Kidney Dysfunction: A Sensitive Predictor of Cardiovascular Risk

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Changes in renal function can be detected in patients suffering from essential hypertension and heart failure. Detection of an increased serum creatinine, a decreased creatinine clearance and of proteinuria or microalbuminuria in hypertensive patients; and the finding of a diminution in the value of estimated creatinine clearance in heart failure patients are very potent predictors for a worse outcome of the patient. The parameters commonly used to evaluate renal function have to be considered in any stratification of cardiovascular risk in hypertensive and heart failure patients. Am J Hypertens 2001;14:213S–217S © 2001 American Journal of Hypertension, Ltd.

Key Words: Cardiovascular risk, renal function, creatinine, proteinuria, estimated creatinine clearance, microalbuminuria.

It is well established that the cardiovascular system of patients with terminal renal failure is profoundly affected. Patients undergoing maintenance hemodialysis have a cardiovascular mortality approximately three times that of age-matched nonuremic control subjects.1 Such an increase has been interpreted as secondary to a higher frequency of atherosclerotic heart disease with myocardial infarction, left ventricular hypertrophy, and congestive heart failure, all favored by a poor control of intravascular volume, the presence of arterial hypertension, and hyperlipidemia.

Recent analysis of the influence of renal function on the cardiovascular outcome in trials performed in patients with essential hypertension2–4 or heart failure5,6 have confirmed the relevance of the kidney in cardiovascular prognosis since the initial stages of renal failure. The diagnosis of a deranged renal function in clinical practice is based on the finding of changes in serum creatinine or its clearance, or the detection of an elevated urinary excretion of albumin either below (ie, in the case of microalbuminuria) or above (ie, macroalbuminuria) the usual laboratory findings. The presence of serum creatinine values > 1.5 mg/dL (132 μmol/L) in men and 1.4 mg/dL (123 μmol/L) in women7,8 or the finding of an estimated creatinine clearance < 60 to 70 mL/min allows the diagnosis of mild renal insufficiency.2,6 The presence of proteinuria (> 300 mg/day) and microalbuminuria (30 to 300 mg/day) can also be interpreted as diagnostic for the presence of an alteration in renal function.9,10

An increase in serum creatinine above normal values, a slight decrease in creatinine clearance, or the presence of proteinuria could constitute the most potent predictors for the future development of cardiovascular death in situations such as essential hypertension or heart failure. The clinical relevance of these findings is reinforced by the simplicity of their consideration in clinical practice.

Value of Serum Creatinine and Other Renal Parameters for Prediction of Increased Cardiovascular Risk in Essential Hypertension

In the absence of antihypertensive treatment, renal involvement is very frequent in primary hypertension. Perera found that proteinuria was present in 42% and chronic renal failure in 18% of 500 patients followed-up until death.11 Interestingly, that report noted that life expectancy after the development of renal involvement by the hypertensive process was no longer than 5 to 7 years. With the advent of antihypertensive therapy the cardiovascular prognosis of hypertensive patients has improved dramatically, and it has generally been agreed that the renal prognosis is excellent when arterial hypertension is treated, with a very small percentage of patients (< 2%) developing chronic renal failure.12,13 However, the prevalence of nephrosclerosis as a cause of end-stage renal failure in patients entering dialysis programs is continuously rising both in the United States and in Eu-
and the estimation of creatinine clearance in the hypertensive population included in the Hypertension Optimal Treatment (HOT) study revealed a significant diminution of this parameter in at least 13% of patients. Interestingly, the existence of a relevant prevalence (8.7% in men and 8.0% in women) of mild renal insufficiency in the community, based on serum creatinine values, has been recently described in the Framingham Heart Study participants. The prevalence of a mild decrease in renal function in the community could be even higher, according to the values of estimated creatinine clearance seen in the Third National Health and Nutrition Examination Survey (NHANES III). Interestingly, in the Framingham population, the presence of mild renal insufficiency did not depend on the existence in this group of patients of a higher prevalence of arterial hypertension. However, the prevalence of left ventricular hypertrophy was 3 to 4 times higher for similar levels of blood pressure in patients with renal insufficiency when compared with those with normal renal function. This indicates that, as in diabetes, the cardiovascular and renal systems of these subjects could be particularly sensitive to very small elevations in blood pressure. On the other hand, the existence of a mild decrease in renal function can contribute to a progressive rise in blood pressure through the various mechanisms involved in the development of arterial hypertension in renal disease.

The presence of hypercreatininemia (≥1.7 mg/dL) at baseline was found to be a very potent predictor for 5- and 8-year all-cause mortality in the Hypertension Detection and Follow-up Program trial. The association of elevated serum creatinine with mortality has been reported in several other studies including the Cardiovascular Health Study, in which baseline serum creatinine values >150 μmol/L were associated with a 70% increase in risk for all-cause mortality in older men and women followed-up for 5 years. Of relevance, the magnitude of risk accompanying the elevation in serum creatinine was similar to that associated with the presence of congestive heart failure at baseline.

Data from the HOT Study, which included >18,000 patients, have confirmed previous observations that serum creatinine values above the cutoff point for mild renal insufficiency predicts an elevated cardiovascular risk—in particular, for total and cardiovascular death—even with excellent blood pressure control. In fact, serum creatinine values were the most powerful predictor, above any of the known accompanying risk factors in the HOT Study. This study investigated the prognostic value of diminished creatinine clearance (as estimated by the Cockcroft and Gault formula), and found that values <60 mL/min were accompanied by a significantly higher cardiovascular risk. The presence of an elevated serum creatinine in the general population is also associated with a high prevalence of cardiovascular disease, which has been attributed, as is essential hypertension, to the coexistence of several cardiovascular risk factors.

The relevance of proteinuria for cardiovascular prognosis in the community was described in the Framingham Heart Study. The presence of proteinuria in essential hypertension varies between 4% and 16% in different series of treated hypertensive patients. The recently published Intervention as a Goal in Hypertension Treatment (INSIGHT) study compared the capacity of a long-acting dihydropiridine and a diuretic to diminish cardiovascular events and death in essential hypertension. In this study, proteinuria was considered for the first time as an associated risk factor, and the analysis of the predictive power of the various risk factors revealed that proteinuria was the most powerful, even more so than the existence of previous myocardial infarction or diabetes.

Attention has been recently paid to the presence of microalbuminuria and its relevance as a predictor of cardiovascular disease. Its prevalence in primary hypertension probably varies between 20% and 30% for untreated hypertensive individuals, and can be as high as 25% in treated patients. Recently it has been shown that the presence of microalbuminuria in primary hypertension correlates with an elevated cardiovascular risk. Microalbuminuria represents the renal expression of a generalized disorder characterized by an increased endothelial permeability, which may be an underlying link between elevated urinary albumin excretion (UAE) and increased risk for cardiovascular disease. Some preliminary data seem to indicate that microalbuminuria is also a predictor of progressive renal function deterioration in primary hypertension.

**Do Nephrosclerosis and Atherosclerosis Evolve in Parallel?**

Hypertensive subjects examined at autopsy are often found to have nephrosclerosis. This condition is characterized by the presence of hyalinization of arterioles and by fibroplastic intimal thickening of small arteries. Interestingly, it has been described that subjects with coronary heart disease exhibit greater hyalinization of renal arterioles than do matched control subjects. Moreover, in autopsy studies, the presence of hyalinization in the renal arterioles has been shown to be a marker of the presence of advanced coronary atherosclerosis in otherwise asymptomatic young persons.

The increase in cardiovascular risk accompanying chronic renal failure since its mildest stages has led to the realization that the identification of predictors of the future development of renal damage in arterial hypertension would be of great clinical value. In this sense, it has been described that African American men with elevated blood glucose and systolic blood pressure have an increased risk of developing impaired renal function. There is greater damage in the renal vessels of hypertensive patients presenting with hyperuricemia in the presence of a normal glomerular filtration rate, and hyperuricemia seems to be linked to a worse renal outcome at equal levels of blood
pressure control. The elevated prevalence of hyperuricemia in previously untreated hypertensive subjects makes this finding of interest, because elevated levels of uric acid are a characteristic of the so-called syndrome X, characterized by the presence of insulin resistance and hyperinsulinism, that contribute to significantly increase cardiovascular morbidity and mortality.

In our experience, nephrosclerosis is associated with higher initial levels of both systolic and diastolic blood pressure, predominantly male sex, higher initial levels of serum uric acid and triglycerides, and lower levels of HDL cholesterol. A multivariate logistic regression analysis identified both systolic and diastolic blood pressure, as well as serum uric acid and triglycerides as independent predictors for the development of nephrosclerosis. Furthermore, in patients with nephrosclerosis and normal fasting serum glucose an oral glucose tolerance test permitted the diagnosis of Type II diabetes in 52% of cases. Data from the Framingham study population also reveal that the presence of mild renal insufficiency is accompanied by the presence of other cardiovascular risk factors, which, in turn, explain the increased cardiovascular risk. Some of the associated risk factors could contribute simultaneously to increase the cardiovascular risk and to facilitate a progressive deterioration in renal function, as is the case with lipid disorders and obesity. In this sense, a recently published study has shown that insulin resistance may predispose mildly hypertensive subjects to renal injury by modifying renal hemodynamics, causing an elevation in filtration fraction secondary to glomerular hyperfiltration. All of these findings indicate that the metabolic alterations that frequently are associated to elevated blood pressure jointly facilitate the progression of atherosclerosis and of nephrosclerosis.

The Kidney as a Predictor of Cardiovascular Risk in Heart Failure

Alterations in renal function play a key role in the pathophysiology of heart failure and are influenced by the treatment of this syndrome. In fact, it has been considered that the adequacy of renal function may be a primary determinant of compensation in patients with heart failure, and therapy capable of improving renal function may delay disease progression.

Low arterial filling represents one major characteristic of the complex mechanisms that lead initially to renal sodium and water retention in heart failure. This situation of decreased fullness of the arterial circulation is sensed by the kidney as similar to that of volume depletion. Thus, the kidney initiates a series of events that, paradoxically, result in an increase of extracellular volume in an attempt to restore the arterial circulation functional integrity. Simultaneously, neurohumoral activation takes place, and the activity of the renin-angiotensin-aldosterone and sympathetic nervous systems, as well as vasopressin release and endothelin production are enhanced. All of these mechanisms will tend to maintain arterial filling and blood pressure within normal range, and to further facilitate the renal retention of sodium and water.

The renal capacity to maintain an adequate sodium balance in response to a high sodium intake is altered since the initial stages of the disease, and a reduction in the renal functional reserve is also seen in the presence of a maintained ejection fraction. More advanced degrees of heart failure are accompanied by significant decreases in renal plasma flow and glomerular filtration rate. The development of progressive renal dysfunction is indeed a frequent complication in heart failure, and represents the consequence of the combined effects of progressive decay in cardiac output and renal perfusion pressure in conjunction with excess renal vasoconstriction. Advanced age (which is common in patients with heart failure), together with a history of hypertension and previous myocardial infarction, contribute to facilitate a decrease in the renal filtering capacity.

Interestingly, decreased renal function, evaluated as the estimation of creatinine clearance, is associated with a significant increment in mortality in heart failure. In fact, impaired renal function could be a better predictor of death than impaired cardiac function (left ventricular ejection fraction and New York Heart Association class) in patients with heart failure. This finding has led to the consideration that therapies improving renal function in patients with heart failure could positively influence outcome.

In summary, it can be proposed that changes in renal function produced by arterial hypertension or accompanying advanced heart failure are associated with a higher cardiovascular morbidity and mortality in both processes. In the case of arterial hypertension, renal vasculature is negatively affected by persistently elevated blood pressure, and nephrosclerosis can develop. When this occurs it seems to run parallel with the development of systemic atherosclerosis, which accounts for the increased cardiovascular morbidity and mortality seen in hypertensive patients. Furthermore, factors known to worsen atherosclerosis seem to be those enhancing the progression of hypertensive vascular damage at the kidney level. Increased serum creatinine, decreased creatinine clearance, and the presence of proteinuria or microalbuminuria confirm the presence of nephrosclerosis and have been shown to be independent predictors of increased cardiovascular morbidity and mortality. In the case of heart failure, a diminution in the estimated value of creatinine clearance carries a significantly increased risk of death. The parameters commonly used to measure renal function must be considered in any stratification of cardiovascular risk in patients with hypertension or heart failure.
References


