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ORIGINAL PAPER

The impact of metaphylaxis of kidney stone disease in the renal function at long term in active kidney stone formers patients

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Abstract A total of 150 patients were included in the analysis. Through chart review, we estimated glomerular filtration rate in the first visit and, at least, 5 years later. All patients were divided into two groups: (1) metaphylaxis adherents ($n = 74$) and (2) metaphylaxis non-adherents ($n = 76$). We followed all patients for at least 5 years. The Scr percentage of patients and GFR <60 mL/min was compared between groups. Variables were compared between groups using t test, χ^2 tests, odds ratios with 95% confidence intervals. There were no differences at baseline between groups. After 5 years of follow-up, GFR was 77.9 mL/min in non-adherent-metaphylaxis group and in the adherent-metaphylaxis group was 87.3 mL/min, with p value of 0.02. After 5 years of follow-up, we had a GFR <60 mL/min in the adherent-metaphylaxis group (4.89 vs. 21.95%) with p value of 0.001 and OR = 5.36; IC-95% = 1.95–14.8. Metaphylaxis of kidney stone disease could prevent chronic kidney disease.

Keywords Urolithiasis · Metaphylaxis · Chronic kidney disease · Prevention

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Introduction

Chronic kidney disease (CKD) and urolithiasis are highly prevalent conditions that have increased in recent decades [1–4]. CKD is a known complication in kidney stone former patients secondary to hereditary diseases, nephrocalcinosis and coraliform stones [5, 6]. Moreover, calcium stones can be associated with CKD [7]. Much experimental evidence shows us that the mechanism of kidney stone formation can, at final analysis, cause interstitial fibrosis and glomerulosclerosis, due to an inflammatory cascade that was initiated in the renal parenchyma [7–16]. All of the above raise question: "Does the metaphylaxis of kidney stone disease decrease the risks of CKD?" We used a historical cohort to evaluate the impact of metaphylaxis of kidney stone disease in the renal function at long term in active kidney stone former patients.

Methods

A total of 150 ambulatory kidney stone former patients who had been treated since 2005 at Stone Clinic were included in the analysis. Inclusion criteria were patients, who had completed the metabolic evaluation and were oriented to metaphylaxis of kidney stone disease.

The metaphylaxis prescribed consisted of: metabolic evaluation: (1) three 24-h urine samples on non-consecutive days, with habitual diet, and measurement of calcium, uric acid, oxalate, citrate, magnesium, sodium, creatinine, (2) measurement of calcium, phosphorus, uric acid, potassium, creatinine in a blood sample, (3) a 72-h nutritional inquiry. The diagnosis of hypercalciuria, urinary calcium >4.0 mg/kg, hyperuricosuria: uric acid >800 mg for men and >750 mg for women, hypocitraturia: citrate

<320 mg, hyperoxaluria: oxalate >50 mg, hypomagnesuria: magnesium <50 mg. After the metabolic diagnosis, all the patients were specifically treated for each one of them. The specific treatment was hypercalciuria: thiazides 0.5–1.0 mg/kg/day and potassium citrate 0.5–1.0 mEq/kg/day, hyperuricosuria: potassium citrate 0.5–1.0 mEq/kg/day and allopurinol 100–300 mg mid, hypocitraturia: potassium citrate 0.5–1.0 mEq/kg/day, hyperoxaluria: the approach to intervention depended on the diet and the urine calcium. If the urine calcium was not high, increasing dietary calcium was considered along with a low oxalate diet, hypomagnesuria: magnesium citrate 100 mg bid. Medical advice to prevent kidney stone disease included individual dietetic orientation including enhanced water ingestion.

Through chart review, we estimated glomerular filtration rate by MDRD formula [17] in the first visit (t0) and, at least, 5 years later (t5). In addition to renal function, we evaluated the following variables: age, body mass index (BMI), gender, extracorporeal shockwave lithotripsy (ESWL) history, hypertension (HTN), diabetes mellitus (DM), hyperuricemia, tobacco smoking, and urinary tract infection (UTI) history. Patients who came to periodic consultations were considered as adherents to metaphylaxis. The patients were instructed to return every 6 months, and were classified as non-adherent if they did not voluntarily return for more than three visits during the follow-up cohort. Having seen this criterion as well as the historical character of the cohort, there were no follow-up data of the non-adherent group. The variables like renal function, and stone recurrence of the non-adherent group were assessed only at the beginning of the observation (t0) and 5 years later (t5) by an active search at the end of 5 years.

All the above criteria permitted us to divide all patients into two groups: (1) metaphylaxis adherents ($n = 74$) and (2) metaphylaxis non-adherents ($n = 76$).

Baseline characteristics were compared at t0, including serum creatinine (Scr) and glomerular filtration rate (GFR) by MDRD formula. At the end of follow-up (t5), we compared Scr and GFR between groups. We also compared the percentage of patients with GFR <60 mL/min in each arm.

Statistical analysis

Statistical comparisons used the t test and χ^2 tests with $p < 0.05$. The strength of the association between CKD and prevention of kidney stones was evaluated using odds ratios and Cornfield's 95% confidence intervals. The results are presented as mean ± 1standard deviation (SD) and rates (%).

Results

There were no differences between groups, at the beginning of the observation, when considering: three 24-h urine samples (Table 1). There was no detectable cystine in the metabolic evaluation of any patient, so suppose that there was no cystine stone in both groups. We did not find staghorn calculi related to infection (struvite stones) in both groups. There were no differences between the groups at the beginning of the observation (t0) about the measurement of calcium, phosphorus, uric acid, potassium, creatinine in a blood sample.

There were no differences between groups, at the beginning of the observation (t0) about 72-h nutritional inquiry. The nutritional inquiry showed in both groups a high ingestion of protein and sodium; low ingestion of calcium, potassium, fibers and fluid (Table 2).

There were no differences at baseline (t0) between groups when considering age, gender, variables related to CKD risk (BMI, HTN, DM and hyperuricemia), ESWL, UTI history, and smoking habits (Table 3).

There were no statistical differences between groups when considering renal function at baseline (t0). After 5 years of follow-up, the serum creatinine was statistically significant lower in the adherent group, when compared with non-adherent group (0.92 ± 0.24 vs. 1.24 ± 0.50) with $p < 0.0001$. GFR was in medium 10 mL/min less in the non-adherent metaphylaxis group (77.9 mL/min) than in the adherent-metaphylaxis group (87.3 mL/min), with $p < 0.02$. After 5 years of follow-up, we had a diminished percentage of patients with GFR <60 mL/min in the adherent-metaphylaxis group than in the non-adherent group (4.89 vs. 21.95%) with $p < 0.001$ and OR = 5.36; IC-95% = 1.95–14.8 (Table 4).

After 5 years of follow-up as a consequence of the treatment in the adherent group, the number of stones/year/patient decreased from 1.7 ± 0.3 to 0.4 ± 0.3 ($p < 0.01$).

The urinary volume increased from 1.3 ± 0.5 to 2.1 ± 0.6 L ($p < 0.01$), 24-h uric acid urinary excretion decreased from 533.2 ± 285.5 to 356.7 ± 112.5 mg

Table 1 Metabolic evaluation between groups in 24-h urine samples at the beginning of the observation

24-h urine samples	Adherent ($n = 74$)	Non-adherent ($n = 76$)	p value
Hypercalciuria	15	14	0.78
Hypocitraturia	30	32	0.30
Hyperoxaluria	12	13	0.09
Hyperuricosuria	14	13	0.37
Hypomagnesuria	5	6	0.74

Table 2 Nutritional inquiry between groups at the beginning of the observation (t0)

Nutritional inquiry	Adherent (SD—medium)	Non-adherent (SD—medium)	*p* value
Calories	2,461 ± 589 kcal (2,398 kcal)	2,582 ± 485 kcal (2,475 kcal)	0.745
Protein	95.6 ± 36.7 g (89 g)	87.6 ± 29.5 g (78 g)	0.089
Calcium	701 ± 419 mg (607 mg)	611 ± 419 mg (561 mg)	0.102
Potassium	2.8 ± 1.0 g (2.7 g)	2.6 ± 1.4 g (2.2 g)	0.321
Sodium	14.1 ± 6.2 g (13.8 g)	13.1 ± 5.6 g (12.9 g)	0.473
Fibers	12.8 ± 6.0 g (14 g)	11.2 ± 5.4 g (11 g)	0.436
Fluid	1,100 ± 203 ml/day	1,160 ± 268 ml/day	0.289

Table 3 Distribution of demographic and clinical variables

	Adherent ($n = 74$)	Non-adherent ($n = 76$)	*p* value	Statistical test
Mean age in years (SD)	48.71 (±13.43)	46.22 (±13.38)	0.25	*t* test
BMI kg/m^2 (SD)	26.56 (±15.6)	25.8 (±4.2)	0.68	*t* test
Gender (f/m)*	35/39	33/43	0.63	χ^2
HTN (%)	19 (25.67)	28 (38.15)	0.10	χ^2
Diabetes (%)	10 (13.51)	19 (25)	0.07	χ^2
Tobacco (%)	10 (13.51)	19 (25)	0.44	χ^2
UTI (%)	15 (20.27)	15 (19.73)	0.07	χ^2
Hyperuricemia (%)	21 (28.37)	26 (34.21)	0.93	χ^2
ESWL (%)	26 (35.13)	24 (31.57)	0.63	χ^2

SD standard deviation

Table 4 Summary of kidney function at baseline (t0 and 5 years later (t5))

	Adherent ($n = 74$)	Non-adherent ($n = 76$)	*p* value OR; CI 95%	Statistical test
Creatinine (t0), mg/dl (SD)	0.91 (±1.97)	0.90 (±1.96)	0.81	*t* test
GFR (t0) ml/min (SD)	90.32 (±21.7)	94.58 (±20.07)	0.24	*t* test
Creatinine (t5) mg/dl (SD)	0.92 (±0.24)	1.24 (±0.50)	<0.0001	*t* test
GFR (t5), ml/min (SD)	87.31 (±20.72)	77.97 (±29.11)	<0.02	*t* test
Patients (%) with GFR <60 ml/min (t5)	7/143	27/123	<0.0001	χ^2
	4.89%	21.95%	OR = 5.36; IC-95% = 1.95–14.8	OR; CI 95%

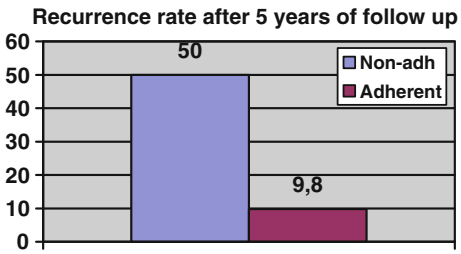
SD standard deviation, *OR* odds ratios and Cornfield's 95% confidence intervals

Table 5 Urinary excretion values before metaphylaxis and after 5 years of treatment in adherent group

Urinary excretion	Before metaphylaxis (t0)	After 5 years of treatment	*p* value
24-h urinary volume	1.3 ± 0.5 L	2.1 ± 0.6 L	0.01
Uric acid	533.2 ± 285.5	356.7 ± 112.5	0.01
Sodium	269.9 ± 153.8	188 ± 96.4	0.01
Calcium	183.8 ± 117.5	110.5 ± 55.7	0.005
Citrate	314.6 ± 228.4	532.3 ± 147.9	0.002
Oxalate	73.8 ± 48.7	31.5 ± 15.7	0.003
Magnesium	84.7 ± 36.7	110.3 ± 29.5	0.01
Creatinine	1.5 ± 0.3 g	1.6 ± 0.5 g	N/S

($p < 0.01$), 24-h sodium urinary excretion decreased from 269.9 ± 153.8 to 188 ± 96.4 mEq ($p < 0.01$), 24-h calcium urinary excretion decreased from 183.8 ± 117.5 to 110.5 ± 55.7 mg ($p < 0.005$), 24-h citrate urinary excretion increased from 314.6 ± 228.4 to 532.3 ± 147.9 mg ($p < 0.002$), 24-h oxalate urinary excretion decreased from 73.8 ± 48 mg to 31.5 ± 15.7 mg ($p < 0.003$) and 24-h magnesium urinary excretion increased from 84.7 ± 36.7 to 110.3 ± 29.5 mg ($p < 0.01$), 24-h creatinine urinary excretion from 1.5 ± 0.3 to 1.6 ± 0.5 g (N/S) (Table 5).

After 5 years, the recurrence rate of new stones of the non-adherent group was 50 vs. 9.8% of the adherent group with $p < 0.0001$.



The evidence that the non-adherent group did not follow dietary advice or take medications were obtained by an active search at the end of 5 years by asking these patients if they compliant the recommendations and all patients replied "no".

Discussion

Our data suggest that adherence to metaphylaxis of kidney stone disease could prevent the development of CKD at long term. Groups were balanced in relation to unfavorable renal variables (such as hypertension, diabetes mellitus, and hyperuricemia), history of UTI, smoking, and ESWL. Although it is an observational study, without a randomization strategy to group allocation, we had an equilibrated distribution of confounding variables, which diminishes the risk of bias, a common artifact in these kind of studies.

More definitive conclusions about the efficacy of metaphylaxis in kidney stone disease preventing CKD at long term would occur only with double-blind-controlled-placebo-clinical trials. Nevertheless, to run a trial like that would be unethical once we already have evidence of the effect of metaphylaxis in recurrence of active kidney stone former patients [17–24].

Epidemiological studies point to urolithiasis as a risk factor to CKD [7, 25, 26], which forecast the attractive hypothesis of CKD prevention using the treatment of kidney stone former patients with metaphylaxis. Although attractive, this hypothesis has not been explored in clinical studies until now.

The question that appears now is: "What would be the mechanisms of lesions and loss of kidney function related to kidney stone disease?" To answer it, we could separate the kidney parenquima aggression related to urolithiasis into four types:

1. Inflammatory lesion related to the binomy infection obstruction. Urease producers agents can cause an increase in ammonium production and consequent alkaline urine, causing tubular lesion, struvite stone formation, urinary stasis, inflammation, and consequent kidney lesion, provoking CKD [27–31],
2. Sterile inflammatory lesion, related to transitory but repeated urinary flux obstruction. It could cause a lesion in tubular cells promoting an inflammation cascade of tubule-interstitial region, with nephronic depletion and glomerulosclerosis, due to a self-sufficient cycle of hyperfiltration and progressive loss of kidney function [7, 8],
3. Cellular lesion induced by crystaluria, for instance, monohydrated oxalate crystals determining a direct toxicity from crystals to tubular cells, starting an oxidative stress cycle and inflammation-repairing-glomerulosclerosis [9–16],
4. Nephrocalcinosis kidney lesion, normally in the medulla, that many times is linked to metabolic syndromes such as primary hyperoxaluria, distal tubular acidosis and primary hyperparathyroidism. In these cases, parenquimal deposition of crystals start an inflammatory injury process leading to interstitial fibrosis, tubular atrophy, and glomerulosclerosis [32, 33].

Randall plaques, which are calcium-protein microparticles, are highly correlated with kidney stone formation and can also be correlated with ectopic calcification in renal parenquima, causing tubular lesion, atrophy, and fibrosis, leading to CKD. Another potential mechanism of lesion is related to sequels associated with invasive treatment of complicated urolithiasis (nephrectomy and hyperfiltration lesion in reminiscent kidney, loss of parenquima and kidney scars that suffers intervention) [34, 35].

Much is discussed about the deleterious effect of ESWL, including CKD risk, without literature support until now [15]. However, in our study, there was no difference between groups when considering the realization of ESWL, reducing bias that could be caused by this potential risk factor.

The hypothesis of prevention of CKD when you reduce lithogenic risk factors through metaphylaxis is reliable in physicopathological terms. When testing this hypothesis in a clinical context, our study had its internal validity increased through the equal distribution of confounding, use of the same treatment proposal, and follow-up of all eligible patients and use of a time interval compatible with the studied disease (at least 5 years), reducing non-systematic errors.

What attracted our attention is the significantly greater GFR in the metaphylaxis adherent group after 5 years of follow-up (almost 10 mL/min greater), which reinforces the potential clinical success of the nephroprotection strategy. Another important fact is the significant difference between groups in the numbers of patients in late stages of CKD (GRF <60 mL/min): 7 patients in the adherent-metaphylaxis group versus 27 in the non-adherent-metaphylaxis groups (the risk of CKD is five times greater when there is no adherence to metaphylaxis).

Despite the intrinsic limitations of the study methodology, including the historic character of the cohort, the results reached statistical and clinical significance. Moreover, our study reinforces the concept that urolithiasis may be only an epiphenomena from a systemic disorder, where all kidney consequences go much farther than the classic painful syndrome caused by stones elimination.

Conclusion

Our study suggests that the adherence to metaphylaxis of kidney stone disease could prevent the CKD, avoiding some mechanism of lesions and loss of kidney function related to kidney stone disease.

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