*https://doi.org/10.31925/farmacia.2022.6.22* **ORIGINAL ARTICLE**

# COMPARISON OF STONE-FREE RATE WITH CITRATURIA LEVELS IN KIDNEY STONES TREATED WITH DIGITAL FLEXIBLE URETEROSCOPY WITH HOLMIUM LASER LITHOTRIPSY

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**Abstract**

The use of citrate treatment (to increase citraturia) may be a solution to help eliminate the remaining fragments (< 5mm) following flexible ureteroscopy and Holmium laser lithotripsy for kidney stones. We performed a prospective, randomized, double-blind trial study on a sample of 149 patients with kidney stones who benefited from digital flexible ureteroscopy with Holmium laser lithotripsy between January 2018 and November 2020. 75 patients then received general treatment with a combination of citrates (975 mg of potassium citrate, 60 mg of magnesium citrate, and 25 mg pyridoxine per sachet) and 74 patients received only general treatment. The sample of patients was divided into two groups (it was not considered whether or not the patient benefited from the combination of citrates): group A consisted of patients who at 90 days obtained stone-free status, while group B consisted of patients who did not obtain this status. The values of citraturia/24 h in group A are statistically significantly increased after 90 days ($p < 0.01$). Following the comparison between the differences between the citraturia at 90 days and the initial ones in the 2 groups (geometric mean), the difference was higher in group A, the effect being statistically significant ($p < 0.05$).

**Rezumat**

Utilizarea tratamentului cu citrați (pentru creșterea citraturiei) poate reprezenta o soluție pentru eliminarea fragmentelor restante (< 5mm) în urma ureteroscopiei flexibile și litotriției cu laserul Holmium pentru calculi renali. Am efectuat un studiu de tip trial controlat, prospectiv, randomizat dublu orb pe un eșantion de 149 de pacienți cu litiază renală care au beneficiat de ureteroscopie flexibilă digitală cu litotriție laser Holmium în perioada ianuarie 2018 - noiembrie 2020. 75 de pacienți au primit apoi tratament general la care a fost adăugată combinație de citrați (975 mg citrat de potasiu, 60 mg citrat de magneziu și 25 mg de piridoxină per plic), iar la 74 de pacienți nu a fost adăugată această combinație. Eșantionul de pacienți a fost împărțit în două loturi (nu a fost luat în considerare dacă pacientul a beneficiat sau nu de combinația de citrați): lotul A a fost format din pacienți care la 90 de zile au obținut statusul stone-free, în vreme ce lotul B a fost format din pacienți care nu au obținut acest status. Valorile citraturiei pe 24 h în lotul A sunt semnificativ statistic crescute după 90 zile ($p < 0.01$). În urma comparației între diferențele dintre citraturiile la 90 zile și inițiale pe cele 2 loturi (medii geometrice), diferența a fost mai mare la lotul A, efectul fiind cu semnificație statistică ($p < 0.05$).

**Keywords**: kidney stones, citraturia, stone-free rate

## Introduction

Among chronic kidney disease patients, kidney stones are a common pathology [1, 2]. Several small variable lithiasis fragments are scattered throughout the renal calyx following flexible ureteroscopy and Holmium laser lithotripsy for kidney stones. It is possible that some of them will not be eliminated, remaining at this level. Increasing favourable results and reducing complications highlight the benefits of flexible ureteroscopy worldwide [3-5]. A significant amount of phytotherapy is used therapeutically in certain parts of the world, especially in developing countries that lack a modern medical system in place to provide for the needs of such people[6]. In recent years, the growth of major pharmaceutical companies and the current trend of industrialization in all fields have contributed to the development of pharmaceuticals [7]. Citrates may be used to treat the remaining fragments.

A balance exists between citrate availability and its excretion from the body based on each individual's physiological requirements. To identify any alterations in their homeostasis, citrate excretion/24 hours is used as a reference point [8]. The average urinary citrate value ranges from 320 to 1260 mg/24 hours, with a higher average value in women (approximately 680 mg/24 hours) than in men (approximately 550 mg/24 hours) [9, 10].

The lower limit of normal citraturia is 320 mg/day. Thus, one can speak of severe citraturia when the values fall below 100 mg/day and moderate-severe citraturia when the values fall between 100 and 320 mg/day [10].

Generally, high levels of citraturia occur during acid-base balance regulation, such as chronic consumption of alkaline substances. It is not necessary to consider hypercitraturia as a pathological condition [11].

Hypocitruria is associated with a risk of 16 - 63% of developing kidney stones containing calcium [12, 13]. Spontaneous crystallization and spontaneous nucleation of calcium oxalate and calcium phosphate occur in cases of kidney stones with hypocitraturia. Potassium citrate is useful in inhibiting this process [14]. According to Nicar *et al*., potassium citrate therapy significantly reduced naturally occurring calcium oxalate precipitation in urine [15].

## Materials and Methods

*Study design*

We conducted a prospective, randomized trial study on a sample of 149 patients with kidney stones who benefited from minimally invasive endoscopic surgery - digital flexible ureteroscopy with Holmium laser lithotripsy, a representative sample for a population of patients with this diagnostic in a highly specialized centre. We evaluated the effect of citrate therapy on patients treated with kidney stones up to 2 cm by the flexible ureteroscopy with Holmium laser digital lithotripsy method, with residual kidney stones up to 5 mm in size, between January 2018 and November 2020 at the "Sf. Ioan" Emergency Clinical Hospital, Bucharest, Romania. We used a ureteral sheath during the entire surgery when we performed Holmium laser lithotripsy. Taking out the fragments at the end of the procedure was done with a Dormia basket. In all cases after surgery, the crystallographic examination was mandatorily performed by infrared spectroscopy or X-ray diffraction. The sample was divided into two groups: the study group (consisting of 75 patients) which benefited from citrate therapy (combination of 975 mg of potassium citrate, 60 mg of magnesium citrate, and 25 mg pyridoxine per sachet) along with general treatment (consisting of 2 - 3 L constant water intake/day - approximately 400 mL every 4 hours and predominantly low-protein foods, especially fruits, vegetables and fibre) and the control group (74 patients) receiving only general treatment. The dose was taken 2 times a day, at 8 am and 8 pm.

*Inclusion criteria*: Patients over the age of 18 who signed consent for inclusion in the study, without active cancer pathology and ongoing or previous cytostatic treatments, without endocrinological pathology, for whom sufficiently large stones could be recovered for crystallographic analysis. For inclusion in the study, the postoperative crystallographic analysis should have resulted in stones consisting of calcium oxalate and/or calcium phosphate, uric acid, or a mixed composition between those.

*Exclusion criteria*: Patients with allergies to previous citrate treatments, those with the pathology associated with a consequent contraindication to citrate administration (severe hepatic or renal failure), and pregnant patients diagnosed with lithiasis during pregnancy were not included in the study. In the case of other types of lithiasis than those mentioned above, patients were also excluded. Cases with major comorbidities (such as advanced heart or respiratory failure, severe coagulation disorders, stroke, or recent myocardial infarction) were an impediment to enrolment in the study. The study aimed to evaluate the role of citrate and pyridoxine therapy in the prevention of lithiasis recurrence in patients with kidney stone pathology. In this case, Holmium laser lithotripsy was used along with flexible digital ureteroscopy.

*Ethics*

The study was conducted following the principles of the Helsinki Declaration, as revised in 2013. The approval was granted by the institutional committee of the Emergency Clinical Hospital "Saint John" Bucharest, Romania. Each patient participating in the study signed an informed consent form regarding the processing of personal data.

*Statistical analysis*

The R program, version 4.0.2 Copyright (C) 2020 The R Foundation for Statistical Computing, R Core Team (2020) was used for statistical analysis. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org. A descriptive analysis of other demographic and clinical variables was performed.

For the inferential analysis the methodology was as follows: the variables of interest were the values of citraturia/24 hours at the time of admission to the hospital before starting treatment and since these variables represent concentrations (titres), their central tendency was assessed with the geometric mean rather than the arithmetic one. Due to these factors, the bidirectional Paired t inferential Tests (which compare the initial citrate values of 24 hours and 90 days) and the bidirectional Welch t-tests (comparing citraturia values in patients without an unfavourable endpoint with citraturia values in patients with unfavourable endpoint) were conducted with natural logarithmic values (in e base) of citrate at 24 h. The test for statistical significance between geometric means is equivalent to the test for statistical significance between natural logarithms of arithmetic means. All tests had a significance level $\alpha = 0.05$, being considered statistically significant for a $p < 0.05$.

## Results and Discussion

The main objective of the study was to determine whether citrauria/24 hours was associated with a favourable outcome (patient without residual lithiasis or recurrence) at 90 days. This was done by dividing the patient sample into two groups (it was not taken into consideration whether the patient was in a study group or control group): group A included patients who had not been diagnosed with residual lithiasis or lithiasis recurrence within 90 days, while group B included patients with this condition.

The main focus of the research was the measurement of citraturia/24 h 90 days after minimally invasive endourological treatment for kidney stones.

In the descriptive statistical analysis, the mean, standard deviation (SD), median, minimum, and maximum distribution were determined for the continuous variables, while the absolute and relative frequencies were determined for the categorical variables.

In terms of the age distribution between the two groups, (Table I) shows a close similarity between them in terms of the average. This was 48.6 for group A and 49.3 for group B. In group B, 52.1% of the patients were males while 47.9% of the patients were females. The proportion of male patients in group A was 50.5% whereas the proportion of female patients was 49.5%.

**Table I**

General characteristics of the patients in the sample

| | **Group A (N = 101)** | **Group B (N = 48)** | **Global (N = 149)** |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) | 48.6 (14.5) | 49.3 (15.9) | 48.8 (14.9) |
| Median [Min, Max] | 47.0 [20.0, 84.0] | 47.5 [23.0, 79.0] | 47.0 [20.0, 84.0] |
| **Sex** | | | |
| F | 50 (49.5%) | 23 (47.9%) | 73 (49.0%) |
| M | 51 (50.5%) | 25 (52.1%) | 76 (51.0%) |
| **Citraturia 24h - Initial** | | | |
| Mean (SD) | 460 (436) | 441 (470) | 454 (446) |
| Median [Min, Max] | 337 [20.3, 2690] | 222 [12.4, 1940] | 311 [12.4, 2690] |
| **Citraturia 24h - 90 Days** | | | |
| Mean (SD) | 945 (811) | 467 (366) | 684 (650) |
| Median [Min, Max] | 740 [56.0, 3510] | 372 [42.1, 1920] | 465 [42.1, 3510] |
| **Urinary pH - Initial** | | | |
| Mean (SD) | 5.57 (0.702) | 5.65 (0.642) | 5.59 (0.682) |
| Median [Min, Max] | 5.50 [5.00, 7.50] | 5.50 [4.00, 7.50] | 5.50 [4.00, 7.50] |
| **Urinary pH - 90 Days** | | | |
| Mean (SD) | 4.92 (1.37) | 5.06 (1.27) | 5.00 (1.30) |
| Median [Min, Max] | 5.00 [3.10, 8.50] | 5.00 [2.20, 7.00] | 5.00 [2.20, 8.50] |

It is worth mentioning that in patients who do not have residual or recurrent kidney stones, the geometric mean of the citrate values at 90 days was 605.52 compared to 303.18 at the beginning of treatment. The differences are statistically significant ($p < 0.01$) at paired t-test ($p < 0.0001$). There is a statistically significant increase in citraturia/24 h values after 90 days among patients who have achieved stone-free status. The results obtained are highlighted in Figure 1.

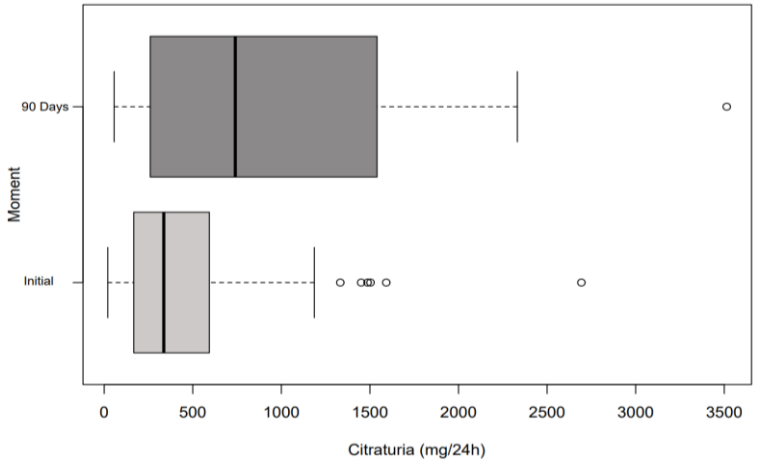


**Figure 1.**

Initial *vs*. 90 Days Citraturia/24h (Group A)

The value of the geometric mean in the group of patients who had residual/recurrent kidney stones was 230.06 initially, and after 90 days of treatment was 350.64. The differences are statistically significant ($p < 0.05$) at Paired t-test ($p = 0.0259$), and the values of citraturia *per* 24 h are statistically significantly increased after 90 days, in patients who had residual kidney stones/lithiasis recurrence. These results can also be viewed in Figure 2.

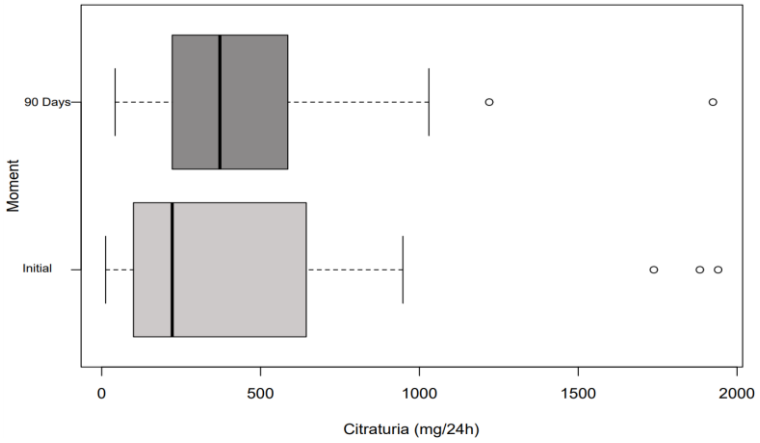


**Figure 2.**
Initial *vs*. 90 Days Citraturia/24h (Group B)

In comparison to the 90-day and initial citraturia/24 h differences between the 2 lots in terms of the geometric mean, it became clear that the difference between groups A and B was significantly wider in group A, 302.34, as compared to 120.58 in group B. P value was 0.0458, which had statistical significance ($p < 0.05$) at bidirectional Welch t-Test. This comparison is also highlighted in Figure 3.

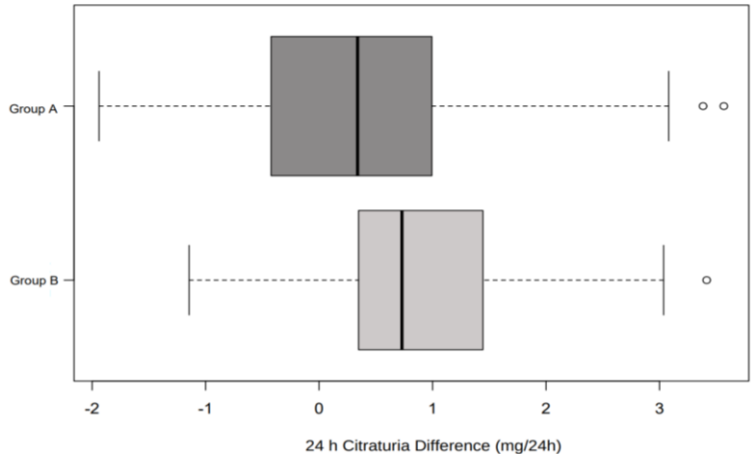


**Figure 3.**
90 Days Citraturia/24h Group A *vs*. Group B

One of the most common treatable causes of kidney stones is hypocitraturia (low excretion of urine citrate). Boothby and Adams first reported this in 1934 [16], followed by Kissin and Locks in 1941 [17]. According to Hodgkinson, hypocitraturia is a unique urinary chemical disorder observed in kidney stone patients [18]. Several studies have demonstrated the effectiveness of potassium citrate in preventing urinary tract stones [19-23].

Based on the results of our study, citrates and pyridoxine can be beneficial in treating kidney stones with hypocitraturia. As noted by Prezioso *et al*. in the chapter "Dietary treatment of hypocitraturia", alkaline citrate salts are recommended in the medical treatment of kidney stones with hypocitraturia and prevention of stone recurrence [24].

A combination of 975 mg potassium citrate, 60 mg magnesium citrate, and 25 mg pyridoxine *per* sachet significantly increased the levels of citraturia in our study. Similar results were obtained in a study by Koenig *et al*. During a study on 14 healthy volunteers, potassium citrate (50 mgEq) and magnesium citrate (25 mgEq) were administered alone as well as their combined administration (49 mEq. Potassium, 24.5 mEq. Magnesium and 73.5 mEq. Citrate), which resulted in significant citraturia variations. However, despite

the differences in the directions analysed by our study and that study, the final results share some similarities. They also demonstrated that administration of different citrate combinations increases citraturia, as so, potassium and magnesium citrate has a higher citraturia level (129 mg/24 h) compared to the exclusive administration of potassium citrate (105 mg/24 h) and magnesium citrate (35 mg/24 h) [25].

A prospective study by Ettinger *et al*. found that patients treated with potassium and magnesium citrate daily (42 mEq. potassium, 21 mEq. magnesium and 63 mEq. citrate) for 3 years had a 12.9% recurrence rate of calcium oxalate kidney calculi. The recurrence rate among those receiving the placebo was 63.6%. Compared to the group of patients receiving placebo treatment, which did not show a statistically significant change in any biochemical or saturation parameters, a significant increase in urinary magnesium, potassium and citrate was observed in those receiving magnesium and potassium citrates, like the results of our study [26].

In a recent literature review, Ferraro *et al*. searched databases using keywords such as "kidney stones", "kidney calculi", "nephrolithiasis" and "urolithiasis". Several studies were identified, but the authors considered only those that could be accessed in full (complete articles, and abstracts were not sufficient) without considering the type of study (retrospective, prospective, matched cases). The authors were also interested in the effects of diet on the risk of developing kidney stones. However, this was less relevant to our study, which had strict dietary criteria for all enrolled patients. According to the chapter "Citrate, Dietary Alkali Load and Magnesium" citrates are protective factors, their increased presence in urine being associated with a decrease in calcium oxalate crystallization, as well as an increase in urinary pH. Additionally, potassium citrate (a compound found in citrus juices) prevents renal lithiasis from developing. A combination of citrates was administered to patients in our study using a similar approach. Considering the evidence found in this review, we see that urinary citrate levels have a very significant protective effect on renal lithiasis. This is based on the results of our study. Some patients in the group did not receive a combination of citrates, but they had high levels of urinary citrate, probably caused by diet and/or metabolic conditions [27].

Rodgers *et al*. performed a study on four groups of patients in which urine was collected before and after administration of citrate, the urine being analysed using a special program (JESS) to determine the form of various elements in urine (Ca, Mg, etc.). The authors noted an increase in calcium phosphocitrate in all 4 groups of patients, a compound that binds ionic calcium and makes it less available to anions, which could have bound it (*e.g.* oxalate or phosphate), and thus a reduction in calcium oxalate occurs. It was only the reduction in calcium ions that reduced calcium oxalate levels in the male patients in the study. In women, these levels are reduced due to a reduction in calcium ions and oxalate ions, which form sodium oxalate when combined with sodium ions. An increase in calcium phosphocitrate was associated with urinary pH, an increase in urinary pH being followed by an increase in calcium phosphocitrate and a decrease in magnesium citrate. The authors link the efficacy of citrate treatment to urinary pH, arguing that a higher urinary pH leads to a higher amount of $PO_4^{3-}$, due to the deprotonation of $HPO_4^{2-}$ and $H_2PO_4^-$, thereby causing a higher amount of triphosphate anion available to be able to form calcium phosphocitrate, so that the favorable response to citrate therapy is dependent not only on the presence of a large amount of citrate in the urine but also on the urinary pH. This may explain the different responses of patients to citrate therapy, which was similarly observed in our study [28].

Another study with results similar to those obtained in our study is the one performed by Conte *et al*. in which a group of 119 patients with calcium oxalate calculi who underwent treatment with potassium citrate for 6 months was compared with a group of 16 patients who did not undergo treatment. The patients who received treatment were previously divided into 2 groups, the first with 61 patients with hypocitraturia, and the second with 58 patients with other urinary disorders (associated with hypocitraturia or normocitraturia). As a result, increases in citraturia values were identified for both groups receiving treatment, but with more favourable outcomes for patients with hypocitraturia from the first group (from 198 ± 13 to 476 ± 35 mg/24 h) [29].

According to the studies mentioned above, the results obtained in our study support the use of citrate therapy in the prevention and treatment of kidney stones, as reported in most studies in the literature.

## Conclusions

In conclusion, we notice that in both groups is an increase in citraturia at 90 days (which is not surprising, since both groups had patients who had received citrate therapy). There is an important difference in outcomes between patients who obtained a stone-free status and patients who had residual kidney stones/lithiasis recurrence. Following a 90-day follow-up, we observed statistically significant increases in citraturia in the patients who achieved stone-free status.

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**Conflict of interest**

The authors declare no conflict of interest.

**References**


1. Lotan Y, Economics and cost of care of stone disease. *Adv Chronic Kidney Dis.*, 2009; 16(1): 5-10.
2. Eisner BH, Goldfarb DS, Halpern J, Shoag J, Risk of chronic and end stage kidney disease in patients with nephrolithiasis. *J Urol.*, 2014; 192(5): 1440-1445.
3. Bagley D, Grasso M, A 7.5/8.2 F actively deflectable, flexible ureteroscope: a new device for both diagnostic and therapeutic upper urinary tract endoscopy. *Urology*, 1994; 43(4): 435-441.
4. Bagley DH, Intrarenal access with the flexible ureteropyeloscope: effects of active and passive tip deflection. *J Endourol.*, 1993; 7(3): 221-224.
5. Bagley DH, Ureteral endoscopy with passively deflectable, irrigating flexible ureteroscopes. *Urology*, 1987; 29(2): 170-173.
6. Chouikh A, Phytochemical profile, antioxidant, analgesic and hypolipidaemic effects of ephedra alata decne. female cones extract. *Farmacia*, 2020; 68(6): 1011-1020.
7. Birsan M, Dragan M, Stan CD, Cristofor AC, Palimariciuc M, Stan CI, Scripcariu S-I, Antonoaea P, Vlad AR, Ciurba A, Patient satisfaction regarding compounded pharmaceutical products and implications on pharmaceutical practice management. *Farmacia*, 2021; 69(4): 806-812.
8. Caudarella R, Vescini F, Urinary citrate and renal stone disease: the preventive role of alkali citrate treatment. *Arch Ital Urol Androl.*, 2009; 81(3): 182-187.
9. Baldini N, Caudarella R, Granchi D, Ulivieri FM, Role of Citrate in Pathophysiology and Medical Management of Bone Diseases. *Nutrients*, 2019; 11(11): 1-30.
10. Pak CY, Resnick IM, Medical therapy and new approaches to management of urolithiasis. *Urol Clin North Am.*, 2000; 27(2): 243-253.
11. Alpern JR, Melnick JZ, Moe OW, Preisig PA, Srere P, Renal cortical mitochondrial aconitase is regulated in hypo- and hypercitraturia. *Kidney Int.*, 1998; 54(1): 160-165.
12. Pak CYC, Medical Management of Urinary Stone Disease. *Nephron Clin Pract.*, 2004; 98: c49-53.
13. Hamm LL, Hering-Smith KS, Pathophysiology of hypocitraturic nephrolithiasis. *Endocrinol Metab Clin North Am.*, 2002; 31(4): 885-893, viii.
14. Chow K, Dixon J, Gilpin S, Kavanagh JP, Rao PN, Citrate inhibits growth of residual fragments in an *in vitro* model of calcium oxalate renal stones. *Kidney Int.*, 2004; 65(5): 1724-1730.
15. Nicar JM, Pak CY, Peterson R, Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. *J Urol.*, 1984; 131(3): 430-433.
16. Adams M, Boothby MW, The occurrence of citric acid in urine and body fluids. *American Journal of Physiology-Legacy Content*, 1934; 107(2): 471-479.
17. Kissin B, Locks MO, Urinary Citrates in Calcium Urolithiasis. *Proceedings of the Society for Experimental Biology and Medicine*, 1941; 46(2): 216-218.
18. Hodgkinson A, Citric acid excretion in normal adults and in patients with renal calculus. *Clin Sci.*, 1962; 23: 203-212.
19. Hill K, Nicar M, Pak CY, Sakhaee K, Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney Int.*, 1983; 24(3): 348-352.
20. Pak CY, Preminger GM, Sakhaee K, Skurla C, Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol.*, 1985; 134(1): 20-23.
21. Pak CY, Preminger GM, Sakhaee K, Alkali action on the urinary crystallization of calcium salts: contrasting responses to sodium citrate and potassium citrate. *J Urol.*, 1988; 139(2): 240-242.
22. Britton F, Fuller C, Pak CY, Preminger GM, Sakhaee K, Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol.*, 1985; 134(1): 11-19.
23. Fuller C, Pak CY, Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med.*, 1986; 104(1): 33-37.
24. Bianchi G, Borghi L, Caione P, Carini M, Caudarella R, Ferraro M, Gambaro G, Lotti T, Prezioso D, Strazzullo P, Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. *Arch Ital Urol Androl.*, 2015; 87(2): 105-120.
25. Alexandrides G, Koenig K, Padalino P, Pak CY, Bioavailability of potassium and magnesium, and citraturic response from potassium-magnesium citrate. *J Urol.*, 1991; 145(2): 330-334.
26. Adams-Huet B, Citron JT, Ettinger B, Pak CY, Thomas C, Vangessel A, Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol.*, 1997; 158(6): 2069-2073.
27. Bargagli M, Ferraro MP, Gambaro G, Trinchieri A, Risk of Kidney Stones: Influence of Dietary Factors, Dietary Patterns, and Vegetarian-Vegan Diets. *Nutrients*, 2020; 12(3): 1-16.
28. Allie-Hamdulay S, Jackson G, Rodgers A, Therapeutic action of citrate in urolithiasis explained by chemical speciation: increase in pH is the determinant factor. *Nephrol Dial Transplant.*, 2006; 21(2): 361-369.
29. Arrabal Martín M, Conte Visús A, Ibarz Navarro JM, Ibarz Servio L, Ruiz Marcellán FJ, Biochemical effects of potassium citrate in the treatment of calcium oxalate lithiasis. *Arch Esp Urol.*, 1994; 47(2): 141-150.