Review

Metabolic Disorders in Patients with Nephrolithiasis in Iran

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Nephrolithiasis is a common disease entity around the world, with an increasing prevalence and incidence. There is no consolidated information available on the cause of kidney stones in Iranian patients. As a result, we decided to review the etiology of kidney stones in Iran. PubMed, Scopus, Web of Science, Google scholar, and Scientific Information Database (SID) were searched with the following keywords "Nephrolithiasis", "Renal stone", "Kidney stone", "Urolithiasis", "Etiology", "Metabolic abnormalities", and "Iran". There was no time period limit for selection of the papers. The inclusion criteria included any paper on evaluation of urine biochemistry regarding stone formation in Iranian adult patients (with or without children) with nephrolithiasis. We found 217 articles, of which 9 were eventually included. In conclusion, 1896 patients with nephrolithiasis from 6 provinces and 7 cities of Iran with different climates from 2000 to 2019 were evaluated collectively. The results showed that in contrast to western countries, hypercalciuria was not the most common biochemical disorder of patients with nephrolithiasis (18.2% vs. 30 to 60%). Low urine volume (49.6%) and hypocitraturia (27%) were the most frequent urine abnormalities in our country.

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INTRODUCTION

Nephrolithiasis is a common problem all over the world. The prevalence and incidence of this disorder are increasing and it is important to pay close attention to its' epidemiology, underlying causes and treatment. Due to the increasing trend of kidney stone frequency, it has been a significant burden on the health care system over the past few years.[1] On the other hand, this disease can lead to chronic kidney disease (CKD), drastically reducing patients' quality of life.[2] Generally, patients with kidney stones are more likely to experience many complications, including cardiovascular and chronic kidney diseases, urinary tract infection (UTI), and fractures.[3,4] In patients with nephrolithiasis, flank pain is the most common symptom that leads to admission to the emergency department.[4] The etiology of most renal stones is non-infectious. Several risk factors are associated with kidney stones, including low fluid intake, high intake of protein, sodium, and carbohydrates, and certain diseases such as obesity, hypertension, and gout.[5]

Laboratory investigation of the etiology of kidney stones is very important for prescription of medications and decision on dietary regimens , which depend on the underlying biochemical disorder. As there is no consolidated information on the epidemiology and underlyring biochemical causes of kidney stones in Iran, we decided to review the etiology of kidney stones in our country according to the published papers.

PubMed, Scopus, Web of Science, Google scholar, and Scientific Information Database (SID) (the national database for Iranian papers) were searched with the following keywords "Nephrolithiasis", "Renal stone", "Kidney stone", "Urolithiasis",

"etiology", "Metabolic abnormalities", "Iran." Every paper irrespective of the time of publication was included and considered for review, if it included biochemical evaluation of urine for stone formation in Iranian. Due to the limited number of papers, studies were included without considering the completeness of the biochemical evaluation.

EPIDEMIOLOGY

The prevalence of renal stones varies in different countries and it is generally higher in the tropical regions.[5] In western countries, the prevalence of nephrolithiasis has been reported between 0.1% to 14.8%. In Asia and Taiwan, it is estimated to be about 9.6%. According to a systematic review in China, the prevalence of urolithiasis was estimated between 1.36% and 13.69%.[4] Studies have shown that stones are more common in men than in women.[6] However, the important thing is that the ratio of males to females reduces. This trend can be due to lifestyle and dietary habits changes related to working activities.[6] An increase in the incidence of renal stones has been observed in adults and children.[3]

BIOCHEMICAL EVALUATION

In addition to a history and a complete physical examination, several blood and urine tests are needed to evaluate a patient with renal stones. Blood laboratory tests included creatinine, sodium, potassium, calcium, phosphorus, magnesium, bicarbonate, uric acid, parathyroid hormone (PTH), and vitamin D (if indicated). The necessary urine laboratory tests are urinanalysis, urine culture, 24-hour urine collection for volume, pH, creatinine, uric acid, sodium, potassium, calcium, magnesium, oxalate, citrate, and cystine.[7]

METABOLIC EVALUATION IN IRAN

We found 217 articles, of which 9 were eventually included. Articles are presented based on the year of publication (Table 1).

Mahmoudi *et al.* conducted a study in 2000; on 79 patients aged ≥ 15 years old in Kashan. Hyperuricemia and hypercalcemia were detected in 8.8% and 2.5% of their patients, respectively. Low urine volume (78.4%), hypercalciuria (27.8%), and hyperuricosuria (11.3%) were the most common metabolic disorders in patients with renal stones. Low urine volume was attributed to excessive heat and sweating, and low fluid intake.[6]

In a cross-sectional study in Shiraz by Hosseini *et al.* in 2010, 376 patients between 3 to 81 years old were evaluated. In addition to laboratory data, age, gender, past medical history of UTI, family history of nephrolithiasis, history of extracorporeal shock wave lithotripsy (ESWL), (percutaneous nephrolithotomy (PCNL), and Transurethral lithotripsy (TUL) were collected by a questionnaire. Low 24-h urine volume (58.2%), hypercalciuria (17.8%), and hyperuricosuria (15.1%) were the most common abnormalities in patients with nephrolithiasis. One of the main findings of this study was that metabolic evaluation must be performed in all patients with renal stones, even those with the first episode of stone formation.[9]

Nouri-Majalan *et al.* conducted a cross-sectional study in Yazd in 2010 on 150 patients with recurrent renal calculi. In these patients, 2 months after stone passage, blood and urine samples were collected and evaluated. The most common metabolic abnormalities in these patients were hypercalciuria and hyperuricosuria in 24% and 14% of patients, respectively. Based on this study, lower urine volume has an important role in nephrolithiasis in hot areas. They concluded that higher urine sodium and uric acid, and lower serum phosphorus correlate with higher urine calcium in stone formers.[10]

In 2012, Goodarzi *et al.* conducted a case-control study on 28 patients in Hamadan. These patients had a history of at least 2 times renal stone removal during the last 2 years. Twenty-seven matched healthy individuals were in the control group. Taking any medications and UTI were the exclusion criteria. There were no significant differences in demographic parameters between the two groups. Calcium phosphate and calcium oxalate were the most prevalent stones (82%) in the study group. The urinary excretion of citrate was lower in the study group ($P < .001$). Forty-three percent of the urolithiasis patients had hypocitraturia. They concluded that the prevalence of hypocitraturia was higher in stone formers than that in healthy volunteers in this study.[11]

Emami-Naini *et al.* performed another study on 437 patients, which had the largest sample size among all studies. All patients were ≥18 years old, with a diagnosis of nephrolithiasis. Receiving any medications and estimated Glomerular

Table 1. Characteristics of the Included Studies

Author	Year	Design	Population	Place	Laboratory Tests	First Author Specialty	Most Common Abnormality
Mahmoudi H.[8]	2000-2001	Cross-sectional	79	Kashan	Blood: [5]Cr, [9]Na, [7]K, Ca, uric acid 24-hour urine: Cr, Ca, uric acid	Urologist	1. Low urine volume 2. Hypercalciuria 3. Hyperuricosuria
Hosseini MM, et al.[9]	2010	Cross-sectional	376	Shiraz	Blood: [3]CBC, Bun, Cr, Na, K, [2]Ca, [10]Ph, uric acid U/A, U/C 24-hour urine: volume, Ca, Ph, [8]Mg, oxalate, citrate, uric acid	Urologist	1. Low urine volume 2. Hypercalciuria 3. Hyperuricosuria
Nouri-Majalan N, et al.[10]	2010	Cross-sectional	150	Yazd	Blood: Cr, K, Ca, Ph, Uric acid 24-hour urine: volume, pH, Cr, Na, K, Ca, uric acid	Nephrologist	1. Hypercalciuria 2. Hyperuricemia
Goodarzi MT, et al.[11]	2012	Case-control	28	Hamadan	U/A 24-hour urine: Cr, citrate, uric acid	-	Hypocitraturia
Emami-Naini A, et al.[12]	2012	Cross-sectional	437	Isfahan	Blood: [1]BUN, Cr, Na, K, Ca, Ph, albumin, uric acid 24-hour urine: volume, Cr, Na, Ca, citrate, oxalate, uric acid, cystine	Nephrologist	1. Hypocitraturia 2. Hyperoxaluria
Ghorbani A, et al.[13]	2012	Case-control	140	Ahwaz	Blood: [6]FBS, Cr, uric acid, [4]Chol, bicarbonate, Ph, [11]PTH [13]U/A: [12]SG, pH [14]U/C 24-hour urine: Na, Ca, Ph, Mg, citrate, oxalate, uric acid, cystine	Nephrologist	1. Hypocitraturia 2. Hyperuricosuria 3. Hyperuricemia
Hadian B, et al.[14]	2018	Cross-sectional	232	Lorestan	Blood: Ca, Ph, uric acid 24-hour urine: Ca, citrate, oxalate, uric acid	Nephrologist	Hyperoxaluria
Pakfetrat M, et al.[15]	2019	Cross-sectional	376	Shiraz	Blood: BUN, Cr, Ca, albumin, uric acid, PTH 24-hour urine: volume, Cr, Na, Ca, Ph, citrate, oxalate, uric acid	Nephrologist	1. Low urine volume 2. Hypercalciuria 3. Hyperoxaluria
Mohammadi Sichani M, et al.[16]	2019	Cross-sectional	78	Isfahan	Blood: BUN, Cr, Ca, Ph, Mg, uric acid, PTH 24-hour urine: volume, Cr, Na, Ca, Ph, citrate, oxalate, uric acid, cystine	Urologist	1. Cystinuria 2. Hyperoxaluria 3. Hypernatriuria

Abbreviations: BUN, blood urea nitrogen; Ca, calcium; CBC, cell blood count; Chol, cholestrol; Cr, creatinine; FBS, fasting blood sugar; K, potassium; Mg, magnesium; Na, sodium; Ph, phosphorus, PTH, parathyroid hormone; SG, specific gravity, U/A, urinalysis, U/C, urine culture

Filtration Rate (eGFR) < 60 mL/min/ 1.73m² were the exclusion criteria. Age, sex, history of nephrolithiasis, and history of concurrent diseases were collected from the medical records. This study, which was performed in Isfahan, had the highest number of biochemical evaluation tests for patients among the reviewed studies. In contrast to similar studies, hypercalciuria was not a frequent metabolic abnormality among nephrolithiasis patients (9.2%) and hypocitraturia and hyperoxaluria were the most frequent metabolic abnormalities (40.5% and 28.8%, respectively). [12]

In 2012, Ghorbani *et al.* studied 140 patients in Ahwaz. Hypocitraturia (59.2%), hyperuricosuria (21.4%), and hyperuricemia (18.5%) were the most common metabolic abnormalities in this study.[13]

In 2018, Hadian *et al.* showed that hyperoxaluria was the most common metabolic abnormality in patients with nephrolithiasis. This study was performed on 232 patients, ≥ 14 years old, while being on the usual diet in Lorestan. Patients with recent hospitalization, past medical history of stone passage during the recent 8 weeks, patients on medical or dietary treatment, or those who were a first stone former were excluded. As mentioned, hyperoxaluria was seen in 93 (40.1%) of the participants, as the most frequent metabolic abnormality. There were no significant differences

in serum calcium and uric acid levels between men and women).[14]

Pakfetrat *et al.* conducted a study with 376 patients in 2019 in Shiraz. Inclusion criteria were bilateral or recurrent renal stones, history of ESWL, TUL or PCNL, and symptomatic renal stone. Exclusion criteria were eGFR less than 60 mL/min/ 1.73m², using medications, and patient non-cooperation. Similar to the study of Hosseini *et al.* in Shiraz, low urine volume (73.7%) and hypercalciuria (23.9%) were the first and second biochemical abnormalities in the patients. However, the third frequent etiology was hyperoxaluria (19.4%).[15]

Mohammadi Sichani *et al.*, evaluated metabolic disorders in patients with staghorn stones in 2019. Patients with a diagnosis of unilateral or bilateral staghorn stones, whose medical record information was complete and filled out the consent form were included in the study. The most common metabolic disorders in these patients were cystinuria (19.2%), hyperoxaluria (16.7%), and hypernatriuria (16.7%), respectively.[16]

CONCLUSION

In conclusion, 1896 patients with nephrolithiasis from 6 provinces and 7 cities of Iran with different climates from 2000 to 2019 were evaluated collectively. In contrast to western countries, hypercalciuria was not the most common biochemical disorder of patients with nephrolithiasis (18.2% vs. 30-60%).[17] Low urine volume (49.6%) and hypocitraturia (27%) were the most frequent urine abnormalities in our country (Table 2).

One of the main limitations of this study was the small number of included articles. Although we searched multiple keywords in various databases, the number of studies that met the inclusion criteria was limited. Most of the studies have been performed on the risk factors of nephrolithiasis based on subjective data. Extensive studies with more participants are helping to decide metabolic abnormalities in nephrolithiasis in our country.

Table 2. Summary of Biochemical Disorders in the Included Studies

	Low Urine Volume	Hypercalcuria	Hyperuricosuria	Hypocitraturia	Hyperoxaluria	Hypernatriuria	Hyperphosphaturia	Cystinuria
Mahmoudi H. et al (n = 79)	62	22	9	Not available	Not available	Not available	Not available	Not available
Hosseini MM, et al. (n = 376)	219	67	57	7	9	Not available	Not available	Not available
Nouri-Majalan N, et al. (n = 150)	Not available	36	21	Not available	Not available	Not available	Not available	Not available
Goodarzi MT, et al. (n = 28)	Not available	Not available	Not available	12	Not available	Not available	Not available	Not available
Emami-Naini A, et al. (n = 437)	71	40	58	177	126	139	Not available	8
Ghorbani A, et al. (n = 140)	Not available	Not available	30	83	Not available	Not available	Not available	Not available
Hadian B, et al. (n = 232)	Not available	55	33	58	93	Not available	Not available	Not available
Pakfetrat M, et al. (n = 376)	277	90	17	69	73	57	12	Not available
Mohammadi Sichani M, et al. (n = 78)	Not available	5	10	10	13	13	0	15
Total (%)	629 (49.6)	315 (18.2)	235 (12.6)	416 (27)	314 (20.9)	209 (23.4)	12 (3.2)	23 (4.5)

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