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COMPARISON OF SOME URINARY BIOMARKERS BETWEEN PATIENTS WITH ONE AND RECURRENT URINARY STONE

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ABSTRACT

Background: Renal stone is common health problem in both developed and developing country; imbalance in the urinary composition of the inhibitor activity against crystal formation is usually noticed in patient with renal stone. It is well known that kidney stones have a marked tendency to recur, with rates in some retrospective studies as high as 50% within 10 years of the first stone episode. However, these rates may be an overestimate since patients without new stones rarely return for visits and are often lost to follow up. Although subsequent prospective study provided more reassuring figures, it remains difficult to establish which patients are likely to have a recurrent stone. **Aim:** To evaluate the biomarkers for the stone formation. **Materials and Methods:** This is a cross sectional study of 100 patient who had kidney stone, the study lasted for one year from 15/1l/2021-15/1/2022.The patient were divided into 2 groups one had renal stone for the first time (n=48). The other group had repeated renal stone (n=25), biochemical examination of urine (24 hours collection) (including specific biomarker for nephrolithiasis). Age, gender, residence, family history, type of food, vegetable intake, soft drink intake, sufficient water intake, and history of recurrent UTI are included in this study. This study was done in Al- Sharq Al-Ausad lab. Mosul-Iraq, the patient who had renal stone attending the lab for biochemical analysis of renal stone after they either passed it after medical treatment or surgical removal. **Results:** The mean age of the sample is 27.98±16.97 years. Males are 75.0% and females are 25.0%. Mean age of group 1 (16.6±14.3) is significantly (p=0.000) lower than that of group 2 (39.4 ±10.7). Males' gender is more frequent than females in both groups, but the difference is a statistically not significant. The stone formation in both groups is higher among urban than rural but statistically has non-significant difference. The family history presents in 41.7% of group1 and 84.6% of group 2 with a statistically significant difference (p=0.000). No significant statistical difference between the study groups regarding type of food, vegetable intake, and soft drink intake. Drinking sufficient water occurs in 66.7% of group1 and 25.0% in group 2, the difference is statistically significant, while insufficient water intake occurs in 8.3% of group 1 in comparison to 75.0% of group 2 and the difference also statistically significant. Recurrent infection and drug intake shows no significant difference. All the biomarkers are significantly higher in group 2 in comparison to that of group1with the exception of the Citric acid which is higher in group 1. **Conclusion:** Testing and analysis of stone composition and biochemical evaluations reveal the role of calcium, uric acid, oxalate, citrate, sodium and calcium in the stone formation in addition to the sufficient water intake and positive family history.

KEYWORDS: Urinary Biomarkers, Renal stone, Recurrence.

INTRODUCTION

Renal stone is common health problem in both developed and developing country; imbalance in the urinary composition of the inhibitor activity against crystal formation is usually noticed in patient with renal stone.[1]

Kidney stone disease often presents between the ages of 20-60 years and more prevalent in hot weather,[1] it affects about 10% of people over their life time.[2]

It is well known that kidney stones have a marked tendency to recur, with rates in some retrospective studies as high as 50% within 10 years of the first stone episode. However, these rates may be an overestimate since patients without new stones rarely return for visits and are often lost to follow up. Although subsequent prospective study provided more reassuring figures, it remains difficult to establish which patients are likely to have a recurrent stone.[1,2]

It is important to plan all necessary investigations to ensure early etiological diagnosis but it can be costly to run through a long series of tests indiscriminately in all patients.[3]

Stone development begins with the formation of crystal in concentrated urine that later on adhere to urethelium which creates the nidus for subsequent stone formation,[1,2] urethelial injury and repair after a stone episode may increase surface expression of these molecules to enhance further crystal deposition [4, 5]. Thus stones beget stones because of presence of residual nucleus on which further stone may be made.

Regarding the risk factors that play an important role in developing kidney stone, firstly Low urine volume is one of the most common metabolic abnormalities encountered among stone formers. In general, a stone former should be encouraged to maintain a urine volume of 2 liters per day [Porena *et al.*, 2007]. Low dietary fluid intake is the most common cause of this abnormality, although fluid losses by other mechanisms, such as chronic diarrhea states, can also result in low urine volume.[6]

Also the gender were men tend to have kidney stone more than female because he tend to have a greater intake of both protein and salt than female,[7] also type of food and some soft drink riching with proteins, oxalate and sodium associated with increase risk of stone formation. Many metabolic disorders that increase secretion of some salt in urine as hyperuricemia and hypercalciemia also may cause renal stone.

Other factors including family history, urban residence, working in hot weather, recurrent UTI and Low concentration of protective factor like citrate and magnisuim can because that trigger stone formation.[8-10]

PATIENTS AND METHODS

The study lasted for one year from 15/1l/2021-15/1/2022. Age, gender, residence, family history, type of food, vegetable intake, soft drink intake, sufficient water intake, history of recurrent UTI and drug intake for treatment of urinary stone are included in this study.

This study was done in Al- Sharq Al-Ausad lab. Mosul-Iraq, the patient had renal stone who attending the laboratory for biochemical analysis of renal stone after they either passed it after medical treatment or surgical removal. 24-hr. urine samples were collected from 100 individuals (72 males and 28 females) with history of kidney stone with different age.

Kidney stones were consisting of calcium oxalate, uric acid calcium phosphate, etc. they were divided into two groups the first is patient with first time having one kidney stone group1 (n=48) and the second group includes the patient with more than one stone group 2 (n-52).

The 24 hr. urine samples were collected in a container added to it 50 ml of 2.2M hydrochloric acid as preservative.

The acidified urine samples of both groups were analyzed for volume, Ph, uric acid, phosphate, sodium, calcium, oxalate, and citrate. The uric acid, phosphate, calcium and magnesium estimation were done by absorbance photometry (mindray BS 240), and sodium and potassium test were done by JOKOH EX-DS device [11] using ion selective electrode technology. While oxalate was used oxalate oxidase ⁄peroxidase method. The estimation of citarate was done by citrate lyse⁄malate method and peroxidase-coupled reactions. Analytical Biochem, 1980; 105: 389-397.

RESULTS

The sample consists of 100 individuals divided into two groups according to the number of stone formation; group1 (n=48) has one stone and a group 2 (n-52) has 2 and more stones.

Table (1) shows the statistical characteristics of sample age and reveals that the mean age is 27.98±16.97 years.

Table (1): Statistical characteristics of sample age.

Mean sample age	Mean	27.9896
	Std. Deviation	16.97512

Figure (1) demonstrates the distribution of the sample according to gender and illustrates that 75.0% of the sample are males and 25.0% are females.

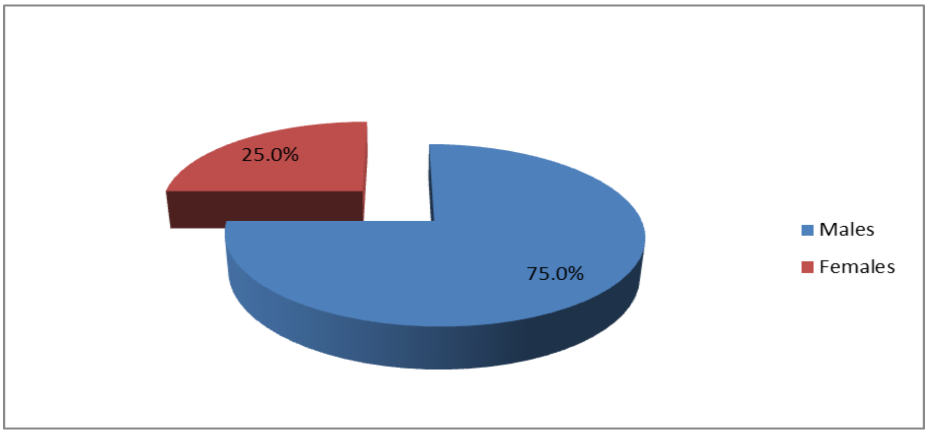

Figure (1): Distribution of the sample according to gender.

Table (2) demonstrates the comparison between study groups concerning age, gender, residence, and family history and shows that mean age of group1 (16.6±14.3) is statistically significant (p=0.000) lower than that of group2 (39.4 ±10.7). Although the males' gender shows higher proportion than females in both groups, but the difference is a statistically non-significant. The stone formation in both groups is higher among urban than rural but statistically has non-significant difference. The family history presents in 41.7% of group1 and 84.6% of group2 with a statistically significant difference (p=0.000).

Table (2): The comparison between study groups concerning age, gender, residence, and family history.

Study variable		**One stone Mean±SD**	**Recurrent stones Mean±SD**	**p-value***
Mean age		16.6±14.3	39.4 ±10.7	0.000
Study variables		**One stone No. (%)**	**Recurrent stones No. (%)**	**p-value****
Gender	Males	32(66.7)	40(76.9)	0.254
	Females	16(33.3)	12(23.1)	
Residence	Urban	28(58.3)	32(61.5)	0.744
	Rural	20(41.7)	20(38.5)	
Family history	Present	20(41.7)	44(84.6)	0.000
	Absent	28(58.3)	8(15.4)	
*t-test for unpaired two samples ** Chi square test				

Table (3) demonstrates the comparison between study groups concerning type of food, vegetable intake, soft drink intake, and sufficient water intake and shows that no significant statistical difference between the study groups regarding type of food, vegetable intake, and soft drink intake. Drinking sufficient water occurs in 66.7% of group1 and 25.0% in group2, the difference is statistically significant, while insufficient water intake occurs in 8.3% of group1 in comparison to 75.0% of group2 and the difference also statistically significant.

Table (3): The comparison between study groups concerning type of food, vegetable intake, soft drink intake, and sufficient water intake.

Study variables		**One stone No. (%)**	**Recurrent stones No. (%)**	**p-value**
Type of food	Barbeque	28(58.3)	32(61.5)	0.744*
	Carbohydrates	8(16.7)	16(30.9)	0.099*
	Leguments	8(16.7)	4(7.6)	0.168**
Vegetable intake	Every day	24(50.0)	28(53.9)	0.701*
	Weekly	4(8.3)	4(7.6)	1.000**
	Seldom	20(41.7)	20(38.5)	0.744*
Soft drink intake	Every day	20(41.7)	20(38.5)	0.744*
	Weekly	8(16.7)	16(30.9)	0.099*
	Seldom	12(25.0)	12(23.0)	0.822*
	Non	8(16.7)	4(7.6)	0.168**
Sufficient water intake	Yes	32(66.7)	24(46.2)	0.039*
	Seldom	12(25.0)	4(7.6)	0.229*
	No	4(8.3)	24(46.2)	0.000**
*Chi square test ** fissure exact test				

Table (4): Demonstrates the comparison between study groups regarding recurrent infection and drug intake and shows non-significant difference.

Study variables		One stone No. (%)	Recurrent stones No. (%)	p-value*
Recurrent infection	Yes	36(75.0)	44(75.0)	0.229
	No	12(25.0)	8(25.0)	
Drug intake	Yes	28(58.3)	32(61.5)	0.744
	No	20(41.7)	20(38.5)	
*Chi square test				

Table (5) demonstrates the comparison between the study groups regarding specific biomarkers for nephrolithiasis and shows statistically significant differences in which the markers are higher in group2 than that of group1with the exception of the Citric acid which is higher in group1.

Table (5): The comparison between the study groups regarding specific biomarkers for nephrolithiasis.

Study variables		One stone Mean±SD	Recurrent stones Mean±SD	p-value*
Oxalic acid	17.5 – 35.1 mg/24 hr	28.4±3.5	31.1±4.2	0.001
Citric acid	Male 116 – 924 mg/24 hr Female 250 - 1160 mg/24 hr	509.7±10.4	221.2±6.77	0.000
Phosphorus	13- 42 mmol/24 hr	16.7±3.8	18.8±5.1	0.022
Calcium	2.5 – 7.5 mmol/24 hr	8.3±1.1	11.1±2.9	0.001
Creatinine	Male 6800 – 19400 µmol /24 hr. Female 6300 –13400 µmol /24 hr	9028.3±86.7	16499.1±100.4	0.000
Uric acid	Less than 800 mg /24 hr	498.7±21.8	826.4±16.9	0.000
Sodium	40- 220 mEq/24hr	248.9±9.7	298.2±5.5	0.000
Cysteine	< 10 mg/24hr	12.6±2.1	17.5±1.5	0.000
*t-test for unpaired two samples				

DISCUSSION

The propensity to form stones varies according to sex, ethnicity and geography. Although historically stones have been 2–3-times more common in men than in women, recent data indicate that this disparity is diminishing.

In present study the patients' age among the one stone group was 16.6±14.3 years which significantly lower than that of recurrent stone group 39.4 ±10.7 years. These results were in line with those of Li *et al.*[12] who discovered that many stone recurrences were substantially linked with early stone production. A retrospective cohort study of pediatric patients was just published by Tasian *et al.*, and it evaluated the population's time to first recurrence. Three years after the initial incident, they discovered a 50% recurrence rate in patients aged 3 to 18 years.[13]

Although the current study didn't found statistical difference between males and females in the study groups, males were more frequently associated with formation of stone in both groups. Similar findings were made by Daudon *et al.*, [14] who discovered that 38,274 stones originated from 26,368 males (68.9%) and 11,906 females, and that 16,336 (42.7% of the patients) had previously experienced a stone occurrence. 11,702 of these patients had recurrent stones, compared to 4,634 of the female patients, showing that men were more likely to have recurrent stones (44.4 vs. 38.9% of the total for each sex, P0.0001). According to data from the US Nationwide Inpatient Sample, the ratio of male to female hospital discharges for stones decreased from 1.7 in 1997 to 1.3 in 2002.[15] In Rochester, Minnesota, USA, the male to female ratio of incidence kidney stones decreased from 3.1 to 1.3 between 1970 and 2000 [16]. The increase in female rates between 1998 and 2004 in Florida (USA) was larger than the increase in male rates, according to an examination of resource use associated to procedures for stones.[17] Between 1991 and 2010, there was a 48% increase in stone therapy in Canada, mostly due to an increase in treatments among women.[18] Although the cause of the rise in female stone disease is unknown, some have hypothesized that it may be related to dietary and lifestyle changes that have led to an increase in female obesity, a known risk factor for stone development.[15]

The present study showed that the urban residence associated with the renal stone formation and the recurrence but the difference was statistically insignificant. Comparable findings from a prospective study.[19] in Missan, in which 270 patients were seen in the departments of surgery at Al-Sader Teaching Hospital and Al-Zahrawi Surgical Hospital from December 2010 to May 2014, revealed that approximately 63.7% of kidney stone patients resided in urban areas, compared to only 36.3% of patients who did so. Additionally, Al-Dabbagh *et al.*, demonstrated that in Al-Mosul Governorate, Iraq, in 1977, the incidence of urolithiasis was greater in urban than rural populations, 52.0 against 30.2 per 100,000 people.[20] A high level of living and renal stones are positively correlated in England, according to Barker *et al.*,[21] Stone prevalence is often higher in hot, arid regions, reflecting environmental risk factors in the geographical heterogeneity of stone illness. The prevalence of kidney stones in the United States is highest in the south and southeast and lowest in the west.[22–26] Sunlight and ambient temperature have been found to be independently linked with the incidence of stones after accounting for other parameters.[24]

Family history was positive in 41.7% of one stone and 84.6% of recurrent stone with statistical significant difference. An earlier study discovered a connection between a family history of kidney stones and a high incidence of kidney stones, which may be due to genetic factors. A recent meta-analysis found 20 loci related with nephrolithiasis, including CYP24A1, DGKD, DGKH, WDR72, GPIC1, and BCR loci, which were anticipated to influence calcium-sensing receptor signaling and vitamin D metabolism, respectively [25]. Patients who had previously experienced renal stones had a higher probability of recurrence, whether they were symptomatic or not. With each subsequent kidney stone occurrence, the likelihood of recurrence rises.[26] Non-obstructing stones also independently predict the return of symptoms [27]. These non-obstructive stones can transit down the road, turn obstructive, and subsequently cause a recurrence of symptoms if they are not surgically removed.[28]

No statistically significant difference found between the present study's groups regarding the types of food, vegetable intake, and soft drink intake. According to recent studies, urolithiasis has become more common over the past few decades in both developed and developing nations. This expanding tendency is thought to be related to dietary changes and other lifestyle alterations.[29–31]

Males in good health tend to consume more than five portions of fruits and vegetables and two thousand millilitres of water daily. These findings, however, do not have statistical significance ($p>0.05$). The consumption of dairy products, meat and meat products, fruit, vegetables, and water by female patients compared to healthy women does not differ statistically ($p>0.05$). In the sample, less than 3 portions of dairy products are consumed daily by 88.9% of patients who have not experienced stone recurrence, 100.0% of patients who have experienced it once or twice, and 92.9% of patients who have experienced it more than twice. In contrast, 77.8% of patients who have not experienced stone recurrence consume more than 5 portions of fruit and vegetables daily, compared to 50.0% of patients who have experienced more than two recurrences. Additionally, 91.8% of patients with two recurrences do not go over the 2000 mL water restriction, as do 66.7% of patients with no stone recurrence. However, there is no statistically significant correlation between the number of stone recurrences and dietary intake.[32] A 13% decrease in the incidence of stone formation was discovered for every 200 mL of fluid consumed daily.[33] But given the wide range of beverages on the market, it stands to reason that not all of them offer the same level of protection. Soda, often known as carbonated soft drinks with added sugar, is steadily gaining popularity among the general public, particularly in the USA.[34] They typically have fructose added and have an average caloric content of 150 calories per 350 mL. Fructose has been linked to an increased risk of kidney stone disease [37] and may increase the excretion of calcium, oxalate, and uric acid.[35,36] It is not surprising, then, that those who consume the most of soft beverages have a higher risk of developing nephrolithiasis.

There is general agreement that a person's daily fluid consumption should be at a level that produces at least 2.0 to 2.5 L of urine [38]. A significant protective effect of fluid intake in preventing stone formation in men was found by Dai *et al.*, [39]. When compared to males who drank less than 500 mL per day, men who drank >2,000 mL/day had a 50% lower risk of developing renal stones. More studies have examined the impact of particular beverages on renal stones in addition to total fluid intake, although their findings are contradictory.

Recurrent infection in the present study found in 75.0% of each study groups with insignificant difference. In a 7-year study of 286 patients with S aureus bacteriuria, Kitano *et al.*,[40] found a significant correlation between the presence of hydronephrosis, renal stones, and indwelling catheters in the former group ($p = 0.002$, 0.04, and 0.001, respectively). This finding further supports the link between renal stone and UTI. In a cohort of 192 urolithiasis patients who presented to the emergency room, Yilmaz *et al.*, study.[41] examined the urine cultures of 27 patients (15.3%), whereas the urine cultures of the remaining 150 patients (84.7%) were negative. The authors concluded that urinary stones may increase the risk of UTI after using ROC analysis to determine that pyuria (over 10 WBCs per HPF), temperature over 37.9 °C, and leukocytosis over 11,300/mm3 were the best predictors of a positive urine culture among patients presenting with urolithiasis. To understand crystal aggregation and stone development, additional molecular pathways have been investigated. The concentration of $Ca(2+)$ and $Mg(2+)$ ions around bacterial cells has been suggested to speed up the crystallization process by bacterial polysaccharides of the genus Proteus, macromolecules with negatively charged residues that can bind them.[42,43]

In the present study, 58.3% of one renal stone and 61.5% of recurrent stones were associated with drug intake although the difference was statistically insignificant. Drugs used to treat a variety of medical conditions may contribute to stone disease. A drug-induced metabolic imbalance may be the cause of a stone event, and treating the condition may completely or significantly reduce stone activity. In contrast, the medication or its metabolites could crystallise and make up the majority of the calculus. When this happens, the medication must typically be stopped, and alternative therapy must be started.[44] Additionally, renal calculi have been reported in up to 64% of newborns with low birth weight who are using furosemide.[45] Additionally, a decreased glomerular filtration rate and immature hepatic function in newborns contribute to furosemide's hypercalciuric impact by making the drug's half-life much longer.[46] These patients' calculi were separated, and they are made entirely of calcium oxalate.[47]

The Oxalic acid, phosphorus, calcium, uric acid, magnesium, potassium, sodium, and cysteine in the present study were associated with formation of renal stone, their levels in one stone group were significantly lower than that in the recurrent stone group, and only the citric acid was lower in the recurrent stone group in comparison to one stone group. The endogenous metabolism of glycine, glycolate, hydroxyproline, and dietary vitamin C produces a significant amount of urine oxalate and because of its limited bioavailability, a large portion of the oxalate in meals may not be easily absorbed. Finally, there can be a sizable difference between people in terms of how much oxalate is absorbed by the digestive system.[48]

Foods high in oxalate should only be consumed in moderation. Individual oxalate absorption varies, so it's crucial to consume enough calcium and water to reduce the quantity of oxalate that is absorbed from the gut. In comparison to typical dietary practises, a trial of dietary supplementation with low-oxalate foodstuffs found a significant improvement in urinary risk factors and probable stone formation in a group of calcium-stone formers.[49] The bulk of research to date have concentrated on the prevention of calcium oxalate nephrolithiasis because calcium makes up about 80% of kidney stones and because calcium oxalate makes up the majority of calcium stones.[50]

A few randomised trials have been conducted to determine if magnesium supplementation affects stone recurrence. The dropout rates were significant when magnesium was administered along with other substances (such thiazide diuretics or potassium citrate). The independent health benefits of magnesium supplementation are unclear. Although there has been no association found in women,[52,53] higher dietary magnesium was linked to a 30% decreased incidence of stone formation in men.[51]

Limiting the potassium intake may lead to more calcium being excreted in urine. Citrate, a key inhibitor of calcium oxalate stone formation, is excreted less often through the urine when hypokalemia stimulates tubular citrate re-absorption. Food also contains potassium in addition to organic anions like citrate, which are converted to bicarbonate during metabolism. Consuming potassium-rich meals, such as fruits and vegetables, acts as an alkali load, increasing the excretion of citrate through the urine. The incidence of kidney stones is negatively correlated with higher potassium intake in men and older women,[52,54] but not in younger women,[53] Generally speaking, potassium citrate is regarded as a relatively secure and often utilised preventive for reducing stone recurrence,[55] In this trial, potassium citrate therapy did not appear to lower the recurrence rate. This might be connected to being impacted by the *Liu et al.,*[56] result. According to their study, potassium citrate prescriptions to patients increased recurrence risk. They hypothesised that confounding by indication may be related to this result.

Renal tubular calcium absorption is decreased by high sodium intake and a consequent decline in proximal sodium absorption. The combined impact of dietary sodium restriction and animal protein restriction on lowering urinary calcium excretion is strongly supported by randomized trial results [57]. Observational studies discovered that sodium consumption is positively and independently associated with the development of new kidney stones in women but not in men [52, 54]. It is unknown what part dietary oxalate plays in the development of calcium oxalate nephrolithiasis. First, estimates for the percentage of urinary oxalate produced from dietary oxalate range from 10 to 50%,[53]

Because sodium and calcium compete for re-absorption in the kidney, high sodium diets are linked to increased calcium excretion in the urine. Salt limitation lowers the risk of kidney stones since sodium is a frequent food preservative. A "no added salt diet," or the equivalent of 2g per day or less, should be the aim of therapy.[58]

CONCLUSION

Testing and analysis of stone composition and biochemical evaluations reveal the role of calcium, uric acid, oxalate, citrate, sodium and calcium in the stone formation in addition to the sufficient water intake and positive family history.

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