Microalbuminuria in Salt-Sensitive Patients
A Marker for Renal and Cardiovascular Risk Factors

Roberto Bigazzi, Stefano Bianchi, Duccio Baldari, Gianpaolo Sgherri,
Giorgio Baldari, Vito M. Campese

Abstract  We previously showed that a high salt diet increases glomerular capillary pressure in salt-sensitive hypertensive patients and suggested that this may underlie the greater propensity of these patients to develop renal failure. Because microalbuminuria is considered an initial sign of renal damage, we have tested whether salt-sensitive patients display greater urinary albumin excretion than salt-resistant hypertensive patients. Twenty-two patients were placed on a low sodium intake (20 mEq/d) for 7 days followed by a high sodium diet (250 mEq/d) for 7 more days. Twelve patients were classified as salt sensitive and 10 as salt resistant. Urinary albumin excretion was greater in salt-sensitive than salt-resistant patients (54±11 versus 22±5 mg/24 h, P<0.01). During the low sodium diet, glomerular filtration rate, renal plasma flow, and filtration fraction were similar between the two groups. During the high sodium intake, glomerular filtration, renal plasma flow, filtration fraction, and calculated intraglomerular pressure did not change in salt-resistant patients; in salt-sensitive patients, however, renal plasma flow decreased, and filtration fraction and intraglomerular pressure increased, whereas glomerular filtration rate did not change. Urinary albumin excretion was significantly correlated with glomerular capillary pressure. Salt-sensitive patients displayed higher serum levels of low-density lipoprotein cholesterol and lipoprotein(a) and lower levels of high-density lipoprotein cholesterol than salt-resistant patients. These studies have shown greater urinary albumin excretion and serum concentrations of atherogenic lipoproteins in salt-sensitive than in salt-resistant hypertensive patients, suggesting that salt sensitivity may be a marker for greater risk of renal and cardiovascular complications. (Hypertension. 1994;23:195-199.)

Key Words  ● hypertension, sodium-dependent ● risk factors ● albuminuria ● renal circulation ● lipoproteins

Patients with essential hypertension manifest variable blood pressure response to high dietary salt (NaCl) intake and accordingly are classified as salt sensitive or salt resistant.1-7 We define as salt sensitive those patients who during a high sodium (Na+) intake (200 mEq/d) display a rise in mean arterial pressure greater than 10 mm Hg compared with a low Na+ intake (20 mEq/d). Several biochemical abnormalities have been described in salt-sensitive patients, including nonsuppressible plasma catecholamine levels,8-10 lower urinary dopamine excretion,11 and lower urinary kallikrein excretion.12-14 Salt-sensitive patients also manifest an abnormal renal function curve and a greater propensity to retain Na+.15 In addition, we have shown recently that in salt-sensitive patients the renal hemodynamic adaptation to a high dietary salt intake differs from that of salt-resistant patients and healthy subjects. During a high NaCl intake, renal vascular resistance, filtration fraction, and intraglomerular pressure increased in salt-sensitive patients but decreased in salt-resistant patients.16

Because salt sensitivity is more prominent among certain categories of patients (such as blacks, the elderly, the obese, and those with diabetes mellitus), who are also more likely to develop renal failure as a consequence of hypertension,17-20 we have suggested that the abnormalities in the renal hemodynamic adaptation to high dietary NaCl intake and particularly the increase in intraglomerular pressure could underlie the greater incidence of renal failure among these patients. Increased urinary albumin excretion (UAE) has been described in some patients with essential hypertension,21-24 and it is considered by some as an early marker of renal involvement. In addition, the presence of microalbuminuria or proteinuria is associated with a greater incidence of cardiovascular morbidity and mortality in patients with essential hypertension.25-28 The reasons for this association have not been established.

We have recently shown that hypertensive patients with microalbuminuria manifest greater serum levels of atherogenic plasma lipoprotein, such as low-density lipoprotein (LDL) cholesterol and lipoprotein(a) [Lp(a)], and we proposed that both microalbuminuria and the attendant greater cardiovascular morbidity could be the result of those lipid abnormalities.29 However, these patients were not classified according to their blood pressure sensitivity to NaCl.

To determine whether salt-sensitive patients manifest a greater amount of UAE and whether microalbuminuria in these patients correlates with alterations in renal hemodynamics and serum lipoproteins, we measured UAE, renal hemodynamics, and lipid profile in a group of hypertensive patients classified according to their salt sensitivity.

Methods  Twenty-two white patients with essential hypertension were included in this study. Twelve were classified as salt sensitive and 10 as salt resistant based on whether during a high NaCl diet their mean arterial pressure increased by 10 mm Hg or more compared with a low NaCl intake. Their clinical characteristics are shown in Table 1. The known duration of hypertension was not different between the two groups.

Patients were considered to be hypertensive if, during three subsequent clinic visits to the outpatient clinic, their diastolic
blood pressure was found to be equal to or greater than 95 mm Hg. Patients with creatinine clearance less than 80 mL/min; a history of myocardial infarction, congestive heart failure, stroke, diabetes mellitus, or liver disease; women with childbearing potential or taking birth control pills; and patients known to abuse drugs or alcohol were excluded from the study. All antihypertensive medications were discontinued at least 4 weeks before entry into the study. A diagnosis of secondary hypertension was adequately excluded by the findings of normal routine blood and urinalysis, electrocardiogram, chest radiograph, and, when clinically indicated, by normal urinary metanephrines, plasma aldosterone, cortisol, diethylenetriamine pentaacetic acid technetium scan, and renal angiogram.

All patients gave informed consent, and the studies were approved by the Human Research Committee of the Spedali Riuniti of Livorno, Italy.

While on their usual diet, all patients selected for the study were instructed to collect 24-hour urine samples on three different occasions, 1 week apart, for measurement of UAE, urinary sodium, and creatinine clearance. After patients had fasted for 12 to 14 hours, venous blood samples were obtained between 8 and 9 AM for measurement of total serum cholesterol, triglycerides, HDL cholesterol, apolipoproteins A and B, and Lp(a). All patients were included in the subsequent phase of the study independent of their UAE and with the investigators kept blind as to the amount of UAE. For the subsequent 2 weeks, patients were instructed as outpatients to adhere to an isocaloric diet containing 1.3 g protein per kilogram, 126 kJ/kg of calories, 800 mg/d of calcium, and 80 mEq/d of potassium, while their sodium intake varied. During the first week, they received a diet containing 20 mEq/d of Na+, and during the remaining 7 days they received a dietary Na+ intake of 250 mEq/d. Food was prepared by the hospital kitchen and provided to the patients on a daily basis. Compliance to the prescribed diet was assessed by measurements of 24-hour urinary Na+ excretion during the last 2 days of each diet. Blood pressure and body weight were measured at the beginning and on days 6 and 7 of each diet between 8 and 9 AM. Patients were weighed after they had voided and before they had eaten breakfast.

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were then measured by inulin and para-aminohippurate (PAH) clearances. Loading doses of inulin (40 mg/kg body wt) and PAH (4 mg/kg body wt) were given, and an infusion of these two compounds was initiated to maintain a serum concentration of approximately 0.2 and 0.02 mg/mL, respectively. After 2 hours of infusion, three separate measurements of inulin and PAH clearance were made 15 minutes apart. The clearance rates of inulin and PAH were corrected to a body surface area of 1.73 m². Filtration fraction (FF) was calculated as GFR/ERPF × 100. The calculation of glomerular pressure and renal segmental vascular resistances was performed according to the analysis used by Gomez and later modified by Hall et al.

Blood pressure was measured with a standard mercury sphygmomanometer after patients had been sitting for at least 5 minutes. Korotkoff sounds I and V were used to record systolic and diastolic blood pressures, respectively. The average of five measurements was recorded.

Total serum cholesterol, triglycerides, HDL cholesterol, apolipoproteins A and B, and glucose were measured immediately after blood drawing. The serum for Lp(a) and insulin was frozen and stored at −25°C and assayed within 15 and 30 days, respectively. Total serum cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic methods. The concentrations of very-low-density lipoprotein and LDL were calculated by the formulas of Friedewald et al. Apolipoproteins A and B were measured by nephelometry with antisera and standard reagents (Behringwerke AG, Marburg, Germany). Serum and urinary sodium and potassium were measured with a flame photometer and serum glucose and creatinine with an autoanalyzer. Lp(a) was measured with an enzyme-immunoassay [Immunozym Lp(a), Immuno AG, Vienna, Austria] and serum insulin by radioimmunoassay. The albumin concentration in the urine was measured by an immunoturbidimetric method. Body mass index was calculated as weight (kilograms) divided by height (meters) squared.

Differences among groups were evaluated by unpaired Student’s t test. Linear regression analysis was performed to determine correlations between different parameters. The results are expressed as mean±SEM.

Results

The clinical characteristics of the salt-sensitive and salt-resistant patients are shown in Table 1. There were no differences in age or body weight between the two groups. During the high NaCl intake, mean arterial pressure increased from 110±2.7 to 125±2.1 mm Hg (P<.01) in salt-sensitive patients but did not change in salt-resistant patients (117±2.3 and 116±2.2 mm Hg, respectively). UAE measured while patients were on an unrestricted diet was significantly greater (P<.01) in salt-sensitive (54±11 mg/24 h) than salt-resistant patients (22±4.7 mg/24 h) (Figure), whereas urinary sodium excretion was similar in salt-sensitive (161±14.6 mEq/d) and salt-resistant patients (172±26.2 mEq/d). During the low NaCl intake, UAE was not significantly different between salt-sensitive and salt-resistant patients (32±5.5 and 18±8.9 mg/24 h, respectively). During the high NaCl intake, UAE was higher (P<.05) in salt-sensitive than salt-resistant patients (43±9.1 and 19±6.2 mg/24 h, respectively).

During the high NaCl diet, salt-sensitive patients displayed renal hemodynamic changes that differed...
from those of salt-resistant patients (Table 2). In salt-sensitive patients, ERPF decreased from 527±36.3 to 415±19.7 mL/min per 1.73 m² (P<.05), renal vascular resistance increased from 10 788±1 016 to 14 863±706 (dyne/s)/cm⁵ (P<.05), and FF increased from 18.8±1.2% to 24.5±2.0% (P<.05). On the other hand, in salt-resistant patients, the high NaCl intake caused no significant changes in GFR, renal vascular resistance, and FF.

In salt-sensitive patients, calculated renal afferent resistance increased from 5231±624 to 7379±533 (dyne/s)/cm⁵ (P<.01), renal efferent resistance increased from 4567±541 to 6539±586 (dyne/s)/cm⁵ (P<.01), and glomerular pressure increased from 58±2.6 to 64±4.3 mm Hg (P<.01) during the high NaCl intake. However, these parameters did not change in salt-resistant patients. During the high NaCl intake, renal afferent resistance, renal efferent resistance, and intraglomerular pressure were significantly (P<.01) greater in salt-sensitive than in salt-resistant patients.

During the high dietary NaCl intake, there was a significant relation between FF and microalbuminuria (r=−.52, P<.03) and between calculated glomerular pressure and microalbuminuria (r=−.49, P<.05). We also observed a significant relation between the changes in FF and microalbuminuria and between the changes in glomerular pressure and microalbuminuria (r=−.51, P<.04) from the low to the high NaCl intake.

Salt-sensitive patients displayed higher (P<.05) serum levels of LDL cholesterol (116±10.9 mg/dL) and Lp(a) (33.5 ±6.5 mg/dL) and lower levels of HDL cholesterol (88.7±7.5, 15.6+4.5, and 63.4±3.7 mg/dL, respectively) (Table 3).

**Discussion**

These studies have shown for the first time that salt-sensitive patients with essential hypertension manifest greater UAE than salt-resistant patients. In this study we have also confirmed in white patients our previous observation in blacks that salt-sensitive patients with essential hypertension display significant alterations of the renal hemodynamic adaptation to a high dietary NaCl intake. In salt-sensitive patients, a disturbance in the relative changes of the afferent and efferent renal vascular resistances during a high NaCl diet results in increased intra-

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### Table 2. Effect of Low (20 mEq/d) and High (250 mEq/d) Dietary Sodium Intake on Renal Hemodynamics in Salt-Sensitive and Salt-Resistant Patients With Essential Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Salt-Sensitive</th>
<th>Salt-Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate, (mL/min)/1.73 m²</td>
<td>98±8.9</td>
<td>102±8.6</td>
</tr>
<tr>
<td>Effective renal plasma flow, (mL/min)/1.73 m²</td>
<td>527±36.3</td>
<td>415±19.7*</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>18.8±1.2</td>
<td>24.5±2.0*</td>
</tr>
<tr>
<td>Renal vascular resistance, (dyne/s)/cm⁵</td>
<td>10 788±1 016</td>
<td>14 863±706*</td>
</tr>
<tr>
<td>Renal afferent resistance, (dyne/s)/cm⁵</td>
<td>5 231±624</td>
<td>7 379±533*</td>
</tr>
<tr>
<td>Renal efferent resistance, (dyne/s)/cm⁵</td>
<td>4 567±541</td>
<td>6 539±586*</td>
</tr>
<tr>
<td>Glomerular pressure, mm Hg</td>
<td>58±2.6</td>
<td>64±4.3*</td>
</tr>
</tbody>
</table>

*P<.01 compared with low sodium (Na⁺) intake.  
†P<.05 compared with salt-sensitive.
glomerular pressure, which could cause greater amounts of UAE.

Thus, the presence of more UAE in salt-sensitive patients could be interpreted as a marker of greater renal damage and potentially as a prognostic indicator for the future progression of renal disease. Renal biopsies could provide useful information to corroborate this hypothesis, but they were not part of this study.

This possibility is supported by the evidence that renal function deteriorates more quickly in salt-sensitive than in salt-resistant models of hypertension in rats. Spontaneously hypertensive rats (SHR) and Dahl salt-sensitive rats are two inbred strains genetically predisposed to develop hypertension, but in SHR the hypertension develops independently of the dietary NaCl intake, whereas in Dahl salt-sensitive rats hypertension develops only if these animals are exposed to a high NaCl intake. The superficial nephrons of SHR adapt to the rise in blood pressure with an increase in renal afferent arteriolar resistance, which protects the kidney from the adverse effects of arterial hypertension.

Dahl salt-sensitive rats, on the other hand, are more susceptible to glomerulosclerosis and proteinuria, because their renal afferent arteriolar resistance fails to autoregulate normally in response to the NaCl-induced rise in blood pressure, a phenomenon that ultimately results in increased glomerular capillary pressure. Takenaka et al confirmed that during a high NaCl diet, Dahl salt-sensitive rats manifest an impairment of the myogenic responsiveness of the renal afferent arterioles to changes in perfusion pressure.

A more accelerated course of renal disease was also observed in other experimental models of salt-sensitive hypertension, such as in the deoxycorticosterone acetate–salt hypertensive rat, the uninephrectomized SHR, the Holtzman postsalt model of hypertension, and the Milan strain of SHR. All of these salt-sensitive models of hypertension manifest a decrease in afferent arteriolar resistance and a rise in glomerular pressure in response to an increase in blood pressure.

In this study, salt-sensitive patients manifested greater serum concentrations of LDL cholesterol and Lp(a) and lower concentrations of HDL cholesterol than salt-resistant patients. This finding raises the intriguing possibility of a link between microalbuminuria and lipid abnormalities in these patients. At least two possibilities should be considered. The first is that the increase in serum levels of lipoproteins may precede and possibly be responsible for the development of microalbuminuria. The second possibility is that microalbuminuria may actually precede and cause dyslipidemia.

A substantial body of evidence supports the notion that lipids may be involved in glomerulosclerosis and the progression of renal disease. Cholesterol-enriched diets may cause albuminuria and glomerulosclerosis in different animal species, particularly when combined with hypertension. In addition, pharmacologic agents that lower serum lipids ameliorate renal injury in several experimental models of renal disease. The mechanisms for the deleterious effects of lipids on glomerular injury are not well established. Because of several functional and structural similarities between glomerular mesangial cells and vascular smooth muscle cells, it is possible that the accumulation of lipids in mesangial cells may cause or accelerate glomerulosclerosis. Klahr et al have suggested that mesangial cells exposed to increased amounts of lipoproteins may incorporate lipoproteins, which in turn could stimulate proliferation of these cells and lead to excessive glomerular basement membrane deposition and progressive glomerulosclerosis. LDL cholesterol also can promote adherence of monocytes to endothelial cells and promote the progression of inflammation and glomerular diseases.

An alternative hypothesis is that microalbuminuria may be an early manifestation of or even precede the development of hypertension. Like in early diabetic renal disease, microalbuminuria may be present in normotensive subjects with a genetic risk for hypertension. According to this hypothesis, the increase in serum levels of atherogenic lipoproteins would be a consequence rather than the cause of microalbuminuria. In support of this notion is the evidence that urinary losses of large amounts of proteins may lead to increased serum levels of total and LDL cholesterol as well as Lp(a). Recent studies have indicated that losses of even small amounts of albumin in the urine may cause substantial alterations of serum lipoprotein levels in diabetic patients.

In conclusion, these studies demonstrate that salt-sensitive patients with essential hypertension manifest a cluster of renal and metabolic derangements that could ultimately lead to a worse renal and cardiovascular prognosis. It remains to be determined whether microalbuminuria is an expression of or a predictor for renal disease in patients with essential hypertension.

We propose that measurements of UAE are a useful marker for salt sensitivity. These studies also suggest that the presence of microalbuminuria is an expression of an unfavorable renal hemodynamic situation that could in the long run result in renal damage. Microalbuminuria is also associated with biochemical abnormalities that in the long run could result in greater cardiovascular complications.

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