Mild Renal Dysfunction and Cardiovascular Risk in Hypertensive Patients

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Abstract. Mild renal dysfunction, defined as GFR <60 to 70 ml/min and/or the presence of increased urinary albumin excretion, is associated with higher cardiovascular morbidity and mortality in primary hypertension. The aim of the present study was to investigate the relationship between renal dysfunction and target organ damage (TOD), namely left ventricular hypertrophy (LVH), retinal vascular changes, and carotid atherosclerosis, in a large cohort of unselected middle-aged hypertensive patients with normal serum creatinine. A group of 934 untreated patients with primary hypertension (543 men, 391 women; mean age 50 ± 11 yr) was studied. Renal function was estimated by the creatinine clearance using the Cockcroft-Gault formula and by the presence of albuminuria, measured as the albumin to creatinine ratio (A/C) in first morning urine samples. LVH was determined according to electrocardiographic criteria, and retinal vascular changes were evaluated by direct ophthalmoscopy in all patients. In a subgroup of patients (n = 340; 208 men, 132 women; mean age 47 ± 9), the presence and extent of cardiac and vascular organ damage was also assessed by ultrasound techniques. Creatinine clearance was on the average 82 ± 20 ml/min. The overall prevalence of ECG-detected LVH and retinopathy was 12 and 49%, respectively. Creatinine clearance was inversely related to duration of disease, systolic BP, serum glucose, total cholesterol, LDL cholesterol, and early signs of TOD, namely retinal vascular changes and LVH. Patients in the bottom quintile of creatinine clearance showed higher prevalence of both ECG-detected LVH (P = 0.04) and retinal vascular changes (P = 0.02). In the subgroup of patients who underwent ultrasound evaluation of cardiovascular structures, the prevalence of mild renal dysfunction was 18%, whereas the prevalence of LVH and carotid plaque was 49 and 26%, respectively. Patients with mild renal dysfunction showed higher left ventricular mass and increased intima-media thickness (P < 0.0001), as well as higher prevalence of LVH and carotid plaque as compared with those with normal renal function. Controlling for duration of hypertension and mean BP, the risk of TOD in our cohort increased by 20% for each 10 ml/min decrease in creatinine clearance and by 30% for each 0.2 mg/mmol increase in Log A/C. In conclusion, mild renal dysfunction is associated with preclinical end-organ damage in patients with primary hypertension. These data may help to explain the observed increase in cardiovascular mortality reported in these patients. The evaluation of creatinine clearance and urinary albumin excretion could be useful for identifying patients who are at higher cardiovascular risk.

The cardiovascular system is profoundly influenced by abnormalities in renal function. In fact, cardiovascular morbidity and mortality have long been known to be significantly increased in patients who are on renal replacement therapy as compared with age-matched control subjects with normal renal function (1). Recently, it has been pointed out that cardiovascular risk progressively increases as the GFR declines and is already significantly elevated even in the earliest stages of renal damage (2). These findings are even more noteworthy when one considers that a mild reduction in renal function is relatively common in hypertensive patients. According to data from the Third National Health and Nutrition Examination Survey, approximately 13% of all non-diabetic adults in the United States have a creatinine clearance <60 ml/min (3). The presence of clinical proteinuria is also a powerful, independent risk factor for cardiovascular complications in this subgroup of patients (4). More recently, the association between urinary protein excretion and cardiovascular morbidity and mortality has been extended to low-grade albuminuria, such as microalbuminuria, both in diabetic and nondiabetic populations (5). Optimal BP control, as indicated by international guidelines, is of the utmost importance both to slow the progression of renal damage and to prevent cardiovascular events (6). However, target BP levels are often very difficult to achieve, and most renal patients remain hypertensive despite treatment (7).

Prevalence and Prognostic Value of Mild Renal Dysfunction

Mild renal dysfunction, defined as a GFR <60 ml/min and/or the presence of increased urinary albumin excretion, varies from 10 to 40% in patients with long-standing primary hypertension (8). Among patients who participated in the MicrAldumunuria: A Genoa Investigation on Complications Study (n = 787; mean age 51 ± 10 yr; mean arterial BP 122...
± 8), approximately 14% had an estimated creatinine clearance below 60 ml/min (9). Several prospective studies have shown that a mild degree of renal insufficiency identifies subgroups of hypertensive patients at higher risk for developing cardiovascular events. In the Hypertension Detection and Follow-up Study carried out on 10,940 patients, a linear correlation between serum creatinine and cardiovascular mortality was observed over a 5-yr follow-up, with a two-times higher risk in patients with serum creatinine >1.7 mg/dl (10). More recently, the Hypertension Optimal Treatment Study evaluated 18,790 hypertensive subjects over 4 yr. Patients with baseline serum creatinine >1.5 mg/dl have a twofold increased adjusted risk for major cardiovascular complications and for all-cause mortality (11). It is interesting that in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, serum creatinine in the upper-normal range was an independent predictor of cardiovascular morbidity regardless of several confounders, such as age, gender, diabetes, smoking habits, lipid profile, or BP load (12).

Mild Renal Dysfunction as a Marker of Target Organ Damage

The high cardiovascular risk reported in patients with mild renal dysfunction cannot be completely attributed to traditional cardiovascular risk factors; therefore, it is likely to be a multifactorial process, in part still unexplained (2). A reduction in GFR per se is associated with several metabolic changes that enhance the atherogenic process at the systemic level. In fact, oxidative stress, inflammation, insulin resistance, endothelial dysfunction, and hyperhomocysteinemia have already been described in the initial stages of renal disease (13–15). However, the impairment of renal function may, in turn, be the manifestation at the level of the kidney of generalized, subclinical atherothrombotic disease. To investigate this issue further, we evaluated the relationship between early renal dysfunction and subclinical target organ damage (TOD), namely LVH, retinal vascular changes, and carotid atherosclerosis, in a large cohort (n = 934; mean age 50 ± 11) of unselected middle-aged hypertensive patients with normal serum creatinine. Creatinine clearance (estimated by means of the Cockcroft-Gault formula) was inversely related to history of hypertension (P < 0.0001), systolic BP (P = 0.001), serum glucose (P = 0.007), lipid profile (P < 0.0001), and prevalence of ECG-determined LVH (P = 0.04) as well as of retinal vascular changes (P = 0.02) observed at fundoscopy. Moreover, in a subgroup of patients (n = 340; mean age 47 ± 9) who also underwent ultrasound evaluation of cardiovascular structures, those with mild renal dysfunction (18%) had a worse global cardiovascular risk profile as compared with those with normal renal function. In fact, they were older, had higher levels of BP and uric acid, had longer history of hypertension, and were more likely to be smokers. Furthermore, they showed higher left ventricular mass and increased intima-media thickness (P < 0.0001), as well as higher prevalence of LVH and carotid plaque as compared with subjects with normal renal function (Figure 1). It is interesting that these differences remained significant (P = 0.02 and P = 0.004, respectively) after adjusting for age, systolic BP, reported duration of disease, and serum uric acid. Controlling for duration of hypertension and mean BP, the risk of ultrasound-determined TOD in our cohort increased by 20% for each 10-ml/min decrease in creatinine clearance and by 30% for each 0.2-mg/mmol increase in Log A/C.

Conclusions

Mild renal dysfunction, regardless of its cause, is a powerful predictor of cardiovascular events in high-risk patients, as well as in the general population (16–18). In hypertensive patients with normal serum creatinine, the presence of microalbuminuria and/or creatinine clearance <60 ml/min is associated with subclinical cardiovascular organ involvement regardless of BP load and other traditional risk factors. These findings may
account for the worse cardiovascular prognosis reported in these patients. In fact, hypertensive TOD is known to precede and predict major cardiovascular events (19). Our results strengthen the usefulness of routinely determining creatinine clearance and urinary albumin excretion in clinical practice, not only to evaluate renal function but also to stratify cardiovascular risk in hypertensive patients. A similar diagnostic approach may also have therapeutic implications. In fact, on the basis of current recommendations, lower BP levels and specific drug classes (i.e., renin-angiotensin system inhibitors) should be used in this subgroup of patients at risk (20,21).

References