence that atherogenic dyslipidaemia, similar to that of the MetS, is a risk factor for progressive renal disease [12]. However, from another point of view, it could be hypothesized that the atherogenic dyslipidaemia observed in individuals with CKD may account for the higher prevalence of the MetS in patients with renal function impairment.

Therapeutic modulation of dyslipidaemia with statins exerts protective effects against both CVD and renal injury. A subgroup analysis of the GREACE study showed that creatinine clearance increased by 12% following atorvastatin treatment, whereas this renal function parameter decreased by 5.2% with non-statin treatment in patients with CHD [6]. Of interest, this benefit of atorvastatin was more prominent in patients in the lower two quartiles of baseline creatinine clearance and with higher doses of atorvastatin treatment [6]. Furthermore, this favourable effect of atorvastatin treatment on renal function independently accounted for statin-related cardiovascular risk reduction (a decrease by 16% in CHD-related events with every 5% increase in creatinine clearance) [6].

Of interest, we noted that among CHD patients participating in the GREACE study, those with the MetS may benefit more from statin (mostly atorvastatin) treatment in terms of renal function improvement as compared to those without the MetS [10]. Namely, eGFR increased by 13.7% among statin-treated patients with CHD and MetS, while the respective post-treatment increase in eGFR was 8.4% among patients without the MetS [10].

Serum uric acid (SUA) levels may represent a metabolic variable that enhances risk for both CVD and CKD [13]. A post hoc analysis of the GREACE study revealed an increase by 9% in the relative risk of vascular events for each 5% increase in SUA levels [10]. Elevated SUA levels are associated with the presence of the MetS [14]. According to our previously published results, untreated patients with CHD and the MetS exhibited a greater increase in SUA levels as compared to corresponding patients without the MetS after a 3-year follow-up. This difference may be responsible for the worse renal outcomes in patients with the MetS [10]. Furthermore, the higher degree of atorvastatin-induced reduction in SUA levels in patients with CHD and the MetS as compared to those without the MetS may account for a greater cardiovascular risk reduction [10]. Of note, multivariate analysis revealed that the relationship between the risk for vascular events and SUA levels vanished when changes of eGFR were included in the regression model. Therefore, there may be a potential link between SUA-related increase in cardiovascular risk and renal injury induced by elevated SUA levels. Furthermore, atorvastatin-provoked cardiovascular benefits may pass through the improvement of renal function derived from this favourable metabolic effect of the statin [10].

The levels of several pro-inflammatory adipokines and enzymes, including visfatin and lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which may also adversely affect endothelial function [15, 16], were found to be elevated in patients with the MetS as compared to healthy controls [17, 18]. Plasma Lp-PLA_2 is suggested to be directly involved in the pathogenesis of atherosclerotic vascular disease, while the levels of this enzyme seem to be higher in patients with CKD compared with healthy subjects [16, 19]. Furthermore, serum visfatin by exerting a proinflammatory role as well as detrimental effects on endothelial function may contribute to both atherogenesis and renal injury [20, 21]. We have shown that high levels of both plasma Lp-PLA_2 and serum visfatin levels are amenable to correction with statin treatment or other hypolipidaemic medications [22, 23].

MetS seems to be a significant risk factor for CVD and CKD as well as a factor which links the pathophysiology of these conditions. Components of the MetS, other than those corresponding to its diagnostic criteria, may increase risk for both diseases and may be favourably affected by treatment modalities used for the treatment of cardiovascular risk factors, such as statin therapy. Early identification of the MetS as well as the appropriate multifactorial approach to treatment of its metabolic disturbances may be useful in the prevention of cardiorenal outcomes.

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