A Follow up Study of Active Urolithiasis at Ain Shams University Hospital-Etiological Factors and Role of Chronic Preventive Strategies

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Abstract: Background: Kidney stone formation or urolithiasis is a complex process that results from a succession of several physico-chemical events. Regardless of etiology, all stone formers should be counseled on dietary measures for stone prevention. The aim was to assess various chronic preventive strategies and different therapeutic modalities. **Patients and Methods:** This case control study was conducted on 100 patients with urinary stones and 40 healthy controls. Each patient was subjected to full clinical history, plain abdominal x-ray, non-contrast helical CT abdomen and baseline laboratory investigations. Data were collected, coded, tabulated, and then analyzed using SPSS® computer package version 16.0. **Results:** The study included 83 males and 17 females; the age of 34% of them ranged from 40-49 years old. Urosurgical intervention (42%) and Oxalate rich diet (41%) were the most prevalent factors favoring urinary stone formation. Mixed Ca stones (50%) were the most commonly retrieved urinary stones. Hyper-calciuria was significantly more prevalent among patients (60% and 32.5% respectively), and hypo-citraturia was highly significantly more prevalent among patients than controls (78% and 42.5% respectively). There was significant increase of urine volume in all groups compliant to dietary modifications. Urinary calcium and oxalate significantly decreased in patients compliant to diet plus 1 drug and those compliant to all prescribed drugs. Urinary citrate significantly increased among patients compliant to 1 drug only in comparison to non compliant patients. **Conclusion:** These results confirm the beneficial effect of the currently available specific treatment options based on metabolic evaluation.

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1. Introduction

Urolithiasis is a major health problem with its high morbidity, high cost management and potential for end stage renal disease [1]. Urinary stones affect 10–12% of the population in industrialized countries. Features associated with recurrence include a young age of onset, positive family history, infection stones and underlying medical conditions [2].

The sequence of events in the formation of any urinary stone can be: Urinary saturation, super saturation, nucleation, crystal growth, crystal aggregation, crystal retention and stone formation [3].

Majority of kidney stones are composed of calcium oxalate (CaOx) and phosphate (CaPh) crystals (~80%). Most of the rest are composed of uric acid (UA; 5-10%) and struvite (5-15%). Other rare constituents are cystine, xanthine, matrix, dihydroxy-adenosine and various drugs (e.g., indinavir, nelfinavir, efavirenz, amprenavir, triamterene) [2].

There are many dietary risk factors. Increased levels of urinary sodium (>150 mg per day) will increase urinary calcium excretion, and may also blunt the hypo-calciuric effects of thiazide medications. Urinary calcium excretion increases by 25 mg for every 100 mmol increase in dietary sodium [4]. Sodium also reduces citrate excretion and increases cystine excretion [5]. Low potassium levels can promote hypo-citraturia [6]. Magnesium is an inhibitor of stone formation, it can complex with renal oxalate, and supplementation with magnesium may increase urinary citrate excretion by decreasing its tubular reabsorption. Poor nutritional status, laxative abuse, and certain malabsorption syndromes are all associated with low magnesium levels. Low magnesium levels are found in up to 7% of stone formers is commonly associated with hypo-citraturia and low urine volume [7]. Increased protein consumption increases stone risk. Urinary analytes, such as phosphorus, sulfate, and urea, can be markers of the amount of animal protein consumption [8].

All patients should undergo a baseline urinalysis, culture, and plain radiograph of the kidneys, ureters, and bladder. Metabolic risk factors include hyper-calciuria, hyper-oxaluria, hypo-

citraturia, hyper-uricosuria, and low urine pH. Environmental risk factors include low total urine volume, elevated urinary sodium, hypo-magnesiuria, and high urine sulfate [9].

Stone formers at high risk also need specific preventive treatment for recurrence, which is usually pharmacological treatment and based on stone analysis [10]. All stone formers, independent of their individual risk, should follow the general preventive measures which focus on 'normalization' of the patient's dietary habits and lifestyle risks. An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [11]. Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre [12]. Some studies have suggested lifestyle factors may influence the risk of stone formation, e.g. being overweight and obesity [13,14].

2.Patients And Methods

This study was conducted upon 140 subjects, 100 patients attended the outpatient nephrology and urology clinics of Ain Shams University hospital with urinary stones and 40 healthy controls. Patients were chosen according to inclusion and exclusion criteria.

Inclusion criteria:

1. Patients with multiple stones at first presentation or
2. Patients with family history of urinary stones or
3. Patients with active urinary stone disease i.e. with recurrent stones, passage of gravels or enlargement of old stones.

Exclusion criteria:

1. Patients with single stone at first presentation, without family history of urinary stones or
2. Patients with past history of urinary stones without evidence of active disease.

Patients group was subjected to:

I. Initial

1- Full clinical history taking; personal history, present history, past history, family history and dietary habits.

2- Radiography; plain abdominal x-ray and non contrast helical CT scan of abdomen.

3- Laboratory investigations:

a) Urine:

Urine analysis (pH, WBC, RBC and crystals)

24 hours urine examination (volume, pH, calcium, uric acid, phosphorus, citrate, oxalate, sodium, creatinine and urinary cystine when indicated)

b) Blood: serum calcium, phosphorus, uric acid and serum creatinine.

c) Creatinine clearance according to Cockcroft-Gault formula : Cr. Cl. = (140 – age) x BW(x 0.85 in females)/72 x serum creatinine and accordingly, patients were divided into those with:

Normal GFR (>90 ml/min)
Mild (60-89 ml/min),
Moderate (30-59 ml/min),
Severe (15-29 ml/min) decrease in GFR
Kidney failure (GFR< 15 ml/min)

d) Chemical analysis of stones or gravel whenever available.

e) Other investigations when needed e.g.

- Parathyroid hormone in patients with elevated serum calcium.
- Urine culture in cases with pyuria (pus cells >5) in urine analysis,
- Arterial blood gas in cases with alkaline urinary pH.

II. Follow up

Follow up was done 2 months following urosurgical intervention and/or dietary modification and/or drug therapy, by repetition of abnormal laboratory results was done. Also follow up by non contrast helical abdominal CT for all patients after 2 months to assess the progression of disease activity.

Control group was subjected to:

1) Urine: urine analysis and 24 hours urinary examination.
2) Plain x-ray urinary tract.

Statistical analysis

Collected data analyzed using SPSS® computer package version 16.0.Description analysis was done of quantitative variables was as mean, SD and range and of qualitative variables was as number and percentage. Chi- square test was used to compare qualitative variables. Unpaired t-test was used to compare two independent groups as regard a quantitative variable. One way (ANOVA test) was used to compare more than two groups as regard quantitative variable. *P* value >0.05 was insignificant, *P*<0.05 significant, *P*<0.001 highly significant.

3. Results

The study included 100 patients; 83% of them were males, 50% had sedentary jobs and 22% of them had positive family history of urolithiasis. The prevalence of urolithiasis among patients was highest among 40-49 age group (34%) and least at 17 (1%) and 70 years old (1%).

Regarding co-morbidities favoring urolithiasis among the studied patients, 49 had one or more co-morbidity; out of who 34 (69.4%) were obese, 16 (32.7%) were diabetic, 7 (14.3%) had gout, 4 (8.2%) had hyper-parathyroidism, and 2 (4.1%) had diarrhea.

Regarding the local factors favoring urolithiasis; prevalence of urolithiasis was highest among patients with history of urosurgical interventions (42%) and lowest among patients with

horseshoe kidney (1%) and caleceal diverticulae (1%).

Studying the dietary risk factors of urolithiasis, 69 patients were on one or more risky diet. The prevalence of urolithiasis among these 69 patients was highest among patients on high oxalate diet 41 (59.4%) and lowest among patients on low calcium diet 7 (10.1%).

Comparison between patients group and control group showed that mean urinary WBC and RBC were highly significantly higher among patients, while mean urinary citrate was highly significantly higher in the control group. And urinary mean calcium was significantly higher among patient group (Table 1).

Table 1: Urine analysis and 24 hours urine examination differences between patients group and control group

Urinary	Patient (n=100)	Control (n=40)	*p* value
	Mean± SD	Mean± SD	
Volume/ml/24h	1411.5±717.24	1243.75±380.14	>0.05
pH	5.85±0.72	5.76±0.81	>0.05
WBC/HPF	21.69±21.69	4.13±1.84	0.001
RBC/HPF	17.79±24.46	2.2±1.55	<0.001
Uric acid (mg/24h)	704.9±1669.36	558.92±802.44	>0.05
Na(meq/24h)	103.04±53.82	101.82±57.81	>0.05
Ca(mg/24h)	748±625.3	440.37±333.79	0.004
Phosphorus(g/24h)	0.3±0.24	0.28±0.2	>0.05
Oxalate (mg/24h)	77.59±70.67	66.8±48.83	>0.05
Citrate(mg/24h)	253.53±187.14	400.22±282.28	<0.001

As regards to 24 hours urinary metabolic abnormalities; low urine volume was significantly more prevalent among control group ($p \leq 0.05$). But hyper-citraturia was highly significantly more prevalent among patients group ($p \leq 0.001$), while crystalluria was significantly more prevalent among patient group ($p \leq 0.05$).

The prevalence of crystalluria among the studied patients was 62%, and Ca oxalate was the most common urinary crystal type (77.4%) of these patients. The most common type of the 44 retrieved stones was mixed Ca stones in 22 (50%) (Table 2).

Table 2: Prevalence difference of crystalluria between patients and control

Type of urinary crystals	**Patients (n=100)**	**Control (n=40)**	*p*
Ca Ox	48 (48%)	13(32.5%)	>0.05
Ca P	10 (10%)	-	<0.05
Uric acid	27 (27%)	5 (12.5)	>0.05
Triple phosphate	7 (7%)	1 (2.5%)	>0.05
Crystalluria	62 (62%)	17 (42%)	0.03

As regards to the number of detected stones; single stone was the most prevalent in 33 patients and multiple stones and gravels were the least prevalent in 8 patients. The most common size of stone ranged from 1.6 to 2.5cm in 39 patients and the least common size was less than 0.5cm in 2 patients. The kidney was the most common site for stone in 73 patients, while the bladder was the least common site for stone in 9 patients. Eighty six patients had radio-opaque stones (Table 3).

After 6 months, only 84 patients have completed their metabolic and imaging follow up studies and have been classified according to the degree of compliance into 5 groups as follows; group 0 non compliant patients (n=15), group 1 patients compliant to diet only (n=11), Group 2 patients compliant to 1 drug only (n=23), group 3 patients compliant to diet plus 1 drug (n=23) and Group 4 = those compliant to all prescribed drugs (n=12).

Out of the 84 followed up patients; 70 had urine volume <2L. Group 3 (diet plus 1 drug) had the highest increase in urine volume while group 0 (non compliant) had the least increase in urine volume. Group 1 (on diet only) had significant increase in urine volume in comparison to group 0 (non compliant). Group 3 (diet and 1 drug) had significant increase in urine volume in comparison with each of group 0 (non compliant), group 1 (diet only) and group 2 (one drug). Group 4 (all drugs) had significant increase in urine in comparison to each of

group 0 (non compliant) and group 2 (one drug) (Table 3).

Table 3: Increased urine volume after treatment according to the degree of compliance (n=81)

		Group 0 (n=12)	Group 1 (n=11)	Group 2 (n=23)	Group 3 (n=23)	Group 4 (n=12)
Mean± SD		-0.04±0.12	-0.42±0.37	-0.23±0.17	-0.74±0.37	-0.52±0.41
p	1		<0.05	>0.05	<0.001	<0.001
	2			>0.05	<0.05	>0.05
	3				<0.001	<0.05
	4					>0.05

Out of the 84 followed up patients; 56 patients had hypercalciuria. Group 3 (diet and 1 drug) had significant decrease in urinary calcium in comparison to each of group 0 (non compliant) and group 2 (one drug). Group 4 (all drugs) had significant decrease of urinary calcium in comparison to the other four groups (Table 4).

Table 4: Decreased urinary calcium after treatment according to the degree of compliance (n=56)

		Group 0 (n=13)	Group 1 (n=3)	Group 2 (n=17)	Group 3 (n=16)	Group 4 (n=7)
Mean± SD		- 0.037±0.19	0.019±0.09	0.015±0.08	0.13±0.11	0.33±0.16
p	1		>0.05	>0.05	0.001	<0.001
	2			>0.05	>0.05	<0.05
	3				<0.05	<0.001
	4					<0.05

Out of 84 followed up patients; 58 patients had hypo-citraturia. Group 2 (one drug) had significant increased urinary citrate in comparison to group 0 (non compliant) and group 1 (on diet only). Group 3 (diet and 1 drug) had significant increased urinary citrate in comparison to group 2 (one drug). Group 4 (all drugs) had significant increased citrate in comparison to group 2 (one drug) (Table 5).

Table 5: Increased urinary citrate after treatment according to the degree of compliance (n=56)

		Group 0 (n=12)	Group 1 (n=7)	Group 2 (n=16)	Group 3 (n=14)	Group 4 (n=9)
Mean± SD		-13.9±0.1	-0.16±0.3	-123.5±1.4	-63.4±0.2	-56.5±0.26
p	1		>0.05	<0.001	>0.05	>0.05
	2			0.001	>0.05	>0.05
	3				<0.05	<0.05
	4					>0.05

Out of the followed up patients; 53 patients had hyper-oxaluria. Group 3 (diet and 1 drug) had significant decrease in urinary oxalate in comparison to each of group 0 (non compliant), group 1 (on diet only) and group 2 (one drug). Group 3 (all drugs) had significant decrease in urinary oxalate in comparison to the other four groups (Table 6).

Table 6: Decreased urinary oxalate after treatment according to the degree of compliance (n=53)

		Group 0 (n=9)	Group 1 (n=5)	Group 2 (n=16)	Group 3 (n=14)	Group 4 (n=9)
Mean± SD		0.096±0.15	0.12±0.11	0.14±0.14	0.33±0.16	0.5±0.16
p	1		>0.05	>0.05	0.001	<0.001
	2			>0.05	<0.05	<0.001
	3				<0.05	<0.001
	4					<0.05

Out of the 84 followed up patients; 32 patients had urinary sodium level >100mg/24 hours. Group 3 (diet and 1 drug) had urinary sodium significantly decreased in comparison to group 2 (one drug). And group 4 (all drugs) showed significant increase of urinary sodium in comparison to group 2 (one drug) (Table 7).

Table 7: Decreased urinary sodium after treatment according to the degree of compliance (n=32)

		Group 0 (n=6)	Group 1 (n=2)	Group 2 (n=12)	Group 3 (n=8)	Group 4 (n=4)
Mean± SD		0.062±0.14	0.032±0.011	-0.044±0.3	0.258±0.18	0.347±0.04
p	1		>0.05	>0.05	>0.05	>0.05
	2			>0.05	>0.05	>0.05
	3				<0.05	<0.05
	4					>0.05

Out of the 84 followed up patients; 13 patients had hyper-uricosuria. But no statistically comparable differences were found between groups as regards to the mean decrease of urinary uric acid.

Out of the 84 followed up patients; 29.8% experienced recurrence of symptoms and 11.9% suffered from either new stone or enlargement of the old stone. The incidence of recurrence of symptoms and new stone formation or enlargement of old stone was highest among group 1 (on diet only). While group 4 (all drugs) showed no recurrence of symptoms, new stone or enlargement of old stone. Insignificant differences were found between the five groups as regards to recurrence of symptoms or CT changes (Table 8).

Table 8: Recurrence of symptoms and CT changes according to the degree of compliance

	Group 0 (n=15)	Group 1 (n=11)	Group 2 (n=23)	Group 3 (n=23)	Group 4 (n=12)	*p*
Recurrent symptoms (n=25(29.8%)	5 (33.3%)	6 (54.5%)	9 (39.1%)	5 (21.7%)	0 (0%)	*p* >0.05
New stone or Enlargement of old stone (n=10 (11.9%)	2 (13.3%)	4 (36.4%)	2 (8.7%)	2 (8.7%)	0 (0%)	*p* >0.05

4.Discussion

In this study, it was found that the mean age of the patients with urinary stones was (45.49 +12.45) years old, with a peak at the 5th decade (40-50) years old. Negri *et al.,* [15] compared the clinical characteristics of 30 "pure" uric acid (UA) stone formers with that of 29 "pure" calcium oxalate (CaOx) stone formers, he found that the mean age of CaOx stone formers was (44.5 +/- 10.0 years) while that for UA stone formers was (53.3 +/- 11.8 years).

The majority of patients in this work (83%) were of the male gender. This finding is similar to Stamatelou *et al.,* [16] who studied the influence of region, race/ethnicity, and gender on stone disease risk, over a 20-year period through a United States National Health and Nutrition Examination Survey, concluded that males were at a greater risk than females, with a male-to-female ratio of 3:1 (except for struvite stones and in black populations, where females had a greater risk).

It becomes difficult to assess whether occupation is a primary factor in stone disease or whether it merely establishes other aspects of environment, such as diet, heat exposure, and water drinking [17]. In this study, patient occupation had no impact on stone formation as it was found that there was equal number of patients with sedentary job and manual works. Blacklock [18] reported that the incidence of urinary calculi was higher in administrative and sedentary personnel than in manual workers.

Family history was present in (22%) of patients included in this study. This is supported by the study of Curhan *et al.,* [19] who found that about 25% of patients with kidney stones had a family history of kidney stones.

The results of this work showed that (49%) of patients had one or more systemic factor favoring the formation of urinary stones. In frequency order, obesity was the most frequent (32%), followed by DM (16%). Negri *et al.,* [15] concluded that obesity and older age associated with low urine pH were the principal characteristic of "pure" UA stone formers. Another recent study conducted by Gebhart [20] found

that (43.5%) of stone formers were obese or morbidly obese and a further (38.8%) were overweight.

This study also showed that (69%) of patients had one or more dietary factor favoring the formation of urinary stones: the most frequent was high dietary oxalate (41%), high salt intake in (37%), low fluid intake in (29%), high animal protein in (17%) and low calcium intake in (7%). Al Zahrani *et al.,* [21] also found statistically greater dietary intake of calories, sodium and carbohydrates in stone formers compared with controls. Rabanal [22] found that rural areas showed high intake of foods rich in oxalic acid (in 84.5% of patients), 68% declared to have high consumption of carbohydrates, with significantly higher intake of animal protein and milky products in (61.2%).

Stitchantrakul *et al.,* [23] found significant differences between stone formers and normal controls in urinary oxalate excretion and urinary calcium/citrate ratio. Also Pourmand *et al.,* [24] comparing urinary citrate, and other inhibitors and promoters of stone formation in 100 calcium stone formers with those in 100 healthy individuals, found that the mean 24-hours urinary calcium, citrate, and oxalate values were 232.6 +/- 95.3 mg and 177.8 +/- 82.7 mg ($P < 0.001$), 132 +/- 103.2 mg and 395 +/- 258.5 mg ($P < 0.001$), and 18.9 +/- 22.5 mg and 10.4 +/- 8.5 mg ($P < 0.001$) in patients and control groups, respectively.

The most frequent urinary abnormality in the present study was low urine volume (< 2 liters) in (84%), followed by hypo-citraturia in (78%), hyper-oxaluria in (61%), hyper-calcuria in (60%), high urinary sodium (> 100 mg/dl/day) in (34%) and the least frequent was hyper-uricosuria in (13%). Stitchantrakul et al [23] found that 69.6%, 15.2%, 10.1%, 7.2% and 1.3% of patients had hypo-citraturia, hyper-calciuria, low urinary volume, hyper-uricosuria and hyper-oxaluria, respectively.

As regards the urine analysis, the prevalence of pyuria and hematuria among the patients in this work was (50%) and (74%) respectively. Crystalluria was present in (62%) of patients and (42%) of the control group with significant difference between both groups (P=0.03). Daudon and Jungers [25] stated that crystalluria examination was a valuable diagnostic method when no stone was available for analysis. The presence of specific crystals (cystine, 2,8-dihydroxyadenine, struvite, ammonium urate) was diagnostic by itself.

In this study also, we found that (50%) of the (44) retrieved stones were mixed Ca stones, (31.8%) were Ca Ox stones, (9.1%) were struvite stones, (4.5%) were Ca P and (4.5%) were uric acid stones. We didn't encounter cystine stones or other rare types. Chou et al [26] collected 1,000 stone samples and found that mixed components of calcium oxalate and calcium phosphate were the most common form of stones (52.3%), followed by calcium oxalate (27.8%) and calcium phosphate (9.3%). Uric acid stones accounted for 7.6%. Magnesium ammonium phosphate stones accounted for 3.0%.

In the present study, the stones were unilateral in (69%), (73%) were in the kidney, (30%) in the lower ureter, (25%) in the upper ureter with only (9%) in the urinary bladder. Coll *et al.,* [27] found that stone location could predict the probability of the spontaneous passage; the rate of spontaneous passage was 48% for proximal ureteral stones, 60% for midureteral stones, and 75% for distal ureteral stones.

Results of this work showed that urinary citrate increased after treatment by a difference varying between (0.16%) in patients receiving diet modification alone to (123.5%) in patients receiving citrate therapy alone (group 2) with significant difference between this group and all other groups 0, 1, 3, 4. (P= <0.001, 0.001, <0.05, <0.05) respectively. In a recent study done by Koffa *et al.,*[28] found that Potassium citrate, but not lemonade, improved citrate levels and urinary pH to a significant degree and concluded that lemonade did not provide improvements in urinary citrate or pH levels but did assist patients in maintaining urine output compared with potassium citrate therapy.

In the study of Smith [29], patients randomized to allopurinol had a 60% reduction in the risk of stones at 12 months. The study of Ettinger *et al.,* [30] reported a 47% reduction in stone recurrence at 24 months of follow-up.

Morton *et al.,* [31] stated that general measures alone, which are advisable for all patients with recurrent stone formation upon a clinic visit, including increasing fluid intake and to reduce animal protein and sodium intake, together with moderate calcium intake, constituted the well-recognized phenomenon of the "stone clinic effect," which, had been suggested to reduce the 5-year stone recurrence rate by 60% and which would have helped to reduce urinary sodium in most of the patients without significant difference between the studied groups.

4. Conclusion

The study confirms the beneficial effect of the currently available specific treatment options based on metabolic evaluation especially the value of a 24 hours urinary collection for Calcium, uric acid and oxalate in comparison to other non specific measures.

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