The Impact of Dietary Modifications and Medical Management on 24-Hour Urinary Metabolic Profiles and the Status of Renal Stone Disease in Recurrent Stone Formers

Yasmin Abu-Ghanem MD, Nir Kleinmann MD, Tomer Ertlich MD, Harry Z. Winkler MD, and Dorit E. Ziberman MD

Department of Urology, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT

Background: Dietary modifications and patient-tailored medical management are significant in controlling renal stone disease. Nevertheless, the literature regarding effectiveness is sparse.

Objectives: To explore the impact of dietary modifications and medical management on 24-hour urinary metabolic profiles (UMP) and renal stone status in recurrent kidney stone formers.

Methods: We reviewed our prospective registry database of patients treated for nephrolithiasis. Data included age, sex, 24-hour UMP, and stone burden before treatment. Under individual treatment, patients were followed at 6–8 month intervals with repeat 24-hour UMP and radiographic images. Nephrolithiasis-related events (e.g., surgery, renal colic) were also recorded. We included patients with established long-term follow-up prior to the initiation of designated treatment, comparing individual nephrolithiasis status before and after treatment initiation.

Results: Inclusion criteria were met by 44 patients. Median age at treatment start was 60.5 (50.2–70.2) years. Male:Female ratio was 3.9:1. Median follow-up was 10 (6–25) years and 5 (3–6) years before and after initiation of medical and dietary treatment, respectively. Metabolic abnormalities detected included: hypocitraturia (95.5%), low urine volume (56.8%), hypercalciciuria (45.5%), hyperoxaluria (40.9%), and hyperuricosuria (13.6%). Repeat 24-hour UMP under appropriate diet and medical treatment revealed a progressive increase in citrate levels compared to baseline and significantly decreased calcium levels (P = 0.001 and 0.03, respectively). A significant decrease was observed in stone burden (P = 0.001) and overall nephrolithiasis-related events.

Conclusions: Dietary modifications and medical management significantly aid in correcting urinary metabolic abnormalities. Consequently, reduced nephrolithiasis-related events and better stone burden control is expected.

KEY WORDS: diet, medical therapy, metabolic profile, nephrolithiasis

Over the past two decades there has been evidence of an increasing role nephrolithiasis plays in the arena of the Western world diseases. Ageing, as well as lifestyle changes and dietary factors, are assumed to contribute the most to the growing numbers of patients treated by a urologist due to kidney stone disease [1,2].

The current prevalence of nephrolithiasis in the United States is reported to be as high as 8.4% [1] and 6.4% in China [3], while in Japan there has been over a twofold increase in the annual incidence over a period of 30 years [2]. Recurrence rates are high, with cited numbers of 50% at 5 years after a single stone episode [4] and 75% at 10 years for recurrent stone formers [5].

The annual budget impact of nephrolithiasis, based on 65 million inhabitants, was found by one study to be 590 million Euros for the payer with annual cost savings of 273 million Euros if high water intake is implemented by 100% of the population [6]. This study concluded that nephrolithiasis prevention could have significantly reduced both the overall stone burden as well as the cost for the payer in the healthcare system.

Despite the potential significance of dietary modifications and patient-tailored medical management in controlling renal stone disease [7], the literature regarding its effectiveness is sparse. In this study we evaluate the influence of dietary modifications and medical management on 24-hour urinary metabolic profiles (UMP) as well as on stone burden and recurrent stone events in nephrolithiasis patients who were previously under regular follow-up but without any medical or dietary intervention.

PATIENTS AND METHODS

Following approval given by our institutional review board, we established a prospective registry database of patients treated at our urology outpatient clinic for nephrolithiasis. Data included demographic details such as patient age and sex as well as 24-hour UMP, stone burden, and stone events (i.e., renal colic, surgical intervention) before treatment.
In accordance with the most recent American Urological Association guidelines for medical management of kidney stones [8], at least one sample of 24-hour urine collection was obtained before treatment and included total volume and levels of creatinine, sodium, potassium, calcium, uric acid, oxalate, and citrate.

Stone burden before treatment was evaluated by radiographic imaging, preferably a non-contrast helical computerized tomography (NCCT). Stone number and diameter of the largest one on each side were recorded. Each and every patient was handed a dietary recommendations datasheet that explained in great detail the need to increase daily fluid intake to a minimum of 2.5 to 3 liters per day to maintain daily urine output of at least 2 L/day. Consumption of sodium, calcium, animal protein, and oxalate-rich foods as well as increasing citrus juices intake were discussed as well.

In accordance with the metabolic workup results, the patients were placed on an individual medical treatment that included potassium-citrate regimens for hypocitraturia, unduly acidic urine, and hypercalciuria; indapamide for hypercalciuria; and vitamin B6 supplements for hyperoxaluria and allopurinol for excessive hyperuricosuria (> 1200 mg/day).

Under individual treatment, patients were followed in 6–8 months intervals with repeat 24-hour UMP and radiographic images (renal ultrasound and abdominal X-ray). Medication doses were titrated individually at follow-up appointments based on UMP results. Nephrolithiasis-related events (i.e., surgery, renal colic) were recorded during the follow-up period.

Participants were at least 18 years old and had at least one 24-hour urine collection before any intervention and one 24-hour urine collection under appropriate dietary and medical treatment.

**Figure 1.** Metabolites level changes in 24-hour urinary metabolic profiles: [A] citrate, [B] potassium, [C] urine volume, [D] calcium
To precisely estimate the effect dietary modifications and medical management in cases of kidney stone disease, we reviewed our database for patients who were previously seen regularly at our outpatient clinic for a long period of time but were not placed on any dietary or medical program. Hence, patients served as their own control.

Cystinuric and renal tubular acidosis patients were excluded from analysis.

Low urine volume (LUV) was defined as < 2000 ml/day. High urinary sodium level was defined as > 200 mEq/day, hypercalciuria was set at > 200 mg/day, hyperuricosuria was set at > 750 mg/day, hyperoxaluria was set at > 45 mg/day, and hypocitraturia was set at < 600 mg/day (for both men and women).

Radiographic stone burden was quantified by number of stones. Possible endoscopic procedures for stone fragmentation were considered when performing the statistical analysis and were eliminated accordingly.

Data are presented as median (interquartile range) or number (percent) unless otherwise specified. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22.0 (SPSS, IBM Corp, Armonk, NY, USA).

Comparisons of changes from baseline conditions were analyzed using the Student t-test (2-tailed, paired). Wherever multiple comparisons were performed, analysis of variance (ANOVA) with repeat measures was used. Whenever appropriate, post-hoc analysis with the Bonferroni correction was applied. Testing was performed at a 95% significance level.

RESULTS

We found 44 patients under meticulous diet, medical treatment, and follow-up, who, prior to treatment start, had an established long-term follow-up without any intervention. Their median age at treatment start was 60.5 years (50.2–70.2 years). Male:Female ratio was 3.9:1. The median follow-up before treatment was 10 years (6–25 years); and under medical and dietary treatment was 5 years (3–6 years).

Metabolic abnormalities from most to least frequent were as follows: hypocitraturia (95.5%), LUV (56.8%), hypercalciuria (45.5%), hyperoxaluria (40.9%), hyperuricosuria (13.6%). High urinary sodium levels were detected in 15.9%.

The change in metabolite levels over time is detailed in Figure 1.

A progressive increase has been observed in both urinary citrate, F(2.3, 62.9) = 10.97, P < 0.001; and potassium levels, F(1.99, 15.9) = 3.7, P < 0.05. The medical treatment effect remained stable, and further increase has been observed throughout the entire follow-up period of the study (Figures 1A and 1B).

Repeat 24-hour urine collection under appropriate diet and medical treatment revealed a progressive increase in urine volume compared to baseline level, F(2.37,92.5) = 3.15, P < 0.05. Unlike the citrate levels, urine volume level rapidly stabilized, and the main effect was observed only on early follow-up [Figure 1C].

The levels of urine Calcium were significantly decreased over time, F(2.8, 44.4) = 3.3, P < 0.05, [Figure 1D]. A slight decrease in oxalate levels was observed at early follow-up; however, recurrent increase over time moderated the overall improvement. Urine levels of sodium and uric acid did not change over time.

With regard to stone burden, a significant decrease was observed over time, F(2.5, 105.9) = 6.4, P < 0.005, [Figure 2]. Normal metabolite levels were recorded in 31% of the hypocitrurics, 48% of LUV patients, 25% of the hypercalciurics, 55% of the hyperoxalurics, 33% of the hyperuricosurics, and 57% of patients with high urinary sodium levels.

Of the 44 patients, 11 patients had a single nephrolithiasis-related event (25%), 6 (13.6%) had 2 events, and 5 (11.4%) had more than two events following treatment.

Median number of stone events per patient before treatment was 3 (3–5) and under medical and dietary treatment 1 (1–2), (P < 0.001).

DISCUSSION

Dietary modification and individual medical management have been found for many years to be the key points in keeping kidney stone formers from recurrent stone episodes [7,9].

Yet, literature searches with regard to the effectiveness of this strategy is sparse, probably as a result of a relatively long observation period required to draw substantial conclusions.

One study retrospectively reviewed stone recurrence rates following percutaneous nephrolithotomy in 70 patients who were either on medical treatment or under observation alone and found that 69% of the patients under medical treatment had no change or decrease in stone burden compared to 19% of the patients under observation [10].

The effect of potassium-citrate supplements on stone recur-
rence rates had been investigated by four different groups [11-14]. Barcelo and colleagues [11] randomly allocated 57 nephrolithiasis patients into two groups: 37 patients were under potassium citrate treatment while the remaining 20 received a placebo. Over a follow-up period of 3 years there was a significant decline in stone forming rate, a phenomenon which was not seen in the control group. Similar results were obtained in another smaller study in which a 93% stone-forming remission rate was achieved in 27 patients over a period of 4.6 years [12].

Apparently, continuous medical treatment is superior to intermittent treatment for stone recurrence prevention. In another study [13], 64 patients under continuous treatment were compared to 80 patients under intermittent treatment. Over a period of 24–60 months, stone recurrence rates were as low as 7.8% in the first group compared with 30% in the second group.

The largest study by far on the impact of potassium citrate therapy on recurrent stone formation was conducted by Robinson and co-authors [14] who retrospectively evaluated 503 patients before and after the introduction of potassium citrate treatment. Over a mean treatment period of 41 months (up to 168 months) there was a 68% remission rate and a 93% decrease in the stone formation rate.

Following the administration of potassium citrate supplements, there has been a consistent and consistent increase in its level, in our study as well as in other studies [12,14-16].

The effect of potassium citrate and other regimens on 24-hour urinary stone risk parameters was investigated by Marchini et al. [15]. They analyzed 137 patients under medical treatment with a mean follow up of 14.4 months and found, similar to us, significant improvement in the levels as a result of their medical intervention.

The same group investigated earlier the effect of dietary counseling only on urinary stone risk parameters [16]. Similar to our study, urinary parameters that were measured included LUV, sodium, calcium, and oxalate. Apparent significant changes were observed in all parameters; however, most of the patients did not normalize their urinary parameters and were advised to receive supplemental pharmacological therapy.

Our current study is an integration of concepts of the previous studies, namely, we reviewed the influence of both dietary and medical treatment on the levels of 24-hour urinary stone risk parameters, stone events, and stone burden over a relatively long period of time. What makes our study unique compared to previous ones is the fact that each established kidney stone former served as his/her own control when exploring the effect of diet and medical management on stone burden.

In our cohort, apparent improvements were observed in urine volume, as well as in urinary levels of calcium, citrate, and potassium with a simultaneous, significant reduction in stone burden category. As stated previously, possible endoscopic procedures for stone fragmentation were considered when performing the statistical analysis and were eliminated accordingly.

LIMITATIONS
There are few weak points in our study that should be addressed. The first is the relatively small number of patients in our cohort and the relatively short follow-up period.

This limitation may explain the apparent decrease in urinary oxalate levels that did not reach statistical significance. Moreover, in too few patients (15.9%, n=7) high urinary sodium levels were detected; therefore, levels improvements could not be well demonstrated.

Another limitation is related to the possible inaccuracy in stone burden estimation. Obviously, mismatches may occur when comparing NCCT to ultrasound or abdominal X-ray findings.

Given the retrospective nature of the present study, compliance to medical treatment could not be quantified or standardized by means of certain tests or questionnaires.

Last, we were unable to estimate cost savings to medical providers; hence, we may not sound convincing enough when claiming that for nephrolithiasis, conservative treatment outweighs observation alone in the long run.

Despite these limitations, our findings obviously validate previous conclusions regarding the high impact of dietary restrictions and medical management on renal stone disease status and emphasize the significance of high patient compliance and regular follow-ups on high stone remission rates.

We believe that with the expected increase in patient number in our cohort and their related urine samples and images, this statement will gain more validity, and hopefully we will continue seeing these patients in an outpatient setting and not in the operating theater.

CONCLUSIONS
High patient compliance to medical treatment and dietary modifications significantly aids in correcting urinary metabolic abnormalities known as risk factors for kidney stone formation. As a consequence, reduced nephrolithiasis-related events and better stone burden control is expected.

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Correspondence
Dr. D.E. Zilberman
Dept. of Urology, Sha’ba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2251
Fax: (972-3) 535-1892
e-mail: dorzie@yahoo.com

References
Severe COVID-19 is characterized by an inflammatory signature, including high levels of inflammatory cytokines, alveolar inflammatory infiltrates and vascular microthrombi. Chakraborty and colleagues showed that patients with severe COVID-19 produced a unique serologic signature, including an increased likelihood of inflammatory cytokines by monocytes, including interleukin-6 and tumor necrosis factor. These results show that disease severity in COVID-19 correlates with including afucosylated IgG1.

Immunological memory after infection with seasonal coronavirus (hCoVs) may potentially contribute to cross-protection against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Ng et al. reported that in a cohort of 350 SARS-CoV-2-uninfected individuals, a small proportion had circulating immunoglobulin G (IgG) antibodies that could cross-react with the S2 subunit of the SARS-CoV-2 spike protein. By contrast, COVID-19 patients generated IgA, IgG, and IgM antibodies that recognized both the S1 and S2 subunits. The anti-S2 antibodies from SARS-CoV-2-uninfected patients showed specific neutralizing activity against both SARS-CoV-2 and SARS-CoV-2 S pseudotypes. A much higher percentage of SARS-CoV-2-uninfected children and adolescents were positive for these antibodies compared with adults. This pattern may be due to the fact that children and adolescents generally have higher hCoV infection rates and a more diverse antibody repertoire, which may explain the age distribution of COVID-19 susceptibility.