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Metabolic Evaluation of Patients with Nephrolithiasis: A Prospective Observational Study from a Tertiary Care Hospital in South India

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Abstract

Objective: To evaluate patients with bilateral, multiple, staghorn and recurrent renal stones for metabolic diseases in Karnataka region.

Methods: All the patients admitted with bilateral, multiple, staghorn and recurrent renal stones and peadiatiric stones on initial evalution in MS Ramaiah hospital were included in the study after obtaining written informed consent. Secondary stones, Single, unilateral renal or ureteric stones on first presentation in adults were excluded.Patient assessment included variables such as age, sex, BMI, dietary pattern, family history, past history, average water intake, alcohol intake and composition of stone. Laboratory investigations included urine routine & microscopy, urine culture, 24 hrs urine analyses for calcium, phosphorous, uric acid, magnesium, oxalate and citrate, serum calcium, phosphorous, uric acid, creatinine, random blood sugar (RBS) and BUN. Imaging was done (USG of abdomen pelvis, NCCT KUB and contrast studies) when indicated. All patients underwent routine pre-operative investigations for treatment of stones with routine testing for s.calcium, phosphrous and uric acid and were repeated only if found to be elevated. After stone had been treated, they underwent urine analyses for metabolic disorder twice on consecutive days.

Results: Maximum number of patients fall in the age group of 20-59 years (81.7%). The males had more preponderance of stone formation than females (M= 41 (68.3%), F=19 (31.7%)). Kidney stones are associated with hypertension, obesity and metabolic syndrome, and may be a harbinger of diabetes. 73.3% of the sample did not have any of the medical comorbidities. One fourth of the sample (N=15, 25%) had Diabetes Mellitus. Our study population had a mean BMI of 28.84 ± 3.53 (27.9-29.8 95% CI) which falls into high BMI (Overweight to Obese). Lifestyle habits and dietary/nutritional factors such as excessive intake of animal proteins and salt and deficiencies of chelating agents like citrate, fiber and alkali foods are all risk factors for nephrolithiasis. Majority of our study population had mixed dietary pattern (91.3%) and good water intake (73.3%). 66.7% of the patients had unilateral stones. 33.3% of the study population had

bilateral stones. 45% of the study sample had recurrence in stone formation. 55% of the patients did not have any history of recurrence.

Conclusions: Metabolic evaluation of patients with NL is necessary as a part of medical management. However it is difficult to comment whether metabolic evaluation should be advised as a mandatory investigation which every patient with NL should undergo. Most of the conducted studies are retrospective studies. Further prospective studies are needed to formulate stringent guidelines for metabolic evaluation in NL.

The major attributes of our study is that we were able to perform metabolic evaluation and stone composition analysis of all patients included in our study. We have performed univariate analysis to understand the risk factors more appropriately. Though our study demonstrates that there are identifiable risk factors for NL, we have a very small size. Hence it may be difficult for us to generate standard protocol for the metabolic evaluation. We recommend that more prospective design studies with multicentre cohort studies with larger sample size should be undertaken to establish specific pathways for metabolic evaluation in NL.

Keywords: NL-Nephrolitiasis; Metabolic evaluation; Haematuria; Urolithiasis.

Introduction

Nephrolithiasis (NL) or Kidney stone disease (KSD) affects about 12% of the world population at some point of life in their living. Neither of the ages, sexes, and races are immune to NL. However it occurs more commonly in men than in women within the age of 20–49 years.[1] The prevalence rate is always increasing, as documented by the National Health and Nutrition Examination Survey III cohort (1988–1994 and 2007– 2010).[2]

The review which is presented and peer-reviewed at the 3rd International Consultation on Stone Disease during the 2014 Société Internationaled 'Urologie Congress in Glasgow has also commented that there is a steady rise in the incidence of stone disease throughout the world with a narrow gender gap.[3]

Nephrolith, is a mass of crystals, that forms a hard lump in one or both the kidneys. It is formed by the solutes and minerals present in the urine and also can remain silent for long durations. When they move, it results in discomfort and severe pain (renal colic) in the back or abdomen that radiates from loin to groin. Other associated symptoms of this disorder includes vomiting, fever, haematuria, pyuria, and dysuria. Most of renal stones pass out of the body through urine without any intervention, while some may require intervention to remove them.

To decrease the incidence of kidney stones, it is important to educate the patients and provide recommendations for their prevention and control of stone formation. A holistic and multidimensional approach is necessary for the management of NL. Detailed history taking including the previous medical, family, social and diet history are all necessary to determine risk factors for each patient after first stone episode.[4]

Diet modifications may decrease the risk of stone formation and its recurrence rate, but there is no conclusive evidence regarding the effectiveness of dietary modifications and recommendations specific for patients with urinary calculi. High fluid intake reduces risk of recurrent nephrolithiasis. Decreased soft drink intake reduced risk of urolithiasis. Data for other dietary interventions were inconclusive, although limited data are present for possibility of benefit from dietary calcium.[5] Each patient with nephrolithiasis should undergo specific evaluation to known the knowledge of the calculus composition. Regardless of the cause of stone disease, a mainstay of treatment is increase in fluid intake to have a daily urine output of 2 litres.[6]

Stone analysis along with basic metabolic evaluation are highly necessary in all patients after stone passage (grade A). All the patients should be categorized to a low-risk or high-risk group in relation to stone formation. It is highly recommended that for low-risk stone formers a general fluid and nutritional intake, as well as lifestyle-related modifications has reduced stone recurrences rate (grade A). High-risk stone formers should undergo specific metabolic evaluation with 24-h urine collection (grade A).[7]

Metabolic evaluation for patients with renal stones disease,when bilateral, multiple or recurrent stones has become important as it helps to identify the major metabolic abnormalities of the person which leads to the formation of stones. Various studies have shown that stone former would have one or more metabolic abnormalities, which when treated, will help to reduce the recurrence of stones formations.[8]

The most common metabolic abnormality occurring in stone formers are hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia. The individual can have one or more of these

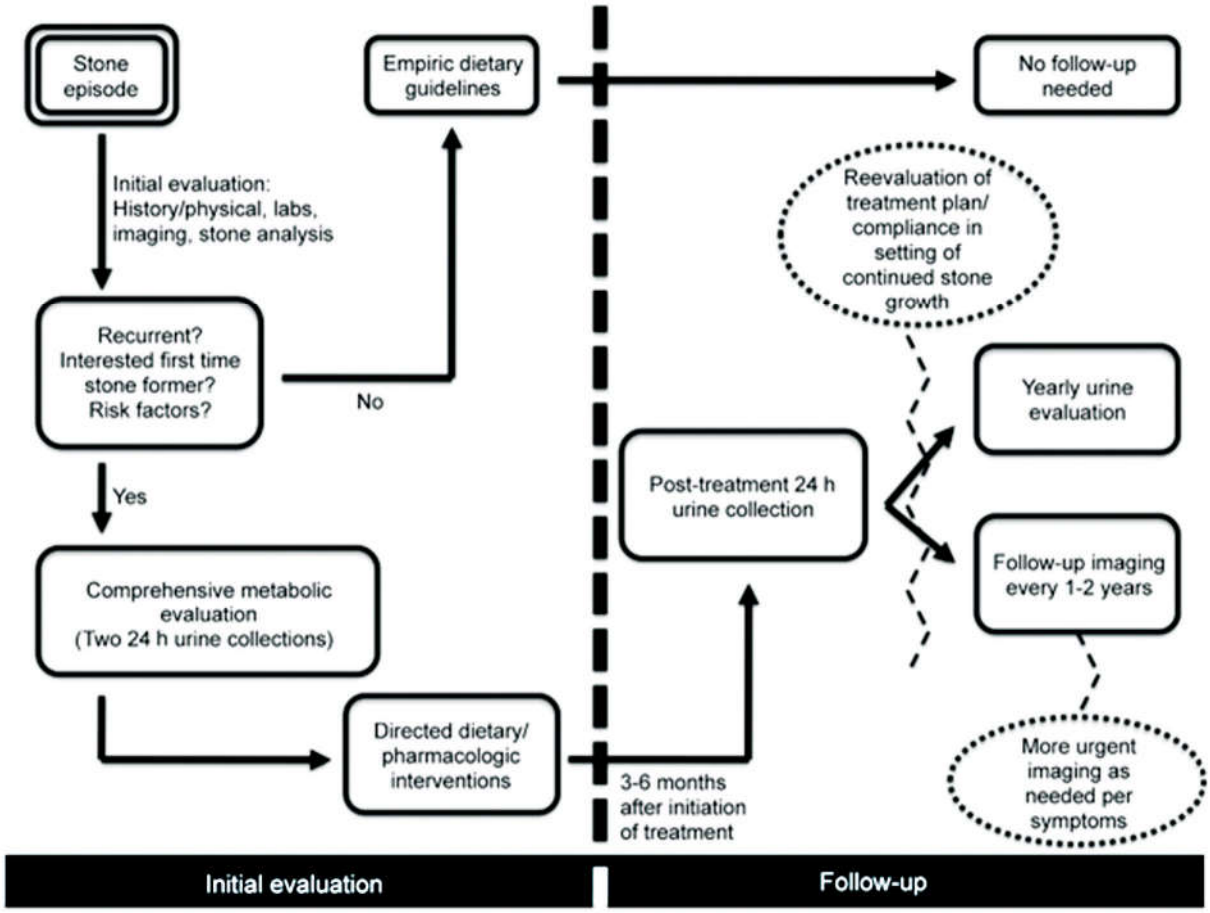

Fig. 1: The figure adapted from Wollin et al. 2018 demonstrates the complete metabolic evaluation of KSD.

metabolic abnormality. Thus, evaluation of the metabolic abnormality and treating them can reduce the incidence of stones formation in these patients and also improve the quality of life. Stone composition is always appropriate. Laboratory evaluation is based on serum chemistries and urinalysis.

24 hour collected urine are most reliable for evaluating patients with recurrent stone formers; but some patients who are motivated to prevent recurrence and have large or complicated stones requiring urologic management might be the ideal persons for complete metabolic assessment. The links between metabolic syndrome, hypertension, and obesity and stones suggest that stones may be a harbinger of important morbidity, particularly an increased risk of diabetes. Single and recurrent stone formers share many similarities in metabolic profiles.[9]

Retrospective review of the studies and identified 146 cases of stone recurrence in a total of 3,985 patients from January 2012 to January 2016 was done by Zeng et al 2019.[10]

They Highlighted the Following Metabolic Parameters

a. 64 out of 146 patients with stone recurrence were obese (43.8%).

b. 86 were hyperlipidemia, 77 had hyperuricemia and 64 had hyperglycemia.

c. 79 had stone of calcium oxalate.

The following results were obtained in Dandapani et al 2016 in which metabolic evaluation was done for 55 patients in the study population of 100 patients, and 23 (41.8%) out of this 55 evaluated were found to have a metabolic abnormality.[11] Uric acid levels were high in 16 patients (29.1%), calcium levels high in 4 patients (7.3%) and creatinine was high in 21 patients (38.2%).

a. Urine pH test was not done in 16.4% of the evaluated patients; it was acidic in 69.1%, neutral in 10.9%, and alkaline in 3.6% of the patients.

b. Hyperuricosuria, hypercalciuria, decreased urine volume, and acidic urine pH were the significant metabolic risk factors Gupta et

al 2013 recruited 39 consecutive patients (29 males and 10 females with mean age 39.3 ± 12.9 years) with unilateral renal stones from the out-patient departments of Urology and Endocri nology at the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.[12]

- 36 patients (92.3%) had at least one identifiable metabolic risk factor, with 23 patients (58.9%) having two or more metabolic abnormalities. The most common etiologies detected were hypo- citraturia (82%) and hyper-oxaluria (56%).
- Hypo-citraturia was found in 32 patients (82%). Incomplete distal RTA was diagnosed in two patients with hypo-citraturia. Other metabolic abnormalities associated with hypo- citraturia.
- Hyper-oxaluric RCD was diagnosed in 56% of the cases. 76 had very high levels of urinary oxalates (>100 mg/day), but none of them had deranged liver, renal or bowel disorder.
- Hypercalciuria was seen in 16 patients (41%). The hyper-calciuric patients were subdivided into renal hyper-calciuria and absorptive hyper- calciuria based on the calcium loading test.[9] patients had renal hyper-calciuria while 7 patients had absorptive hypercalciuria.

It is clear that the metabolic work up of patients with urinary tract stone disease should be individualized according to stone type and severity of the disease and that the different therapeutic approaches are closely associated with the availability of therapeutic tools and motivation by the patient.

Aim and Objective of Study

To evaluate patients with bilateral, multiple, staghorn and recurrent renal stones for metabolic diseases in Karnataka region.

Methods and Material

A hospital based prospective study was carried out on patients diagnosed to have bilateral, multiple, staghorn and recurrent renal stones. All the patients admitted with bilateral, multiple, staghorn and recurrent renal stones in MS Ramaiah hospital were included in the study after obtaining written informed consent. Patient assessment included variables such as age, sex, BMI, dietary pattern, family history, past history, average water intake, alcohol intake and composition of stone. Laboratory investigations included urine routine & microscopy, urine culture, 24 hrs urine analyses for calcium, phosphorous, uric acid, magnesium, oxalate and citrate, serum calcium, phosphorous, uric acid, creatinine, random blood sugar (RBS) and BUN. Imaging was done (USG of abdomen pelvis, NCCT KUB and contrast studies) when indicated.

All patients underwent routine pre-operative investigations for treatment of stones. Testing for serum calcium, phosphorous and uric acid were included in preoperative investigations. They were repeated only if found to be elevated. After stone had been treated, they underwent urine analyses for metabolic disorder twice on consecutive days.

Sample size was calculated using the Dandpani et al study. The study had observed that metabolic disorders were associated with 41.8% of patients with bilateral, multiple, staghorn and recurrent stones. In the present study expecting similar result with 25% relative precision and 90% confidence level, the study required a minimum of 60 subjects.

Inclusion Criteria

- All patients diagnosed to have bilateral, multiple and staghorn stones on first presentation and recurrent stones (unilateral/ bilateral).
- Pediatric patient at first presentation will be included in the study.

Exclusion Criteria

- Secondary stones.
- Single, unilateral renal or ureteric stones on first presentation in adults.

Statistical Analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram and pie diagram.[13]

Results

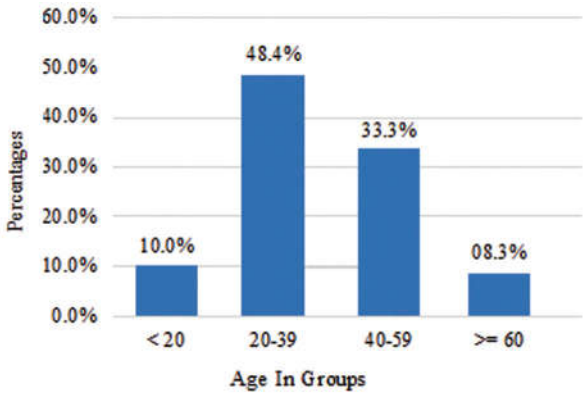

Fig. 1: Bar chart of age in groups in the study population (N=60).

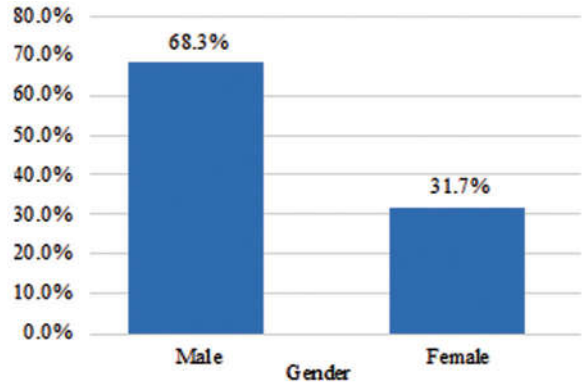

Fig. 2: Bar chart of gender in the study population (N=60).

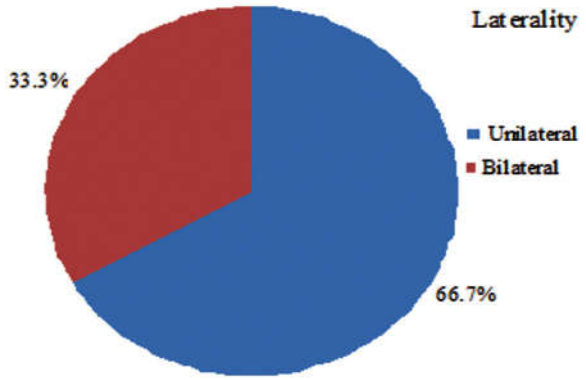

Fig. 4: Pie chart of laterality in the study population (N=60).

Demographic factors

The mean age of our study population is 38.52 ± 15.41 years of age (Table 1), maximum number of patients fall in the age group of 20-59 years (81.7%) (Figure 1). The males had more preponderance of stone formation than females [M= 41 (68.3%), F=19 (31.7%)] (Table 3) (Figure 2).

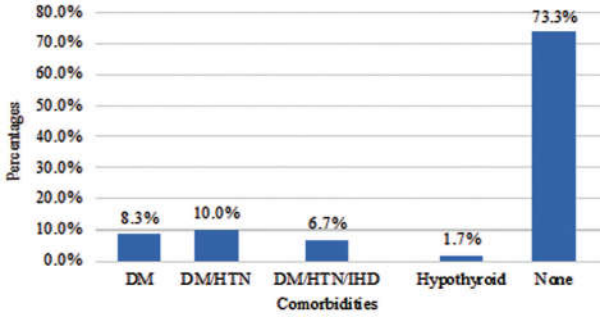

Fig. 3: Bar chart of comorbidities in the study population (N=60).

Medical Comorbidities

Kidney stones are associated with hypertension, obesity and metabolic syndrome, and may be a harbinger of diabetes. 73.3% of the sample did not have any of the medical comorbidities. One fourth of the sample (N=15, 25%) had Diabetes Mellitus (Figure 3). Our study population had a mean BMI of 28.84 ± 3.53 (27.9-29.8 95% CI) which falls into high BMI (Overweight to Obese).

Dietary habits and Water intake

Lifestyle habits and dietary/nutritional factors such as excessive intake of animal proteins and salt and deficiencies of chelating agents like citrate, fiber and alkali foods are all risk factors for nephrolithiasis. Majority of our study population had mixed dietary pattern (91.3%) and good water intake (73.3%).

66.7% of the patients had unilateral stones. 33.3% of the study population had bilateral stones (Figure 4).

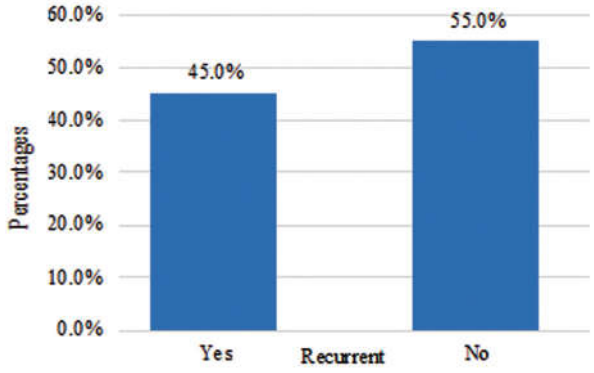

Fig. 5: Bar chart of recurrent in the study population (N=60).

45% of the study sample had recurrence in stone formation. 55% of the patients did not have any history of recurrence (Figure 5).

Stone analysis was done after the stone (what intervention was done to remove the stone??). 35 (58.3%) of the study population had calcium stones. 25 (41.7%) of the patients had uric acid stones.

- Mean Calcium levels were 8.54 ± 0.55 mg/dl (normal range- 8.5-10.5mg/dl). Mean Phosphorus levels were 4.06 ± 0.3 mg/dl (normal range- 2.5- 4.5mg/dl). Mean uric acid levels were 6.68± 1.05 mg/dl (normal range- 3.5-7mg/dl). Mean creatine levels were 1.35±0.31 mg/dl (Normal range Adults- upto 1.2 mg/dl, upto 1 mg/dl for 3-18 yrs, upto 0.7 mg/dl for 3 yrs old). Mean BUN levels were 21.06 ± 4.36 mg/dl (Normal range- 7-20 mg/dl for adults, 4-15 mg/dl upto 2yrs old, 5-20 for more than 2yrs old).
- Serum Calcium and Serum Phosphorus was normal in the majority of the sample (53.3% and 98.3% respectively). Hyperuricemia (24) was found in 40% of the patients.

- Urinary pH was found to be acidic in 48.3% of the sample. 51.7% of the patients had alkaline urinary pH.
- Mean urinary calcium levels were 264.75 ± 36.32 mg/day (normal range- 100-300 mg/day). Mean urinary phosphorus levels were 602.97 ± 86.7 mg/day (normal- 800 mg/day). Mean urinary uric acid levels were 628.08 ± 110.37 mg/day (normal- 800 mg/day). Mean urinary citrate levels were 290.45 ± 36.61 mg/day (normal- 320 mg/day). Mean urinary oxalate levels were 34.73 ± 4.25 mg/day (normal- 45 mg/day). Mean urinary magnesium levels were 24.55 ± 3.04 mg/day (normal- 25 mg/day).
- Urinary calcium and phosphorus levels were in the normal range (98.3% and 100% respectively). Urinary Uric acid levels were also normal (96.7%). 90% of the sample showed normal urinary citrate levels. Hypo-oxaluria was recorded in 98.3% of the sample. The distribution of sample for magnesium levels was equivalent for both urinary hyper and hypo- magnesimia (48.3% each).
- Univariate binary logistic regression analysis was performed to understand the influence of various parameters on recurrent in the current study population. None of the parameters were found to be significant ($p<0.005$). If we consider the unadjusted odds ratio then diet, gender and serum creatine levels, serum potassium levels, serum uric acid levels form the main risk factors.
- Univariate binary logistic regression analysis was performed to understand the influence of various parameters on laterality in the current study population. Diabetes mellitus, high creatine and BUN levels, hyperkalemia and hyperuricemia were found to be the risk aaw3factors with high significance ($p<0.005$).

Conclusions

Metabolic evaluation of patients with NL is necessary as a part of medical management. However it is difficult to comment whether metabolic evaluation should be advised as a mandatory investigation which every patient with NL should undergo. Most of the conducted studies are retrospective studies. Further prospective studies are needed to formulate stringent guidelines for metabolic evaluation in NL.

Nonetheless for an individual patient with history of recurrence in NL, metabolic evaluation will further add to the medical management of NL. The major attributes of our study is that we were able to perform metabolic evaluation and stone composition analysis of all patients included in our study. We have performed univariate analysis to understand the risk factors more appropriately.

Though our study demonstrates that there are identifiable risk factors for NL, we have a very small size. Hence it may be difficult for us to generate standard protocol for the metabolic evaluation. We recommend that more prospective design studies with larger sample size should be undertaken to establish specific pathways for metabolic evaluation in NL. Multicentre cohort studies also should be considered in order to remove the heterogeneity in the studies. This can aid us in understanding the metabolic profile of patients with NL in an enormous way.

Discussion

Time and now there have been multiple studies in various parts of the world discussing the medical management of nephrolithiasis. Nephrolithiasis remains one of the important causes of recurrent renal disease which has significant impact on the quality of life of the patients. The metabolic evaluation and medical management of nephrolithiasis varies on several patient and practitioner-related factors. Furthermore due to lack of sufficient data from the Indian studies the grey area in the management of high risk stone formers remains unexplored. A thorough history, clinical examination and metabolic evaluation would help us in holistic management of stone formers. Hence there is a need for discussion on protocol based evaluation of metabolic parameters involved in stone formation which can aid the improvement in the management of nephrolithiasis. Based on the results obtained in our study we would be highlighting certain important aspects to be taken in to account during evaluation of stone formers.

Demographic Factors

The mean age of our study population is 38.52 ± 15.41 years of age, maximum number of patients are in the age group of 20-59 years (81.7%). The males had more preponderance of stone formation than females (M= 41 (68.3%), F=19 (31.7%). This is in keeping in line with the epidemiological data across the world which states that males in the age group of 20-49years are at risk for stone formation.[14] Age and gender did not prove to be statistically significant factors for the assessment of laterality and recurrence in stone formation in our study.

The previous studies in the Indian scenario have also concluded that neither of the age and gender categories are immune to stone formation.[11,12]

Medical Comorbidities

Taylor et al 2004 utilized three large epidemiological prospective cohort studies to examine 4 827 kidney stone incidents over a combined 46 years of follow-up. They showed that body mass index (BMI) and waist circumference, two distinct measures of obesity, were associated with an increased risk of kidney stone formation.[15] A systematic review and meta-analysis to clarify the association between physical activity adiposity and diabetes and the risk of kidney stones was done by Aune D et al 2018.[13] cohort studies were included. The results suggested a positive association between adiposity and diabetes and the risk of kidney stones, but no association with physical activity.[16]

Kidney stones are associated with obesity, hypertension, and metabolic syndrome, and may be a harbinger of diabetes. 73.3% of the sample did not have any of the medical comorbidities. One fourth of the sample (N=15, 25%) had Diabetes Mellitus. Our study population had a mean BMI of 28.84 ± 3.53 (27.9-29.8 95% CI) which falls into high BMI (Overweight to Obese) category.

Dietary Habits

Diet plays an undeniable role in KSD. There have been enormous epidemiological data on the association of dietary factors and risk of KSD. The impact of calcium, sodium, oxalate, animal protein and fluid intake are well documented.[17] Majority of our study population had mixed dietary pattern (91.3%). A strict dietary advice is mandatory as part of medical management of KSD.

Urinary and Metabolic Parameters

The requirement of detailed metabolic evaluation of stone formers has been a topic for debate for over a decade now. Yet there are no conclusive guidelines which form the baseline for testing all the parameters considered as risk factors for KSD. With the available studies we can extrapolate that there is a certain benefit in carrying out metabolic evaluation of bilateral, stag horn, multiple and recurrent stone formers. The data on metabolic evaluation of first time stone formers is scarce.

Urine pH

A negative correlation between BMI and urinary pH has been reported by several studies. In a large group of stone formers, Maalouf et al 2004 reported a significantly negative correlation between urine pH and body weight. Eisner et al 2010 demonstrated that patients with type 2 diabetes mellitus had more acidic urine. Urinary pH was found to be acidic in 48.3% of the sample. Wrobel et al 2012 reported a similar negative correlation between BMI and urine pH in a group of calcium oxalate stone formers.[18,19,20]

Stone Composition

It has been established that the majority of staghorn calculi are of metabolic stone types. While there is some controversy regarding the incidence of metabolic defects in pure struvite stone formers, contemporary studies show that the prevalence of such defects in these patients exceeds 50%. Correspondingly, a significant portion of staghorn stones—regardless of metabolic versus infection stone type—are associated with specific metabolic abnormalities. Therefore, it is reasonable for all patients with stag horn stones to undergo metabolic evaluation, 2135 (58.3%) of the study population had calcium stones. 25 (41.7%) of the patients had uric acid stones.

A retrospective chart review of 589 adult stone formers who completed 24-hour urine collections from April 2004 through August 2015 was performed at the University of Alabama-Birmingham School of Medicine by Wood et al 2019. Most patients were CaOx stone formers (67.5%), with calcium phosphate (CaP) and UA stones being the second and third most common, 18.1% and 12.2%, respectively.[22] Zeng et al 2019 retrospectively reviewed medical records and identified 146 cases of stone recurrence in a total of 3,985 patients from January 2012 to January 2016. Chemical composition analysis showed that most recurrent stones were of calcium oxalate followed by calcium oxalate plus hydroxyapatite, calcium oxalate plus magnesium ammonium phosphate and uric acid plus calcium oxalate.[10] 35 (58.3%) of the study population had calcium stones. 25 (41.7%) of the patients had uric acid stones.

Serum and Urinary Metabolic Parameters

Metabolic disorders such as excess calciuria, oxaluria, uricosuria and reduced citraturia history of gout (defective metabolism of uric acid) are well established risk factors.[23,24] Serum Calcium and Serum Phosphorus was normal in the majority of the sample (53.3% and 98.3% respectively). Hyperuricemia 24 was found in 40% of the patients.Urinary calcium and phosphorus levels were in the normal range (98.3% and 100%

respectively). Urinary Uric acid levels were also normal (96.7%). 90% of the sample showed normal urinary citrate levels. The distribution of sample for magnesium levels was equivalent for both urinary hyper and hypo-magnesimia (48.3% each). The univariate analysis done to identify the risk factors for recurrence showed that presence of Diabetes Mellitus (p 0.003), Serum Creatine and BUN levels (p 0.000), Serum uric acid and potassium levels (p 0.001 and 0.000 respectively) correlated significantly with the recurrent stone formation. These findings are similar to the results obtained by Dandapani et al.[11]

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