The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Nephrolithiasis:

An Update on Current Concepts

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Professor of Nephrology
Isfahan University of Medical Sciences

TEHRAN 2023

Outline

1. A tale of 100 kidney stone
2. Introduction
3. Epidemiology
   - ROKS
4. Diagnosis
5. Management
6. Two articles from Iran
7. Take-Home Message

kidney INTERNATIONAL

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Articles Publish Topics About Contact

NEPHROLOGY IMAGE | VOLUME 99, ISSUE 6, P1502, JUNE 2021

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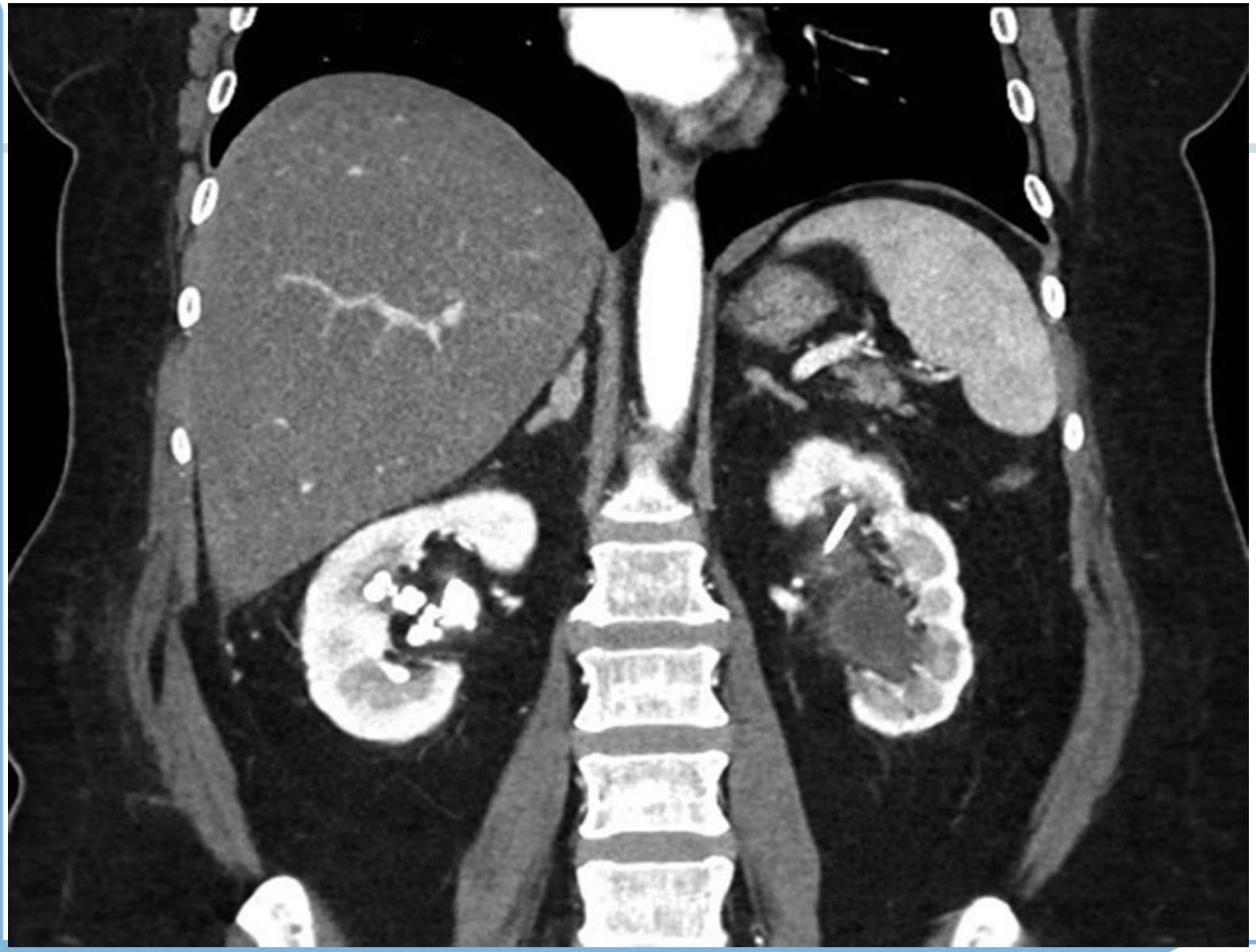
A tale of 100 kidney stones

Janina Paula T. Sy-Go • Prince Singh • James R. Gregoire

DOI: https://doi.org/10.1016/j.kint.2020.09.012 • Check for updates

A 58-year old woman with a history of Crohn's disease status



A coronal view of the CT scan showing multiple stones in the RK & a stent in the LK

Removal of > 100 kidney stones via right PCNL

AJKD

Kidney Stone Pathophysiology, Evaluation and Management: Core Curriculum 2023

Shani Shastri, Jiten Patel,* Kamalanathan K. Sambandam, and Eleanor D. Lederer*

Kidney stone disease, also known as nephrolithiasis or urolithiasis, is a disorder in which urinary solutes precipitate to form aggregates of crystalline material in the urinary space. The incidence of nephrolithiasis has been increasing, and the demographics have been evolving. Once viewed as a limited disease with intermittent exacerbations that are simply managed by urologists, nephrolithiasis is now recognized as a complex condition requiring thorough evaluation and multifaceted care. Kidney stones are frequently manifestations of underlying systemic medical conditions such as the metabolic syndrome, genetic disorders, or endocrinopathies. Analysis of urine chemistries and stone composition provide a window into pathogenesis and direct ancillary studies to uncover underlying diseases. These studies allow providers to devise individualized strategies to limit future stone events. Given its complexity, kidney stone disease is best addressed by a team led by nephrologists and urologists with input from multiple other health professionals including dietitians, endocrinologists, interventional radiologists, and endocrine surgeons. In this installment of *AJKD*'s Core Curriculum in Nephrology, we provide a case-based overview of nephrolithiasis, divided by the individual stone types. The reader will gain a pragmatic understanding of the pathophysiology, evaluation, and management of this condition.

Complete author and article information provided at end of article.

**S.S. and J.P. contributed equally to this work.*

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doi: 10.1053/j.ajkd.2023.03.017

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Shastri S. AJKI. 2023

Introduction

- ✓ Nephrolithiasis describes a **syndrome** characterized by the development of solid crystalline masses within the urinary space of the kidney.
- ✓ Predisposing factors can be genetic, metabolic, & environmental.
- ✓ Nephrolithiasis is now recognized as a marker for **systemic disease** & a predictor of metabolic & CV complications.

Shastri S. AJKI. 2023

The Medical Community's Perspective on Nephrolithiasis

Primarily urologic illness

→ Chronic medical condition requiring long-term surveillance & management

Shastri S. AJKI. 2023

Epidemiology

- ✓Nephrolithiasis is common, affecting approximately 1 in 11 people in the US.
- ✓By age 70, 19.1% of men & 9.4% of women report ever having a kidney stone.

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Epidemiology

- ✓The M/F ratio has decreased from 3:1 to about 2:1 in the past 2 decades, attributed to an increasing prevalence of obesity.
- ✓Obesity & DM are strongly associated with a history of kidney stones in multivariate models, particularly for women.

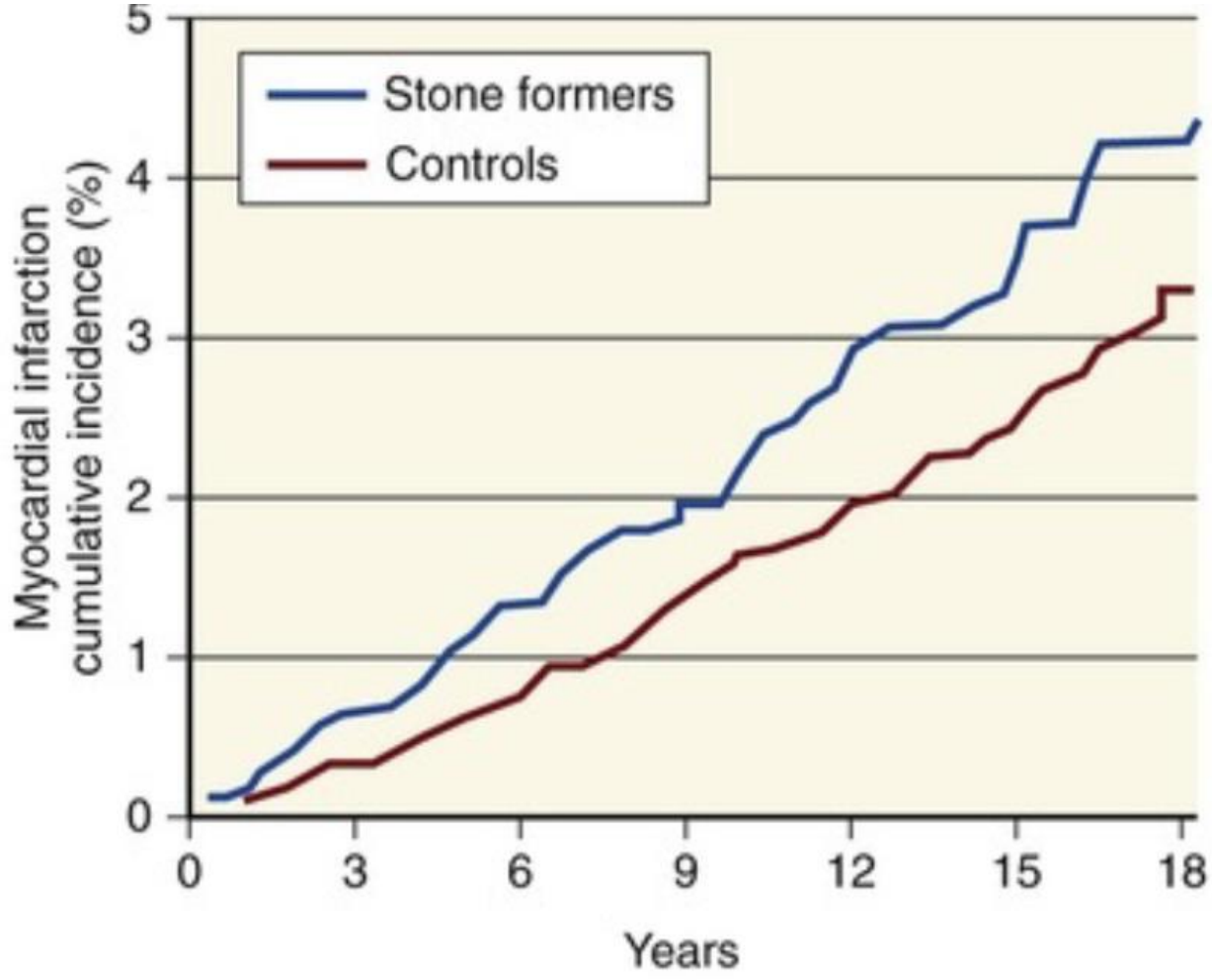
Shastri S. AJKI. 2023

Epidemiology

- ✓Nephrolithiasis has been associated with significant morbidity beyond the urologic system including:
  - CKD
  - Cardiovascular disease
    - HTN
    - Possibly increased carotid wall thickness
    - MI
  - Reduced BMD & fractures

Shastri S. AJKI. 2023

Increased Risk for MI in Stone Formers



Incidence (no. at risk)

Control	0 (10,860)	0.8 (6,689)	2 (3,184)	4.2 (1,010)
Stone formers	0 (4,564)	1.3 (2,686)	3 (1,276)	5.2 (404)

During a mean of 9 ys of f/u, stone formers had a 38% (95% CI 7 - 77%) increased risk for MI, which remained at 31% (95% CI 2 -69%) after adjustment for CKD & other comorbidities.

Rule AD. JASN.2010

Epidemiology

✓The risk of stone recurrence: 50% in 5-10 ys & 75% in 20 ys.

✓Risk factors for recurrent stones:

- Multiple prior stone episodes
- Younger age of onset
- Male gender
- FH of kidney stones
- Higher BMI
- Presence of ≥ 2 stones across both kidneys, the presence of stones in the renal pelvis or lower kidney pole
- A stone composition consisting of uric acid, struvite, or brushite

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Epidemiology

✓The online Recurrence of Kidney Stone (ROKS) nomogram estimates the risk of recurrence at varying time points in symptomatic stone-formers using baseline characteristics.

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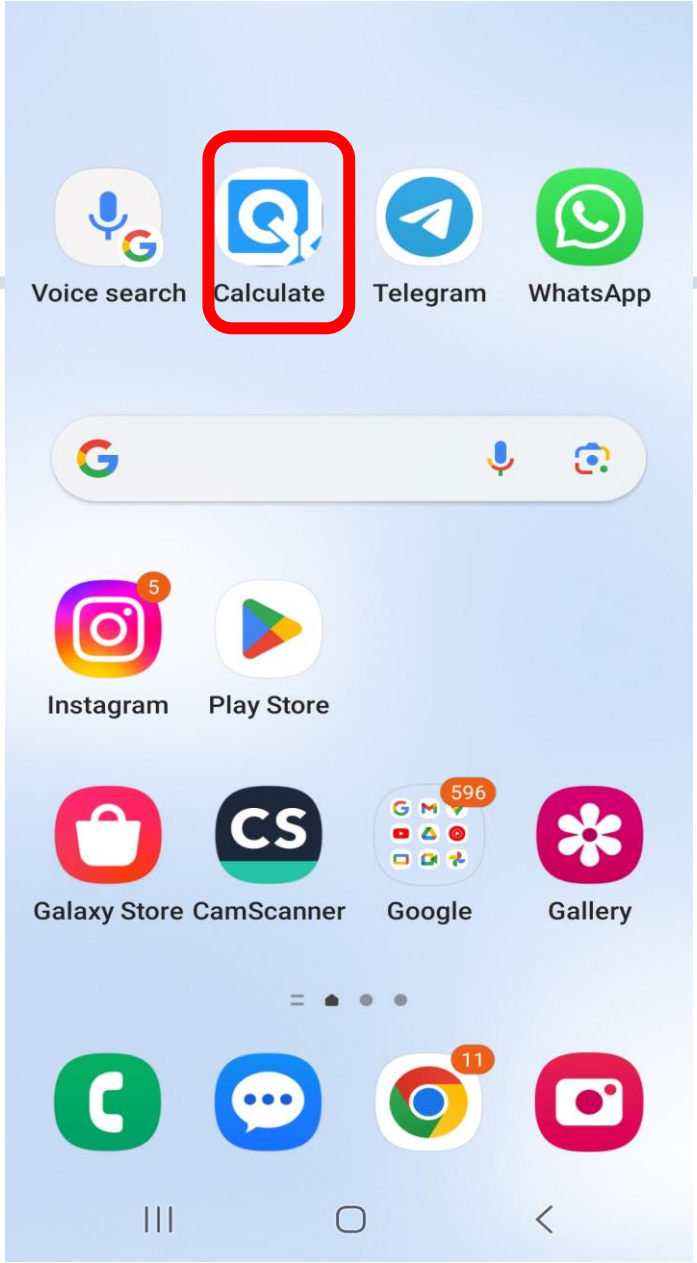
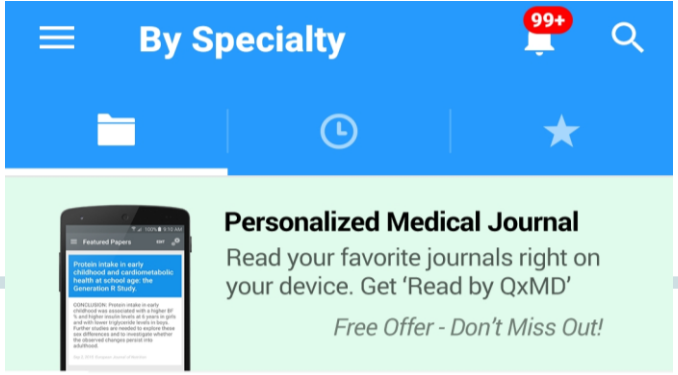
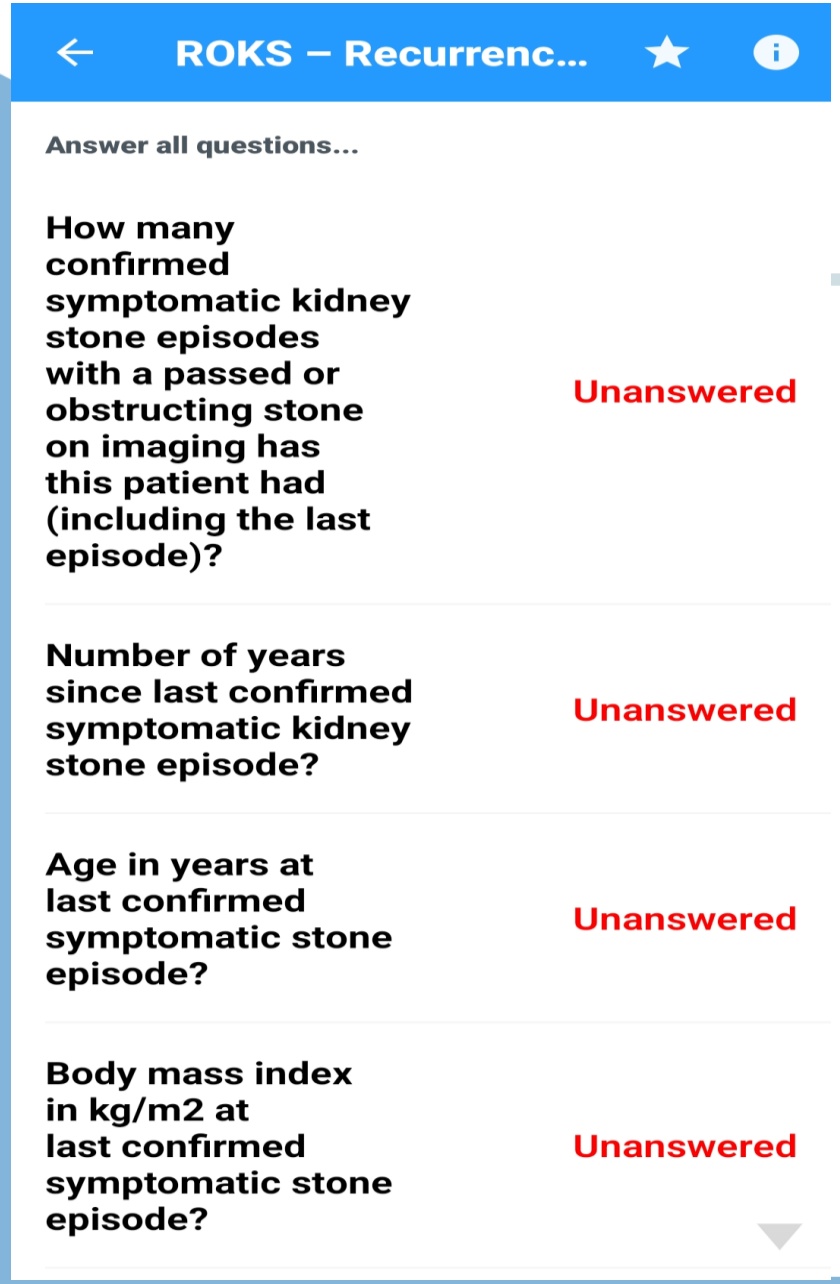
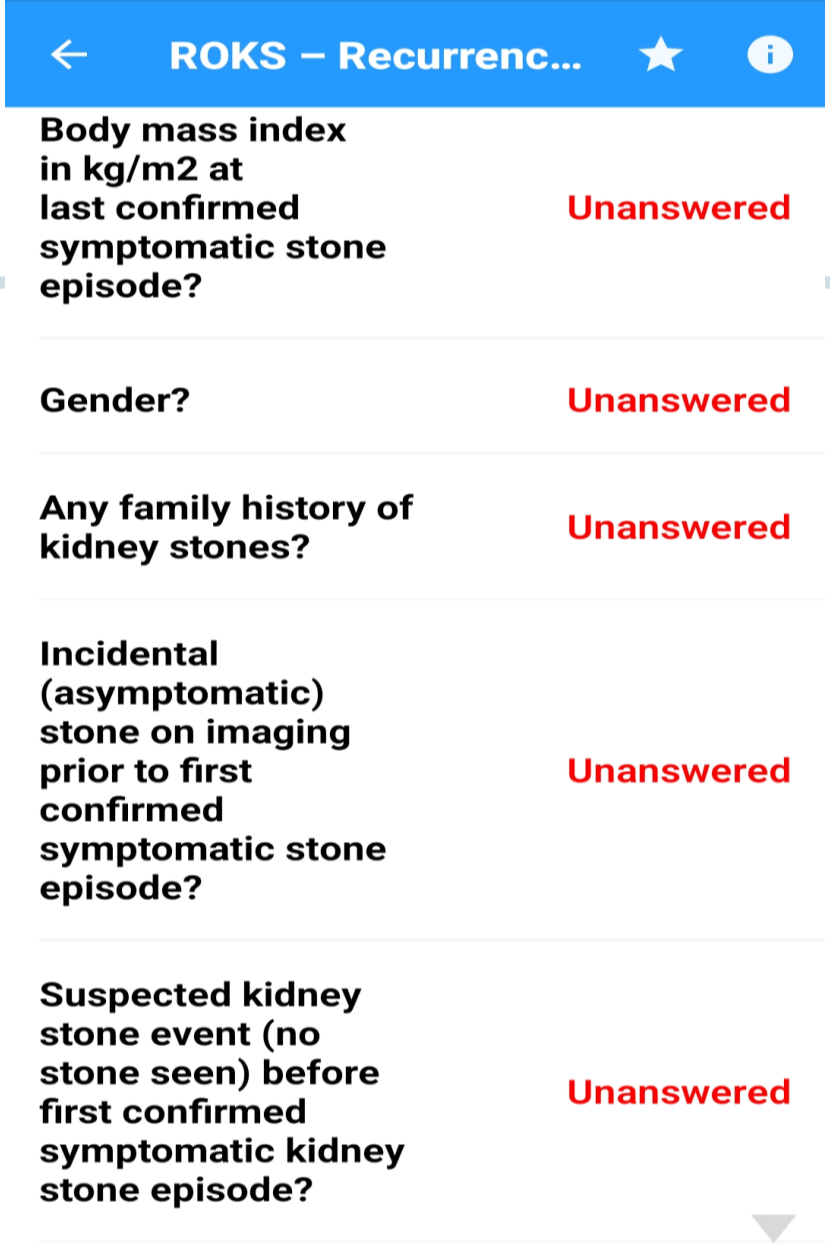
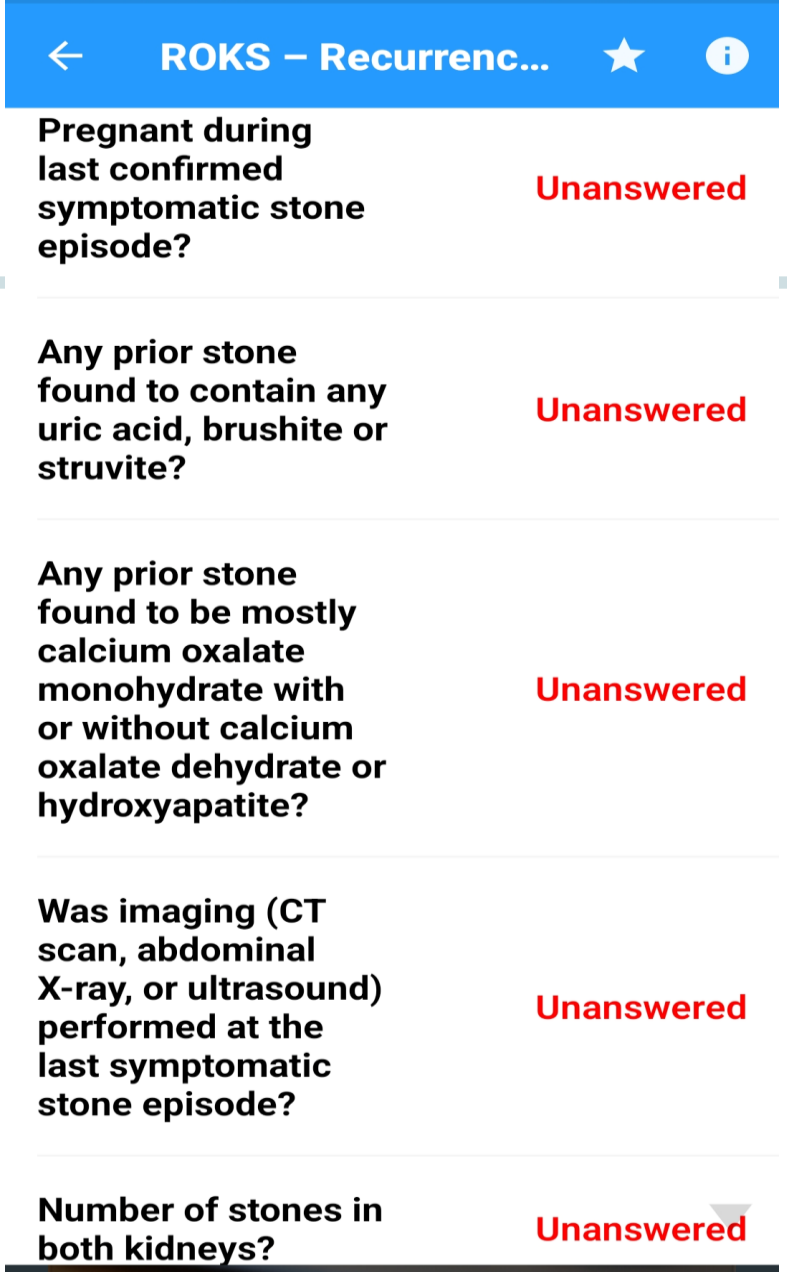


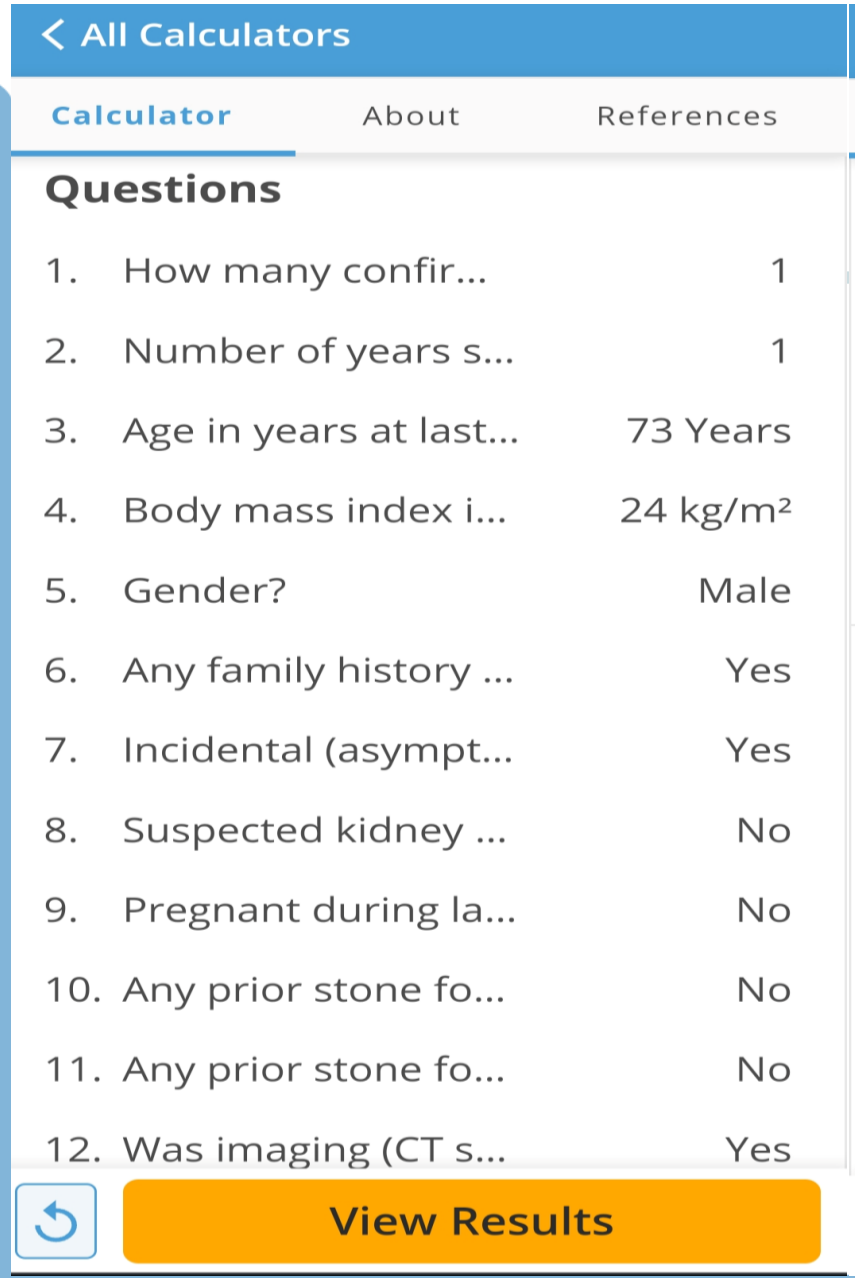


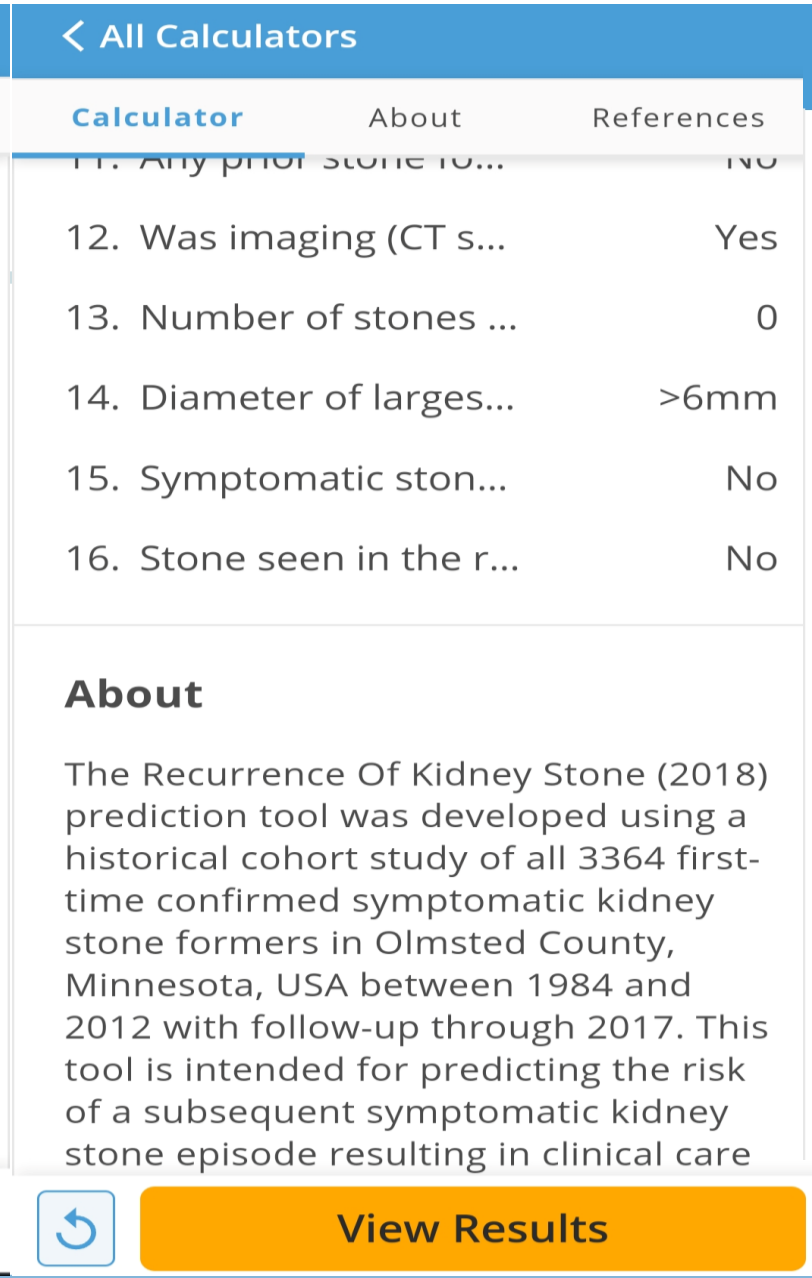
- General Calculators
- Nephrology
  - Acute Kidney Injury
  - Nephrolithiasis
    - ROKS - Recurrence Of Kidney Stone (2014)
      Predict risk of recurrent kidney stones
    - ROKS – Recurrence Of Kidney Stone (2018)
      Predict the risk of a future symptomatic kidney stone after the last symptomatic
  - Pathology

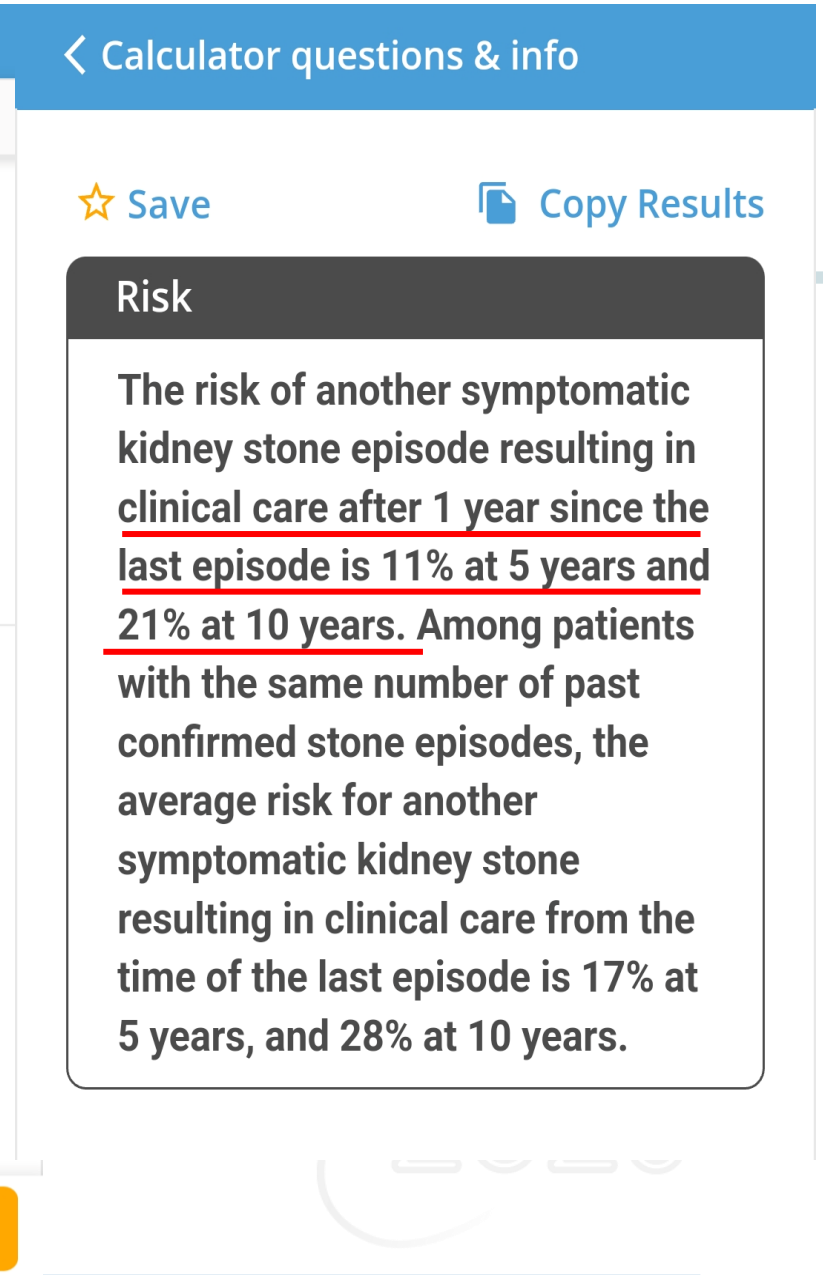

ROKS – Recurrenc...
Answer all questions...
How many confirmed symptomatic kidney stone episodes with a passed or obstructing stone on imaging has this patient had (including the last episode)?
Unanswered
Number of years since last confirmed symptomatic kidney stone episode?
Unanswered
Age in years at last confirmed symptomatic stone episode?
Unanswered
Body mass index in kg/m2 at last confirmed symptomatic stone episode?
Unanswered


ROKS – Recurrenc...
Body mass index in kg/m2 at last confirmed symptomatic stone episode?
Unanswered
Gender?
Unanswered
Any family history of kidney stones?
Unanswered
Incidental (asymptomatic) stone on imaging prior to first confirmed symptomatic stone episode?
Unanswered
Suspected kidney stone event (no stone seen) before first confirmed symptomatic kidney stone episode?
Unanswered


ROKS – Recurrenc...
Pregnant during last confirmed symptomatic stone episode?
Unanswered
Any prior stone found to contain any uric acid, brushite or struvite?
Unanswered
Any prior stone found to be mostly calcium oxalate monohydrate with or without calcium oxalate dehydrate or hydroxyapatite?
Unanswered
Was imaging (CT scan, abdominal X-ray, or ultrasound) performed at the last symptomatic stone episode?
Unanswered
Number of stones in both kidneys?
Unanswered


All Calculators
Calculator
About
References
Questions
1. How many confir... 1
2. Number of years s... 1
3. Age in years at last... 73 Years
4. Body mass index i... 24 kg/m²
5. Gender? Male
6. Any family history ... Yes
7. Incidental (asympt... Yes
8. Suspected kidney ... No
9. Pregnant during la... No
10. Any prior stone fo... No
11. Any prior stone fo... No
12. Was imaging (CT s... Yes
View Results


All Calculators
Calculator
About
References
12. Was imaging (CT s... Yes
13. Number of stones ... 0
14. Diameter of larges... >6mm
15. Symptomatic ston... No
16. Stone seen in the r... No
About
The Recurrence Of Kidney Stone (2018) prediction tool was developed using a historical cohort study of all 3364 first-time confirmed symptomatic kidney stone formers in Olmsted County, Minnesota, USA between 1984 and 2012 with follow-up through 2017. This tool is intended for predicting the risk of a subsequent symptomatic kidney stone episode resulting in clinical care
View Results


Calculator questions & info
Save
Copy Results
Risk
The risk of another symptomatic kidney stone episode resulting in clinical care after 1 year since the last episode is 11% at 5 years and 21% at 10 years. Among patients with the same number of past confirmed stone episodes, the average risk for another symptomatic kidney stone resulting in clinical care from the time of the last episode is 17% at 5 years, and 28% at 10 years.

Diagnosis

clinical investigation

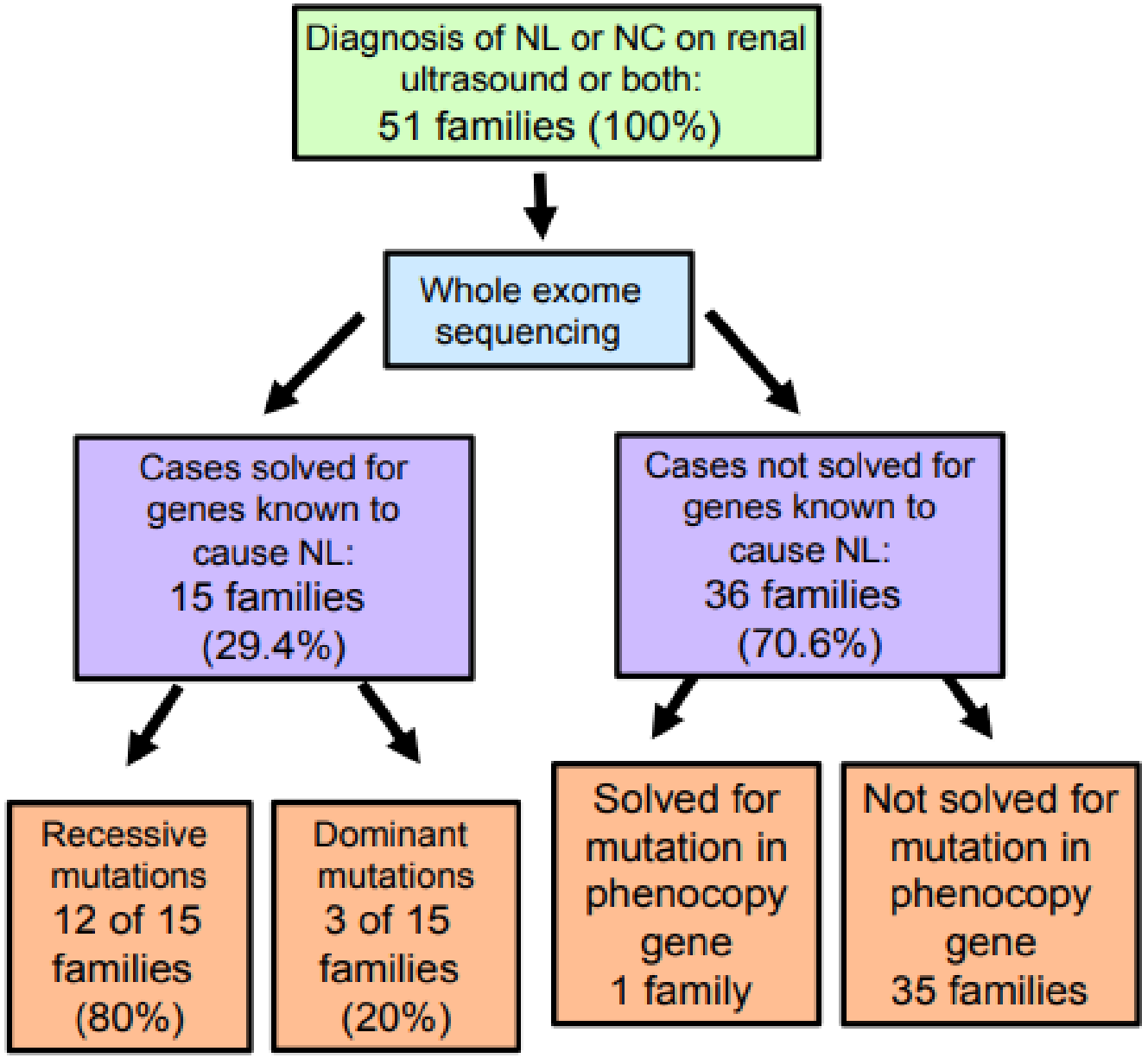
www.kidney-international.org

2018

Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis

see commentary on page 15

Ankana Daga[1,20], Amar J. Majmundar[1,20], Daniela A. Braun[1], Heon Yung Gee[2], Jennifer A. Lawson[1], Shirlee Shril[1], Tilman Jobst-Schwan[1], Asaf Vivante[1], David Schapiro[1], Weizhen Tan[1], Jillian K. Warejko[1], Eugen Widmeier[1], Caleb P. Nelson[3], Hanan M. Fathy[4], Zoran Gucev[5], Neveen A. Soliman[6,7], Seema Hashmi[8], Jan Halbritter[9], Margarita Halty[10], Jameela A. Kari[11], Sherif El-Desoky[11], Michael A. Ferguson[1], Michael J.G. Somers[1], Avram Z. Traum[1], Deborah R. Stein[1], Ghaleb H. Daouk[1], Nancy M. Rodig[1], Avi Katz[12], Christian Hanna[12], Andrew L. Schwaderer[13], John A. Sayer[14], Ari J. Wassner[15], Shrikant Mane[16,17,18], Richard P. Lifton[16,17,18], Danko Milosevic[19], Velibor Tasic[5], Michelle A. Baum[1] and Friedhelm Hildebrandt[1]



Flow diagram on detection by whole exome sequencing of causative monogenic mutations in 30% nephrolithiasis or nephrocalcinosis or both (NL/NC) genes in 51 families with NL/NC

Daga A. KI.2018

Conclusion

We established WES as an efficient approach toward a molecular genetic diagnosis in individuals with nephrolithiasis/nephrocalcinosis who manifest before age **25** years.

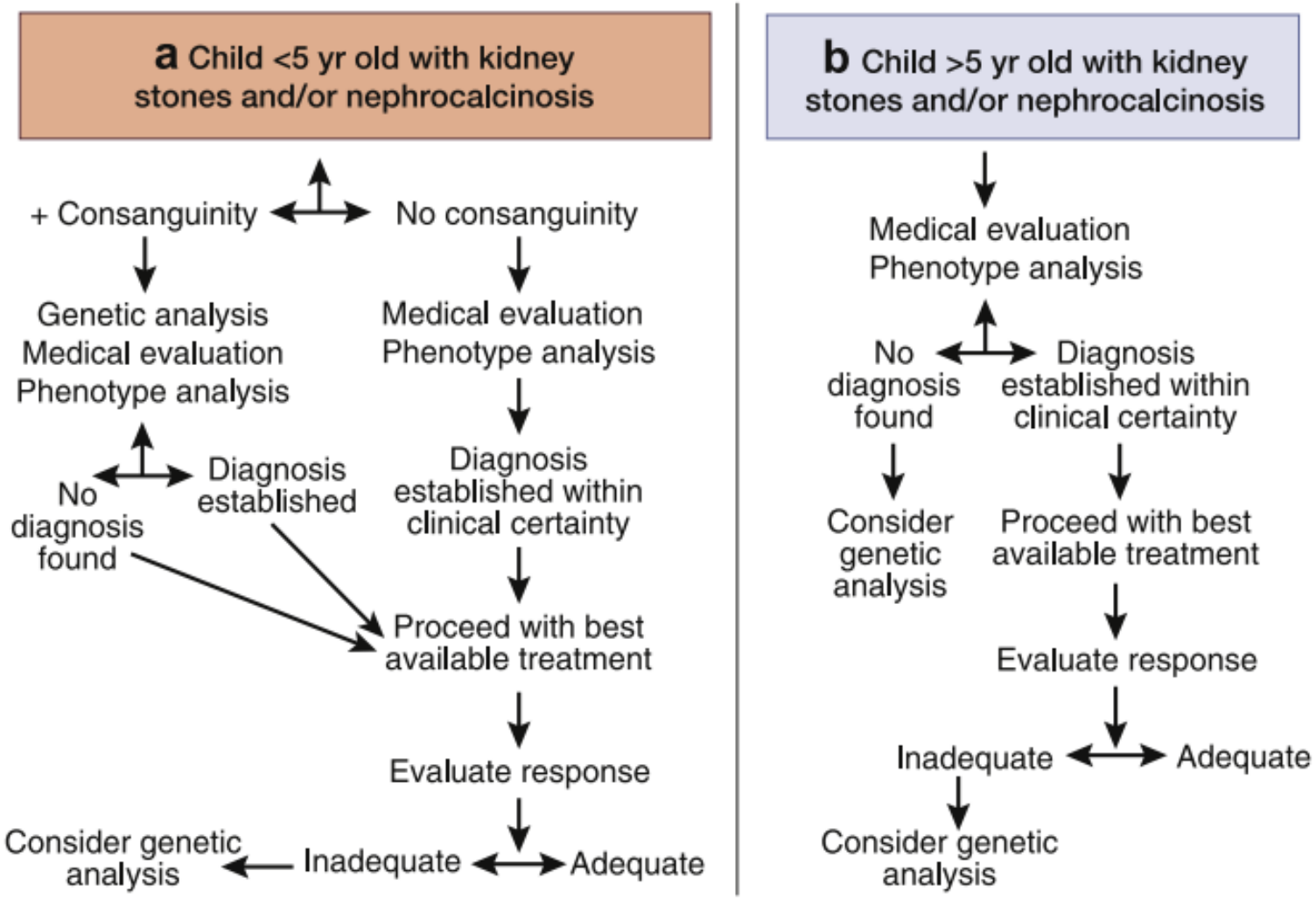
A rational approach to the use of sophisticated genetic analyses of pediatric stone disease

Craig B. Langman[1]

Kidney stone disease in the childhood years has a genetic underpinning in some. The relationships between clinical phenotype, medical evaluation, and genetic etiologies were investigated using whole-exome sequencing by the Hildebrandt laboratory. At this time, a genetic evaluation of pediatric nephrolithiasis should be reserved for specific circumstances when clinical uncertainty of the reason for the presence of the stone or therapy is not satisfactory.

Kidney International (2018) **93,** 15–18; https://doi.org/10.1016/j.kint.2017.08.023

see clinical investigation on page 204



Diagnostic approach to the care of the pediatric patient with nephrolithiasis &/or nephrocalcinosis

Langman CB. KI. 2018

Kidney Stones 2012: Pathogenesis, Diagnosis, and Management

Khashayar Sakhaee, Naim M. Maalouf, and Bridget Sinnott

Department of Internal Medicine, Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Context: The pathogenetic mechanisms of kidney stone formation are complex and involve both metabolic and environmental risk factors. Over the past decade, major advances have been made in the understanding of the pathogenesis, diagnosis, and treatment of kidney stone disease.

Evidence Acquisition and Synthesis: Both original and review articles were found via PubMed search reporting on pathophysiology, diagnosis, and management of kidney stones. These resources were integrated with the authors' knowledge of the field.

Conclusion: Nephrolithiasis remains a major economic and health burden worldwide. Nephrolithiasis is considered a systemic disorder associated with chronic kidney disease, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. Further understanding of the pathophysiological link between nephrolithiasis and these systemic disorders is necessary for the development of new therapeutic options.
***(J Clin Endocrinol Metab* 97: 1847–1860, 2012)**

Simplified ambulatory metabolic evaluation	Extensive ambulatory metabolic evaluation	Expected daily values	Results interpretation
Random 24-h urinary profile	Random 24-h urine profile and 24-h urine profile after 1 wk of dietary restrictions		
Total volume	Total volume	≥2.5 liter	Indicative of daily fluid intake. This value diminishes with low fluid intake, sweating, and diarrhea
pH	pH	5.9–6.2	Values < 5.5 increase UA precipitation. Commonly found in UA stone patients, subjects with intestinal disease and diarrhea, and in those with intestinal bypass surgery. Values > 6.7 increase CaP precipitation. Commonly found in patients with dRTA, primary hyperparathyroidism, alkali overtreatment, and carbonic anhydrase treatment. Values > 7.0–7.5 indicate a urinary tract infection as a result of urease-producing bacteria
Creatinine	Creatinine	15–25 mg/kg body weight	15–20 mg/kg body weight in females; 20–25 mg/kg body weigh in males
Sodium	Sodium	100 mEq	Reflective of dietary sodium intake, given a lack of excessive sweating and/or diarrhea
Potassium	Potassium	40–60 mEq	Reflective of dietary potassium intake, given a lack of diarrhea
Calcium	Calcium	≤250–300 mg	There may be differences in male and female subjects. A higher value is expected in males
Magnesium	Magnesium	30–120 mg	Low urinary magnesium is detected with low magnesium intake, intestinal malabsorption (small bowel disease), and after bariatric surgery
Oxalate	Oxalate	≤45 mg	Commonly encountered with intestinal fat malabsorption and after bariatric surgery. Values > 100 mg/d may indicate primary hyperoxaluria
Phosphorus	Phosphorus	≤1100 mg	Indicative of dietary phosphorus intake and absorption. A higher excretion may increase the risk of CaP stone formation
UA	UA	600–800 mg	Hyperuricosuria is encountered with the overindulgence of purine-rich foods such as red meat, poultry, and fish
Sulfate	Sulfate	≤25–30 mmol	Sulfate is a marker of an acid-rich diet that occurs as a result of increased oxidation of sulfur-rich amino acids (methionine) found in meat and meat products
Citrate	Citrate	≥320 mg	An inhibitor of calcium stone formation. Hypocitraturia is commonly encountered in metabolic acidosis, dRTA, chronic diarrhea, excessive protein ingestion, strenuous physical

Diagnostic evaluation & interpretation of laboratory profiles

Sakhaee K. J Clin Endoc Metab. 2012

Ammonium	Ammonium	30–40 mEq	Ammonium is a major buffer that neutralizes hydrogen protons secreted by the kidney. Its excretion corresponds with urinary sulfate (acid load). A higher ammonium:sulfate ratio indicates gastrointestinal alkali loss
Chloride	Chloride	100 mEq	Chloride values also correspond with sodium intake
Cystine	Cystine	<30–60 mg	Cystine has a limited urinary solubility at 250 mg/liter
	2-h fasting Ca:Cr ratio	<0.11 mg/100 ml glomerular filtrate	Elevated fasting Ca:Cr, high serum calcium, and elevated PTH are suggestive of primary hyperparathyroidism. Elevated fasting Ca:Cr, normal serum calcium, and normal or suppressed PTH are suggestive of resorptive hypercalciuria. Elevated fasting Ca:Cr, normal serum calcium, and elevated PTH are suggestive of renal hypercalciuria
	4-h Ca:Cr ratio after a 1-g oral calcium load	≤0.20 mg/mg Cr	Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciuria
Simplified fasting blood chemistries	Extensive fasting blood chemistries		
Complete metabolic panel	Complete metabolic panel	Variable[a]	Low serum potassium, high serum chloride, and low serum total CO_2 content are suggestive of a diarrheal state of dRTA
PTH	PTH	10–65 pg/ml[a]	High serum calcium, low serum phosphorus, and high PTH are suggestive of primary hyperparathyroidism
	$1,25(OH)_2D$	Variable[a]	Normal serum calcium, normal PTH, and elevated $1,25(OH)_2D$ are suggestive of absorptive hypercalciuria. Normal serum calcium, normal PTH, low serum phosphorus, and elevated $1,25(OH)_2D$ are suggestive of renal phosphorus leak
	Other evaluations		
	Bone mineral density measurements (DXA)	Z-score > −2; T-score > −2.5	Z-score < −2 or T-score < −2.5 indicates bone loss. This finding may be more prevalent in hypercalciuric kidney stone formers

These limits are mean + 2 SD (for calcium, oxalate, UA, pH, sodium, sulfate, and phosphorus) or mean − 2 SD (for citrate, pH, and magnesium) from normal. ACE, Angiotensin-converting enzyme; DXA, dual-energy x-ray absorptiometry.

Sakhaee K. J Clin Endoc Metab. 2012

Interpreting 24-Hour Urine Studies to Address Risk for Recurrent Stones

Creatinine
- Allows an assessment of the completeness of 24-hour collection.
- Expect 15-20 mg/kg/d for females and 20-25 mg/kg/d for males.

Total Volume
- A goal of 2.5 L/d, sometimes more, is typical for reducing recurrence risk.

Calcium
- Though > 4 mg/kg is clearly excessive, a graded increase in stone risk is noted with levels > 150 mg/d.
- Correlate with urine sodium to determine of hypercalciuria is driven by excessive sodium intake.

Sodium
- A goal of <100 mg/d is sought if hypercalciuria is present.

Oxalate
- Values > 40 mg/d are excessive, though lower excretion rates may also increase risk.
- For values > 80 mg/d, consider primary hyperoxaluria.

Citrate
- Values > 400 mg/d may limit risk for calcareous stones, with even higher levels sometimes needed.

pH
- Values < 6.0 may increase the risk of uric acid stones.
- Values > 6.0 with metabolic acidosis suggests renal tubular acidosis and a risk for calcium phosphate stones.
- Values > 7.0 may indicate urine infection by bacteria with urease and a risk for struvite stones.

Uric Acid
- Consider xanthine oxidase inhibitor or reduced purine intake if >750-800 mg/d and other measures for calcium oxalate stones or uric acid stones fail.

Ammonium
- Values of >45 mmol/d suggest excess acid production from diet, chronic diarrhea, or other cause.

Sulfate
- Values of >30 mmol/d suggest excessive dietary animal protein.

Cystine
- Normal individuals typically excrete < 30 mg/d.
- Patients with cystinuria generally excrete > 400 mg/d.
- For cystinuria patients, target a concentration < 250 mg/L to limit stone risk.

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Management

Tips to Reduce Your Sodium Intake

- ✓ Adults should aim to consume **< 2.3 gr/d**
- ✓ One teaspoon of table salt has 2.3 g of sodium
- ✓ Check the %DV for Na on the Nutrition Facts label found on many foods.
- ✓ Low in Na is ≤ 5%, & high in Na is ≥ 20%.

National Institute of Diabetes and Digestive and Kidney Diseases

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 2, 2023 VOL. 388 NO. 9

Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Nasser A. Dhayat, M.D., Olivier Bonny, M.D., Ph.D., Beat Roth, M.D., Andreas Christe, M.D., Alexander Ritter, M.D., Nilufar Mohebbi, M.D., Nicolas Faller, M.D., Ph.D., Lisa Pellegrini, M.D., Giulia Bedino, M.D., Reto M. Venzin, M.D., Philipp Grosse, M.D., Carina Hüsler, M.D., Irene Koneth, M.D., Christian Bucher, M.D., Rosaria Del Giorno, M.D., Luca Gabutti, M.D., Michael Mayr, M.D., Urs Odermatt, M.D., Florian Buchkremer, M.D., Thomas Ernandez, M.D., Catherine Stoermann-Chopard, M.D., Daniel Teta, M.D., Bruno Vogt, M.D., Marie Roumet, Ph.D., Luca Tamò, Ph.D., Grazia M. Cereghetti, Ph.D., Sven Trelle, M.D., and Daniel G. Fuster, M.D.

ABSTRACT

Dhayat NA. NEJM. 2023

Methods

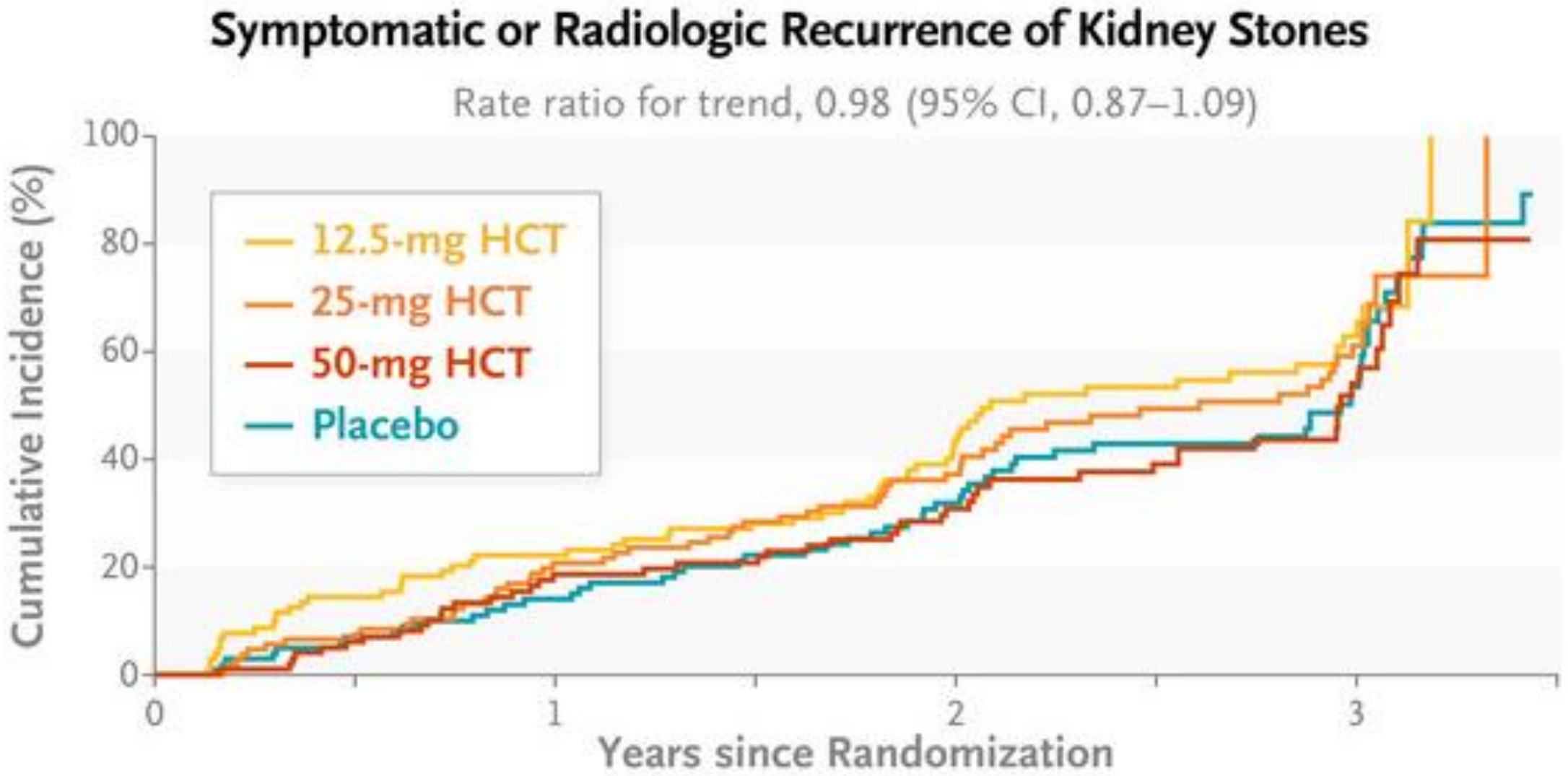
- ✓In this double-blind trial, we randomly assigned patients with recurrent ca containing kidney stones to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily.
- ✓The main objective was to investigate the dose–response effect for the primary end point, a composite of symptomatic or radiologic recurrence of kidney stones.
- ✓Safety was also assessed.

Dhayat NA. NEJM. 2023

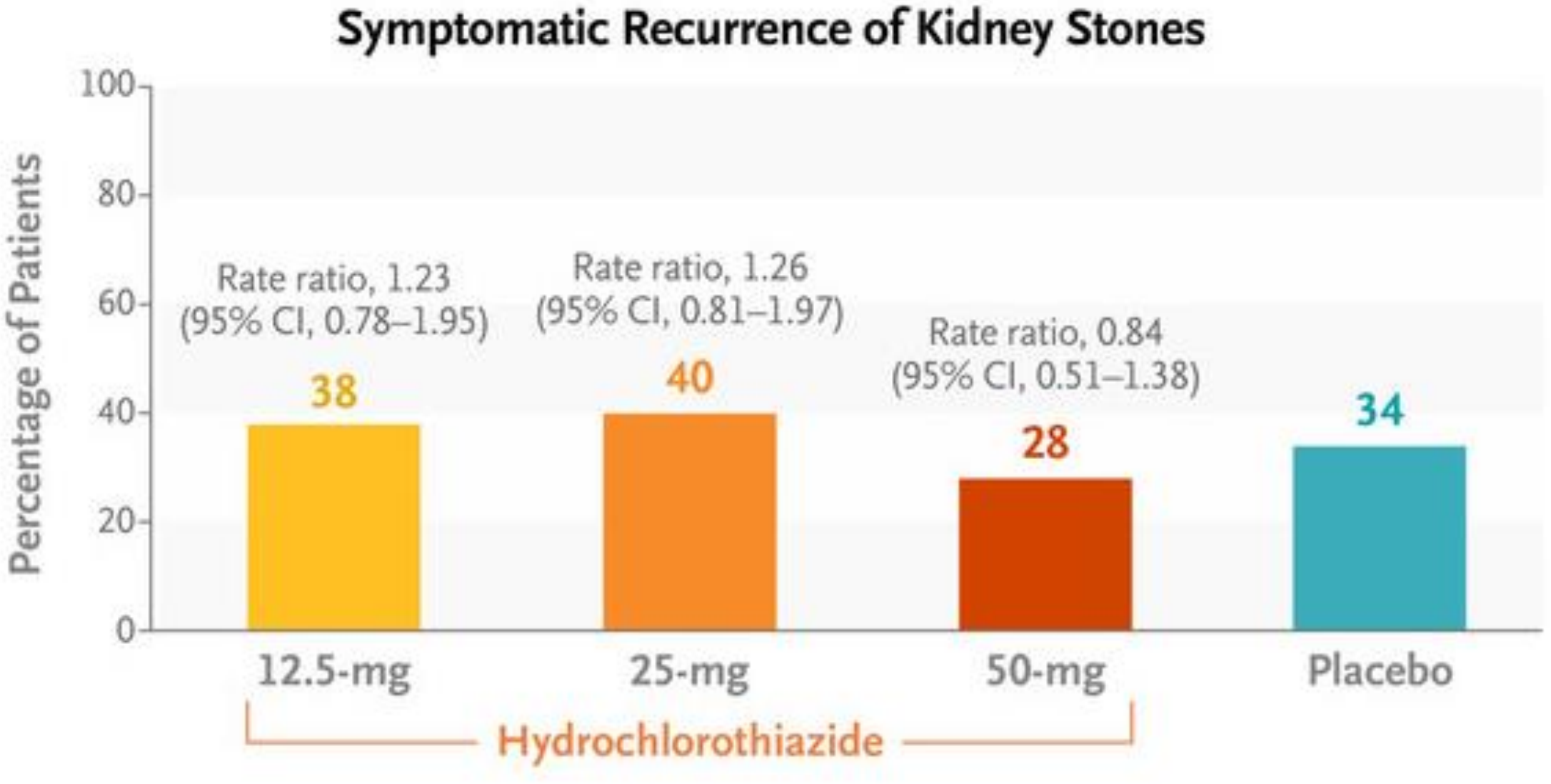
Results

- ✓In all, **416** patients underwent randomization and were followed for a median of **2.9** ys.
- ✓A primary end-point event occurred in:
  - 60 of 102 patients (59%) in the placebo group
  - 62 of 105 patients (59%) in the 12.5-mg hydrochlorothiazide group
  - 61 of 108 patients (56%) in the 25-mg hyd. group
  - 49 of 101 patients (49%) in the 50-mg hyd. group.
- ✓There was no relation between the hydrochlorothiazide dose & the occurrence of a primary end-point event (P=0.66).

Dhayat NA. NEJM. 2023

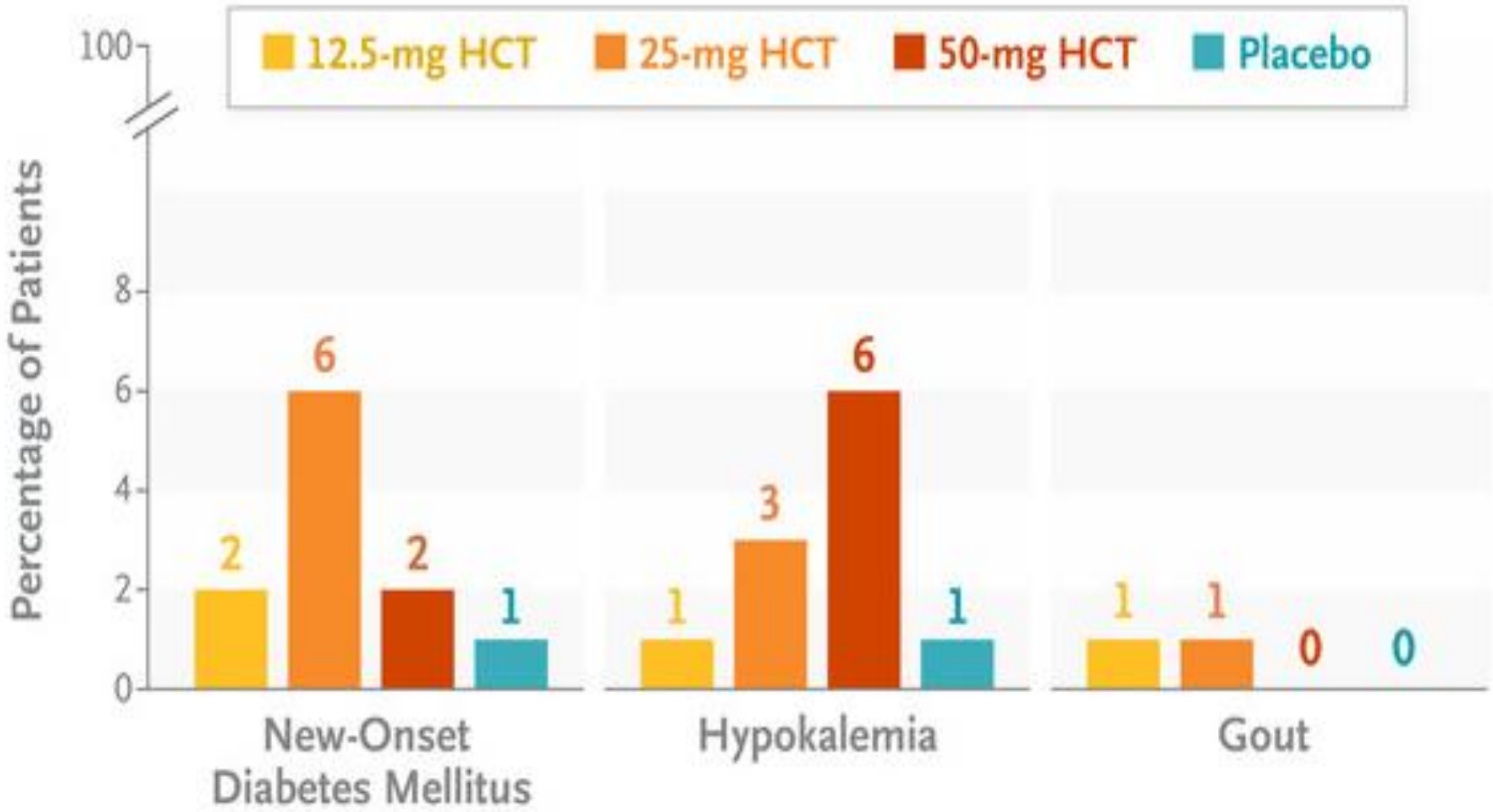


Dhayat NA. NEJM. 2023



Dhayat NA. NEJM. 2023

Selected Adverse Events of Special Interest



Dhayat NA. NEJM. 2023

Conclusion

- ✓ Among patients with recurrent kidney stones, the incidence of recurrence **did not appear** to differ substantially among patients receiving hydrochlorothiazide once daily at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily.

Dhayat NA. NEJM. 2023

clinical nephrology

Leave NOSTONE unturned: are thiazides useless in preventing kidney stone recurrence?

François Brazier[1,2], Nicolas Cornière[1,2] and Dominique Eladari[1,2]

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Correspondence: Dominique Eladari, Centre de dépistage et de Médecine de précision des Maladies Rénales, Service de Néphrologie, Centre Hospitalier Universitaire Amiens-Picardie, 1 rond-point du Professeur Christian Cabrol, F-80000 Amiens, France. E-mail: dominique.eladari@inserm.fr

Refers to: Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and prevention of kidney-stone recurrence. *N Engl J Med*. 2023;388:781–791.

Kidney International (2023) **104,** 640–643; https://doi.org/10.1016/j.kint.2023.06.030

KEYWORDS: diuretics; kidney stones; nephrolithiasis; urolithiasis

Nephrolithiasis, or kidney stone disease, is the second most frequent kidney disease after hypertension, affecting up to approximately 20% of men and approximately 10% of women in industrialized countries. The prevalence of nephrolithiasis has consistently increased over the last 50 years.[1] Nephrolithiasis represents a considerable burden for health care systems, with the total health care expenditure for kidney stones exceeding US $10 billion in 2006 in the United States alone.[2]

Kidney stones are commonly recurrent, with up to 15%, 30%, and 50% of individuals experiencing a second episode within 3, 5, or 10 years of their initial presentation,

Are thiazides useless in preventing kidney stone recurrence?

1. At randomization, half of the participants in NOSTONE exhibited a urine Na output 168 mmol/24 hs (equivalent to daily NaCl intake of approximately 9 g/24 hs), indicating very poor dietary control.
2. Poor dietary control persisted throughout F/U with mean urine output remaining < 2.15 liters/24 hs & mean urine Na excretion >181 mmol/24 hs.
3. Urine oxalate excretion was also relatively high during the F/U period.

Brazier F. KI. 2023

Are thiazides useless in preventing kidney stone recurrence?

✓Indeed, thiazide diuretics are generally recommended as second-line therapy after dietary control which includes:

- Increased water intake of > 2.5 liters/d
- The reduction of salt

Brazier F. KI. 2023

Conclusion

✓The NOSTONE trial provides:

- Hydrochlorothiazide is ineffective at reducing the recurrence of symptomatic kidney stones at 3 ys in the absence of dietary control including abundant water intake & reduced dietary Na.
- However, additional studies are required to conclude that hydrochlorothiazide is a useless therapy for kidney stone recurrence

Clinical Follow-up

- ✓ Annual clinical visit

1. Medical history
2. PE
3. Laboratory examination for full serum chemistries & urine profiles
4. Ultrasonography

Sakhaee K. J Clin Endoc Metab. 2012

Overview of K.Citrate Administration in Different Types of Calculi

Type of calculus	Indication	Urinary pH goal	Dose
Calcium	• Low urinary pH or hypocitraturia • Added to thiazide despite normal urine calcium level on thiazide • Recurrent calculus formers whose metabolic profile is normal or has been normalized (alone or combined with thiazide)	5.5 to 6.5	10 mEq to 20 mEq, 2 to 3 times per day
Uric acid	All	6.0 to 7.0	10 mEq to 20 mEq, 3 times per day
Cystine	All	7.0 to 7.5	15 mEq to 30 mEq, 3 times per day

Shadman A. IJKD. 2017

Indication for Cystine-binding Thiol Drugs

✓Cystine-binding thiol drugs should be prescribed in patients with:

- Large calculus burden
- Keep forming calculi on conservative treatment
- Fail to achieve the desirable urinary pH (7.0 to 7.5) on medical treatment
- Fail to lower urine cystine concentration < 243 mg/L
- Persistent cystine crystals in urinalysis despite conservative management.

✓ Tiopronin is preferred over D-penicillamine due to fewer adverse events & possibly more effectiveness.

Shadman A. IJKD. 2017

An Epidemiological Survey on Kidney Stones and Related Risk Factors in the Iranian Community

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Abstract- Increasing number of patients with kidney stones is a major worldwide concern that needs more attention for recognizing the disease in order to set up suitable prevention systems. In this study, we aimed to assess the prevalence and related risk factors of kidney stones in our local area (Isfahan, Iran). In 2011, we celebrated World Kidney Day (WKD) with several training programs for informing people about kidney diseases. A questionnaire containing demographic data, past medical history, and familial and self-history of kidney disease was fulfilled by each individual who participated in WKD. Blood pressure and body mass index (BMI) were also measured using standard methods. Statistical analysis with SPSS-20 software was done. 556 participants with a mean age of 44.69±15.32 were included in the study, of which 107 cases (19.2%) with a mean age of 50.24±12.33 had a kidney stone, and 449 cases (80.8%) with a mean age of 44.69±15.32 had no

Variables		History of kidney stone		Total	P
		Yes	No		
Daily work	High activity	16(21%)	60(13.4%)	76(13.7%)	0.91
	Low activity	91(85%)	389(86.6%)	480(86.3%)	
Place of living	Isfahan (Urban area)	64(59.8%)	271(60.3%)	335(60.3%)	0.92
	Rural area near Isfahan	37(34.6%)	157(35%)	194(34.9%)	
	Other cities	6(5.6%)	21(4.7%)	27(4.8%)	
Diabetes Mellitus	Present	23(21.5%)	64(14.2%)	87(15.6%)	0.64
	Absent	84(78.5%)	385(85.8%)	469(84.4%)	
Cardiovascular diseases	Present	13(12.1%)	26(5.8%)	39(7%)	0.02
	absent	94(87.9%)	423(94.2%)	517(93%)	
Hypertension	Present	36(33.6%)	86(19.1%)	122(21.9%)	0.001
	Absent	71(66.4%)	363(80.9%)	434(78.1%)	
Vitamin C consumption	Yes	2 (1.9%)	9(2.1%)	11(1.9%)	0.21
	No	105 (98.1%)	440(97.9%)	545(98.1%)	
Vitamin D consumption	Yes	2(1.9%)	11(2.5%)	13(2.3%)	0.13
	no	105(98.1%)	438(97.5%)	543(97.7%)	
Familial history of kidney stone	No	57(53.3%)	343(76.4%)	400(71.9%)	<0.001
	First degree	46(43%)	93(20.7%)	139(25%)	
	Second degree	4(3.7%)	13(2.9%)	17(3.1%)	
Total		107(19.2%)	449(80.8%)	556(100%)	-

Probable risk factors of kidney stone

KIDNEY DISEASES IJKD

Review

Metabolic Disorders in Patients with Nephrolithiasis in Iran

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Keywords. Nephrolithiasis, Urolithiasis, Kidney Stone, Renal Calculi, Metabolic Disease, Etiology, Iran

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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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

Characteristics of the Included Studies

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)

Take-Home Message

1. Nephrolithiasis is a common problem that is increasing in prevalence & is associated with significant morbidity.
2. Although urinary supersaturation is a necessary substrate for stone formation, it is not sufficient.
3. Local & systemic factors interact with supersaturated solutes to cause stones.
4. These systemic factors can have important consequences beyond the urologic system, including adverse effects on bone & cardiovascular health.

Take-Home Message

5. Lowering supersaturation is a fundamental principal in management.

6. Additional interventions are tailored to the type of stone formed as well as the clinical context.

7. Often a multidisciplinary approach led by nephrologists & urologists is needed for optimal management.

Thanks for Your Attention

TEHRAN 2023