



Original Article

Impact of the adherence to medical treatment on the main urinary metabolic disorders in patients with kidney stones



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KEYWORDS

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Citrate;
Oxalate;
Lithiasis

Abstract *Objective:* To assess the effect of the adherence to medical treatment on urinary parameters in the 24-h metabolic study of patients with kidney stones.

Methods: A retrospective, longitudinal, descriptive, and observational study was carried out by reviewing the hospital electronic medical record from 2014 to 2018. The adherence to drug treatment was measured 6 months after its initiation, and the numerical values of the metabolic studies were compared. Wilcoxon tests were performed to compare the difference before and after treatment.

Results: Ninety patients were evaluated, with 73.3% of adherence. The 180-day overall adherence rate was 61.2% in patients treated with a single drug and 85.4% in patients treated with multiple drugs. There is a statistically significant increase in citrate levels in patients with good adherence in comparison with non-adherent patients ($p=0.031$ vs. $p=0.528$).

Conclusions: Medical treatment and dietary measures in patients with kidney stones have an initial impact at 6 months on the values of the main urinary metabolic alterations that predispose to calculi formation; the most significant is seen in those patients with adherence to medical treatment for hypocitraturia.

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1. Introduction

The recurrence rate of renal stones is about 50% at 5-year follow-up if pharmacologic treatment is not given [1–3]. The most critical factors that contribute to calcium stones formation are hypercalciuria, hypocitraturia, hyperuricosuria, and hyperoxaluria [4,5]. Nowadays, the 24-hour urine collection is the gold standard method to identify such abnormalities to guide the pharmacological treatment and dietary modifications [6].

Adherence to an established treatment is defined as the extent to which patients take medications prescribed by their health care providers. Also, adherence is a cornerstone for an adequate response and resolution of any human disease like all metabolic disorders responsible for kidney stones [7–10]. Additionally, adherence is a crucial gauge of health care quality, and nonadherence is associated with poor health outcomes and substantial economic costs [11]. Despite the above, nonadherence to drug therapy is one of the main limitations in the treatment of chronic diseases, reducing the benefits that could be obtained [12]. Efforts to accurately measure and improve adherence have received increasing attention from patients, physicians, payers, and all the rest of healthcare stakeholders.

Unfortunately, today there is no consensual standard for what adequate adherence constitutes and how to measure it adequately. A 50% adherence rate has been described for chronic illness such as hypertension and type 2 diabetes in a 6-month follow-up [13]. Prior studies on this topic have reported a 70% compliance rate for stone patients followed explicitly in a comprehensive kidney stone center. It is likely that compliance for the typical patient, in a non-specialized center, is significantly lower [14]. Therefore, the purpose of the current study was to describe the patients' compliance rates to the stone prevention regimens and to evaluate its influence in the 24-hour urine parameters at 6 months of follow-up.

2. Methods

A retrospective cohort study was conducted, with a longitudinal, descriptive, and observational design approved by the ethics committee with the registration number (CI/HRAEB/2019/040). From 2014 to 2018, we analyzed all adult patients with kidney stones diagnosis and stone-free state after their surgical procedure. All patients had two metabolic studies, including 24-hour urine panel and urinary pH determination in single sample separately with dipstick (Chemstrip® by Roche Diagnostics, Indianapolis, USA), and a reflectance photometer (Urisys 1100, Diagnostics, Laval QC): The first one performed at the time of determining stone-free status and the second in the follow-up after medical intervention at 6 months. Medical treatment was directed depending on the patient's metabolic abnormality in the first metabolic evaluation. We defined hypocitraturia as urine citrate of <320 mg/day, hyperoxaluria as a urine oxalate of >0.4 mmol/day, hypercalciuria >200 mg/day and hyperuricosuria as a urine uric acid of >0.7 g/day. All patients received a printed sheet with the dietary recommendations corresponding to each

metabolic alteration. Standardized treatment regimens were as follows: For hypocitraturia were given potassium citrate (KCit) 2 g PO BID bid; for hypercalciuria were given hydrochlorothiazide (HCT) 25 mg PO QD; for hyperuricosuria were given allopurinol (Allo) 300 mg PO QD, and finally, hyperoxaluria was managed with low oxalate/calcium-rich diet [15]. For patients with two or more alterations of 24-hour urine composition, they received multiple treatments with two or more prescriptions, as well as combined dietary modifications (Supplementary material). Compliance or adherence to dietary modifications was evaluated by self-reported dietary compliance as described by previous authors [16,17].

2.1. Determination of adherence

Adherence to drug treatment was determined by reviewing the electronic medical record. To estimate adherence, we use the formula for the proportion of days covered (PDC) described by Dauw et al. [18]. The PDC is calculated as the number of days covered by a specific drug divided by the total number of days in the follow-up period. For patients taking more than one medication, we estimated the adherence by calculating the average class-specific PDC values. We used a follow-up period of 180 days after the first drug prescription in our study, and then we multiplied the PDC by 100 to express it as a percentage. According to previous studies, we defined a good adherence if this percentage was equal or greater than 80%. Patients with less than 80% and those who lost the prescription or had irregular follow-up were considered as having poor adherence.

2.2. Statistical analysis

The program used for statistical purposes was IBM SPSS version 25 (IBM Corp., Armonk, NY). A univariate analysis was carried out using frequencies and percentages for categorical data and measures of central tendency and corresponding dispersion according to the distribution of the data in the quantitative variables, following the Kolmogorov-Smirnov normality test. Wilcoxon tests were performed to compare the difference before and after medical treatment. A $p < 0.05$ and a 95% bilateral confidence interval were considered statistically significant.

3. Results

Ninety patients met inclusion criteria (*i.e.*, stone-free status after surgery and at least 180 days of follow-up for metabolic stone evaluation and treatment). The demographic data of the 90 patients are presented in Table 1. The relative prevalence of the 24-hour urine abnormalities, taking into account that many patients had more than one disorder, was as follows: Hypocitraturia (41.26%), hyperuricosuria (14.28%), hypercalciuria (16.40%) and hyperoxaluria (28.04%) (see Table 1).

Of the 90 patients included in this study, 36 (40%) were treated with monotherapy (single drug); the most frequent treatment was KCit ($n = 29$), followed by HCT ($n = 7$) and no single patient had monotherapy treatment with allopurinol. Forty-one (45.5%) patients were treated with multi-drug

Table 1 Baseline and demographic characteristics.

Characteristics	Patients	Percentage (%)
Gender, <i>n</i>		
Male	50	55.6
Female	40	44.4
Age (year)	45.4 (13.2) ^a	
DM2, <i>n</i>	8	8.9
HTN, <i>n</i>	25	27.8
BMI (kg/m ²)	28.8 (4.3) ^a	
Normal, <i>n</i>	17	18.9
Overweight, <i>n</i>	42	46.7
Grade I Obesity, <i>n</i>	30	33.3
Grade II Obesity, <i>n</i>	1	1.1
Stone volume (mm ²)	252 (124–447.3) ^b	
Number of Stones, <i>n</i>	2 (1–3) ^b	
Urinary Metabolic Disorders, <i>n</i>	189	
Hypocitraturia	78	41.26
Hyperoxaluria	53	28.04
Hypercalciuria	31	16.40
Hyperuricosuria	27	14.28

DM2, Type II Diabetes; HTN, hypertension; BMI, body mass index.

^a Mean (Standard Deviation).

^b Median (Quartile).

therapy. The most frequent combination was KCit+HCT (*n*=12), KCit+Allo (*n*=9), KCit+HCT+Allo (*n*=8), HCT+Allo (*n*=6), KCit+Mg (*n*=3), Cit+Calcitriol (*n*=3). Thirteen (14.4%) patients with hyperoxaluria were managed just with dietary therapy. The 180-day overall adherence rate was 73.3% (61.2% in patients treated with a single drug and 85.4% in patients treated with multiple drugs). The overall differences in the urine parameters of patients after pharmacologic treatment are seen in Table 2.

Patients were sub-stratified by medication therapy and divided into good and poor adherence to medical treatment (Tables 3 and 4). When comparing patients who were

adherent versus those who were not, a statistical difference was seen in potassium citrate-adherent patients showing a significant increase (Table 3) in the urine citrate (from 60 mg/day to 141.5 mg/day) (*p*=0.031). Non-adherent patients (Table 4) failed to demonstrate such an increase in the urine citrate (130 mg/day to 248.5 mg/day) (*p*=0.5).

For patients with hyperuricosuria, there was a decrease of 25% in uric acid levels. In those patients with hypercalciuria, there was a decrease of 12% in calcium levels. Finally, in those patients with hyperoxaluria, there were no changes in the urine oxalate levels. However, neither adherent nor non-adherent patients demonstrated a statistically significant difference in urinary parameters at six-month follow-up (*p*=non significant for all). These results are shown in Tables 3 and 4.

4. Discussion

Adherence to medical treatment is a complicated issue to evaluate. Some strategies to evaluate this include surveying the patients, directly observing medication taking, measuring drug or metabolites in plasma/urine, or using electronic medication monitors. Previous studies evaluating compliance used the self-reporting patients (directly surveying the patients) being the simplest to achieve and considered to be reliable in the published literature [11,12]. Similar to Dauw et al. [18], we evaluated patient's adherence to the proportion of days formula in order to evaluate the impact of the adherence to medical treatment and dietary modifications on the primary metabolic disorders that predispose to stone formation in patients diagnosed with kidney stones.

Reducing recurrence is the main objective of preventive treatment, and it should be individualized concerning the specific metabolic alteration of each patient. Thiazides are the standard management for idiopathic hypercalciuria; compared to placebo, a significant decrease in stone recurrence (more than 60% of reduction) has been documented [15]. Hypocitraturia is treated by alkali

Table 2 Differences between the first metabolic study and its control 6 months after the start of medical treatment.

Metabolic disorder	Before, mean (range)	After, mean (range)	<i>p</i> -Value
Hypocitraturia (<i>n</i> =78)			
Urinary pH	6 (5–7)	6 (5.5–6.75)	0.473
24 h urine Cit (mg/d)	62 (20.5–208)	189 (40–274)	0.015*
24 h volume (mL)	1900 (1485–2585)	2210 (1600–2740)	0.561
Hyperuricosuria (<i>n</i> =27)			
Urinary pH	6 (5.5–6.7)	6 (5.5–6.8)	0.606
24 h urine UA (g/d)	0.8 (0.5–10)	0.7 (0.5–0.9)	0.021*
24 h volume (mL)	2100 (1780–2800)	2145 (1500–2970)	0.764
Hypercalciuria (<i>n</i> =31)			
Urinary pH	6 (5.3–6.5)	6 (5.8–6.5)	0.425
24 h urine Ca (mg/d)	302.4 (172.2–367.4)	261.8 (208–342)	0.854
24 h volume (mL)	2200 (1720–2970)	2360 (1700–2920)	0.984
Hyperoxaluria (<i>n</i> =53)			
24 h urine Ox (mmol/d)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.906
24 h volume (mL)	2390 (1845–2950)	2440 (1800–2965)	0.468

*Statistically significant. Wilcoxon tests were performed to compare the difference before and after medical treatment. A *p*<0.05 and a 95% bilateral confidence interval were considered statistically significant.

Table 3 Changes showed in the 24-hour urine parameters in patients with adherence to medical and dietary treatment.

Metabolic alteration	Variable	Before, mean (range)	After, mean (range)	p-Value
Hypocitraturia (n=78)	24 h Cit (mg/d)	60 (18–191.5)	141.5 (29.2–274)	0.031*
Hyperuricosuria (n=27)	24 h UA (g/d)	0.8 (0.4–22.6)	0.6 (0.4–0.9)	0.088
Hypercalciuria (n=31)	24 h Ca (mg/d)	297.5 (167.7–366.9)	261.8 (191.7–342.0)	0.889
Hyperoxaluria (n=53)	24 h Ox (mmol/d)	0.6 (0.5–0.8)	0.6 (0.4–0.7)	0.286

*Statistically significant. Wilcoxon tests were performed to compare the difference before and after medical treatment. A $p < 0.05$ and a 95% bilateral confidence interval were considered statistically significant.

preparations based on citrate and has been shown to maintain stone-free rates of 92% in surveillance vs. 58% in placebo patients [19]. Allopurinol has been indicated for the treatment of calcium oxalate stones associated with hyperuricosuria; its use has shown up to a 50% decrease in the recurrence of lithiasis vs. placebo [20]. In hyperoxaluria, the reduction of dietary oxalate is essential; only 52% of patients have adequate compliance with dietary measures and fluid consumption, achieving a significant decrease in urinary oxalate levels [16,21,22].

In the current study, we found that adherence to prescribed measures described above resulted in significant differences in 24-hour urine composition only in patients taking potassium citrate. At first glance, this is somewhat surprising, considering that hypercalciuric patients received a thiazide diuretic and hyperuricosuric patients received allopurinol. We feel that the best possible explanation for these findings is likely the diet that is typical of the region in Mexico where our patients come. This diet is a diet rich in sodium and animal protein. Sodium is known to reduce or block the hypocalciuric effects of thiazide diuretics, and a diet rich in animal protein may result in increased urinary uric acid excretion and reduce the uric acid lowering effects of allopurinol. On the other hand, these dietary tendencies would not be expected to reduce the effects of potassium citrate, which works by causing systemic alkalization, inducing citrate excretion into the urine. Another finding to assess was that urinary pH did not change significantly after potassium citrate treatment, as is commonly expected. We use the urine dipstick (Urisys® by Roche) as the pH determination evaluation method, and it has been described that this kind of study (photometry readers) has considerable inaccuracy that could cause bias in our results [23].

In our study, 73.3% (61.2% in single drug and 85.4% with multiple drugs) of patients showed adherence to medical treatment and dietary recommendations. This adherence rate is a high percentage compared to the reported in previous studies. One possible explanation for the high adherence of our population is that the majority of patients treated in our center (a tertiary referral center for complex

stone disease) have experienced recurrent or persistent complicated urinary stones. Therefore, our patients may be highly motivated to comply with preventive measures and treatments that were given. Additionally, opposite to previous studies, our patients submitted to multiple therapies for more than one metabolic alteration, showed higher compliance. A big concern, suffering, and even the loss of one renal unit could be one reason for this high adherence in patients with multiple metabolic diagnoses, but this needs to be further studied. Nonetheless, we observed, as described above, that adherence to therapy only resulted in significant changes in patients with hypocitraturia.

These findings may be unique to our patient population. As described above, there exists level 1 evidence that each of the three medication therapies: Potassium citrate, thiazide diuretics, and allopurinol results in a significant reduction in recurrent stone events. However, these studies were all performed in a distinct population (United States) where dietary habits may be different from those of our patients [20,24,25]. We feel that our findings have significant implications for the treatment of patients in Mexico with recurrent calcium oxalate stone disease. One could assume if future studies confirm these findings, that the optimal medication for stone prevention for patients in this region of Mexico would be potassium citrate-based therapies.

Our study has several limitations, which are inherent in a retrospective study, such as the definition of adherence. As reported in previous studies, it is not possible to assess accurately if the patient took or not the medication, despite the records in the file and pharmacy. Previous studies have been based on self-patient reporting to measure compliance or adherence to medical treatment and dietary measures. Also, non-adherent patients could have taken another dietary or herbal treatments not reported to doctors that could affect their metabolic profile. The study was conducted in a third level hospital, with a specialized lithiasis clinic, in which complex and recurrent cases of kidney stones are treated so that it could be not representative of the general population. Although the follow-up time of our population could be considered a short time

Table 4 Changes showed in the 24-hour urine parameters in patients with no adherence to medical and dietary treatment.

Metabolic alteration	Variable	Before, mean (range)	After, mean (range)	p-Value
Hypocitraturia (n=78)	24 h Cit (mg/d)	130 (32–322)	248.5 (80.7–281.5)	0.528
Hyperuricosuria (n=27)	24 h UA (g/d)	0.8 (0.6–5.9)	0.7 (0.6–4.9)	0.327
Hypercalciuria (n=31)	24 h Ca (mg/d)	305.1 (226.1–305.1)	228.7 (213.2–228.7)	0.655
Hyperoxaluria (n=53)	24 h Ox (mmol/d)	0.4 (0.3–0.7)	0.6 (0.5–0.8)	0.374

follow-up for chronic diseases, all the previous studies evaluating adherence to medical treatment have reported just 6 months of follow-up [16–18]. Long-term follow-up is necessary to document the constancy to adherence in chronic treatments and to observe changes in the 24-hour urinary metabolic study and its long-term effect on recurrence rate changes, stone re-formation, emergency visits, and even loss of kidney function.

5. Conclusion

Medical treatment and dietary measures in patients with kidney stones have an initial impact at 6 months on the values of the main urinary metabolic alterations that predispose to calculus formation; the most significant is seen in those patients with adherence to medical treatment for hypocitraturia.

Author contributions

Study concept and design: Jose Ernesto Torres, Braulio Omar Manzo, Jose David Cabrera.

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Critical revision of the manuscript: Braulio Omar Manzo, Esteban Emiliani, Brian Howard Eisner.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajur.2020.07.002>

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