Hypertension in Kidney Stone Patients

Abstract
The prevalence of arterial hypertension (HT) was investigated in 258 patients (171 m, 87 f, 22–68 years) with a history of primary stone disease. HT was detected in 64 patients (24.8%), with no difference between males (25.7%) and females (23.0%). The prevalence of HT by age was very similar to that of a general population, especially in the calcium stone group. The discriminant analysis demonstrated that the composition of stones, other than the age and body weight of the patients, were the main factors associated with HT.

As far as the different kind of stone is concerned, the prevalence of HT was higher in patients with uric acid (17/37, 45.9%) and struvite stones (11/27, 40.7%) than in calcium stone formers (35/188, 18.6%) (χ² 16.31, p < 0.001). The prevalence of hypercalciuria was higher in the calcium stone group than in uric acid or struvite stone patients (36.4 vs. 9.7 vs. 13.7%; χ² 10.35, p < 0.01). Furthermore, the hypercalciuria showed a trend to be more prevalent in the untreated (47.0%) than in the treated (31.2%) hypertensives, or normotensives (35.1%). Uric acid stone formers were older, heavier and with higher triglycerides and uric acid plasma levels than calcium or struvite patients. Also the struvite stone formers were older than the calcium stone ones.

Our data suggest that the prevalence of HT in kidney stone patients and particularly in calcium stone formers is similar to that of a general population. The role of hypercalciuria as the link for HT-urolithiasis association seems quite uncertain. Struvite and uric acid stone formers have higher risk for HT than calcium stone formers, probably due to the old age or to the associated metabolic abnormalities.

Introduction
An independent clinical association between arterial hypertension (HT) and kidney stone disease was recently described [1, 2]. In fact, studies performed on a general population showed that a history of kidney stones was approximately 2 or 3 times more frequent in hypertensive than in nonhypertensive subjects [1]. Since urinary calcium excretion is increased in hypertensives [3–5], the hypercalciuria was regarded as the pathogenetic link between HT and urolithiasis.

Conversely, to our knowledge, data concerning the prevalence of HT in stone patients, as well as the differences related to the stone composition, are not available in the literature.

In our opinion, it is of great importance that the analysis of the relationship between urolithiasis and HT takes into account the different chemical stone composition.
because (1) it is often associated with epidemiological and clinical features that can influence the risk of HT, and because (2) the hypercalcemia is a well-known risk factor for calcium urolithiasis [6–8], but not for the other types of kidney stones.

The aim of this study was to evaluate the prevalence of HT and of hypercalcemia in a cohort of patients with well-documented kidney stone disease, having the purpose to look for the differences associated with the stone composition.

**Patients and Methods**

Only patients with a definite history of kidney stone disease (stones passed or removed by surgery, urological maneuvers or ESWL, or detected by sonography or X-ray methods) were considered for the study.

Stone patients aged <20 or >70 years, with serum creatinine >1.2 mg/dl, hypercalcemia, bone diseases, primary hyperparathyroidism, diabetes, polycystic kidney disease, obstructive nephropathy, or with clinical or laboratory signs of secondary HT were excluded.

Two hundred and fifty-eight stone patients (171 males and 87 females, aged 22–68 years) were selected; calcium stone disease was the most frequent (72.8%), followed by uric acid (14.3%), struvite (10.5%) and cystine (2.3%). The patients having a diastolic blood pressure >95 mm Hg on at least three measurements performed in different days, as well as the patients having a previous diagnosis of essential HT and for this already on antihypertensive treatment at the time of observation, were classified as hypertensives.

Blood pressure was measured by a physician, using a mercury sphygmomanometer, after 5 min of rest with the patient in an upright position. Data regarding age, body weight, plasma levels of creatinine, electrolyte, total cholesterol and triglycerides, urinary calcium and urea excretion, were collected at the time of the first visit in our stone clinic. All the assays were performed using the standard laboratory procedures. Hypercalciuria was defined as daily urinary calcium excretion >4 mg/kg b.w. The results have been expressed as mean ± SD.

Statistical evaluation was performed using Student’s t test for unpaired data, analysis of variance (one-way ANOVA), $\chi^2$ test, discriminant analysis (by software 'SOLO' BMDP); p values <0.05 were regarded as statistically significant.

**Results**

Hypertension was present in 64 out of the 258 stone patients (24.8%). Thirty-two of them were untreated hypertensives, whereas 32 have been taking antihypertensive drugs for more than 6 months. The drugs employed were angiotensin-converting enzyme (ACE) inhibitors (12 patients), calcium channel blockers (10), clonidine (6) and β-blockers (5); in 8 patients thiazides were used in association with ACE inhibitors, clonidine or β-blockers. The prevalence of HT was similar in males (25.7%) and in females (23.0%), as well as in the recurrent (26.4%) or in the single (19.4%) stone formers.
Table 3. Age, sex and serum biochemistry in patients affected by calcium, uric acid or struvite stone disease

<table>
<thead>
<tr>
<th>Stone composition</th>
<th>Calcium</th>
<th>Uric acid</th>
<th>Struvite</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>129/59</td>
<td>29/8</td>
<td>9/18</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>41.7 ± 11.9</td>
<td>50.9 ± 11.2**</td>
<td>53.6 ± 11.4**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>71.3 ± 12.5</td>
<td>80.0 ± 13.1***</td>
<td>65.0 ± 9.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>127±68</td>
<td>198±131***</td>
<td>136±52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>199±39</td>
<td>210±44</td>
<td>211±44</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>4.8±1.3</td>
<td>5.8±2.0*</td>
<td>4.6±1.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001 vs. calcium and struvite. * p < 0.05; ** p < 0.001 vs. calcium group.

Data regarding hypertensive and normotensive patients are shown in table 1. In the former, age, body weight and triglyceride plasma levels were significantly higher than in the latter. In our series, discriminant analysis showed that HT mainly correlated with the composition of stones (specificity 86%, sensitivity 42%), followed by the age and body weight of the patients. The highest values of specificity (88%) and sensitivity (43%) were reached when the type of stone, age and body weight were considered together. As expected, the prevalence of HT increased with age, particularly in the calcium stone group (fig. 1) in which the prevalence of HT by age was very similar to that reported in the general population [9, 10]. As far as the different type of stone disease was concerned (table 2), in uric acid and struvite nephrolithiasis the prevalence of HT was greater than in calcium stone disease (χ² 16.31, p < 0.001). Patients with uric acid stone disease were older, heavier and with higher plasma levels of uric acid and triglycerides than calcium or struvite stone patients (table 3). Also in the struvite group the age was higher than in the calcium stone group (table 3).

As expected, the prevalence of hypercalciuria was significantly higher in the patients forming calcium stones than uric acid or struvite stones (respectively 36.4 vs. 9.7 vs. 13.7%; χ² 10.35, p < 0.01). Furthermore, in the calcium stone group, the hypercalciuria showed a trend higher in the untreated (47.0%) than in the treated (31.2%) hypertensives or in normotensives (35.1%).

Discussion

The results of our study demonstrate that the prevalence of HT in stone formers is quite similar to that observed in the general population [9, 10]. The types of stone, other than the body weight and the age of the patients, are the main factors associated with HT. In fact, the prevalence of HT in uric acid and struvite patients was higher than in calcium stone patients (table 2), in the latter (fig. 1) being very similar to that reported in a general population [1, 9, 10].

Uric acid stone formers were heavier and older than calcium stone patients and showed elevated triglycerides and uric acid serum levels (table 3): these features are often associated with HT. In addition, chronic pyelonephritis is often present in struvite stone patients who are also older than calcium stone formers. These arguments can account for the higher prevalence of hypertension in uric acid and struvite stone patients.

The prevalence of hypercalciuria is much higher in calcium stone formers than in uric acid or struvite stone patients, accordingly to its role of risk factor for calcium urolithiasis. Notwithstanding, the risk of hypertension is higher in the uric acid (and struvite) stone disease than in
calcium stone formers (table 2) where the prevalence of HT is quite similar to that of a general population [9, 10]. Consequently, at least in stone patients, hypercalciuria does not seem the link for HT-urolithiasis association.

Increased urinary calcium excretion has been described in patients with essential HT. It is caused by a defective renal tubular handling of calcium, dependent [4] or not [3] on sodium urinary excretion. This study failed to clearly demonstrate a significantly greater prevalence of hypercalciuria in the untreated hypertensives in respect to the nonhypertensives. It could be due to the presence, in the stone patients, of changes in dietary intake, or in intestinal, renal and bone calcium metabolism that are additional factors able to affect urinary calcium excretion [11–13].

In this study the hypercalciuria showed a trend to be higher in the untreated hypertensive than in the treated hypertensives. There is evidence that the increased urinary calcium excretion in hypertensive patients is primary to, and not induced by, the elevated blood pressure per se [14]. Then, the trend to a lower prevalence of hypercalciuria in the treated patients could be due to the antihypertensive treatment. Thiazides are well-known agents capable of lowering urinary calcium, and also β-blockers decreased the fasting excretion of calcium [15]. On the contrary, ACE inhibitors or calcium channel blockers, in particular dihydropyridine derivatives [15, 16], do not induce major changes in urinary calcium excretion; instead, nifedipine reduces urinary calcium excretion in hypercalcemic patients [17]. In addition, it is possible that the patients already on antihypertensive treatment were also on a restricted sodium diet, contributing to the underestimation of the prevalence of hypercalciuria in the treated hypertensive stone formers.

In conclusion, the prevalence of HT in calcium stone formers seems to be quite similar to that of the general population, and the role of hypercalciuria in the HT-urolithiasis association is quite uncertain. Instead, the uric acid and struvite stone formers present an increased risk of HT and this can be influenced, at least in part, by other associated factors such as overweight and old age.

In our opinion, the next studies concerning the relations between kidney stones and HT must not leave aside the chemical composition of stones, that is associated with different etiopathogenetic factors and clinical features.

References