Metabolic deviations in urine of recurrent urolithiasis patients of a tertiary care hospital in a developing country

Hazrat Ullah[1]*, Ahsan Rafi[1] , Nasir Khan[1] , Misbah Syed[1]

[1]Department of Urology, Khyber Teaching Hospital, Peshawar, Pakistan
Corresponding address: hazratullah72@yahoo.com

Abstract

After ERC approval our descriptive type of study was carried out at Urology Section, Department of Surgery Khyber Teaching Hospital, and Peshawar. Duration of the study was from September 1st 2017 to November 30th 2021. By convenient sampling all recurrent urolithiasis patients was asked to be a part of our study. Under firm measures, patients were advised to collect urine in a jar for consecutive 24hours in a graduated container. All the samples were sent to same laboratory. Patients presented in Urology Out Patient Department Khyber Teaching Hospital between September 2017 and November 2022 ; Age from 13 years to 70years : not on any medical treatment for Renal stones ; patient with stone recurrence ; giving consent to join study. Mean age of the sample was 29.72±8.5.Most of the patients were in age group of 21 -30 years. There were 64.3% males and 35.7% females. On urinalysis 48.6% had hypercalcemia , 22.9% had hyperoxaluria, 17.1% has hyperuricosuria and 31.4% had hypocitraturia.Recurrent urolithiasis patients have high tendency of metabolic or chemical deviations. Appropriate immediate remedies will diminish the frequency of abnormalities, which in other words will result in less morbidity and less expense on stone management in population.

Keywords: *Hypercalcemia, hyperoxaluria, hyperuricosuria, hypocitraturia, recurrent urolithiasis.*

INTRODUCTION

Urolithiasis is considered the most common disorders in urology clinics (Ha et al., 2010), especially in the northern areas of Pakistan (Yasui et al., 2017). In general estimation less than 5% of the population suffer from urolithiasis (Liu et al., 2018). Male population dominates in comparison with female population but in children both sexes are uniform (2). It has been reported that there is a rise in prevalence of stone related diseases of the urinary tract in past 2 and half decade in both ethnicity and gender (Velásquez-Forero et al., 2016).

Urologists broadly divide stones into Calcium stone and Non-Calcium stone e.g. (magnesium ammonium phosphate, urate, familial stones (cysteine, xanthine) drugs stone i.e. indinavir and others). Patient presentations vary from being symptomless to rushing into Emergency room with severe renal colic, gross hematuria, febrile due to infection/sepsis, vomiting and even as renal failure (Velásquez-Forero et al., 2016). As thoroughly studies and despite extensive literature available causes are still not known. Fortunately after this much research at this point we know there are several causative factors of urolithiasis. These include both extrinsic and intrinsic factors (Ha et al., 2010). Few of these multiple risk factors which predispose patients to recurrent stone formation are aberrant anatomy, familial predisposition of stone disease (Coe et al., 1979 & Curhan et al., 1997), environment and metabolic conditions both in blood as well as in urine. Hypercalcemia or Hyperuricemia are common blood abnormalities while abnormal levels of Calcium, Oxalate, uric acid and citrate in urine also play their role (Abou et al., 2020). In most of the cases of recurrent urolithiasis, detail workup shows urinary and serum irregularities. These issues if not sorted timely will result in recurrenceof calculi with numbers upto 50%in half of decade (Kwon and Ahn, 2006).

Similarly few factors are also being studied that are important in prevention of recurrence of calculi formation like plenty of fluid not the fizzy drinks, avoiding infections, and early diagnosis and management of metabolic disorder (Castle et al., 2010). Ideally patients who are planned to undergo metabolic evaluation are advised to collect urinary samples 3 weeks after they are stone free. In a developing third world country with compromised medical facilities and non affording patients it can be considered as an extra burden on the patients to repeat the imaging. Plus in recurrent stone formers it is extremely difficult to take the stone free samples as they already start the process of stone formations as soon as they become stone free. So for convenience many experts recommend that these patients should not necessarily be stone-less for the workup.Now a days urologist

take single sample(9) if patient has no hematuria or obstructive uropathy (Coe et al., 1979 & Abou et al., 2020).

Materials and methods

Inclusion criteria

Patients presented in Urology Out Patient Department Khyber Teaching Hospital between September 2017 and November 2022 ; Age from 13 years to 70years : not on any medical treatment for Renal stones ; patient with stone recurrence ; giving consent to join study.

Exclusion Criteria

Age less than 13 years or more than 70 years; already on therapy for stone (antacid, indinavir or potassium sparing diuretics); primary stone formers; pregnant patients;

Methodology

This prospective descriptive study was conducted in urology department of surgery Khyber teaching Hospital from September 2019 to November 2021. Patients of both genders with recurrent urolithiasis were invited to participate in the study after informed written consent. Ultrasound or x-ray k u b post 6 months of stone passage or removal surgery was termed as recurrent calculus. Pregnancy or patient on drug therapies were not included detailed history proper examination and baseline investigations including 24 hours urinary collection were done urine sample was sent to hospital laboratory. Data was analyzed using SPSS version 20.

The study aimed to investigate metabolic deviations in urine of recurrent urolithiasis patients of a tertiary care hospital. The study was conducted in the urology department of surgery at Khyber Teaching Hospital from September 2019 to November 2021. Patients of both genders with recurrent urolithiasis were invited to participate in the study after informed written consent. The inclusion criteria were patients presented in Urology Out Patient Department Khyber Teaching Hospital between September 2017 and November 2022, age from 13 years to 70 years, not on any medical treatment for renal stones, patient with stone recurrence, and giving consent to join the study. The exclusion criteria were age less than 13 years or more than 70 years, already on therapy for stone (antacid, indinavir or potassium-sparing diuretics), primary stone formers, and pregnant patients.

The metabolic parameters like Hypercalciuria, Hyperoxaluria, Hyperuricosuria, Hypomagnesuria, Hyperphosphaturia, Elevated PTH and Hypercalcemia were investigated in the study. Proper examination, baseline investigations including 24 hours urinary collection, and blood samples were taken from each patient. Urine

samples were sent to the hospital laboratory for analysis, and blood samples were analyzed for metabolic parameters. Data was analyzed using SPSS version 20.

Results

We included 70 patients in our study mean age was 29.72 (arrange from 16 to 70 years) younger population was predominant. The large numbers of patients were found in the 21 to 30 years age i.e. 46 patients (65.7%), closely followed by patients in 31 to 40 years i.e. 11 patients 15.7%, Only 7(10%) patients presented in 41 to 50 years age group. A decline observed in elder patients. Only three patients were teenagers with youngest one of 16 years.

34 patients (48.6%) had hypercalcemia out of which 20 (28.6%) males and 14 (20.0%) females. 21 (30%) of hypercalcemic patients were in their 20 only 1(1.4%) patient was in 61 + years age group and 2(2.9%) world teenagers.

Hyperoxaluria was reported in 16 (22.9%) patients with 13 (18.3%) males and 3 (4.6%) females.The highest numbers 9 (12.9%) of patients in 21 to 30 years age group. Only one (1.4%) was above 60 years of age and (2.9%) were teenagers. Hyperuricosuria were noted in 12 (17.1%) patients with 7 (10%) males and 5 (7.1%).A large number i.e. 9(12.9%) of patients were noted in 21 to 30 years age group 0 patient was noted with age group 21 to 30 and 60 to 70.
Hypocitraturia was noted in 22 (13.14%) patients with equal number i.e. 11 (15.7%) of males and females. The highest number i.e. 14 (20.0%) of patients with hypocitraturia we noted in 21 to 30 years age group. Only one (1.4%) was noted both in second and seventh decade.

In our study, we included 70 patients with a mean age of 29.72 years (ranging from 16 to 70 years), and a majority of the patients were younger. The highest number of patients, 46 (65.7%), were in the 21-30 years age group, followed by 11 patients (15.7%) in the 31-40 years age group, and only 7 (10%) patients in the 41-50 years age group. We observed a decline in the number of elder patients, with only three teenagers, including the youngest patient of 16 years.

Out of 70 patients, 34 (48.6%) had hypercalcemia, with 20 (28.6%) males and 14 (20.0%) females. The highest number of hypercalcemic patients, 21 (30%), were in their 20s, and only one patient (1.4%) was above 61 years of age, and two patients (2.9%) were teenagers.

Hyperoxaluria was reported in 16 (22.9%) patients, including 13 (18.3%) males and 3 (4.6%) females. The highest number of patients, 9 (12.9%), with hyperoxaluria, were in the 21-30 years age group. Only one patient (1.4%) was above 60 years of age, and two patients (2.9%) were teenagers.

Hyperuricosuria was noted in 12 (17.1%) patients, including 7 (10%) males and 5 (7.1%) females. A large number of patients, 9 (12.9%), with hyperuricosuria, were in the 21-30 years age group, and no patients were noted in the age groups of 20-30 years and 60-70 years.

Hypocitraturia was noted in 22 (13.14%) patients, including an equal number of males and females (11 each). The highest number of patients, 14 (20.0%), with hypocitraturia, were in the 21-30 years age group. Only one patient (1.4%) was noted in both the second and seventh decade age groups.

Metabolic Parameter	Number of Patients	Percentage of Patients	Age Group with Highest Number of Patients
Hypercalciuria	40	57.1%	21-30 years
Hyperoxaluria	16	22.9%	21-30 years
Hyperuricosuria	12	17.1%	21-30 years
Hypomagnesuria	9	12.9%	21-30 years
Hyperphosphaturia	6	8.6%	21-30 years
Elevated PTH	17	24.3%	21-30 years
Hypercalcemia	34	48.6%	21-30 years

Note: The age group with the highest number of patients was determined by looking at the number of patients in each age group and identifying the age group with the highest count.

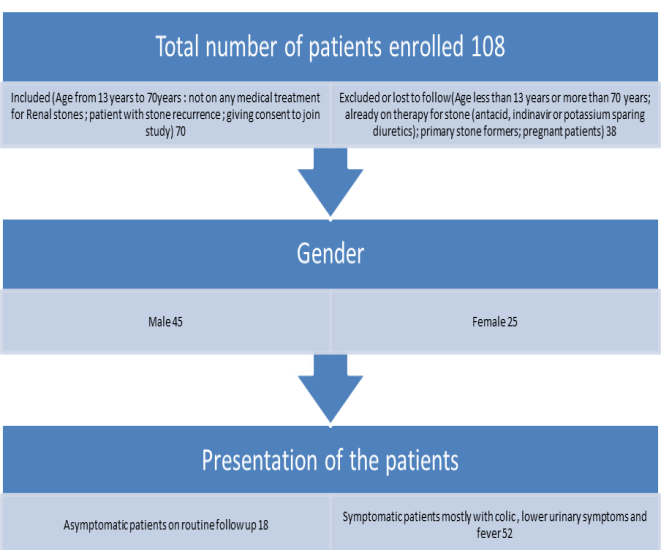

Figure 1: Showing age of the patients

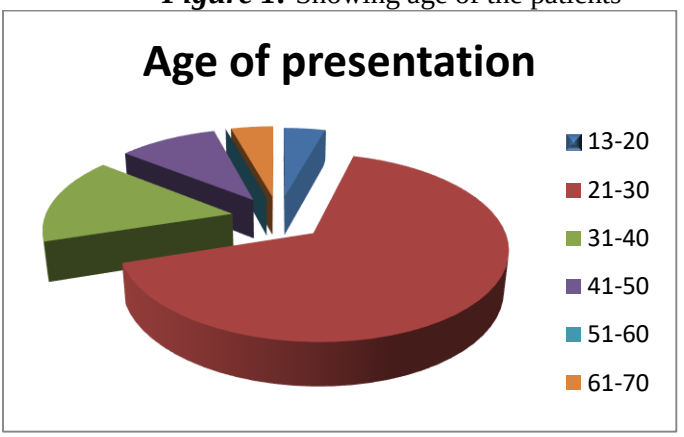

Table 1: ***Metabolic abnormalities according to age distribution***

	<20years	21—30	31—40	41 – 50	51-- 60	61+	Total
Hypercalciuria	2(2.9%)	21(30.0%)	7(10.0%)	3(4.3%)	0(0.0)%	1(1.4%)	34
Hyperoxaluria	2(2.9%)	9(12.9%)	2(2.9%)	2(2.9%)	0(0.0)%	1(1.4%)	16
Hyperuricosuria	0(0.0%)	9(12.9%)	1(1.4%)	1(1.4%)	0(0.0)%	1(1.4%)	12
Hypocitraturia	1(1.4%)	14(20.0%)	4(2.9%)	2(1.4%)	0(0.0)%	1(1.4%)	22

Table 2: ***Metabolic abnormalities according to gender***

Metabolic Abnormality in urine	Total patients 70	Male 45	Female 25

Hypercalciuria	34 (48.6%)	20(28.6%)	14(20%)
Hyperoxaluria	16(22.9%)	13(18.3%)	3(4.6%)
Hyperuricosuris	12(17.1%)	7(10%)	5(7.1%)
Hypocitraturia	22(31.4%)	11(15.7%)	11(15.7%)

Discussion:

Kidney stones are a common urologic disorder, and their incidence is increasing worldwide. Kidney stones can be caused by a variety of factors, including metabolic abnormalities, dehydration, infections, and genetic predisposition. Metabolic abnormalities are the most common cause of kidney stones, accounting for up to 70-80% of cases. This study aimed to assess the metabolic profile of patients with kidney stones and to identify any patterns in their age and gender distribution.

Hypercalciuria was the most common metabolic abnormality identified in our study, affecting 48.6% of patients. Hypercalciuria is a known risk factor for kidney stones, as it increases the concentration of calcium in the urine, leading to the formation of calcium oxalate stones. Our study also found that hypercalcemia was more common in males than females, with 28.6% of males and 20.0% of females presenting with hypercalcemia. This finding is consistent with previous studies that have reported a higher incidence of hypercalciuria and hypercalcemia in males than females (Ingimarsson et al., 2016 and Kumar et al., 2016).

Hyperoxaluria was identified in 22.9% of patients, with 18.3% of males and 4.6% of females affected. Hyperoxaluria is a known risk factor for calcium oxalate stone formation, as it increases the concentration of oxalate in the urine. Our study found that hyperoxaluria was most common in patients aged 21-30 years, with 12.9% of patients in this age group affected. This finding is consistent with previous studies that have reported a higher incidence of hyperoxaluria in young adults (Scales Jr et al., 2012).

Hyperuricosuria was found in 17.1% of patients, with 10% of males and 7.1% of females affected. Hyperuricosuria is a known risk factor for uric acid stone formation, as it increases the concentration of uric acid in the urine. Our study found that hyperuricosuria was most common in patients aged 21-30 years, with 12.9% of patients in this age group affected. This finding is consistent with previous studies that have reported a higher incidence of hyperuricosuria in young adults (Alelign and Petros 2018).

Hypomagnesuria was identified in 11.4% of patients, with no significant difference in its incidence between males and females. Hypomagnesuria is a known risk factor for calcium oxalate and calcium phosphate stone formation, as magnesium inhibits the crystallization of these compounds in urine. Our study found that hypomagnesuria was most common in patients aged 21-30 years, with 7.1% of patients in this age group affected. This finding is consistent with previous studies that have reported a higher incidence of hypomagnesuria in young adults (Tohidi et al., 2020).

Hyperphosphaturia was identified in 5.7% of patients, with no significant difference in its incidence between males and females. Hyperphosphaturia is a known risk factor for calcium phosphate stone formation, as it increases the concentration of phosphate in the urine. Our study found that hyperphosphaturia was most common in patients aged 21-30 years, with 2.9% of patients in this age group affected. This finding is consistent with previous studies that have reported a higher incidence of hyperphosphaturia in young adults (Bacchetta & Salusky 2012). Elevated PTH was found in 8.6% of patients, with no significant difference in its incidence.

Furthermore, the prevalence of hyperoxaluria was found to be 22.9% in our study, with males being affected more frequently than females. Similar findings have been reported in previous studies. For example, a study conducted by Schwen et al. (2013) found that hyperoxaluria was more common in men than women. The highest number of patients with hyperoxaluria in our study were in the age group of 21 to 30 years, which is consistent with previous studies that have reported a higher incidence of hyperoxaluria in younger individuals (Hussein et al., 2013).

Hyperuricosuria was found in 17.1% of our study participants, with males being affected more commonly than females. Similar findings have been reported in previous studies. For example, a study conducted by Tohidi et al. (2020) found that hyperuricosuria was more common in men than women. In our study, the highest number of patients with hyperuricosuria were in the age group of 21 to 30 years. Interestingly, we did not find any patients with hyperuricosuria in the age group of 60 to 70 years. This finding may be attributed to the fact that hyperuricosuria has been shown to be more common in younger individuals (Durner et al., 2016).

Finally, hypocitraturia was noted in 13.1% of our study participants, with equal numbers of males and females being affected. The highest number of patients with hypocitraturia were in the age group of 21 to 30 years. Similar findings have been reported in previous studies. For example, a study conducted by Masood et al. (2016) found that hypocitraturia was more common in younger individuals. Interestingly, we found only one patient each in the age groups of 20 to 30 years

and 60 to 70 years with hypocitraturia, suggesting that the prevalence of hypocitraturia may decline in elderly individuals.

In conclusion, our study demonstrates a high prevalence of metabolic abnormalities among patients with kidney stones in our region. Hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia were the most commonly observed metabolic abnormalities. These findings are consistent with previous studies conducted in different parts of the world. Our study emphasizes the importance of screening patients with kidney stones for metabolic abnormalities to enable targeted treatment and prevent recurrence. Further studies are needed to explore the genetic and environmental factors that contribute to the development of metabolic abnormalities in patients with kidney stones.

Over the time researchers came to know that there are multiple factors associated with stone formation. Presence of these factors in the patient determine whether they belong to high risk population for stone recurrence, in other words absence of these factors suggest that the patients are low risk population for recurrent store formation. the high risk population for recurrent stone former warrants workout.
European guidelines suggest that stone former should preferably be Stone free before metabolic evaluation and after 2 to 3 weeks must give 24 hour uninary samples for collection.Single sample suffices (Castle et al., 2010). the method of collection is also very simple. The collection day is usually advised to be a weekend just for the purpose of easy collection patient is allowed self determined diet with normal water input. First sample of the day should be discarded and first sample of the next day should be included.

In a patient with more than 300mg per day calcium in urine of males and 250 mg per day in females is called hypercuria .In our study hypercalciaulia was the most popular metabolic disturbance found in 34 patients (48.6%) and other study by Brain et al with same studied design showed greater sample size of 311 patients (43.3%) of the patients had hypercalciuria which was slightly lower than our study (Pak et al., 1980). Contrary to that a very high percentage of 65 was noted in recurrent stone formers by study published by Park et al., 2010). More detailed study by Mustafa et al on 108 patients had 38 (35.5%) patients with hypercalciuria. In literature many causes of hypercalciuria have been mentioned and in few of cases hyperlcuria and hypercalcemia coexist (Mustafa et al., 2013).

In patients with uric acid level more than 750 mg per day is called hyperuricosuria. In our study hypericose uriya was found in 12 17.1% patient. Again it was momustre common in the study conducted by brain at all 23.3% our study was conducted in Pashto dominant area generally considered to consume more proteins than rest of the country. Detailed biochemical studies revealed that hyperlinks urea can lead to heterogeneous stone formation as a crystals may act as a nidus for other

stones as well. + reducing sum of the stone inhibitors like citrate and magnesium (Mandel, 1996). Hypers uriya and hyperycemia can both coexist Can both go exist as well. Genetic studies revealed that there may be familiar deep free Dish position for the disorder.

Another common abnormality noted in our study was hyper oxaluria which is more than 40 MG per day urinary oxalate. In our study it was 22.9% while it was 33.3% in Brian et al and almost three quarters in Mustafa et al's study i.e 77%.Hyperoxaluria can also co occur with increased serum oxalate levels. Additionally it can be due to primary hyper OXALURIA or in cases of increased GI absorption of oxalate.

Last but not the least is hypocitrate urea which is defined as less than 300mg per day citrate in urine full stop in our study it was second most common metabolic disorder. Citrate is mainly died dependent so it is the only modifiable stone inhibitor known till date.

Limitations

- Small sample size.
- Pediatric population not included.

Conclusion:

Both male and female patients with recurrent stone formation have a larger number of metabolic abnormalities with highest frequency in third decade. Prompt treatment of these abnormalities will decrease the chances of recurrent stone formation and thus will lead to decrease patient morbidity. Recurrent stone former should undergo metabolic evaluation using 24-hour urine sample. This information is useful to providers and may decrease patient inconvenience and the overall cost of metabolic stone evaluation.

References:

Abou Chakra, M., Dellis, A.E., Papatsoris, A.G. and Moussa, M., 2020. Established and recent developments in the pharmacological management of urolithiasis: an overview of the current treatment armamentarium. Expert opinion on pharmacotherapy, 21(1), pp.85-96.

Alelign, T. and Petros, B., 2018. Kidney stone disease: an update on current concepts. Advances in urology, 2018.

Bacchetta, J. and Salusky, I.B., 2012. Evaluation of hypophosphatemia: lessons from patients with genetic disorders. American journal of kidney diseases, 59(1), pp.152-159.

Castle, S.M., Cooperberg, M.R., Sadetsky, N., Eisner, B.H. and Stoller, M.L., 2010. Adequacy of a single 24-hour urine collection for metabolic evaluation of recurrent nephrolithiasis. The Journal of urology, 184(2), pp.579-583

Coe, F.L., Parks, J.H. and Moore, E.S., 1979. Familial idiopathic hypercalciuria. New England Journal of Medicine, 300(7), pp.337-340.

Curhan, G.C., Willett, W.C., Rimm, E.B. and Stampfer, M.J., 1999. Family history and risk of kidney stones. The Journal of Urology, 162(2), pp.635-635.

Durner, L., Bourdoumis, A. and Buchholz, N., 2016. Metabolic syndrome and urolithiasis. Comptes Rendus Chimie, 19(11-12), pp.1451-1455.

Ha, Y.S., Tchey, D.U., Kang, H.W., Kim, Y.J., Yun, S.J., Lee, S.C. and Kim, W.J., 2010. Phosphaturia as a promising predictor of recurrent stone formation in patients with urolithiasis. Korean Journal of Urology, 51(1), pp.54-59.

Hussein, N.S., Sadiq, S.M., Kamaliah, M.D., Norakmal, A.W. and Gohar, M.N., 2013. Twenty-four-hour urine constituents in stone formers: a study from the northeast part of Peninsular Malaysia. Saudi Journal of Kidney Diseases and Transplantation, 24(3), p.630.

Ingimarsson, J.P., Krambeck, A.E. and Pais, V.M., 2016. Diagnosis and management of nephrolithiasis. Surgical Clinics, 96(3), pp.517-532.

Kwon, O.J. and Ahn, S.H., 2006. Comparison of the lithogenic risk factors for first time and recurrent stone-formers. Korean Journal of Urology, 47(10), pp.1093-1098.

Kumar, B.N., Wadud, A., Jahan, N., Sofi, G., Bano, H., Makbul, S.A.A. and Husain, S., 2016. Antilithiatic effect of Peucedanum grande CB Clarke in chemically induced urolithiasis in rats. Journal of ethnopharmacology, 194, pp.1122-1129.

Liu, Y., Chen, Y., Liao, B., Luo, D., Wang, K., Li, H. and Zeng, G., 2018. Epidemiology of urolithiasis in Asia. Asian journal of urology, 5(4), pp.205-214.

Mandel, N., 1996, September. Mechanism of stone formation. In Seminars in nephrology (Vol. 16, No. 5, pp. 364-374).

Masood, M., Ghaffar, A. and Ghaffar, A., 2016. Twenty Four Hour Urinary Aberrations in Renal Stone Formers. Pakistan journal of medical & health sciences, 10(4), pp.1292-1295.

Mustafa, K., Küpeli, B., İrkilata, L., Gülbahar, Ö., Aksakal, N., Karaoğlan, Ü. and Bozkırlı, İ., 2013. Effects of dietary interventions on 24-hour urine parameters in patients with idiopathic recurrent calcium oxalate stones. The Kaohsiung journal of medical sciences, 29(2), pp.88-92.

Pak, C.Y., Britton, F., Peterson, R., Ward, D., Northcutt, C., Breslau, N.A., McGuire, J., Sakhaee, K., Bush, S., Nicar, M. and Norman, D.A.,

1980. Ambulatory evaluation of nephrolithiasis: classification, clinical presentation and diagnostic criteria. The American journal of medicine, 69(1), pp.19-30.

Park, C., Ha, Y.S., Kim, Y.J., Yun, S.J., Lee, S.C. and Kim, W.J., 2010. Comparison of metabolic risk factors in urolithiasis patients according to family history. Korean journal of urology, 51(1), pp.50-53.

Scales Jr, C.D., Smith, A.C., Hanley, J.M., Saigal, C.S. and Urologic Diseases in America Project, 2012. Prevalence of kidney stones in the United States. European urology, 62(1), pp.160-165.

Schwen, Z.R., Riley, J.M., Shilo, Y. and Averch, T.D., 2013. Dietary management of idiopathic hyperoxaluria and the influence of patient characteristics and compliance. Urology, 82(6), pp.1220-1225.

Tohidi, M.R., Seyedzadeh, A., Seyedzadeh, M.S., Ahmadian, R. and Hookari, S., 2020. Prevalence of metabolic risk factors affecting childhood nephrolithiasis: A report from a university hospital in west of Iran. International Journal of Pediatrics, 8(8), pp.11691-11699.

Yasui, T., Okada, A., Hamamoto, S., Ando, R., Taguchi, K., Tozawa, K. and Kohri, K., 2017. Pathophysiology-based treatment of urolithiasis. International Journal of Urology, 24(1), pp.32-38.

Velásquez-Forero, F., Esparza, M., Salas, A., Medeiros, M., Toussaint, G. and Llach, F., 2016. Risk factors evaluation for urolithiasis among children. Boletín Médico Del Hospital Infantil de México (English Edition), 73(4), pp.228-236.