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Essential arterial hypertension and stone disease

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Essential arterial hypertension and stone disease.

Background. Cross-sectional studies have shown that nephrolithiasis is more frequently found in hypertensive patients than in normotensive subjects, but the pathogenic link between hypertension and stone disease is still not clear.

Methods. Between 1984 and 1991, we studied the baseline stone risk profile, including supersaturation of lithogenic salts, in 132 patients with stable essential hypertension (diastolic blood pressure of more than 95 mm Hg) without stone disease and 135 normotensive subjects (diastolic blood pressure less than 85 mm Hg) without stone disease who were matched for age and sex (controls). Subsequently, both controls and hypertensives were followed up for at least five years to check on the eventual formation of kidney stones.

Results. Baseline urine levels in hypertensive males were different from that of normotensive males with regards to calcium (263 vs. 199 mg/day), magnesium (100 vs. 85 mg/day), uric acid (707 vs. 586 mg/day), and oxalate (34.8 vs. 26.5 mg/day). Moreover, the urine of hypertensive males was more supersaturated for calcium oxalate (8.9 vs. 6.1) and calcium phosphate (1.39 vs. 0.74). Baseline urine levels in hypertensive females were different from that of normotensive females with regards to calcium (212 vs. 154 mg/day), phosphorus (696 vs. 614 mg/day), and oxalate (26.2 vs. 21.7 mg/day), and the urine of hypertensive females was more supersaturated for calcium oxalate (7.1 vs. 4.8). These urinary alterations were only partially dependent on the greater body mass index in hypertensive patients. During the follow-up, 19 out of 132 hypertensive patients and 4 out of 135 normotensive patients had stone episodes (14.3 vs. 2.9%, chi-square 11.07, $P = 0.001$; odds ratio 5.5, 95% CI, 1.82 to 16.66). Of the 19 stone-former hypertensive patients, 12 formed calcium calculi, 5 formed uric acid calculi, and 2 formed nondetermined calculi. Of the urinary factors for lithogenous risk, those with the greatest predictive value were supersaturation of calcium oxalate for calcium calculi and uric acid supersaturation for uric acid calculi.

Conclusions. A significant percentage of hypertensive subjects has a greater risk of renal stone formation, especially when hypertension is associated with excessive body weight. Higher oxaluria and calciuria as well as supersaturation of calcium oxalate and uric acid appear to be the most important factors. Excessive weight and consumption of salt and animal proteins may also play an important role.

Key words: calcium oxalate, renal stones, body weight, urine calcium, urolithiasis, calciuria, blood pressure.

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A possible association between nephrolithiasis and hypertension has been suggested by a number of studies conducted in animals and humans. Naturally occurring kidney stones are rare in animals, but strains of spontaneously hypertensive rats were found to be more prone to developing kidney stones than normotensive ones [1]. In a trial conducted on a study population of 895 men, aged 50 years at the time of examination, 6.8% were diagnosed as having kidney stones [2]. When the participants were classified according to their blood pressure level, the rate of nephrolithiasis increased from 1.1% in the lower blood pressure class to 13.3% in the upper one, which also included treated hypertensive subjects. The relationship between blood pressure and rate of kidney stone disease was found to be statistically significant.

Furthermore, among patients affected with nephrolithiasis, the incidence of hypertension was found to be higher than that of the general population, and a higher mean pressure level was reported in stone formers as opposed to controls [3–5].

The pathogenic link between hypertension and stone disease is not fully understood. Hypercalciuria is the most frequent risk factor for renal stones [6, 7], and some studies have reported calcium metabolism disorders in both patients and animals with hypertension, including a higher calcium excretion rate [8–11]. Furthermore, epidemiological surveys have found a significant correlation between arterial pressure and calcium excretion [12–14].

These observations suggest that the pathogenic link between hypertension and nephrolithiasis might be a high calcium level. The formation of kidney stones is, however, a multifactorial event [15], and many other urinary stone risk factors have not been tested in hypertensive subjects.

This study began in 1984 with the aim of obtaining a more complete urinary stone risk profile in subjects with stable essential arterial hypertension, but who had no

history of stone disease or silent calculi, versus normotensive control subjects.

Both hypertensive patients and controls were then followed up for a minimum period of five years in order monitor any possible stone formation.

METHODS

Patients and controls

Between 1984 and 1991, 140 normotensive subjects (controls, 70 male and 70 female) and 140 patients with stable essential arterial hypertension requiring pharmacological treatment (hypertensive subjects, 71 male and 69 female) were enrolled in the study, all ranging from 35 to 50 years of age, this being the high-risk age group for nephrolithiasis [16–18].

Selection of controls. Every year, for a period of eight years, a random sample population of 1000 persons (half male and half female), aged between 35 and 50, was selected from the records kept by the Births, Deaths, and Marriages Registration Office, and information was sent to them regarding the study. Healthy subjects wishing to volunteer were invited to contact one of the physicians involved in the research project.

A total of 492 persons volunteered, but only 204 fulfilled inclusion criteria requirements, which included diastolic pressure that was equal or inferior to 85 mm Hg, no use of drugs, no medical history of renal lithiasis or suspected colic, no medical history of bone disease or other relevant alterations, no silent kidney stones (verified by renal echography and abdominal x-ray), normal renal function (glomerular filtration rate by creatinine clearance of more than 80 ml/min), and normal serum glucose, uric acid, calcium, and phosphate levels.

In order to be absolutely certain that the subjects enrolled were normotensive, we followed them for at least two months, measuring their arterial pressure on at least six occasions using a mercury sphygmomanometer in accordance with the recommendations of the Subcommittee of the AHA Postgraduate Education Committee [19]. As a result, a further 64 subjects were excluded from final enrollment because they presented with a mean diastolic pressure (calculated on the six measurements taken) greater than 85 mm Hg. The 140 subjects finally judged to be absolutely normotensive were definitively enrolled for evaluation of the urinary lithogenous risk and subsequent follow-up (discussed later in this article). They were asked not to change their dietary habits in any way.

Selection of hypertensive subjects. Each year, an average of 50 hypertensive subjects are referred by their general physicians to our university hospital for an initial diagnostic assessment and to exempt them from payment for antihypertensive drugs.

From this "pool" of approximately 400 patients, we selected those aged between 35 and 50 with a negative personal history of nephrolithiasis and with a diastolic blood pressure level of over 95 mm Hg. We asked the 193 subjects fitting this description to collect two 24-hour urine samples over a Sunday and a workday (for collection procedure and analysis, see the **Urinary stone risk evaluation** section).

We decided to collect urine samples before the screening period in order to avoid the sort of "stone clinic effect" that can modify diet and urinary physical chemistry [20].

These subjects were then screened for secondary causes of hypertension (3 subjects) and silent urolithiasis (8 subjects) in accordance with a standardized protocol, which included a renal echography and intravenous pyelography.

During the screening period, we also measured the patient's body weight, height, and blood pressure.

The importance of body weight, physical exercise, and diet for arterial hypertension was explained to each patient.

Following the guidelines for the treatment of hypertension [21], we identified the patients with stable hypertension, and only the subjects who continued to present with a diastolic pressure equal to or greater than 95 mm Hg throughout the entire screening period (two to three months), despite the dietary measures and physical precautions taken, were included in the study.

In this way, over a period of eight years, we were able to enroll 140 patients who were definitely affected by stable essential arterial hypertension requiring pharmacological treatment but not suffering from stone disease. As per the controls, the arterial pressure reported is the mean value calculated on a minimum of six readings.

Both controls and hypertensive subjects were classified as having a family history of stone disease if they had at least one grandparent, one parent, or one sibling with a history of kidney stones (family history self-reported).

Urinary stone risk evaluation

For each control and hypertensive subject, we arranged two days of urine collection over a Sunday and a workday, in normal lifestyle and free diet conditions. The subjects were specifically asked not to change their eating and drinking habits, and each received written instructions relative to urine collection methods.

None of the subjects were under pharmacological treatment at the time of the urine collection. As published elsewhere, the evaluation of urinary stone risk in our laboratory included 24-hour urine volume, pH (pH meter), creatinine (Jaffé method), sodium, potassium, calcium and magnesium (atomic absorption spectrophotometry), chloride (electrochemical titration), uric acid (uricase method), sulfate, phosphorus and oxalate (ion-chromatographic technique), citrate (citrate lyase method), urea (urease method), ammonium (colorimet-

ric method by Berthelot), cystine (colorimetric method by phosphotungstic acid), and glycosaminoglycans (GAG; hexuronic acid determination) [22].

Supersaturation calculations for calcium oxalate, calcium phosphate, uric acid, and struvite were obtained using the computer program Equil [23]. A result of less than one indicates undersaturation, whereas a result of more than one indicates supersaturation.

For all of the urinary stone risk factors reported, the mean value of the two measurements was calculated.

Follow-up

Both controls and hypertensive subjects were fully informed of the nature of the study, and all of them consented to a follow-up of at least five years, involving an annual clinical examination and renal echography to check for the formation of stones.

Once the baseline study had been concluded, the hypertensive subjects began pharmacological treatment with one or more antihypertensive drugs in order to keep pressure values under control. At the outset these drugs were Ca antagonists, angiotensin-converting enzyme inhibitors, or thiazides. During the follow-up, the patients' family doctors were responsible for controlling pressure and prescribing pharmacological treatment, and we were not informed as to changes made in dosages or drugs. Both controls and hypertensive subjects were only required to report to us once a year for the echography specified by the protocol or following the symptoms of renal stones.

The natural expulsion of a stone, the presence of a silent stone revealed by echography, a typical renal colic with the expulsion of gravel and hematuria were all considered to be stone episodes. When silent stones were revealed by echography, an abdominal x-ray was also carried out, and if judged to be the best course of action, appropriate measures were taken to remove the calculi.

The stones passed, or their fragments were analyzed by wet chemical methods or by an x-ray diffraction technique when material was very scarce.

Statistics

All data are expressed as a mean ± SEM.

Levene's test for equality of variances and Student's unpaired *t*-test for equality of means were used to compare mean values in hypertensive patients and controls, which were subdivided according to sex.

Associations among variables were assessed by Pearson's correlation coefficients.

Analyses of covariance were used to adjust urinary stone risk factors for body mass index (BMI).

Differences in frequency were tested by chi-square analysis. In addition, the odds ratio and 95% confidence interval were taken as an approximate estimate of the relative risk of stone formation associated with blood hypertension.

Stepwise discriminant analysis was performed among hypertensive stone formers and hypertensive nonstone formers in order to identify independent abnormalities and stone predictors among the baseline urinary stone risk factors.

All statistical analyses were performed on a personal computer using the SPSS software package.

RESULTS

Because nephrolithiasis can be affected by occupation [15, 24, 25], an analysis was carried out "a posteriori" on the types of occupation, and no differences were observed between the normotensive and hypertensive group.

Five controls (four men and one woman) and eight hypertensive subjects (five men and three women) failed to respect the follow-up time and were therefore considered as dropouts and were not included in the calculations.

The characteristics of the subjects who successfully finished the study are shown in Table 1.

The glomerular filtration rate was higher in hypertensive men, but when it was corrected for 1.73 m^2 body surface area, the difference ceased to exist.

Both male and female hypertensive subjects differed from controls regarding anthropometric data in that the body weight, BMI, and body surface area were higher.

Serum and urine baseline study

No differences in baseline serum levels of glucose, urea, calcium, phosphate, magnesium, sodium, and potassium were found between hypertensive patients and controls (data not reported).

In hypertensive men, the mean values of serum cholesterol (217 ± 5 vs. 201 ± 5 mg/dl, $P = 0.021$), triglycerides (158 ± 9 vs. 124 ± 5 mg/dl, $P = 0.003$), and uric acid (5.7 ± 0.1 vs. 5.2 ± 0.08 mg/dl, $P = 0.012$) were higher than in control men.

In hypertensive women, only the mean values of serum cholesterol were higher than in control women (210 ± 5 vs. 191 ± 3 mg/dl, $P = 0.005$).

The urinary baseline stone risk profile in essential hypertensive patients and controls is shown in Table 2.

The urine of hypertensive men differed from that of control men in that they had a higher excretion of calcium, magnesium, uric acid, and oxalate. Furthermore, the urine of hypertensive men was more supersaturated for calcium oxalate and calcium phosphate.

The urine of hypertensive women differed from that of control women with regards to a higher excretion of calcium, phosphorus, and oxalate. It was also more supersaturated for calcium oxalate.

Table 1. Characteristics of hypertensive patients and controls

	Men			Women		
	Controls ($N = 66$)	Hypertensives ($N = 66$)	P	Controls ($N = 69$)	Hypertensives ($N = 66$)	P
Age *years*	41.6 ± 0.6	42.9 ± 0.6	0.11	42.7 ± 0.7	42.6 ± 0.6	0.95
Weight *kg*	74.4 ± 0.9	82.7 ± 1.7	0.0001	58.7 ± 0.8	64.8 ± 1.6	0.001
Height *cm*	173 ± 0.8	174 ± 0.8	0.70	162 ± 0.7	162 ± 0.6	0.57
BMI kg/m^2	24.6 ± 0.3	27.2 ± 0.4	0.0001	22.2 ± 0.3	24.7 ± 0.6	0.0001
BSA m^2	1.88 ± 0.01	1.97 ± 0.02	0.001	1.62 ± 0.01	1.68 ± 0.02	0.01
SBP *mm Hg*	129 ± 1	151 ± 1.4	0.0001	122 ± 1.5	147 ± 1.4	0.0001
DBP *mm Hg*	77 ± 0.6	102 ± 0.8	0.0001	75 ± 0.7	100 ± 0.6	0.0001
MBP *mm Hg*	95 ± 0.7	118 ± 0.9	0.0001	91 ± 0.9	116 ± 0.8	0.0001
C_{Cr} *ml/min*	115 ± 2	126 ± 3	0.01	101 ± 2	103 ± 2	0.60
Corr. C_{Cr} *ml/min*	106 ± 2	110 ± 2	0.20	108 ± 2	106 ± 2	0.52
Family history of stone disease	13.6%	19.7%	0.35	15.9%	16.7%	0.91

Data are mean ± SEM; P value is by Student's t-test for unpaired data.
Abbreviations are: BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure, MBP, mean blood pressure; C_{Cr}, creatinine clearance; Corr. C_{Cr}, corrected creatinine clearance ($C_{Cr} \times 1.73/BSA$).

Table 2. Baseline urinary stone risk profile in hypertensive patients and controls

	Men			Women		
	Controls ($N = 66$)	Hypertensives ($N = 66$)	P	Controls ($N = 69$)	Hypertensives ($N = 66$)	P
Volume *ml/day*	1425 ± 64	1501 ± 69	0.42	1263 ± 57	1357 ± 65	0.20
Sodium *mmol/day*	178 ± 7	183 ± 8	0.60	145 ± 5	147 ± 6	0.81
Potassium *mmol/day*	56 ± 2	60 ± 3	0.21	51 ± 2	54 ± 2	0.37
Chloride *mmol/day*	178 ± 7	194 ± 9	0.15	146 ± 6	150 ± 6	0.63
Calcium *mg/day*	199 ± 10	263 ± 14	0.0001	154 ± 8	212 ± 11	0.0001
Phosphorus *mg/day*	777 ± 29	847 ± 32	0.09	614 ± 26	696 ± 25	0.026
Magnesium *mg/day*	85 ± 4	100 ± 4	0.01	72 ± 4	76 ± 3	0.44
Urea *g/day*	24.6 ± 0.8	26.8 ± 0.9	0.09	19.4 ± 1.1	18.7 ± 0.8	0.64
Sulfate *mmol/day*	21 ± 0.5	22 ± 0.8	0.15	17 ± 0.4	18 ± 0.5	0.35
Ammonium *mmol/day*	39 ± 1	38 ± 1	0.64	29 ± 1.1	28 ± 1.1	0.43
Uric acid *mg/day*	586 ± 21	707 ± 30	0.001	501 ± 22	498 ± 17	0.90
Oxalate *mg/day*	26.5 ± 1.2	34.8 ± 1.3	0.0001	21.7 ± 0.8	26.2 ± 0.9	0.001
Cystine *mg/day*	81 ± 5	80 ± 5	0.95	73 ± 4	72 ± 5	0.79
Citrate *mg/day*	566 ± 28	530 ± 29	0.37	689 ± 34	650 ± 30	0.39
GAG *mg/day*	(31) 7.1 ± 0.3	(43) 7.7 ± 0.5	0.34	(37) 5.7 ± 0.2	(28) 5.6 ± 0.3	0.74
pH, *24 hr*	5.85 ± 0.05	5.91 ± 0.06	0.45	6.07 ± 0.06	5.95 ± 0.06	0.19
CaOx SS	6.1 ± 0.5	8.9 ± 0.5	0.0001	4.8 ± 0.3	7.1 ± 0.4	0.0001
CaP SS	0.74 ± 0.05	1.39 ± 0.13	0.0001	0.87 ± 0.09	1.00 ± 0.8	0.33
Uric acid SS	2.9 ± 0.2	3.2 ± 0.3	0.45	2.1 ± 0.2	2.5 ± 0.3	0.28
Struvite SS	0.06 ± 0.02	0.13 ± 0.05	0.19	0.12 ± 0.03	0.08 ± 0.02	0.33

Data are mean ± SEM; P value is by Student's t-test for unpaired data.
Abbreviations are GAG (glycosoaminoglycans) were detected in some of the subjects (the number is in brackets); CaOx SS, CaP SS, Uric acid SS, and Struvite SS, supersaturations by Equil 2 for calcium oxalate, calcium phosphate, uric acid and struvite.

No differences were detected for the other urinary stone risk factors evaluated.

Because hypertensive subjects tend to have a greater body size and because the BMI was positively correlated to many of the urinary parameters giving different values compared with normotensive subjects (Pearson's correlations BMI calcium $r = 0.34$, $P = 0.0001$; BMI phosphorus $r = 0.43$, $P = 0.0001$; BMI uric acid $r = 0.44$, $P = 0.0001$; BMI oxalate $r = 0.36$, $P = 0.0001$; BMI magnesium $r = 0.30$, $P = 0.0001$), we divided the hypertensive patients into two groups: those with a normal BMI and those with a high BMI ($< 26 >$ male and $< 24 >$ female).

Table 3 shows that in overweight hypertensive males, the urinary stone risk factors (calcium, oxalate, and uric acid) were higher than in hypertensive males with a normal BMI, whereas less significant differences were observed in the stone inhibitors (magnesium, citrate, and GAG).

These data, referred to as nutritional markers, suggested that a higher intake of salt and animal proteins existed in overweight hypertensive males; that is, these patients had higher levels of sodium, urea, sulfate, phosphorus, and creatinine.

In overweight hypertensive females, these differences

Table 3. Urinary parameters in hypertensive men and women, divided by normal or high body mass index (BMI)

	Hypertensive men ($N = 66$)			*Hypertensive women* ($N = 66$)		
	BMI < 26 ($N = 23$)	BMI > 26 ($N = 43$)	*P*	BMI < 24 ($N = 32$)	BMI > 24 ($N = 34$)	*P*
Urinary parameters						
Stone risk factors						
Calcium *mg/day*	208 ± 16	293 ± 17	0.003	180 ± 15	243 ± 14	0.003
Oxalate *mg/day*	29 ± 1.4	37.9 ± 1.7	0.0001	26.2 ± 1.5	26.1 ± 1.2	0.93
Uric acid *mg/day*	562 ± 35	784 ± 36	0.0001	464 ± 21	530 ± 26	0.058
Stone inhibitors						
Magnesium *mg/day*	88 ± 5	106 ± 6	0.052	71 ± 5	80 ± 5	0.22
Citrate *mg/day*	505 ± 40	543 ± 39	0.53	574 ± 44	723 ± 36	0.011
GAG *mg/day*	(17) 6.5 ± 0.6	(26) 8.5 ± 0.8	0.073	(13) 5.5 ± 0.6	(15) 5.7 ± 0.4	0.79
Nutritional markers						
Sodium *mmol/day*	160 ± 12	196 ± 11	0.038	135 ± 7	158 ± 9	0.066
Potassium *mmol/day*	56 ± 5	62 ± 3	0.31	50 ± 3	58 ± 3	0.09
Urea *g/day*	22.2 ± 1.3	29.3 ± 1.1	0.0001	17.2 ± 1.1	20.1 ± 1.3	0.10
Sulfate *mmol/day*	19.7 ± 1.2	23.9 ± 0.9	0.012	16.7 ± 0.8	18.7 ± 0.6	0.065
Phosphorus *mg/day*	724 ± 35	913 ± 42	0.001	605 ± 32	782 ± 32	0.0001
Creatinine *mg/day*	1557 ± 46	1947 ± 76	0.0001	1171 ± 53	1246 ± 40	0.26

Data are mean ± SEM; *P* value is by Student's *t*-test for unpaired data.
GAG (glycosoaminoglycans) were detected in some of the subjects (the number is in brackets).

Table 4. Mean values adjusted for body mass index (BMI) of the urine parameters found different in hypertensive patients

	Controls	Hypertensives	*P*
Men			
Mean calcium adjusted *mg/day*	215	247	0.069
Mean magnesium adjusted *mg/day*	89	95	0.31
Mean uric acid adjusted *mg/day*	625	668	0.23
Mean oxalate adjusted *mg/day*	27.9	33.5	0.004
Mean CaOx SS adjusted	6.5	8.6	0.009
Mean CaP SS adjusted	0.84	1.29	0.005
Women			
Mean calcium adjusted *mg/day*	156	209	0.0001
Mean phosphorus adjusted *mg/day*	630	682	0.14
Mean oxalate adjusted *mg/day*	21.9	26.0	0.003
Mean CaOx SS adjusted	4.9	7.0	0.001

were less evident, but it was possible to demonstrate distinctly higher urinary calcium and citrate values. Concerning the nutritional markers, data suggesting greater salt and animal protein consumption in overweight hypertensive females showed a less marked trend as compared with males, although the trend was nonetheless detectable.

Potassium values did not show any significant differences in either males or females with regards to overweight subjects and subjects with a normal BMI.

Following the adjustment for the BMI (Table 4), the differences in calcium excretion, magnesium and uric acid decreased in males, whereas in females, only the difference in phosphorus excretion decreased. In hypertensive males, oxalate and supersaturations of calcium oxalate and calcium phosphate remained higher, whereas in hypertensive females, calcium, oxalate, and supersaturation of calcium oxalate remained higher.

Follow-up study

The mean length of the follow-up was 7.78 ± 0.17 years in the control group (range 5.25 to 12.41 years) and 7.59 ± 0.19 years in the hypertensive group (range 5.08 to 12 years).

During this period, 4 out of 135 normotensive subjects and 19 out of 132 hypertensive patients had a renal stone episode: 2.9 and 14.3%, respectively (chi-square value 11.07, $P = 0.001$).

The risk of stone formation was significantly higher in hypertensive patients than in normotensive controls (odds ratio 5.5, 95% CI, 1.82 to 16.66).

Table 5 reports some clinical information on subjects who had stone episodes during the follow-up.

Among the controls, we were able to identify stone composition in three out of four subjects (two calcium and one uric acid stone). Among the hypertensive patients, when it was not possible to analyze the stone, x-ray radiopaque material was defined as a calcium stone, and x-ray radiolucent material was defined as a uric acid stone. In this way, we were able to establish a calcium stone composition in 12 out of 19 patients (patients numbers 1 to 12) and a uric acid stone composition in 5 out of 19 (patients numbers 13 to 17); in two patients, it was not possible to define stone composition (patients 18 and 19) because the stone was not seen (the likely cause of the renal colic and hematuria was gravel).

In seven other cases, the formation of stones in hypertensive subjects occurred asymptomatically and was only ob-

Table 5. Clinical information about subjects who had a stone episode during the follow-up period

	Sex	BMI	Composition	Time	Presentation	Removal
Controls						
1	M	26.2	CaOx 100% (fragments)	5.58	Silent	ESWL
2	M	25.3	CaOx 100%	6.41	Renal colic	Expulsion
3	M	23.8	Unknown	3.66	Hematuria	Gravel?
4	F	25.3	Uric acid 100%	7.25	Renal colic	Expulsion
Hypertensives						
1	M	26.9	CaOx 95% + CaP 5%	2.33	Renal colic	Expulsion
2	M	21.9	CaOx 100%	3.66	Renal colic	Expulsion
3	M	32.1	CaOx 65% + CaP 35%	7.75	Renal colic	Basket
4	M	22.4	CaOx 90% + CaP 10%	6.75	Renal colic	Expulsion
5	M	27	X-ray opaque (calcium)	4.41	Silent	No removal
6	M	25.3	CaOx 100% (fragments)	3.58	Silent	ESWL
7	M	29.2	X-ray opaque (calcium)	6.16	Silent	No removal
8	M	35.8	CaOx 90% + CaP 10%	4.66	Renal colic	Expulsion
9	F	27.5	CaOx 100% (fragments)	3.08	Silent	ESWL
10	F	24.2	X-ray opaque (calcium)	4.66	Silent	No removal
11	F	35.4	CaOx 95% + CaP 5%	6.25	Renal colic	Basket
12	F	25.6	CaOx 100% (fragments)	5.58	Silent	ESWL
13	M	29.4	Uric acid 100%	5.16	Hematuria	Expulsion
14	M	27.5	Uric acid 80% + CaOx 20%	6.16	Renal colic	Expulsion
15	M	26.4	X-ray radiolucent (uric acid)	6.33	Silent	No removal
16	M	26.7	Uric acid 100%	10.75	Renal colic	Basket
17	F	23.5	Uric acid 100%	5.5	Renal colic	Expulsion
18	M	31.5	Unknown	8.33	Renal colic	Gravel?
19	F	22.9	Unknown	11.33	Hematuria	Gravel?

Definitions are: BMI, body mass index; composition, type of stones formed; time, years passed between baseline study and stone discovery; presentation, way of stone discovery; removal, kind of stone removal.

served during the periodical echographic and radiographic examinations carried out during the follow-up period; three of these seven cases were subsequently treated with extracorporeal shock wave lithotripsy (ESWL) with a final confirmation that they were actually renal stones.

Table 5 also shows the BMI of stone formers, recorded at the beginning of the follow-up period. Among the 23 subjects who produced stones, 16 were overweight. A statistical comparison between stone formers and non-stone formers gave a statistically significant result regarding the BMI (chi-square value, 6.9, $P = 0.009$), suggesting a higher lithogenous risk in overweight subjects.

The urinary baseline characteristics of the 12 hypertensive calcium stone formers and the 5 hypertensive uric acid stone formers were studied by stepwise discriminant analysis and were compared with the urinary baseline characteristics of the hypertensive subjects who remained calculi free during the follow-up. The discriminant function (Table 6) identified calcium oxalate supersaturation in calcium stone formers and uric acid supersaturation in uric acid stone formers as the main urinary predictors. The percentage of "grouped" cases correctly classified was 72.8% by calcium oxalate supersaturation and 78.8% by uric acid supersaturation.

Table 6. Discriminant analysis of the urinary characteristics that differentiate between hypertensive stone formers and hypertensive calculi free

		Predicted group membership	
CaOx SS in hypertensive calcium stone formers			
Actual group	No. of cases	Stone formers	Calculi free
Calcium stone formers	12	8 (66.7%)	4 (33.3%)
Hypertensive calculi free	113	30 (26.5%)	83 (73.5%)
Uric Acid SS in hypertensive uric acid stone formers			
Actual group	No. of cases	Stone formers	Calculi free
Calcium stone formers	5	3 (60%)	2 (40%)
Hypertensive calculi free	113	23 (20.4%)	90 (79.6%)

DISCUSSION

This article suggests that patients with stable essential arterial hypertension, especially when overweight, are in a category at risk for the formation of renal calculi because they present certain urinary abnormalities commonly encountered in stone formers.

In fact, baseline urinary values in hypertensive males were different than those of normotensive males inasmuch as they had greater amounts of calcium, oxalate, and uric acid, and although they contained greater levels of magnesium, they were more supersaturated with regards to calcium oxalate and calcium phosphate. Also, in hypertensive females, the urine values were characterized by higher excretion of calcium and oxalate resulting in a higher supersaturation of calcium oxalate.

Over the last 50 years, the incidence of arterial hypertension and nephrolithiasis has markedly increased, becoming an important social and economic problem.

Some epidemiological studies have confirmed that there is a positive association between the two diseases [2, 26–29], and recently, it was reported that a history of hypertension was the only clinical parameter correlated to papillary calcification in cadaveric kidneys [30]. The reasons behind this association are not yet fully understood. In chronological terms, it appears that nephrolithiasis manifests itself before arterial hypertension [29], but this does not necessarily imply that there is a causal relationship between the two. A possible hypothesis might be that a portion of hypertensive subjects with calculosis tends to have a common genetic, metabolic, and nutritional substrate that expresses itself in early life in the form of nephrolithiasis and in later life in the form of arterial hypertension.

We compared two groups of patients, matched for age and sex, with no history of kidney stones and with markedly different diastolic pressure levels.

We found that the basic lithogenous risk is, in fact, higher for a significant percentage of the hypertensive subjects and that part of them tend to form stones, even when the hypertension is pharmacologically treated.

Hypercalciuria is undoubtedly an important risk factor for the formation of calcium oxalate calculi, and research has revealed the existence of calcium metabolism alterations, including increased renal excretion both in hypertensive animals [1, 31–33] and humans [10, 11, 34–40].

We confirm this finding and are in agreement with the authors who advance the hypothesis that increased renal calcium excretion could be a pathogenic link between hypertension and nephrolithiasis [41–45].

However, it also emerged from our study that urinary oxalate levels were higher in hypertensive subjects of both sexes, and that hypertensive men tended to have higher urinary uric acid levels.

It is a well-known fact that a small increase in urinary oxalate increases the lithogenous risk for calcium oxalate [46], whereas hyperuricosuria can favor the formation of both uric acid and calcium stones [6, 47–49].

On the whole, these findings suggest that hypertensive subjects usually harbor a higher lithogenous risk than normotensive ones, and this might explain the frequent association between the two diseases.

The scope of our work does not allow us to make a pathogenic interpretation of these findings, but we can, nonetheless, advance some hypotheses.

Cell alterations concerning abnormal transport of sodium, calcium, and oxalate [50–58] have been described for both stone forming and hypertensive subjects. These alterations could form a kind of genetic substrate favoring the onset of both diseases [44]. Some hormonal similarities are also to be found between hypertensive and stone-forming subjects, such as, for example, increased levels of $1,25(OH)_2D$ and parathyroid hormone [59–62], which could explain the discovery of hypercalciuria in a significant subgroup of these subjects.

Other epidemiological studies, on the other hand, seem to suggest that hypertensive subjects and stone formers have similar dietary habits, characterized above all by a low calcium intake [63–65], which, as is well-known, can lead to increased oxaluria as a result of augmented intestinal absorption of oxalate [66, 67]. This hypothesis is born out by the fact that a calcium-rich diet seems to favor the reduction of arterial pressure levels and the risk of renal stone formation [68, 69].

Still on the subject of nutrition, both hypertensive subjects and stone formers generally have a higher body weight when compared with control groups, leading to the conclusion that body weight must play a role in both diseases. Recent wide-reaching epidemiological studies confirmed that an increase in body weight, even slight, is strongly correlated to the risk of hypertension and stone disease [70, 71].

The scope of our study did not allow us to carry out an in-depth investigation of diet, but certain elements suggest a different metabolic–nutritional picture in the hypertensive patients in our study versus the normotensive subjects.

Both males and females had higher cholesterol serum levels. The males also had higher serum levels for triglycerides and uric acid, whereas both males and females had a higher BMI.

These data are indicative of a diet rich in calories, fats, and carbohydrates, which has been associated with a higher metabolic production of uric acid and oxalate [72–74].

The BMI is a particularly significant element because oxalate excretion has recently been found to correlate directly with body size in normal subjects as well [75].

In our hypertensive patients, the BMI correlated well to excretion of the most important stone risk factors: calcium, oxalate, and uric acid, and when hypertensive subjects were divided into groups with a normal or high BMI, significant differences were observed in the urinary excretion of lithogenous factors as well as of certain known nutritional markers.

In particular, it was observed that the urine of overweight hypertensive subjects showed a higher stone risk associated with higher levels of sodium, urea, sulfate, phosphorus, and creatinine, which in the presence of normal renal function are acknowledged to be valid markers of the dietary intake of salt and animal proteins [76–79].

These differences were more evident in hypertensive males but were also observed in the females. Of course, the detection of a higher creatinine excretion level in hypertensive males with a high BMI, a phenomenon not encountered in the females, could also be due to the greater muscle mass peculiar to this group of subjects.

It is, however, well-known that a high sodium intake increases the stone risk as it may induce hypercalciuria [80–87] and that an excess of animal proteins can cause marked increases in the excretion of calcium, oxalate, and uric acid [88, 89].

It should be underlined that in our personal experience, the role of NaCl intake seems to be considerable in many hypertensives in that it maintains a high blood pressure and induces a high calcium excretion.

In all of our subjects, there was no relevant difference in NaCl excretion between hypertensives and controls; however, a hypersensibility to salt is proven in many hypertensive subjects, and it is associated with genetic factors, which were recently analyzed and supposed to be a possible pathogenic mechanism of salt-dependent hypertension [90].

In these conditions, the volume expansion caused by NaCl retention may be produced by an excretion defect, and it may play an important role in calcium excretion increase on the same NaCl supply.

In addition, an extracellular volume expansion and a salt-dependent hypertension has been often noticed in overweight subjects [91, 92].

When, however, the urinary data relative to lithogenous risk were corrected for the BMI, a persistent difference was observed in the levels of oxalate and in the supersaturation values for calcium oxalate in hypertensive males as well as females.

This finding suggests that hypertension *per se* may be accompanied by higher levels of urinary oxalate with mechanisms that are still unknown.

The role of body size also has been confirmed by the follow-up data.

In fact, of the 23 subjects who developed nephrolithiasis (19 of whom were hypertensive and 4 of whom normotensive), 16 were overweight, and the statistical analysis was in favor of a significant association with BMI.

The aim of our study was not to assess the prevalence of nephrolithiasis in hypertensive subjects, a topic that would require an extensive epidemiological assessment that did not fall within the scope of our investigation.

The percentage of stone formers (14.3%) that was recorded in our group of hypertensive subjects may seem high if we fail to take into account the fact that we were investigating a selected group in an age range that is particularly at risk for the formation of stones [16–18]. Furthermore, it must also be stressed that in 7 out of 19 cases, the early formation of silent calculi was detected, and this would not have been identified in an analysis based on only the clinical expression of lithiasic disease. On the other hand, even though not directly comparable with our study, reports concerning the history of nephrolithiasis in hypertensive subjects quote percentages of up to 13.3% in 50-year-old males [2], 20.3% in nontreated hypertensive males, and of up to 32.8% in hypertensive males treated with antihypertensive drugs [27].

Regarding the chemical composition of the stones formed by the hypertensive subjects, we were able to establish that 12 were calcium stones and 5 uric acid stones.

The stepwise discriminant analysis pointed out that the most important predictive factor in the 12 subjects who had formed calcium stones was calcium oxalate supersaturation, whereas in the 5 subjects who had formed uric acid stones, the most discriminating factor was uric acid supersaturation.

This result is fully consistent with a recent article that reported an excellent correspondence between the supersaturation levels of lithogenous salts and the type of stones produced in a large population of stone formers [93].

Concerning the type of antihypertensive treatment followed by the hypertensive patients, it was not possible to reach any conclusion.

The pharmacological treatment was administered by the family doctor who would increase or modify the dosage with a view to maintaining the best possible pressure levels. In general, the drugs used were thiazides, calcium antagonists, angiotensin-converting enzyme inhibitors, β-blockers, and clonidine. Loop diuretics were never administered over long periods of time. In a small number of cases, the treatment was stopped within this time period, as it was possible to keep the blood pressure under control with nonpharmacological methods. In any event, we do not have the necessary data to be able to say whether the type of pharmacological treatment administered or pressure control methods used actually influenced the formation of renal stones.

The only observation that we were able to make was that none of the subjects who formed stones had used thiazides on a regular basis.

In summary, this study has demonstrated that a significant percentage of the subjects who suffer from stable essential arterial hypertension present a urinary physiochemical profile with a greater stone risk than normotensive subjects matched for sex and age. This greater risk appears to be, at least partially, of a metabolic–nutritional nature, but this aspect requires to be further investigated.

The most important predictive factors for chemical composition appear to be the supersaturation of lithogenous salts, calcium oxalate, and uric acid.

From a practical point of view, this study suggests that hypertensive subjects, especially when overweight, would do well to adopt the preventive dietary measures that are generally recommended to subjects who have had previous stone episodes: a reduction in the intake of calories and animal protein and salt while maintaining a normal intake of calcium and increasing water consumption. The possible role played by antihypertensive

drugs in this specific problem requires further investigation.

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