OPEN ACCESS
Scholars International Journal of Biochemistry
Abbreviated Key Title: Sch Int J Biochem
ISSN 2616-8650 (Print) |ISSN 2617-3476 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Epidemiological Risk Factors Influencing the Formation of Renal Calculi, their Chemical Composition and Association with Urinary Tract Infections

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DOI: 10.36348/sijb.2020.v03i12.005 | **Received:** 13.12.2020 | **Accepted:** 24.12.2020 | **Published:** 30.12.2020

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Abstract

This study was conducted to assess the influence of epidemiological risk factors in the formation of renal calculi, their compositionand association with urinary tract infections (UTI) among the ethnic population of Khammam district, Telangana state. This study included 56 subjects attending the urology department, Mamata General Hospital, Khammam. Out of 56 patients with renal calculi, 50 are male, 46 from rural areas, 22 were farmers and 26 were manual labor. Twenty six belonged to socioeconomically lower middle class, 38 were non-vegetarians and 47 were consuming bore/tank water. Results of this study suggest a significant association between all the epidemiological risk factors viz., gender, residence, occupation, socio economic status, diet, and source of water and formation of renal calculi. Structural analysis of stones demonstrated that 78.6% of stones were mixed. Overall, calcium oxalate as pureor mixed with otherchemicals was the main component of stones matrix, seen in 38 (67.9%) patients. In this study, struvite is present in 21.4% of the stones. Thirty (53.6%) of 56 urine specimens were culture positive and 26 (46.4%) were sterile. All the positive urine cultures yielded a single organism and 26of 30 isolates were positive for urease enzyme. *Klebsiella* was the most common organism and was isolated from 16 (28.6%) urine samples. Results suggest that there is a significant association between UTI and renal calculi formation.

Keywords Epidemiological risk factors. Renal calculi. Chemical composition. Urinary tract infection.

INTRODUCTION

Renal calculus formation is seen as a common worldwide clinical problem; basically the formation of calculi occur in kidney (nephrolithiasis), ureter (ureterolithiasis) and urinary bladder (cystolithiasis) by the succeedingphysico-chemicalevents of super saturation, nucleation, aggregation, andfinally preservation [1]. The crystal is formed by the components like calcium oxalate, calcium phosphate, calcium carbonate, magnesium-ammonium phosphate, uric acid, and cysteine [2]. Calcium stones are predominant renal stonescomprising about 80% of all urinary calculi [3]. Struviteor Magnesium Ammonium Phosphate stones occur to the extent of 10–15% and havealso been referred to as infection stones and triple phosphate stones. Struvite stones occur among patients with chronic urinary tract infections that produce urease [3, 4]. Women's are likely to develop this type of stone than the male.Uric Acid Stonesaccount for approximatelyfor 3–10% of all stone types [3, 5]. Diets high in purinesespecially those containing animal protein diet such as meatand fish, results in hyperuricosuria, low urine volume, andlow urinary pH (pH < 5.05) exacerbates uric acid stone formation [4, 6, 7].

Renal calculi are perceived as acute disorder but the growing stage of urolithiasis is a systemic disease that can lead to end stage renal disorder.Formation of kidney stones is common worldwide; often debilitating that has different etiology, pathophysiology and affecting all geographical regions throughout the globe. Annual approximate prevalence is 3-5% and approximate life time prevalence is 15-25%. Nephrolithiasis tend to be recurrent in most of the renal calculi patients. Recurrence rates of renal stone are approximately 10% year, 50% over a period of 5-10 years and 75% over 20 years period [8].The incidence rate of renal calculi varies with geographical region of an individual country. Incidence is 13% in North America, 5-9% in Europe and 1-5% in Asia [9, 10].Geographically, high frequency was foundin United States, Middle East, Mediterranean countries, Scandinavian countries, the British Isles, and Central Europe. In Asia, a stone-forming belt has been reported to extend across India, Indonesia, Iran, Myanmar, Pakistan, the Philippines, Saudi Arabia, Sudan, Thailand and the United Arab Emirates [11]. In India, the incidence of kidney stones is 15% (approximately 5 to 7 million) [12]. Approximate 2 million people in India is affected with nephrolithiasis every year and some parts of country has name denoted as a stone belt that is, Gujarat, Maharashtra, Punjab, Rajasthan, Delhi, Haryana and part of states on North East side [13]. Renal calculi are also found in south India due to high intake of tamarind in regular diet [14].

In most countries, males are predisposed to renal calculi,with male to female ratio ranging from 1.3 to 5 [15-17]. Overall, the incidence of urinary tract stones increasedwith age, which peaked in the age group of 30-60 years and decreased afterwards [18]. Patientswith urine volume is <1 L/day are prone to develop renal stones [19] and patients with renal stones are instructed to maintain a high fluid intake in order to produce at least 2.5 L of urine in 24 hours [20, 21]. This multi-factorial disease occurs as a result of the combined influence of epidemiological, biochemical, genetic, and metabolic risk factors [22].

Bacteria and renal calculi are clinically associated because they often occur in the same patients and patients with renal calculi often have positive urine and/or stone cultures. The relationship between renal calculi and urinary tract infections (UTI) is complex and difficult to analyze bothon a pathophysiological and clinical point of view. Bacteria have long been recognized to contribute to struvite urinary stones; however, the role of bacteria in the development of the more common calcium oxalate and calcium phosphate stones has not been extensively investigated. Several recent studies also indicate a possible association between urinary stones and bacteria, including the high rate of UTI in urinary stone patients and multiple case series of culture-positive urinary stones, including stones composed of calcium oxalate or calcium phosphate [23]. Calcium-based stones might also become secondarilyinfected with urease-splitting organismsand result in secondary struvite stone formation. These stones may contain a mixture of struvite and other materials [24, 25]. Previous reports suggest increased crystal clumping in the presence of bacteria, bacteria-induced lower urine citrate levels and increased CaOx deposits and stone matrix protein expression when bacteria are present as opposed to CaOx deposits alone [23].

Prevention of renal calculi recurrences remains to be a serious problem in human health [26]. Prevention of stone recurrencerequires better understanding of risk factors and the mechanismsinvolved in stone formation. Hence, this study is taken up to assess the influence of epidemiological risk factors like age, gender, occupation, socioeconomic status, source of water and dietary habits of an individual'son kidney stone formation among the ethnic population of Khammam district, Telangana. This study also aimed at determining the association between formation of renal calculi and urinary tract infections.

PATIENTS AND METHODS

This study included 56 patients, out of whom 50 were male and 6 female patients.Patients who underwent surgery for vesiclecalculus at Mamata General and Super Specialty Hospital, Khammam, from March 2018 to March 2019 were included in this study. Patients with calculi ≥2.5cm were included to compare trans-urethral cysto-lithotripsy and open cysto-lithotomy. Patients having bladder stones in augmented bladder were excluded from the study.Patient's written consent and study methodology approval by the institutional ethical committee was obtained.

Patients were subjected to the preformatted study methodology including detail history taking, clinical examination, routine laboratory investigations, relevant special investigations (Ultrasound abdomen/ X-ray KUB/ IVP/ CT-KUB). Samples were taken from the removed stones at the time of operation and samples of urine were obtained through simultaneous bladder catheterization. After washing the stone several times with normal saline and softening the stone fragments, a homogenous dilution of the softened stone was prepared in saline. Samples from these prepared specimens were sent for chemical analysis [27]. Urine specimens were inoculated onto appropriate culture media for identification of urease-producing bacteria as well as common gram positive and gram negative bacteria. The results of urine cultures were considered positive if growth of ≥100.000 CFU/mL was observed after 24 h. The negative cultures were re-examined after an additional 24 h for confirmation.Bacterial isolates were subjected to a series of biochemical tests for identification. Results were analyzed by using the SPSS-20.0 version (Non-Parametric chi-square analysis). The results were considered significant at $p<0.05$ level.

RESULTS

The present study was conducted to assess the influence of epidemiological risk factors in the formation of renal calculi.Out of 56 patients with renal calculi, 50 are male, 46 from rural areas, 22 were farmers and 26 were manual labor (Table-1). Twenty six belonged to socioeconomically lower middle class, 38 were non-vegetarians and 47 were consuming bore/tank water (Table-1).

Structural analysis of stones demonstrated that 44 (78.6%) of 56 were mixed. We have found that 19 (34%) of 56 stones were formed with the combination of calcium oxalate, calcium phosphate stones, and 7

(12.5%) of 56 stones were composed of calcium oxalate &magnesium ammonium phosphate (Struvite) (Table-2). Overall, calcium oxalate as pureor mixed with other chemicals was the main component of stones matrix, seen in 38 patients (67.9%) (Table-2).

Thirty (53.6%) of 56 urine specimens were culture positive and 26 (46.4%) were sterile (Table 3). All the positive urine cultures yielded a single organism and 26 (Klebsiella species-16 and Proteus species-10) of 30 isolates were positive for urease enzyme. Klebsiella was the most common organism and was isolated from 16 (28.6%) urine samples. Proteus was isolated from 10 (17.9%) urine samples, followed by Escherichia coli (5.4%) and Staphylococcus aureus (1.8%).

The chi-square values for all the epidemiological risk factors viz., gender, residence, occupation, socio economic status, diet, and source of waterarefound to be significant (Table-4). The chi-square values for urine culture and stone chemical composition were also significant (Table-4).

Table-1: Influence of epidemiological risk factors for stone formation

Parameters	Observed	Expected	Residual
Gender			
Male	50	28.0	22.0
Female	6	28.0	-22.0
Residence			
Rural	46	28.0	18.0
Urban	10	28.0	-18.0
Occupation			
Manual Labor	26	14.0	12.0
Farmer	22	14.0	8.0
Business	5	14.0	-8.0
Student	2	14.0	-12.0
Socio economic status			
Lower Middle	26	11.2	14.8
Upper lower	13	11.2	1.8
Upper middle	11	11.2	-0.2
Upper	3	11.2	-8.2
Lower	3	11.2	-8.2
Diet			
Non-vegetarian	38	28.0	10.0
Vegetarian	18	28.0	-10.0
Source of water			
Bore/tank	47	28.0	19.0
Mineral water	9	28.0	-19.0

Table-2: Structural analysis of renal calcul

Parameters	Observed	Expected	Residual
Stone Analysis			
Calcium oxalate mixed with calcium phosphate	19	4.3	14.7
Calcium oxalate mixed with magnesium ammonium phosphate (Struvite)	7	4.3	2.7
Calcium oxalate (Pure)	5	4.3	0.7
Uric acid (pure)	4	4.3	-0.3
Uric acid mixed with calcium phosphate	4	4.3	-0.3
Calcium phosphate mixed with magnesium ammonium phosphate (Struvite)	4	4.3	-0.3
Calcium phosphate (pure)	3	4.3	-1.3
Uric acid mixed with magnesium phosphate	2	4.3	-2.3
Calcium oxalate mixed with ammonium urate	2	4.3	-2.3
Uric acid mixed with calcium oxalate	2	4.3	-2.3
Calcium oxalate mixed with calcium phosphate, and ammonium urate	2	4.3	-2.3
Calcium phosphate mixed with ammonium urate	1	4.3	-3.3
Calcium oxalate mixed with Calcium phosphate, and magnesium ammonium phosphate (Struvite)	1	4.3	-3.3

Table-3: List of urinary bacterial isolates from patients with renal calculi

Bacteria	Observed	Expected	Residual
Klebsiella species	16	11.2	4.8
Proteusspecies	10	11.2	-1.2
Escherichia coli	3	11.2	-8.2
Staphylococcus aureus	1	11.2	-10.2
Sterile (No growth)	26	11.2	14.8

Table-4: Chi-Square analysis

Parameter	Chi-Square	Difference	Asymp.Sig
Gender	37.7	1	0.00
Residence	23.14	1	0.00
Occupation	29.14	3	0.00
Socio Economic Status	31.85	4	0.00
Diet	7.14	1	0.00
Source of water	25.78	1	0.00
Urine Culture	37.03	4	0.00
Stone Chemical Analysis	62.39	12	0.00

DISCUSSION

The male (n=50) preponderance of renal stonesin our study was similar to that of other studies [22, 28-30]. Reports from most of the countries suggest that males are predisposed to develop renal calculi, with male to female ratio ranging from 1.3 to 5 [15-17]. This may be attributed to the different dietary habits and hormonal effects [31].Welshman and McGeown demonstrated increasedcitrate concentrations in the urine of women [32]. It has been postulated that this mayaid in protecting females from development of calcium stones since citrateinhibits nucleation of calcium oxalate crystals [33]. Testosterone might promote the formation of urinary stones, while estrogen appears to inhibit by regulating the synthesis of 1,25-dihydroxy-vitamin D [18].Additionally, anatomical differences in urinary tract between males and females; in male the urethra is longer than in female which may cause accumulation and stagnation of urine in the bladder for longer times.

In our study, 46 (82.1%) of 56 patients were residing in rural areas. This result is in line with Stamatiou and colleagues [34] report, in their study they have shown that a significant percentage of the population with urolithiasis in rural areas (15.2%). Wang et al., [35] did not observe any significant differences in the prevalence of kidney stone formation between urban and rural populations. Sas et al., [36] also reported that there were no differences in the incidence of renal calculi in children from urban and rural areas, but these results cannot be directly compared to the adult population. However, Prakash et al., [37] reported that the incidence of kidney stones was higher in the urban population.

The role of occupation or education level in the formation of renal calculi is still controversial [38]. Some research reports suggested that people with sedentary jobs (usually with high education level) are more prone to develop kidney stones; however, other reports suggested a positive relationship between kidney stones and people with more physical works (less educated). In the present study, 48 (85.7%) of 56 patients were farmers and manual labors. The risk of developing kidney stones in people working outdoors or exposed to high temperatures is twice compared to people working at room temperature [39-41]. Hussein et al., [17] also reported that kidney stone patients are more likely to be physical workers with lower education level in Thailand and Malaysia. The reason for the high incidence of kidney stones in outdoor workers is that hot temperature might lead to dehydration, and people in these conditions have less access to drinking water. Excessive exposure to sunlight results in more production of vitamin D and this after conversion to 1,25-dihydroxy-vitamin D in kidneys, can promote calcium absorption in the gut [42].

According to Kuppuswamy [43] socio economic status classification, we have categorized our patients into 5 different groups. In the present study, 26 (46.4%) of 56 patients with renal calculi belonged to lower middle class. Our results are in line with a recent report from India [37]. However, reports from other countries are quite different from our result [44, 45].

In this study, 38 (67.9%) of 56 patients with renal calculi were non-vegetarians. Excessive consumption of meat protein might increase the risk of developing kidney stones because meat causes the over acidification of urine. Acidic urine causes the increased excretion of oxalate, calcium and uric acid, and decreases the excretion of citrate - which provides protection against stone formation. Dietary oxalate contributes to about half of the urinary oxalate [46].

This study shows that 47 (83.9%) of 56 patients with renal calculi were consuming bore/tank water. This result is similar to the findings of a study from Italy [47]. They havefound that the extra meal intake of hard water enhances the risk for stone recurrence in patients since, being associated with an increased excretion of calcium and constant urinary levels of oxalate; it induces a relative super saturation of the calcium-oxalate product. They also reported that hard water enhances the risk for renal stones by the marked increase of the calcium-citrate index. However, a recent study from India, reported the high incidence of kidney stones in people consuming tap water compared to bore well water [37].

Results of this study suggest a significant association between all the epidemiological risk factors viz., gender, residence, occupation, socio economic status, diet, and source of water and formation of renal calculi (Table-4).

Most of the calculi were mixed variety (78.6%) and commonest components noted were calcium oxalate in 38(67.9%), calcium phosphate in 34 (60.7%), magnesium ammonium phosphate (struvite) in 12 (21.4%), and uric acid in 12 (21.4%). Ogaili et al., [48] reported that calcium oxalate (64.6%) was the most common chemical composition in their study, followed by uric acid (6.3%) and calcium phosphate (0.6%). Even in a study conducted in Pakistan, it was seen that calcium oxalate was the most common composition (87.5%), while uric acid, calcium phosphate, cystine and struvite were predominant compositions in 6.5%, 1.29%, 0 % and 4.3% respectively [49]. Khan et al., [50] reported that calcium oxalate the most common stone component in 78%, uric acid in 19% and struvite in 3 %. Chemical analysis by Janakiram et al., [51] revealed that among 125 stones, the incidence of calcium oxalate stones was 36.8%, calcium phosphate 24%, mixed 19.2%, struvite 12%, Magnesium phosphate 6.4% and uricacid phosphate 1.6%. Alatab et al., [52] reported that the calcium oxalate (90% vs. 75%) and uric acid calculi (15% vs. 5%) are more common in developed countries than in developing countries, while the reverse is true for struvite stones (7% vs14%). Even in this study, struvite is present in 12 (21.4%) of 56 stones.

The present study indicated that 53.6% of patients with renal calculi were complaining from UTI and this result is in consistent with other studies [30, 53, 54]. In this study, 26 (86.7%) of 30 isolates were positive for urease enzyme. Previous studies suggested that there is a significant association between UTI caused by urease-producing organisms and stone formation [55-58]. Infection is frequently a coexistent lithogenic factor. Residual urine from outlet obstruction predisposes to infection, and combination of these factors may result in stone formation. Benway and Bhayani [59] reported that between 22-34% of bladder calculi are associated with UTI and most commonly with Proteus organisms. In our study also 53.6% of stones are associated with UTI and Proteus was isolated from 10 (17.9%) urine samples. Urease is necessary to split urea to ammonia and CO2, making urine more alkaline which elevates pH (typically > 7). Phosphate is less soluble at alkaline versus acidic pH, so phosphate precipitates on to the insoluble ammonium products to for struvite stones. Until recently, only struvite stones were considered to be derived from bacterial infection. However, other types of stones such as calcium - based stones might also become secondarily infected with urease-splitting organisms and result in secondary struvite stone formation. These stones may contain a mixture of struvite and other materials [24, 25]. In this study, struvite is present in 21.4% of the stones. Results suggest that there is a significant association between UTI and renal calculi formation (Table-4).

CONCLUSION

This study has identified the epidemiological risk factors for formation of renal calculi and their composition among the ethnic population of Khammam district, Telangana, India. This study also attempted to determine the association between stone formation and UTI. We feel that small sample size is the limitation of this study and further studies with larger samples may be needed to determinethe association between stone formation and UTI.

Compliance with Ethical Standards

Funding: The authors received no specific funding for this work.

Conflict of interest: The authors declare that they have no conflict of interest.

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