The Kidney as a Sensor of Cardiovascular Risk in Essential Hypertension

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Abstract. Renal damage as a consequence of uncontrolled arterial hypertension is well recognized. Antihypertensive therapy has come to very significantly decrease the vascular damage in the kidneys of hypertensive patients. However, prevalence of mild renal insufficiency remains present in a significant proportion of the hypertensive population. This is accompanied by a marked increase in cardiovascular risk, as a consequence of the clustering of other cardiovascular risk factors and of insufficiently controlled BP. Prevention and protection of renal and cardiovascular damage in these patients will be one of the most relevant tasks in the future.

The kidney plays a relevant role in the origin of essential hypertension in humans (1–3) and can suffer the consequences of the subsequent elevation in systemic BP (4). Nephrosclerosis constitutes together with diabetic nephrophy the most common renal substrates leading to the development of end-stage renal disease (5). However, the literature published in the last decade transmits the idea that, with an “adequate” BP control with standard antihypertensive therapy, the kidney is well protected and very few hypertensive patients, less than 2%, will develop renal damage as a consequence of arterial hypertension (6). A small percentage of patients suffering the renal consequences of a very prevalent process (more than 20% of the population is hypertensive) is enough to explain the high prevalence of nephrosclerosis as a cause of end-stage renal disease (3). The aim of this short review is to show that the prevalence of renal damage is higher than previously thought in essential hypertension and also that the presence of mild renal insufficiency constitutes an excellent predictor of increased global cardiovascular risk.

Prevalence of Mild Renal Insufficiency in Essential Hypertension

The diagnosis of renal dysfunction in clinical practice is usually based on the finding of an elevated serum creatinine level, or of a decrease in GFR usually measured as creatinine clearance, and/or in the detection of an elevated urinary excretion of albumin below (microalbuminuria) or above (macroalbuminuria) the usual laboratory methods to detect proteinuria.

Mild renal insufficiency has recently been defined as serum creatinine values above 1.5 mg/dl (132 μmol/L) in men and 1.4 mg/dl (123 μmol/L) in women (7) or by the finding of estimated creatinine clearance values below 60 to 70 ml/min (8,9,10).

Table 1 summarizes the prevalence of renal damage defined as an increment in serum creatinine above normal limits or a decrease in estimated creatinine clearance in three recently published studies, HOT (8), INSIGHT (9), and HOPE (10), and in a recently published survey performed in 47 hospital-based hypertension units in Spain (11). The global cardiovascular risk of the population included in the three studies differs, with the top corresponding to the HOPE study, in which patients on secondary prevention or diabetics with at least one accompanying risk factor were included, followed by the INSIGHT study, in which hypertensive patients with one or more associated risk factors were present, and finally the HOT trial, which may be said to represent the generality of the hypertensive population. Finally, most patients followed in hypertension units present an elevated degree of global cardiovascular risk (11). As can be seen in Table 1, the prevalence of mild renal insufficiency is higher than previously thought; a direct relationship seems to exist between the level of cardiovascular risk and the prevalence of the renal disorder being detected either as an elevation of serum creatinine or as a diminution of estimated creatinine clearance. This association is not explained by the simultaneous existence of diabetes (8,9,10).

Mild Renal Insufficiency in the General Population and its Relation to BP

Recently, Culleton et al. (12) described an elevated prevalence of mild renal insufficiency, around 8% in both men and women, defined as the finding of an elevated serum creatinine in the Framingham population. The authors did not relate their finding to the existence of arterial hypertension (defined as a BP in excess of 140/90 mmHg) because the prevalence of elevated BP did not greatly differ among those with and without a deranged renal function. However, the article describes that the prevalence of left ventricular hypertrophy in those patients with an augment in serum creatinine levels was 3 to 4 times higher than in the group with preserved renal function. This finding indicates that the threshold BP to clas-
sify people with mild renal insufficiency as being hypertensives cannot be 140/90 mmHg but must be lower. Probably in agreement with the consideration of the recent guidelines (13,14), this level must be 130/85 mmHg or even lower.

More recently, a prevalence of mild renal insufficiency defined by a serum creatinine in excess of 1.4 mg/dl of 3% has been described (15) in the general population of United States. The elevated serum creatinine levels strongly correlated with an inadequate BP control. Furthermore, the estimation of creatinine clearance in the same survey (NHANES III) has revealed that with a cut-off point of 70 ml/min the prevalence of a decreased renal function is surprisingly elevated in the US population, as can be seen in Table 2 (16).

**Table 1.** Prevalence of mild renal insufficiency

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Serum Creatinine &gt;1.5 mg/dl in men and &gt;1.4 mg/dl in women (%)</th>
<th>Estimated Creatinine Clearance &lt;60 to 70 ml/min (%)</th>
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<tbody>
<tr>
<td>HOT</td>
<td>18790</td>
<td>2.5</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>6321</td>
<td>3.1</td>
</tr>
<tr>
<td>HOPE</td>
<td>9173</td>
<td>10.5</td>
</tr>
<tr>
<td>Hypertension units</td>
<td>3822</td>
<td>12.1</td>
</tr>
</tbody>
</table>

*According to values in patients included in HOT (9), INSIGHT (10), and HOPE (11) studies. Data from a survey performed in 47 hospital-based hypertension units in Spain (11) are also included.

The fact that elevated serum creatinine concentrations frequently coexist with several cardiovascular risk factors (3,12).

Some data indicate that nephrosclerosis, often found in hypertensive patients, is associated with atherosclerosis of the large arteries. Nephrosclerosis is characterized by hyalinization of arterioles and fibroplastic intimal thickening of small arteries. Interestingly, hyalinization of renal arterioles is more marked in patients with coronary heart disease than in matched control subjects (19). Conversely, in autopsy studies, the presence of hyalinization in the renal arterioles is a marker of the presence of advanced coronary atherosclerosis in otherwise asymptomatic young individuals (20).

**Table 2.** Prevalence of an estimated creatinine clearance <70 ml/min in the US population of (NHANES III) (17)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>%</th>
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<tbody>
<tr>
<td>20 to 39</td>
<td>6.3</td>
</tr>
<tr>
<td>40 to 59</td>
<td>28.5</td>
</tr>
<tr>
<td>60 to 79</td>
<td>65.0</td>
</tr>
<tr>
<td>&gt;80</td>
<td>87.2</td>
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</table>

The relevance of proteinuria for cardiovascular prognosis in the community was documented by the Framingham Heart Study (21). The presence of proteinuria in patients with treated essential hypertension varies between 4 and 16% in different series of treated hypertensive patients (22). The INSIGHT Study compared the capacity of a long-acting dihydropyridine and a diuretic to diminish cardiovascular events and death in essential hypertension. This study assessed the role of proteinuria as a risk factor and confirmed that proteinuria was accompanied by a very significant increase in cardiovascular risk similar to that accompanying an elevated serum creatinine or the existence of a previous myocardial infarction (23).

Attention has recently been drawn to microalbuminuria and its relevance as a predictor of cardiovascular disease (24). Its prevalence varies between 20 and 30% of untreated patients and up to 25% in treated patients. Recently, it has been shown that the presence of microalbuminuria in primary hypertension carries an elevated cardiovascular risk (10,25). According to a persuasive hypothesis, microalbuminuria constitutes the renal expression of a generalized disorder characterized by increased endothelial permeability. This hypothesis provides an explanation for the link between increased urinary albumin excretion and elevated cardiovascular risk (24). Some preliminary data indicate that microalbuminuria is also a predictor of progressive deterioration of renal function in primary hypertension (3,26).
Table 3. Therapeutic attitudes in patients with mild renal insufficiency and hypertension

<table>
<thead>
<tr>
<th>Lifestyle changes</th>
<th>Strict BP control</th>
<th>Control of associated risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• salt intake</td>
<td>• &lt;130/80 mmHg</td>
<td>• lipids, statins, fribates</td>
</tr>
<tr>
<td>• body weight</td>
<td>• combination therapy required in most cases</td>
<td>• insulin resistance; insulin sensitizers (metformin, glitazones?)</td>
</tr>
<tr>
<td>• smoking</td>
<td>• blockade of angiotensin II effects is required</td>
<td>• platelet aggregation; aspirin; others?</td>
</tr>
</tbody>
</table>

Can We Prevent the Development of Mild Renal Insufficiency Related to High BP?

Development of renal damage can be the consequence of uncontrolled arterial hypertension (4), but it also seems to coexist with small elevations of BP in a percentage of the population characterized by the simultaneous presence of several other cardiovascular risk factors (3,12,15). In this case, the development of mild renal failure is accompanied by a significant increase in global cardiovascular risk mostly as a consequence of the clustering of other cardiovascular risk factors. This situation mimics diabetes mellitus where renal and cardiovascular risk are very high, and subtle elevations in BP can cause great microvascular and macrovascular damage.

Prevention of this disorder would then need an early identification of the people at risk to develop renal damage in conjunction with small BP elevations in the presence of several associated cardiovascular risk factors. This group of patients could constitute one of the intermediate phenotypes deserving genetic investigation (27).

Table 3 summarizes the therapeutic attitudes that must be considered when renal insufficiency is present. They contemplate the simultaneous performance of cardiovascular and renal protection. First are lifestyle changes; among them, three are of particular relevance: diminishing salt intake, avoidance of overweight and obesity, and withdrawal from smoking. A high salt intake makes BP control difficult as soon as the renal function is slightly deranged (28); obesity can cause a further fall in renal function while making more difficult the control of arterial hypertension (29); and smoking has been shown to clearly facilitate the progression of renal damage (30).

Strict BP control (probably below 130/80 mmHg) is required and will probably need the administration of a combination of drugs. We recently published (31) that the presence of an angiotensin-converting enzyme inhibitor in this combination significantly improves the long-term renal outcome of patients with nephrosclerosis.

Strict control of the other cardiovascular risk factors present is also required. The presence of mild renal insufficiency in hypertensives is accompanied by higher initial levels of both systolic and diastolic BP, a predominantly male gender, higher initial levels of serum uric acid and triglycerides, and lower levels of HDL-cholesterol (3). A multivariate logistic regression analysis identified systolic and diastolic BP, as well as serum uric acid and triglycerides as independent predictors for the development of nephrosclerosis. Therapies such as statins with good effects beyond the effects on serum cholesterol levels (32) and drugs improving insulin sensitivity (33) deserve to be investigated in this disorder.

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