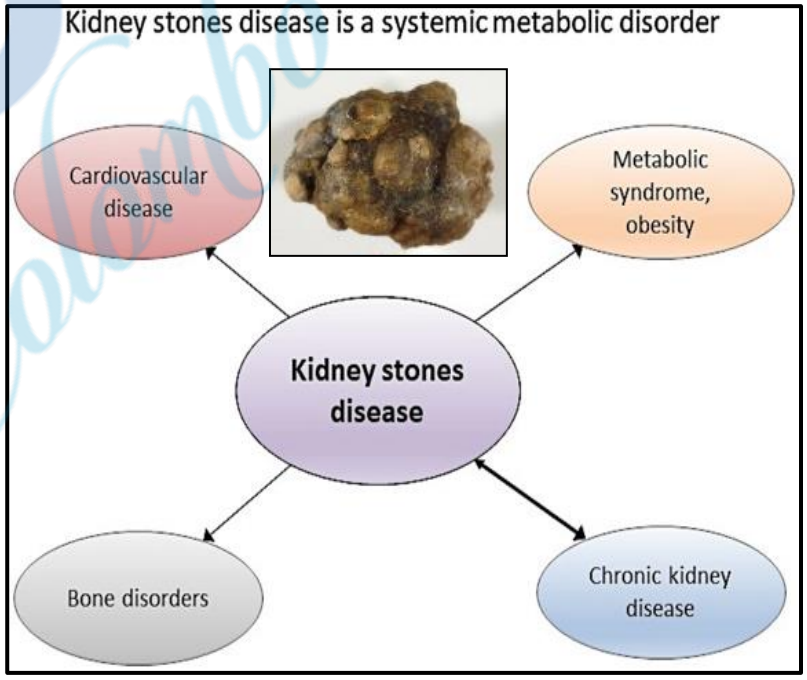
Stones, Bones, Metabolic Syndrome: shared pathophysiological features and treatment strategies

Virginia L Hood MBBS, MPH, MACP, 2025

Objectives:

- Describe overlapping pathogenic, dietary and metabolic features of kidney stones, osteoporosis and metabolic syndrome
- Discuss evidence for dietary changes and medications to treat and reduce risk factors for these conditions
- Outline monitoring strategies



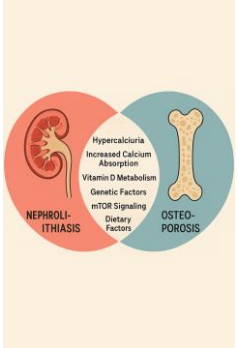
Disclosures: none; **Acknowledgements:** Desiree DeWaal, MS, RD

Common threads connecting stones, bones and metabolic syndrome

Epidemiology:

Consequences: Morbidity, mortality, cost, associated conditions

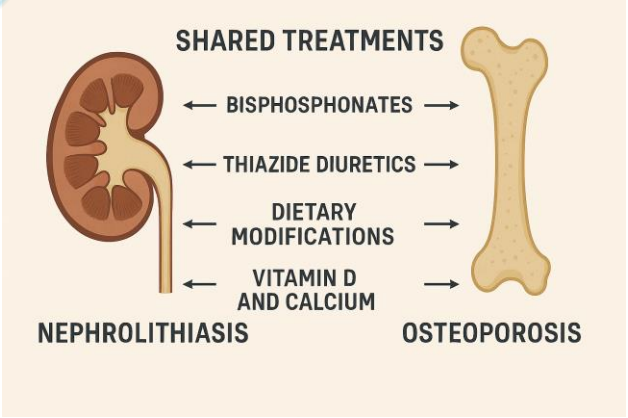
Pathogenesis:



- Environmental
- Genetic
- Metabolic: hypercalciuria, hypocitraturia,
- Diet: protein, calcium, sodium, citrate, processed foods
- Lifestyle: exercise, supplements
- Disorders, medications

Treatments:

- Dietary modification
- Thiazide diuretics
- SGLT2i, GLP1 agonists
- Bisphosphonates
- Citrate supplements



Monitoring:

24 h urines, spot urines, renal imaging, DXA, other markers

Kidney stones and osteoporosis have a high prevalence globally and are increasing and costly

- **1/10 people over a lifetime have a kidney stone**
  increased from 3.8% (1976-80) to 8.8% (2007-10), *NHANES*
  rates vary from 13% in North America, 9% in Europe, 5% in Asia [3,4.]
- **recurrence rate: 75% over 20 years**
  more common in M and those with FH of stones
- **cost for stones: US $ 2.55 B in 2024; will be $4.02B in 2034**

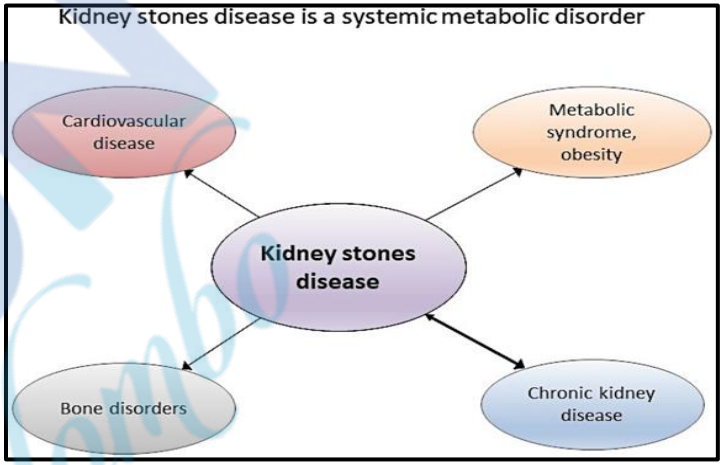
- **osteoporosis affects > 20% F & > 11% M worldwide (2021)**
  Fragility fracture risk in those > 50y is 40% for F and 20% for M over their remaining lifetime[1,2, 5]
- **cost for fractures will increase. $57B before 2019, $95B in 2040[5]**

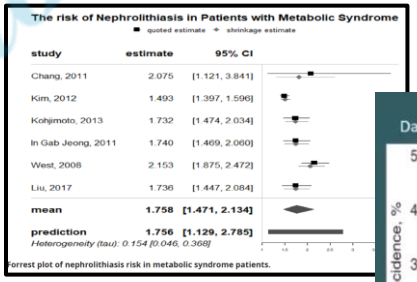
- **Metabolic syndrome affects 1/3 people globally; 42% central obesity, 40% BP>130, 29% high HDL** (Global Burden of Disease 2019)

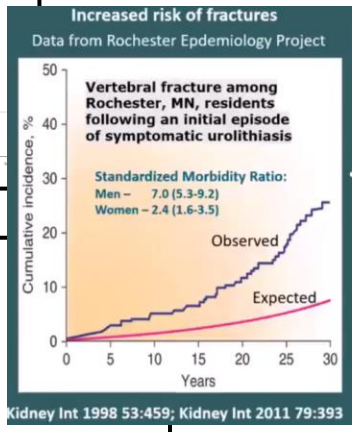
1. LeBoff et al, Osteoporosis Int, 2022, 33:249-2102; 2. Rendina et al, International Journal of Medical Sciences, 2020, 21:8183-8200; 3. Ziemba et al, Investig Clin Urol, 2017; 58:299-306; 4. Vergatti et al, Archivio Italiano di Urologia, 2025; 97: 13870-13878; 5. Cosmon, Osteoporosis Int 2014, 25: 2359.

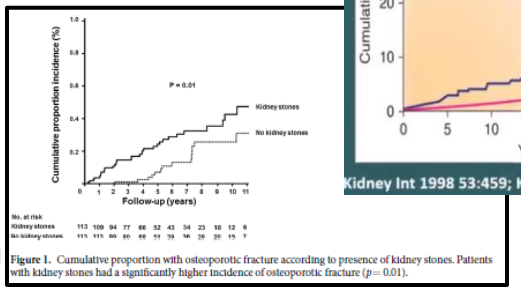
Kidney stone disease is part of a systemic metabolic disorder involving vascular, kidney, bones and gut

- **Increased risk of CKD** in those with stones *CJASN l4: 804–811, 2009*
- CaOx, CaP crystals implicated in CKD progression, *ASN 2021*
- **Increased risk of CAD** in women with stones *JAMA 310:408-15. 2013*
- Acidosis of CKD associated with high stone risk, *Tangri CKJ 16: 1113-21, 2023*
- **Increase risk of osteoporosis and DM** in those with kidney stones *Dong, NHANES 2007-2020, Int Urol. Nephrol. 2025, 57:1615*
- **Increased risk of fracture in patients with nephrolithiasis** *Kidney Int 1998, 53:459, 2011,79:393*
- **Increased incidence of osteoporotic fracture in CKD (3-4)** in those with kidney stones**.** *nature.com/scientific reports (2019) 9:1929 https://doi.org/10.1038/s41598-018-38191-1*







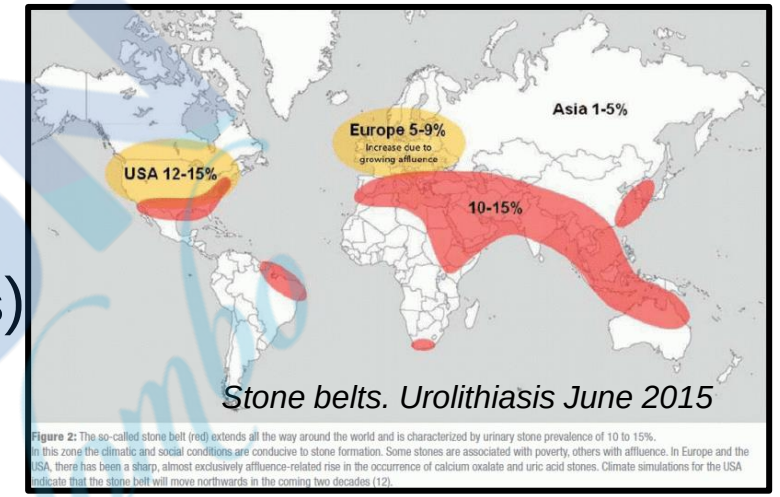


- **Metabolic syndrome (hypertension, diabetes mellitus, obesity, dyslipidemia) is associated with increased risk of kidney stones including calcium oxalate & uric acid - four traits doubles risk** *Rahman, F1000 Research 2021,November 2021*
- **Increased risk of new onset DM in those with stones and increased stones in those with DM**. *Prochaska et al, CJASN, 2025, 000837R2*

❖ **Common pathogenic mechanisms link metabolic syndrome with low bone mass and fracture risk** *Nutrients 2016, 8, 347*

Persons with kidney stones & osteoporosis have common causes and risk factors: modifiable and non-modifiable

- geography: stone belts, climate change
- genetic predisposition:
  (family history – 3-16 fold risk for stones)



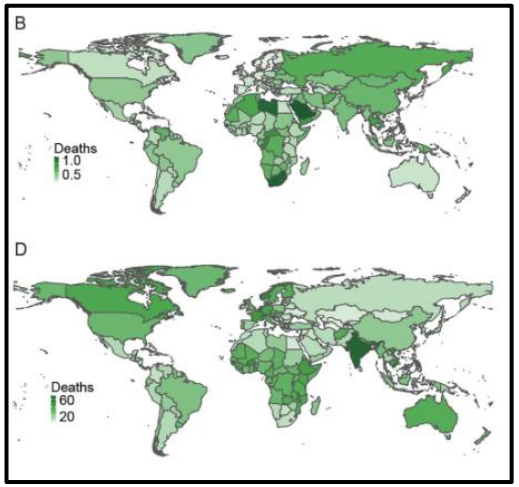
Stone belts. Urolithiasis June 2015

Table 1. Genes associated to occurrence of osteoporosis and nephrolithiasis.

Gene	*HGNC Symbol*	*Location*	Ref.
Calcium-sensing receptor	*CASR*	*3q13.3-q21.1*	[124–126]
Vitamin D receptor	*VDR*	*12q13.11*	[127–132]
Alkaline phosphatase	*ALPL*	*1p36.12*	[133,134]
Osteopontin	*SPP1*	*4q22.1*	[135,136]
Claudin 14	*CLDN14*	*21q22.13*	[137–139]
Type 2a sodium–phosphate cotransporter	*SLC34A1*	*5q35.3*	[140]
Fibroblast growth factor 23	*FGF23*	*12p13.32*	[141]
25(OH)D-24-hydroxylase	*CYP24A1*	*20q13.2*	[142]

HGNC: Human Genome Organisation (HUGO) Gene Nomenclature Committee.

Idiopathic Osteoporosis and Nephrolithiasis:Two Sides of the Same Coin? Rendina et al. Int. J. Mol. Sci. 2020, 21, 8183;



B. premenopausal, D. post menopausal death attributed to low bone mass in 2021. *Global burden of disease*

- aging and hormones for bones
  Ding, Aging and Disease, 2020, 11: 438-447
- gut microbiomes affect stones and bones - diet, antibiotics Wildkins, Sci Rep, 2019, 9:129

Physiological factors that bones & stones have in common

- Skeleton is 15% of body weight - *LeBoff, Osteoporosis Int, 2022, 33:2049*
- Bone is 60% hydroxy apatite ($CaPO_4OH$), 10% water and 30% organic material - collagen protein. 85-90% stones contain calcium
- Bone contains 90% of total body citrate -*Costello, HSOA J Hum Endocrinol.2016, 1:1*
- Bone is maintained by balance of osteoclasts and osteoblasts
  - imbalance leads to osteoporosis or low bone mass
  - bone loss results in loss of protein and minerals: calcium and phosphorus
- Bone is an endocrine organ that produces FGF23 causing phosphaturia and decreased PTH and increased 1,25 Vit D3 – all affecting calcium absorption and excretion
- Bone produces osteopontin, an inhibitor of stones
- Gut microbes can increase bone mass by reducing bone resorption and influence gut absorption of calcium, oxalate, citrate. *Hrncr, Microorganisms 2022, 10:578*

Pathogenic factors that bones and stones have in common

Pathogenic factors for low bone density and stones

- age, genetic epigenetic, hormones
- diet: – high sodium, chloride, protein, sugar, low citrate diet, all
  - increase calciuria,
  - reduce citraturia
  - facilitate acidosis increasing bone resorption
- sub-optimal calcium or vitamin D3 intake *Munoz-Garache, Nutrients 2020 12:1986*
- physical inactivity, smoking

LeBoff, Osteo. Int, 2022, 33:2049
Giannini, Euro. J. Endo. 2003, 149:209

Idiopathic Osteoporosis and Nephro-lithiasis: Two Sides of the Same Coin?
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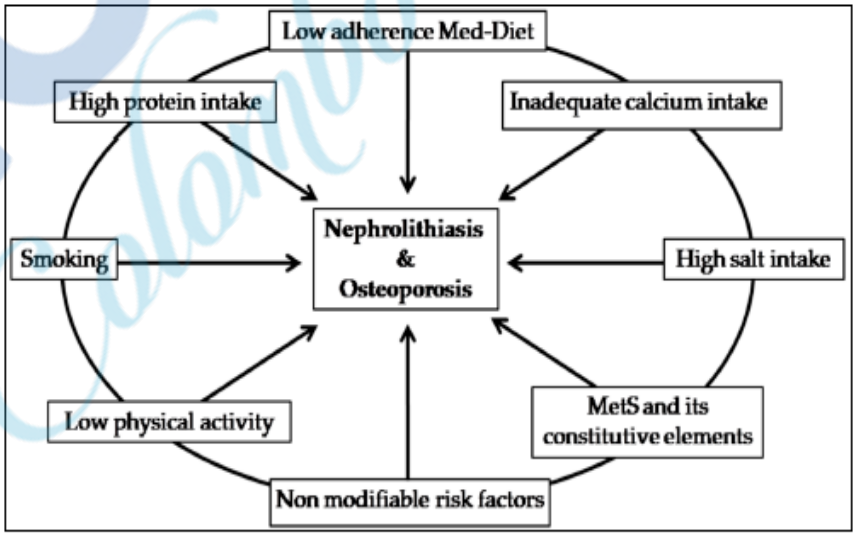


Figure 1. Common pathogenic factors between osteoporosis and nephrolithiasis. Med-I Mediterranean Diet; MetS: Metabolic Syndrome. MetS constitutive elements: diabetes and/or h fasting plasma glucose, abdominal obesity, dyslipidemia and elevated blood pressure.

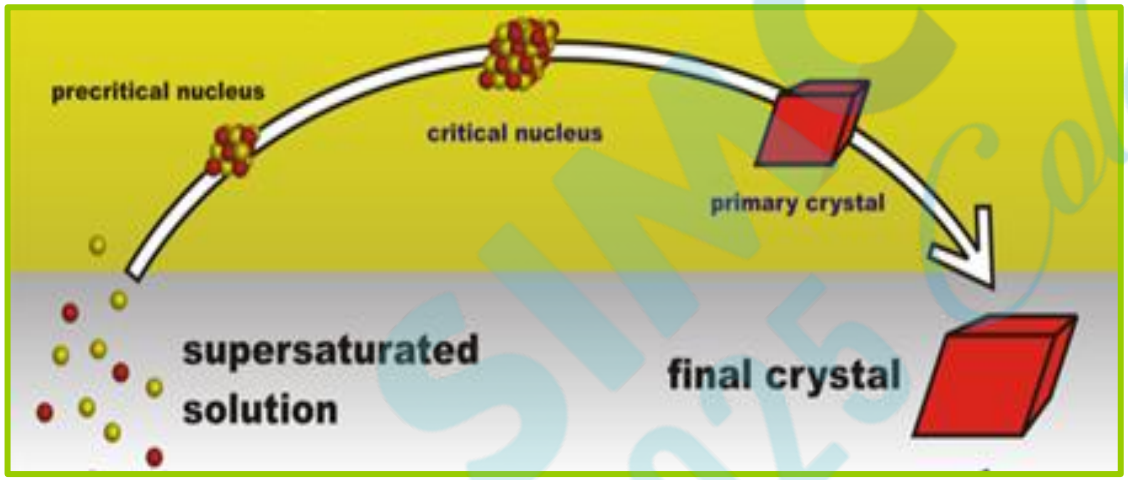
❖ **Hypercalciuria is present in 20-30% of those with low bone mass and 50% of those with kidney stones**

Stones grow from crystals formed in urine supersaturated with stone forming elements and lacking inhibitors

Supersaturation (SS) is influenced by

- concentration: too little solvent- low volume; too much solute - calcium, oxalate, phosphate, uric acid, cystine, mixed

- pH: too high for phosphate or too low for uric acid or cystine



Nano Today, Volume 6, Issue 6, December 2011, Pages 564-584

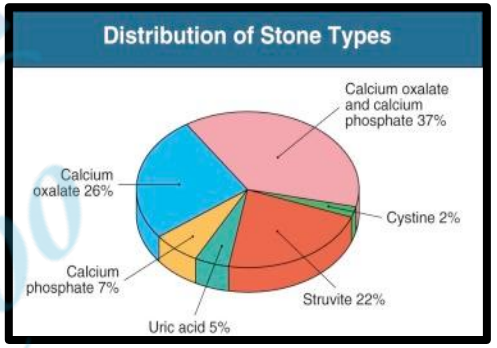
Crystallization is facilitated by seeds (crystals, aggregated proteins, biological nano particles) **and reduced by inhibitors.**

- **SS** increases risk of stone formation
- **SS** emphasizes the importance of concentration, not just daily excretion
- **SS** varies over the course of the day; greatest risk at night
- **SS** can help predict stone type
- Lowering **SS** helps prevent stone recurrence

Factors affecting supersaturation: solute - hypercalciuria

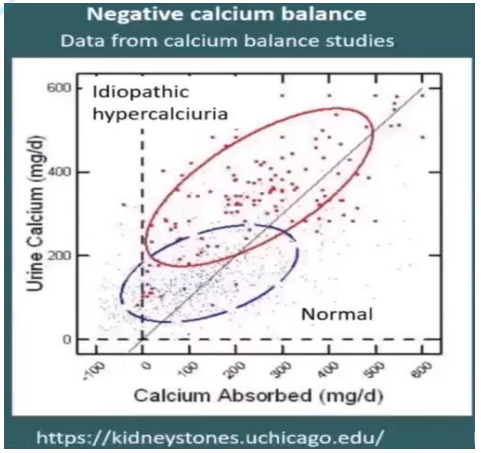
hypercalciuria >250 mg/d **-** present in 50% of stone formers and 20-30% of those with low bone mass

90% stones contain calcium



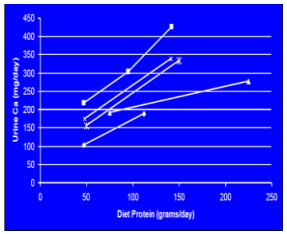
- **hypercalcemia**: PTH, malignancy, sarcoidosis
- **increased gut absorption of calcium**
  - excessive Vitamin D and or
  - **calcium supplements/antacids**,
  - sarcoidosis or conditions with
    1α OHase: – 25OHD3 activated to 1,25 $(OH)_2$ D3
- **bone reabsorption with age or disease**

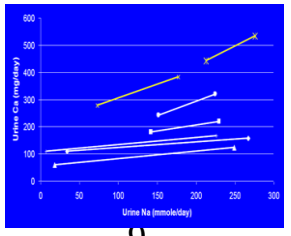
Giannini, Euro J Endo 2003, 149:209



- **diet high in protein** acid load increases calcium loss from bone and renal excretion
- **diet high in sodium** increases urine calcium
- **diet high in chloride** increases bone resorption and hypercalciuria

- renal leak, proximal tubule Na/P transporter defects



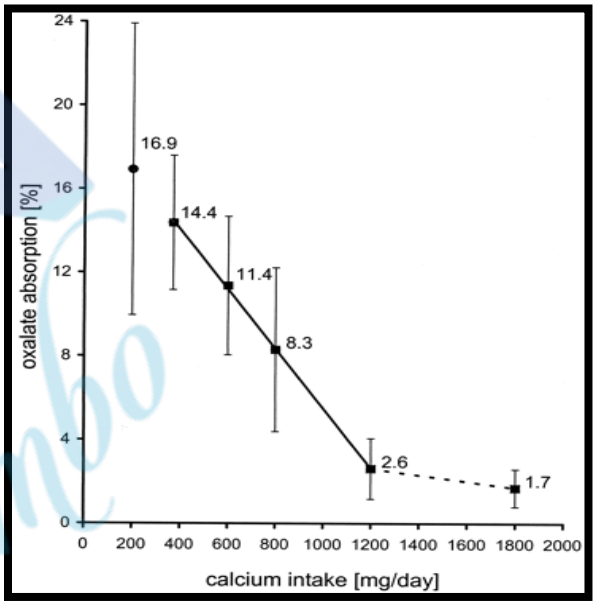


from studies 1967-1993, and 1972-1981, courtesy John Asplin

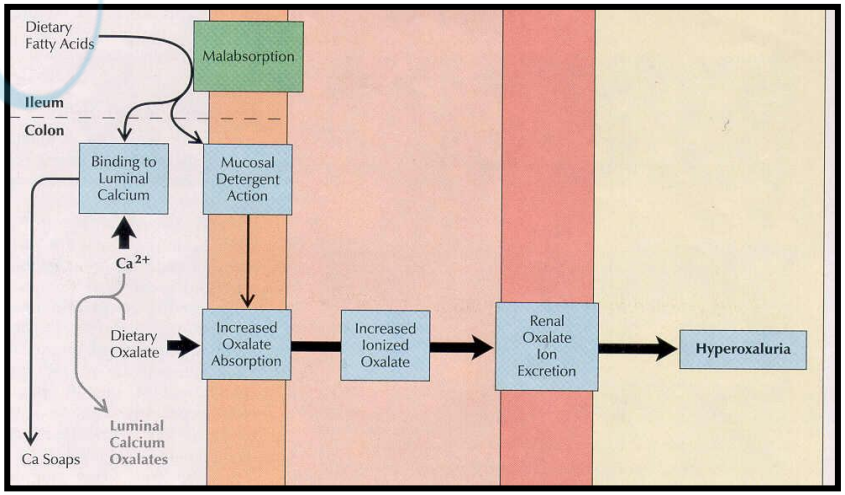
Factors affecting supersaturation: solute: oxalate

hyperoxaluria > 40 mg/d

- **low calcium diet**
- **malabsorption of fat: saponifies Ca, increasing gut Ox absorption**
  - **short bowel syndromes;**
  - **inflammatory bowel diseases,**
  - **bariatric surgery (Roux-en-Y)**
- high oxalate diet-with low dietary calcium
- abnormal gut flora
  - after antibiotics
  - low oxalobacter
- primary hyperoxaluria –
  - autosomal recessive disorder with mutations in genes stopping normal breakdown of glycoxylate which can then form oxalate
- high dose Vitamin C
- ethylene glycol toxicity



von Unruh et al JASN, 15:1567-1573, 2004



Kupin, W.L. Hospital Practice March 15, 1995

Factors affecting supersaturation: solute: hyperphosphaturia

- Diets high in processed foods such as packaged snacks, convenience foods, and fast food, contain 10,000 additives; **phosphate and sodium are highly absorbed by the gut**

- Consumption of excess dairy products, high-phosphorus meats and very high protein diets

- Phosphate-containing beverages, like dark sodas and some bottled teas

- *Phosphorus is added to extend the shelf life of foods and not required to be on the Nutrition Facts label.*

Phosphorus absorbed from food:

Vegetable sources: 50% due to the high level of phytates found in vegetables.
Animal sources: 70% is absorbed during digestion.
Phosphorus additives: 100% of phosphorus found in food additives and processed foods is absorbed.

Di- or tri-sodium phosphate
Monosodium phosphate
Sodium hexametaphosphate
Trisodium triphosphate
Sodium tripolyphosphate
Tetrasodium pyrophosphate
Phosphoric acid
Calcium phosphate
Dipotassium phosphate

Nutrition Facts

Serving Size (75g)
Servings Per Container 1

Amount Per Serving	
Calories 280	Calories from Fat 50
	% Daily Value*
Total Fat 6g	9%
Saturated Fat 5g	25%
Trans Fat 0g	
Cholesterol 5mg	2%
Sodium 180mg	8%
Potassium 380mg	11%
Total Carbohydrate 38g	13%
Dietary Fiber 2g	8%
Sugars 28g	
Protein 20g	40%

Vitamin A 25%	• Vitamin C 25%
Calcium 25%	• Iron 45%
Vitamin E 25%	• Thiamin 25%
Riboflavin 25%	• Niacin 25%
Vitamin B6 25%	• Folate 30%
Vitamin B12 25%	• Biotin 25%
Pantothenic Acid 25%	• Phosphorus 30%
Iodine 25%	• Magnesium 25%
Zinc 30%	• Copper 50%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Saturated Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500 mg	3,500 mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g
Protein		50g	65g

Factors affecting crystallization: inhibitors

Inhibitors

- **Tamm-Horsfall protein (uromodulin)**
  inhibits aggregation, attachment and endocytosis
  uromodulin secretion is increased by water loading *CJASN July 2023*

- **citrate - complexes calcium**

- **pyrophosphate**
  inhibits crystal formation by making weak/soluable complexes with calcium
  Baumann et al, ClinSci.MolMed,53:141-148,1977
  bisphohonates are analogues of pyrophosphate

- **magnesium**
  complexes oxalate (weak)
- **peptides (nephrocalcin, osteopontin)**
  inhibit crystal nucleation, aggregation and growth

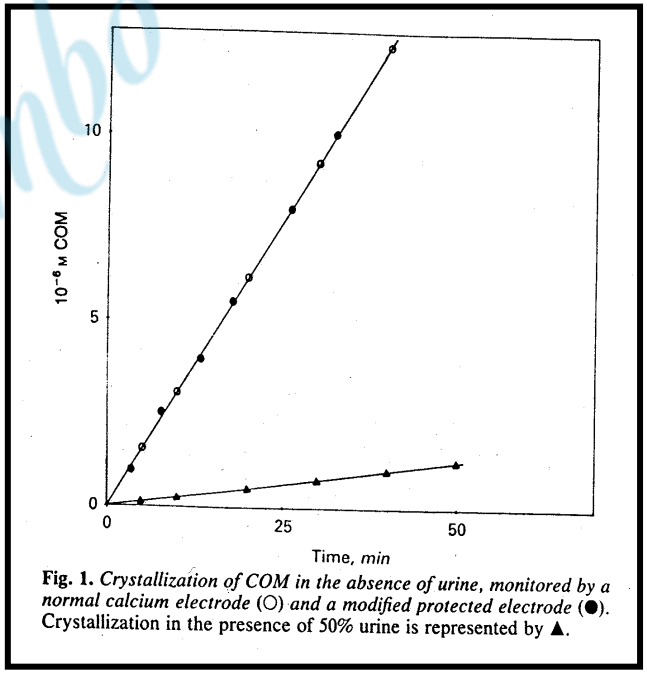


Fig. 1. *Crystallization of COM in the absence of urine, monitored by a normal calcium electrode* (○) *and a modified protected electrode* (●). Crystallization in the presence of 50% urine is represented by ▲.

Gaur and Nancollas, KI, 26:767-768, 1984

Note: osteopontin is formed in bone

Some facts about citrate and hypocitraturia

- **20-40% of stone formers have low citrate**
- **90% body citrate is in bones**
- **Increased acid load in body releases citrate from bones and reduces BMD**
  (Vergatti et all, Archivio Italiano di Urologia, 2025; 97:13870

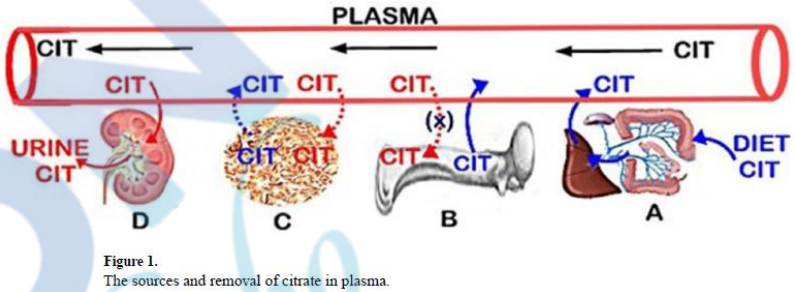


Figure 1.
The sources and removal of citrate in plasma.

Costello, HSOA J Hum Endocrinol. 2016 ; 1(1):

- **Citrate** comes from TCA cycle and diet. Citrate is filtered and if not reabsorbed in proximal tubule is excreted in urine as **base that does not alkalinize urine**
- Urine citrate is reduced by systemic or intracellular acidosis and increased by systemic alkalosis by changing PT reabsorption
- **Ingested K or Na citrate is metabolized to bicarbonate in the liver which can alkalinize urine** - 1 mmol citrate = 3 mmol bicarbonate

Causes of Hypocitraturia

- **Acidosis**
  - **Distal renal tubule acidosis**
  - **Diarrhea**
  - **Exercise (lactic acidosis)**
- **Hypokalemia (intracellular acidosis)**
  - **Medication induced (diuretics)**
  - **Diarrhea**
  - **High-sodium intake**
- **Urinary tract infection**
- **Idiopathic**

People who have kidney stones want advice about prevention

HC, 31 years old has passed many calcium stones over 5 years. His brother and father have also had kidney stones. He is told he should eat less calcium in his diet and wants to know if this is good advice.

IBD, 36 years old, with Crohn's disease, had an obstructing stone removed with a laser via endo-urologic manipulation and now seeks advice about how not to have another stone.

MS, 59 years old, weight 118 kg, with metabolic syndrome is passing more stones and wants to understand what they are and how to stop them.

Investigations to prevent kidney stones and assess bones

- **H&P** **predisposing conditions**
  medications

family history;
UTI, obstruction;
ileostomy; GI disease,
gastric bypass surgery;
bone disease

sodium
animal protein
fruit / vegetables
(K, Mg, citrate)
calcium, oxalate,
fructose (soda)
processed foods
(phosphorus)
supplements
(protein)

diet

-

fluid intake

amount and timing

especially night-time

calcium, antacids
vitamin D, vitamin C
triamterene - crystalluria
indinavir - crystalluria
furosemide - calciuria
acetazolamide (type 2 RTA)
topiramate (type 2 RTA)
uricosuric agents
antibiotics

- **examine the stone**
- urinalysis – pH, pyuria, hematuria, crystals, culture
- blood and urine chemistries
- assess stone burden – ultrasound, non contrast CT
- **examine bones – DXA scans**

Metabolic stone profile investigations to identify blood, urine and dietary factors contributing to stone formation and assessment of diet contributors to osteoporosis

- **blood tests**
  - calcium, phosphorus, uric acid, potassium, bicarbonate, creatinine, (PTH, Vitamin D if indicated)

- **24 hour urine excretion to assess**
  - **stone forming factors**: calcium, oxalate, uric acid, phosphate, cystine; SS correlates with type of stone
  - **stone inhibitors in urine**: citrate, magnesium
  - **dietary factors that influence stone forming factors and bone mass and density**
    sodium, potassium, urea nitrogen (protein intake), citrate
  - **other**: **SS**, **volume**, **pH**, creatinine (for collection accuracy)

❖ 10-15% have no measurable metabolic defect

Stone Risk Factors / Cystine Screening: Negative (06/30/2016)

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
08/07/17	S24281191	3.04	4.14	358	28	254	1.30	6.081	0.45	0.772
02/06/17	S22426084	2.42	6.70	297	42	455	2.53	6.874	0.10	0.771
10/23/16	S20187718	2.98	7.56	401*	49*	546	2.00	6.494	0.18	0.723
06/26/16	S19466608	1.44	5.38	197	29	220	0.37	5.201	3.66	0.829
REFERENCE RANGE		0.5 - 4L	6 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.800 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
08/07/17	S24281191	178	50	100	1.516	58	167	51	14.59	1.1
02/06/17	S22426084	157	78	116	0.963	37	144	54	10.75	0.9
10/23/16	S20187718	183	83	119	1.117	45	208	47	15.34	1.1
06/26/16	S19466608	255	65	102	1.569	61	271	61	15.16	
REFERENCE RANGE		50 - 150	20 - 100	30 - 120	0.6 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

Normalized Values

DATE	SAMPLE ID	WEIGHT	Cr 24	Cr 24/Kg	Ca 24/Kg	Ca 24/Cr 24
08/07/17	S24281191	104.3	2416	23.2	3.4	148
02/06/17	S22426084	97.5	2427	24.9	3.0	123
10/23/16	S20187718	102.5	2147	20.9	3.9	187
06/26/16	S19466608		2477			79
REFERENCE RANGE				male 18-24 female 15-20	<4	<140

Serial 24 hour urine collections reflect volume

- changes over time
- adequacy of urine collection
- amount of stone forming factors
- amount of stone inhibiting factors
- dietary intake
- urine super-saturations, pH

HC, 31 years old has passed many calcium stones over 5 years. His brother and father also have kidney stones. He was advised to reduce calcium in his diet and wants to know if this is the right advice?

What dietary changes should be followed by this patient?

Problems:

stone forming factors

- hypercalciuria
- hyperphosphaturia
- highish oxaluria
- High SS CaOx and CaP

not ideal diet

- high urine sodium
- high UUN, sulfate, phosphorus

indicating high animal protein diet and processed food diet

stone inhibiting

- good volume
- adequate citrate, magnesium, potassium

Stone Risk Factors / Cystine Screening: Negative (02/24/2010)

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
11/01/16	S21979339	2.49	2.78	159	20	1223	0.27	5.750	0.68	0.517
04/12/16	S17609427	2.65	5.65	425	33	1474	1.64	6.231	0.31	0.634
07/16/15	S13236811	1.89	7.54	448	28	1426	1.01	5.579	1.12	0.519
02/22/10	5609951	1.81	5.84	299	23	984	2.48	6.335	0.26	0.457
REFERENCE RANGE		0.8 - 4L	9 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.600 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
11/01/16	S21979339	39	90	96	0.708	24	72	35	7.24	0.9
04/12/16	S17609427	201	121	125	1.100	28	222	54	13.59	1.4
07/16/15	S13236811	148	93	136	1.162	36	190	43	10.91	1.1
02/22/10	5609951	188	42	81	1.017	20	159	31	8.55	0.9
REFERENCE RANGE		80 - 150	20 - 100	30 - 120	0.8 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

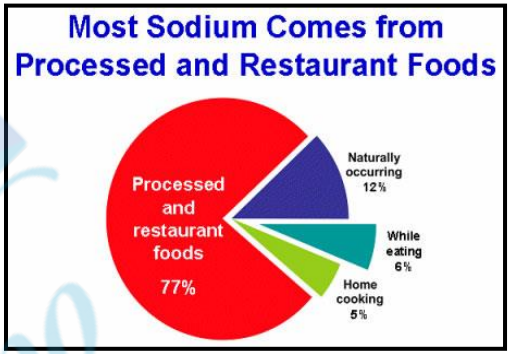
Normalized Values

DATE	SAMPLE ID	WEIGHT	Cr 24	Cr 24/Kg	Ca 24/Kg	Ca 24/Cr 24
11/01/16	S21979339	68.0	1484	21.8	2.3	107

Dietary factors influencing risk for kidney stones and bone density: calcium, sodium and protein

- **high dietary sodium causes high urine sodium**
  - **increases urine calcium decreases urine citrate increasing stones and low bone density**

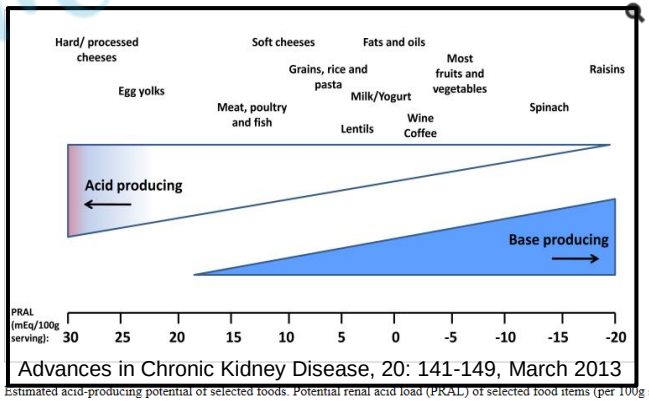
  Kleeman, Proc . Soc. Exp Biol.Med, 1964, 115: 29-32; Rendina; Sackee, J. Urol, 1993 150:310; Moe, Current Opinin. Nephrol. Hypertension 2005, 14:368



- **high dietary protein**
  - **increases acid production and excretion**
  - **bone buffering, reduced bone density**
  - **decreases urine citrate**
  - **increases urine calcium**
  - **decreases urine pH**
  - **increases uric acid production & excretion**

Meats, grains, cheeses contribute the largest acid load; fruits and vegetables contribute base

Figure 1



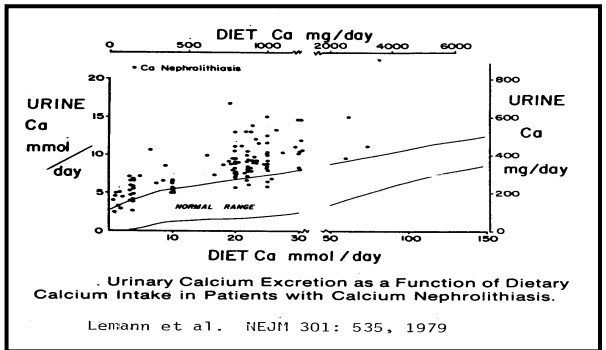
Advances in Chronic Kidney Disease, 20: 141-149, March 2013

Estimated acid-producing potential of selected foods. Potential renal acid load (PRAL) of selected food items (per 100g s
from estimates performed by Remer (22), and calculated as: PRAL (mEq/d) = 0.49 × protein (g/d) + 0.037 × P (mg/d) −
0.026 × Mg (mg/d) − 0.013 × Ca (mg/d).

- **low dietary calcium:**
  - **increase oxalate absorption & excretion**

  Borghi, NEJM 2002, 346:77-84)
  - **reduces bone density**

  Munoz-Garache, Nutrients 2020 12:1986
- **high dietary calcium**
  - **increases calciuria**
  - **does not increase bone density**

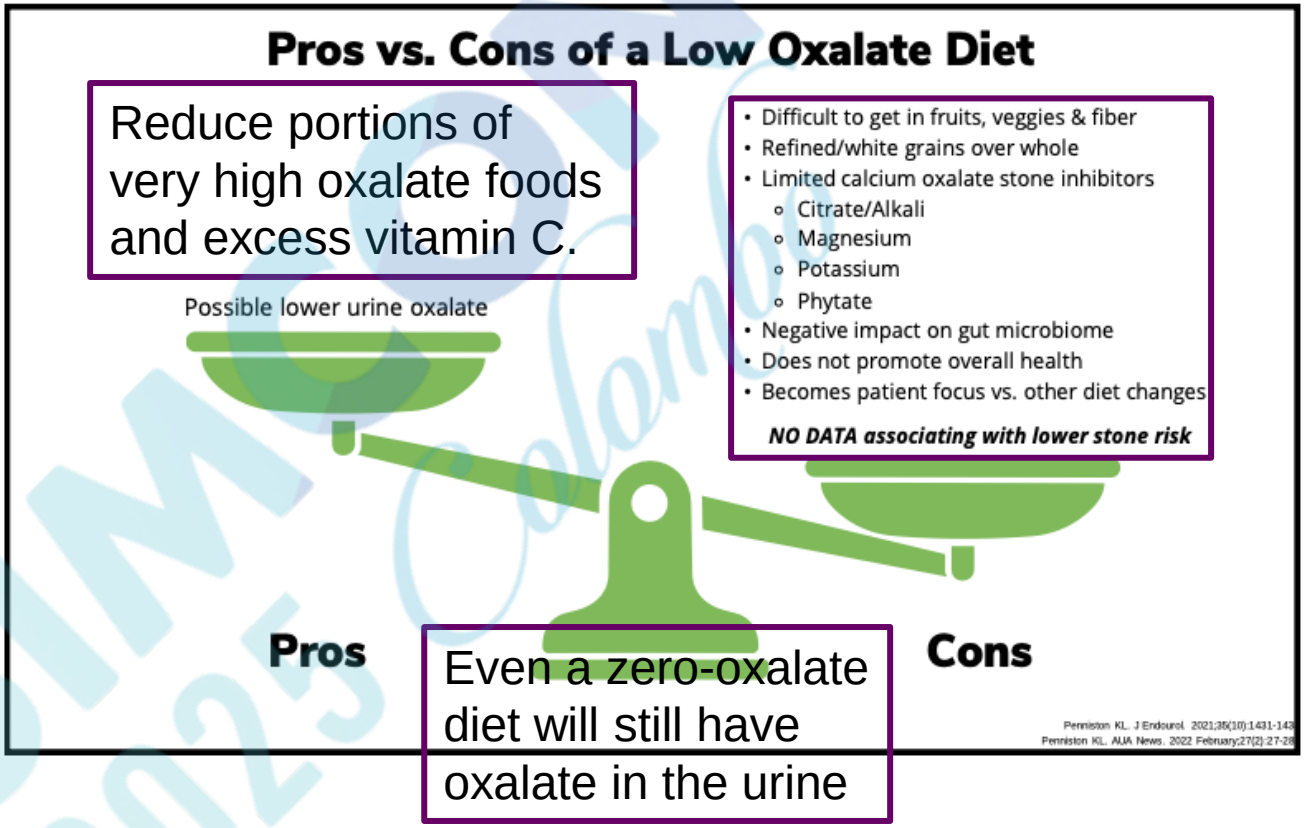


Urinary Calcium Excretion as a Function of Dietary Calcium Intake in Patients with Calcium Nephrolithiasis.

Lemann et al. NEJM 301: 535, 1979

Treatment for dietary factors influencing risk for kidney stones and bone density: low oxalate diets are ineffective

- **Treatment for hyperoxaluria is adequate dietary calcium eaten with meals to bind oxalate and phosphate in gut and prevent absorption**



Evidence: Urinary lithogenic risk profile in recurrent stone formers with hyperoxaluria: a RCT comparing **DASH-style and low oxalate diets.** *Noori et al AJKD, 2014:63:456-463.*

- There was a trend for calcium oxalate supersaturation to decrease in the DASH versus the low-oxalate group in association with an increase in magnesium and citrate excretion and increased urine pH in the DASH versus low-oxalate group.

Increase urine citrate (hypocitraturia)

Diet recommendations:

- decrease protein (0.8-1g/kg IBW)
- increase citrus based products (lemons/lime juice: 3-4 oz/100ml)
- Increase fruits and vegetables

Medications and supplements:

- potassium or magnesium citrate (15-30 meq once or twice a day)
- products developed by nephrologists: Litholyte® or Moonstone® (Stone Stopper Drink Mix)

Correct intra or extracellular acidosis (diarrhea, RTA, CKD):

- sodium bicarbonate 30-60 meq/d

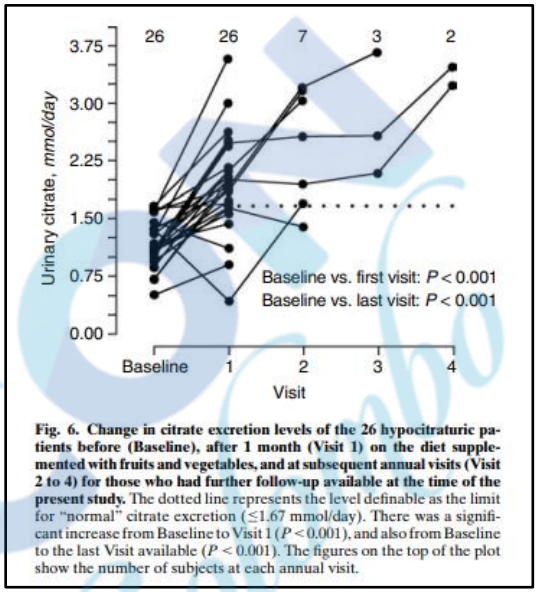


Fig. 6. Change in citrate excretion levels of the 26 hypocitraturic patients before (Baseline), after 1 month (Visit 1) on the diet supplemented with fruits and vegetables, and at subsequent annual visits (Visit 2 to 4) for those who had further follow-up available at the time of the present study. The dotted line represents the level definable as the limit for "normal" citrate excretion (≤1.67 mmol/day). There was a significant increase from Baseline to Visit 1 ($P < 0.001$), and also from Baseline to the last Visit available ($P < 0.001$). The figures on the top of the plot show the number of subjects at each annual visit.

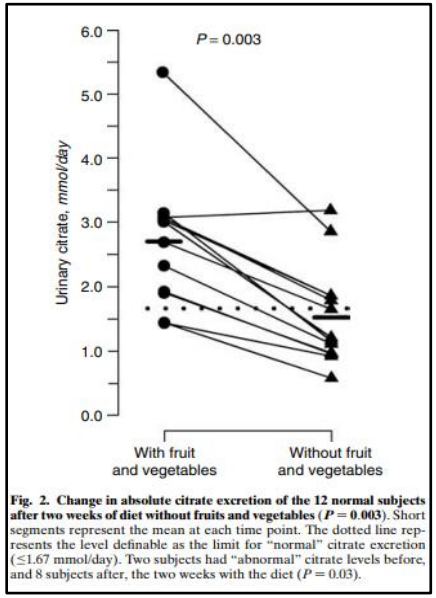
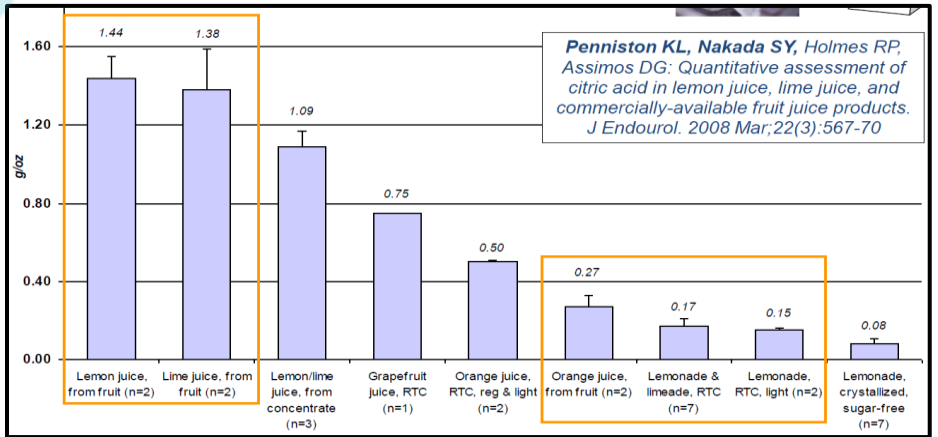


Fig. 2. Change in absolute citrate excretion of the 12 normal subjects after two weeks of diet without fruits and vegetables ($P = 0.003$). Short segments represent the mean at each time point. The dotted line represents the level definable as the limit for "normal" citrate excretion (≤1.67 mmol/day). Two subjects had "abnormal" citrate levels before, and 8 subjects after, the two weeks with the diet ($P = 0.03$).

Before and after increasing fruits and vegetables in hypocitraturic patients and before and after reducing fruits and vegetables in normal subjects.

Meschi et al, KI, 66 (2004):2402–2410

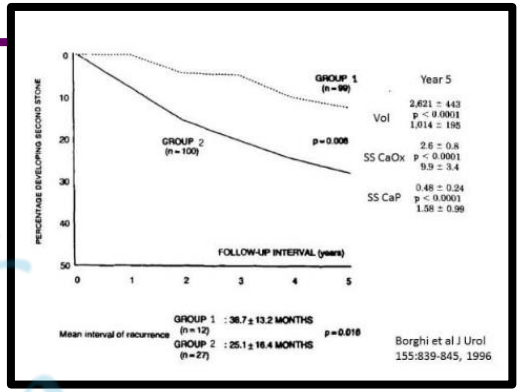


Evidence for dietary based prevention of stones

Fluids: urine volume 2.6 L/day

Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study.
Recurrence was 12% v 27% with 2.6 v 1 L water/day

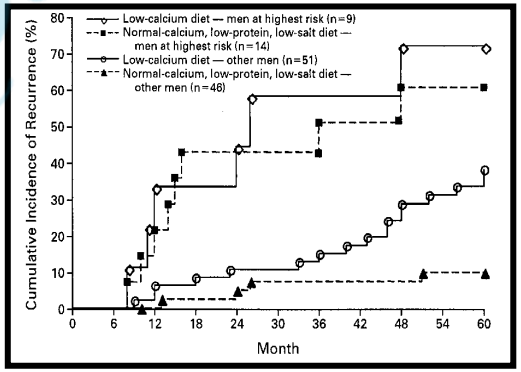
Borghi. J Urol,155:839-843,1996



Diet: low sodium, normal calcium and low animal protein

Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *50mmol Na, 52g animal (93g) protein, 1200 mg Ca diet v 400 mg Ca diet*
Low sodium, low protein diet reduced SS CaOx & stones (50%) more than low calcium diet which did not decrease calcium excretion but increased oxalate excretion.

Borghi, NEJM, 346:77-84, 2002



Medical management to prevent recurrent nephrolithiasis in adults:
A Systematic Review of 28 RCT. *Ann Intern Med. 2013; 158:535-543.*
In patients with 1 past calcium stone stone risk was reduced by 50% with increased fluid intake; 20% with reduced soft-drink consumption

DASH-Style Diet was Associated with Reduced Risk for Kidney Stones.

Taylor et al. JASN: 2009, 20: 2253–2259

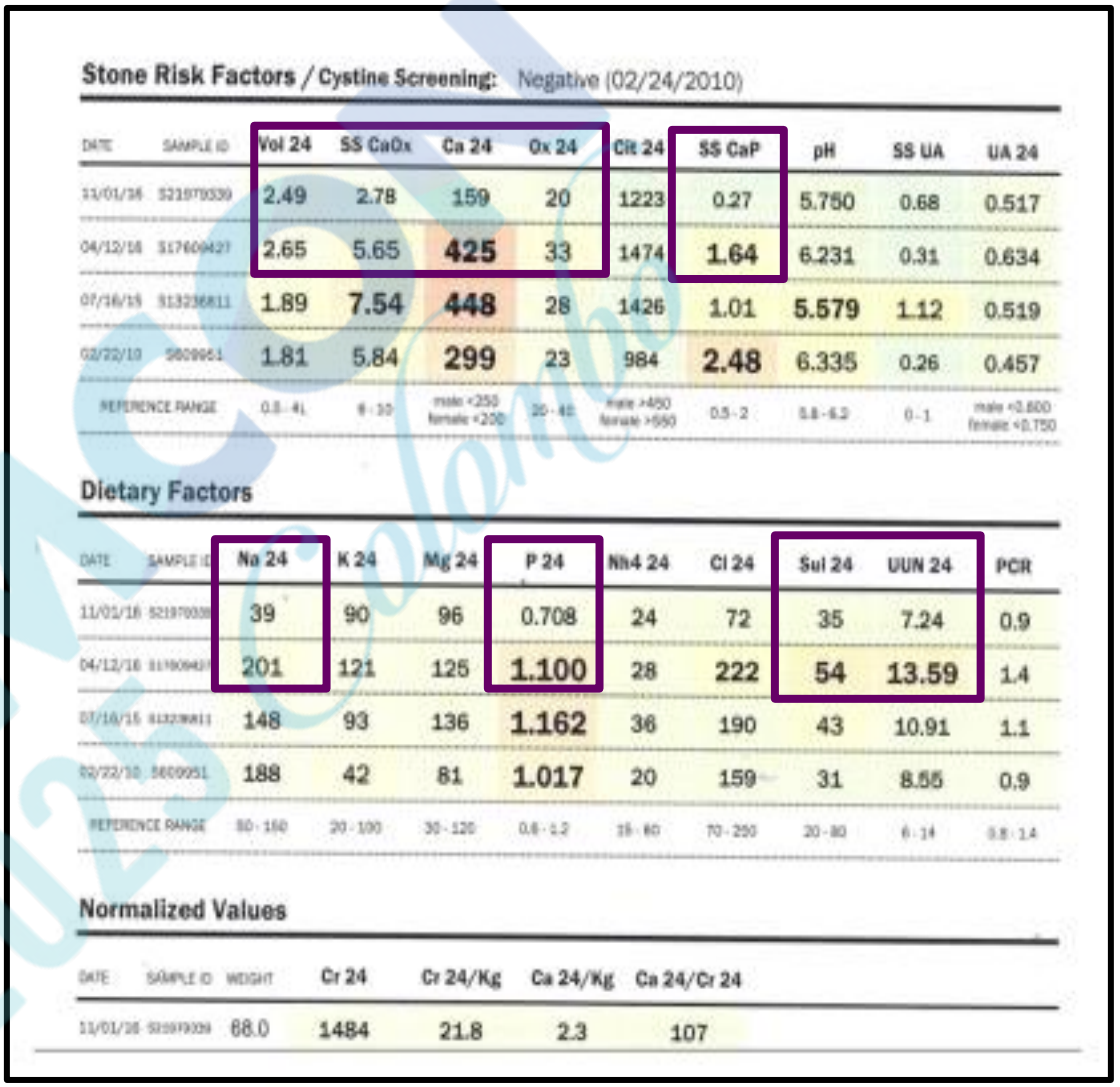
Zisman, A, Effectiveness of Treatment Modalities on Kidney Stone Recurrence. *CJASN 2017,12: 1699-1708,*
Penniston, K, Nonpharmacologic methods of stone risk reduction. *Urol Clin N Am, 2025, 52:343-363*

HC, 31 years old has passed many calcium stones over 5 years. His brother and father have kidney stones. He was advised to reduce calcium in his diet and wants to know if this is the right advice?

Dietary changes for HC included

- **DASH diet – more fruits and vegetables**
- **Normal calcium**
- **Reduced sodium**
- **Reduced animal protein** as reflected in urine UUN, sulfate and phosphorus

❖ **All of these were associated with reduced calcium, oxalate and phosphorus excretion and SS calcium oxalate and calcium phosphate**



Stone Risk Factors / Cystine Screening: Negative (02/24/2010)

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
11/01/16	521979339	2.49	2.78	159	20	1223	0.27	5.750	0.68	0.517
04/12/16	517609427	2.65	5.65	425	33	1474	1.64	6.231	0.31	0.634
07/16/15	513236811	1.89	7.54	448	28	1426	1.01	5.579	1.12	0.519
02/22/10	5609951	1.81	5.84	299	23	984	2.48	6.335	0.26	0.457
REFERENCE RANGE		0.8 - 4L	6 - 10	male <250 female <200	20 - 40	male >480 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.600 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
11/01/16	521970339	39	90	96	0.708	24	72	35	7.24	0.9
04/12/16	517609427	201	121	125	1.100	28	222	54	13.59	1.4
07/16/15	513236811	148	93	136	1.162	36	190	43	10.91	1.1
02/22/10	5609951	188	42	81	1.017	20	159	31	8.55	0.9
REFERENCE RANGE		80 - 150	20 - 100	30 - 120	0.8 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

Normalized Values

DATE	SAMPLE ID	WEIGHT	Cr 24	Cr 24/Kg	Ca 24/Kg	Ca 24/Cr 24
11/01/16	521979339	68.0	1484	21.8	2.3	107

Evidence for treatments to prevent stone recurrence when diet inadequate

Medical Management to Prevent Recurrent Nephrolithiasis in Adults: Systematic Review for an American College of Physicians Clinical Guideline. *Ann Int M 2013; 158:535-543*

- **28 RCTs through September 2012 were examined**

  In patients with 1 past calcium stone recurrent composite stone risk was reduced by 50% with increased fluid intake; 20% with reduced soft-drink consumption–symptomatic, 50% with reduced sodium and animal protein diet

- **In patients with multiple past calcium stones (moderate strength evidence) further composite stone recurrence risk was reduced by**
  - **48% with thiazides,** but (2023) study did not confirm this
  - **75% with citrates** and spinal bone loss *Pak, J Urol 2002 Jul;168(1):31-4*
  - **41% with allopurinol**

Current pharmacological options

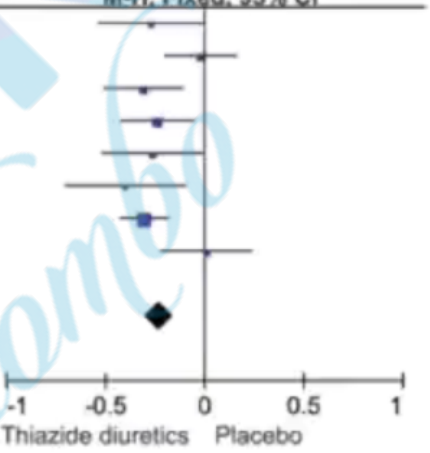
- Thiazide diuretics
- SGLT2i, GLP1 agonists
- Bisphosphonates
- Citrate supplements

Thiazide diuretics lower urine Ca by increasing proximal tubule reabsorption of Na and Ca

Meta-analysis of 8 RCT of thiazides to prevent stones

Study or Subgroup	Thiazide diuretics Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Borghi 1993	3	19	9	21	7.0%	-0.27 [-0.54, -0.00]
Brocks 1981	5	33	5	29	10.9%	-0.02 [-0.20, 0.16]
Ettinger 1988	6	42	14	31	12.6%	-0.31 [-0.51, -0.10]
Fernández-Rodriguez 2006	16	50	28	50	17.6%	-0.24 [-0.43, -0.05]
Laerum 1984	5	23	12	25	8.4%	-0.26 [-0.52, -0.00]
Mortensen 1986	0	12	4	10	3.8%	-0.40 [-0.71, -0.09]
Ohkawa 1992	11	82	41	93	30.7%	-0.31 [-0.43, -0.18]
Scholz 1982	6	25	6	26	9.0%	0.01 [-0.22, 0.24]
Total (95% CI)		**286**		**285**	**100.0%**	**-0.23 [-0.30, -0.16]**
Total events	52		119			

Heterogeneity: Chi² = 12.38, df = 7 (P = 0.09); I² = 43%
Test for overall effect: Z = 6.42 (P < 0.00001)

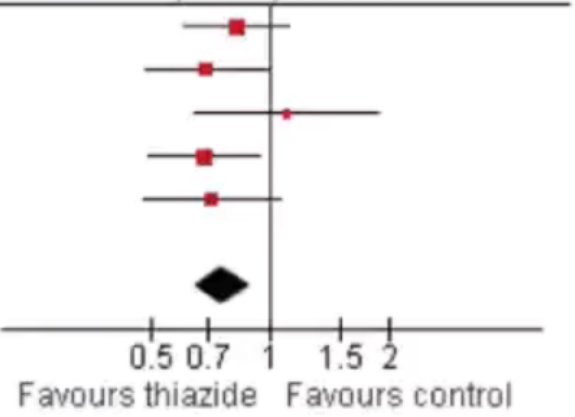


Li et al, J Transl Med, 2020

Meta-analysis of effect of thiazides on hip fracture

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Cauley 1993	-0.19845	0.15907124	27.6%	0.82 [0.60, 1.12]
Feskanich 1997	-0.37106	0.18419048	20.6%	0.69 [0.48, 0.99]
Guo 1998	0.09531	0.2707287	9.5%	1.10 [0.65, 1.87]
LaCroix 1990	-0.38566	0.16519749	25.6%	0.68 [0.49, 0.94]
Schoofs 2003	-0.34249	0.20446899	16.7%	0.71 [0.48, 1.06]
Total (95% CI)			**100.0%**	**0.76 [0.64, 0.89]**

Heterogeneity: Chi² = 2.93, df = 4 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)



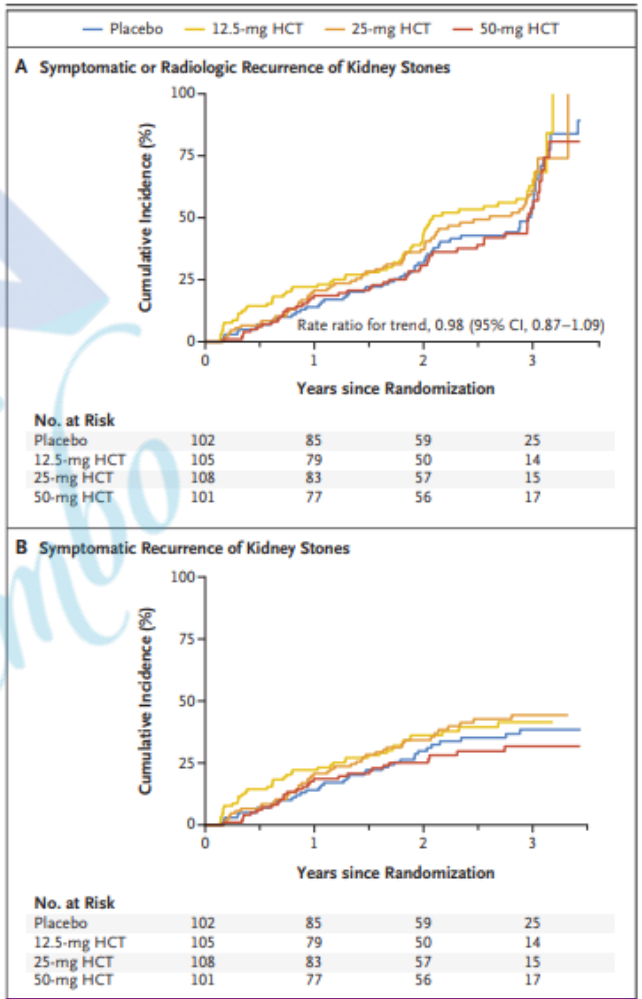
Aung and Htay, Cochrane Database Syst Rev 2011

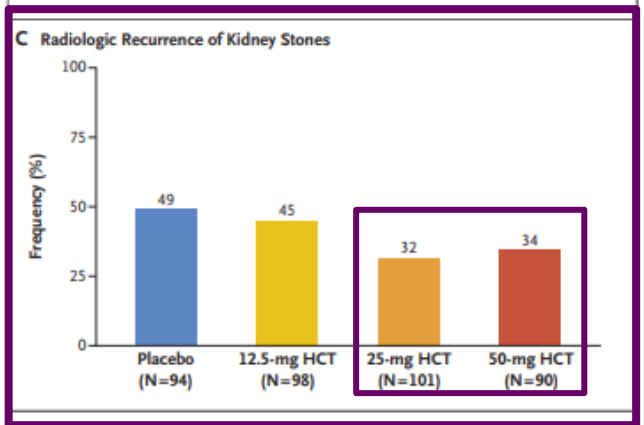
Hydrochlorthiazide and prevention of kidney stone recurrence. *NEJM 388: 781-791, 2023*

Methods: RCT with follow up 2.9 y.
n= 416 with at least 2 recurrent calcium stones.
Rx: Placebo v HCTZ 12.5, 25, 50 mg/d
Outcomes: radiological recurrence using CT (RadR) and symptomatic recurrence (SymR)

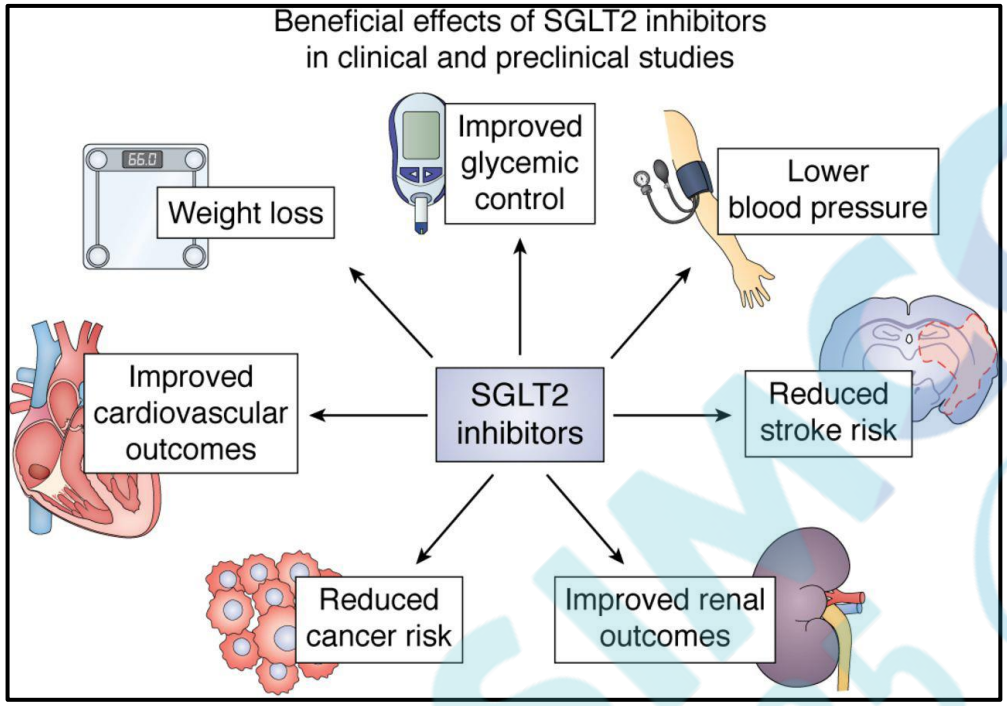
Results: no relationship with dose and combination of RadR and SymS. **RadR lower in 25 & 50 mg v. 12.5 & placebo groups**
Other effects: small urine calcium decrease, more oxalate, more hypokalemia, gout, DM with HCTZ

Limitations:
- low power for dosing groups and follow up
- HCTZ short acting and used once a day
- diet higher in sodium than earlier studies
- SymS recurrence didn't exclude existing stones





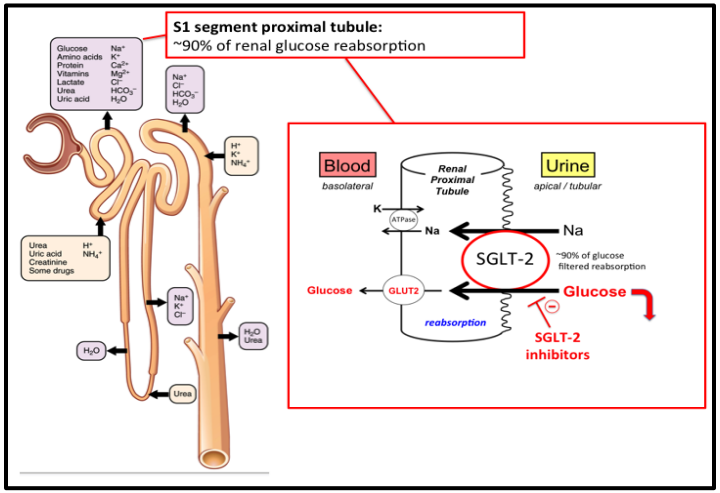
SGLT2i can prevent kidney stones, don't hurt bones and improve outcomes for those with metabolic syndrome



Sodium-glucose cotransporter-2 inhibitors: Understanding the mechanisms for therapeutic promise and persisting risks - Journal of Biological Chemistry

Potential mechanisms for stone risk reduction

- **osmotic diuresis**
- **increased urinary citrate**:
- **reduced supersaturation** uric acid and calcium oxalate
- may increase urine pH in uric acid stone formers
- **anti-inflammatory Effects**:



SGLT2i can prevent kidney stones, don't hurt bones and improve outcomes for those with metabolic syndrome

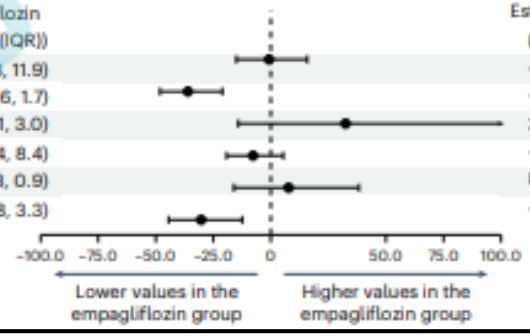
SGLT2 Inhibitors and their effect on Urolithiasis: Current evidence and Future directions. *Dika et al, J. Clin. Med 2024, 13: 6017*

- A **retrospective cohort** study of the risk of nephrolithiasis **among 1,378462 patients with type 2 diabetes** who initiated sodium-glucose cotransporter 2 inhibitors (SGLT2i) compared to those who started glucagon-like peptide-1 receptor agonists (GLP-1RA) or dipeptidyl using 3 data bases. After propensity score matching, the **hazard ratios for nephrolithiasis were 0.69 for SGLT2i versus GLP-1RA and 0.74 for SGLT2i versus DPP4i**, indicating a significantly lower risk of kidney stones among SGLT2i users. *Paik, JAMA Int Med, 2024, 184:265-274*

- **A systematic review and meta-analysis** assessed the relationship between SGLT2 inhibitor use and kidney stone incidence. The analysis included **six studies with a combined total of 4,963,542 participants**. The pooled odds ratio for kidney stone prevention was **0.80 (95% CI: 0.72–0.89)**: *Sisakht, J Renal Inj Prev, 2024, e32292*

- In a **double blind cross over placebo controlled** single center RCT in 53 non-diabetic persons with calcium or uric acid stones, empaglifozin 25 mg reduced SS CaP; SS uric acid and increased urine citrate over 2 week periods. *Anderegg, Nature Medicine, 2025, 31:286*

Type of SF	Primary outcomes	N[a]	Placebo (median (IQR))	N[b]	Empagliflozin (median (IQR))	Estimated relative difference (% (95% CI))[c]	P value[d]
Calcium	Calcium oxalate supersaturation	25	8.9 (7.7, 13.4)	25	9.1 (7.3, 11.9)	-1 (-15 to 16)	0.921
Calcium	Calcium phosphate supersaturation	25	1.9 (1.0, 2.7)	25	1.0 (0.6, 1.7)	-36 (-48 to -21)	<0.001*
Calcium	UA supersaturation	25	1.3 (0.9, 2.3)	25	2.2 (1.1, 3.0)	32 (-14 to 104)	0.204
UA	Calcium oxalate supersaturation	21	6.6 (4.4, 10.0)	21	5.8 (4.4, 8.4)	-8 (-19 to 5)	0.236
UA	Calcium phosphate supersaturation	21	0.5 (0.3, 0.8)	21	0.4 (0.3, 0.9)	8 (-16 to 38)	0.559
UA	UA supersaturation	21	3.3 (2.6, 5.4)	21	2.5 (1.8, 3.3)	-30 (-44 to -12)	0.002



- **A meta analysis of 20 RCT's in 12,764 patients with diabetes showed no association between SGLT2i and elevated fracture risk** or affects on bone metabolism markers. *Wang, Osteoporosis Int, 2023, 12:2013-2025*

GLP-1A and kidney stone risk

WCET 2025: The Impact of GLP-1 Receptor Agonists on Nephrolithiasis Amongst Patients with Obesity: Insights from a Real-World Data Analysis. *Qiuchen Li*

- TriNetX U.S. Collaborative Research Network, queried for patients over the age of 18 years diagnosed with obesity, but without diabetes in the recent 20 years (n=255,916).
- categorized into those who have and have not had a history of nephrolithiasis, then those who have and have not been on GLP-1A treatment.
- **findings suggest a consistent, independent association between GLP-1A use and reduced kidney stone risk, regardless of prior stone history**

Table 1: Rates of nephrolithiasis in nondiabetic patients with obesity with and without GLP-1 Receptor Agonist Therapy

		GLP-1 Treated (n, %)	non-GLP-1 Treated (n, %)	Risk ratio	p-value
Patients with obesity and history of stone formation	Before propensity matching	7,243 (28.0%)	100,015 (43.5%)	0.64	<0.001*
	After propensity matching (n=23,885)	6,855 (28.7%)	7,821 (32.8%)	0.87	<0.001*
Patients with obesity and no history of stone formation	Before propensity matching	1,731 (0.54%)	54,410 (1.18%)	0.46	<0.001*
	After propensity matching (n=237,800)	1,189 (0.50%)	1,505 (0.63%)	0.79	<0.001*

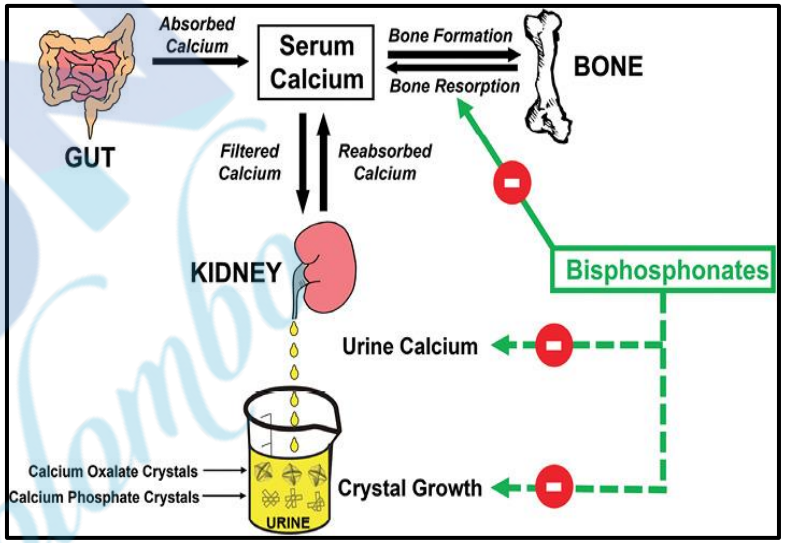
Changes in 24-Hour Urine Chemistry in Patients with Nephrolithiasis during Weight Loss with Glucagon-Like Peptide 1–Based Therapies

Karen Feghali, Xilong Li , Naim M. Maalouf, Kidney 360 5: 1706–1712, 2024

- **In obese kidney stone formers, weight loss with glucagon-like peptide-1 (GLP)-based therapy was associated with a significant decline in 24-hour urine oxalate and sulfate excretion rates.**

Treatment of kidney stones used for low density bone disease: bisphosphonates: observational but no RCT trials

- **Potential mechanisms**: inhibit calcium oxalate & phosphate crystallization; bind to hydroxyapatite in bone/alter bone calcium dynamics; ? reduce hypercalciuria

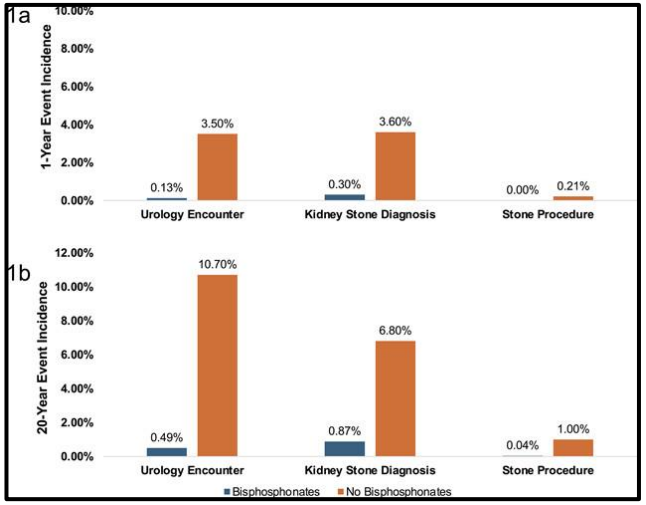


Jan, 2024: AUA news

- In NHS II, low bone density was associated with higher risk of kidney stones and higher urine calcium excretion. **Bisphosphate use was independently associated with lower risk of incident kidney stones among participants with low bone density** but not 24 h urine calcium excretion. *Prochaska. CJASN 12: 1284, 2017*

- Bisphosphonate Use May Reduce the Risk of Urolithiasis in Astronauts on Long-Term Spaceflights. Reduced calcium & Type 1 collagen excretion in a weightless environment. *Okada, 2021,JBMR Plus, 6:1-10*

- Bisphosphonate treatment is associated with lower incidence of urology encounters, kidney stone diagnoses and procedures. *Sheetz, J.of Urol, 2025, 213:e1160*



Sheetz et al, Journal of Urology, 2025, 213:e1160

Summary: prevention of kidney stones, preserve bones and address metabolic syndrome: lifestyle

- **Exercise**: weight bearing for bones, stones and well being
- **FLUID INTAKE**: 2-3 L/day to have urine volume >2.5 L
  ingest evenly through day and night so urine is dilute to reduce urine SS
- **Diet**: - ≤ 70-80 g/d protein to reduce hypercalciuria & acid load on bones
  - ≤ 2.3 g (100 meq) sodium to reduce hypercalciuria & BP
  - 0.8-1.2 g calcium from food with meals to maintain bones and reduce oxalate absorption from gut especially in those with plant-based diets
  - avoid processed foods to reduce phosphorus, sodium, sugars
  - avoid excess sugary drinks
  - 5-9 fruits and vegetables or 3-4 oz lemon/lime to increase citrate
  - DASH or mediterranean diet for western populations

Supplements: No calcium, protein, vitamins (except D3,1000u/d)

❖ **It is about the HOW not just the WHAT**
Consult with dietitian in person or online

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Melanie
Melanie Betz MS, RD, CSR, LDN, FAND
www.thekidneydietitian.org

Summary: prevention of kidney stones, preserve bones and address metabolic syndrome: pharmacology

Drugs:

- **thiazides** (for hypercalciuria, calcium phosphate stones and bones)
- **citrates, potassium,** magnesium or sodium for hypocitraturia or to alkalinize urine, *Litholyte* or *Moonstone* better tolerated than pills)
- **allopurinol** (for hyperuricosuria or hyperuricemia with gout)
- **SGLT2 inhibitors** (increase urine flow, increase citrate excretion, reduce urine SS for calcium oxalate and uric acid)
- **bisphosphates** for bones with density < T2.5 and ? stones (? reducing hypercalciuria, reducing CaOx and CaP crystallization)
- **GLP1** for DM, metabolic syndrome and obesity and ? stones

Monitor:

- **24 h urine** for metabolic and dietary risk factors, pH, volume and SS
  Spot urines don't accurately reflect daily excretion or intake
  (*Ferraro et al, Nephrol. Dial. Transplant, 2021,37: 2171-2179)*

share results with patient

- **imaging of kidneys** to assess **stone burden**

- DXA **scans of bones** to assess **bone density**

Stone Risk Factors / Cystine Screening: Negative (06/30/2016)

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
08/07/17	S24281191	3.04	4.14	358	28	254	1.30	6.081	0.45	0.772
02/06/17	S22426084	2.42	6.70	297	42	455	2.53	6.874	0.10	0.771
10/23/16	S20187718	2.98	7.56	401*	49*	546	2.00	6.494	0.18	0.723
06/26/16	S19466608	1.44	5.38	197	29	220	0.37	5.201	3.66	0.829
REFERENCE RANGE		0.5 - 4L	6 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.800 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
08/07/17	S24281191	178	50	100	1.516	58	167	51	14.59	1.1
02/06/17	S22426084	157	78	116	0.963	37	144	54	10.75	0.9
10/23/16	S20187718	183	83	119	1.117	45	208	47	15.34	1.1
06/26/16	S19466608	255	65	102	1.569	61	271	61	15.16	
REFERENCE RANGE		50 - 150	20 - 100	30 - 120	0.6 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

Normalized Values

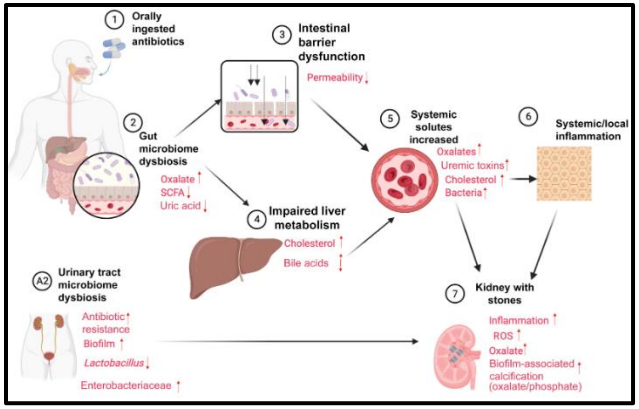
DATE	SAMPLE ID	WEIGHT	Cr 24	Cr 24/Kg	Ca 24/Kg	Ca 24/Cr 24
08/07/17	S24281191	104.3	2416	23.2	3.4	148
02/06/17	S22426084	97.5	2427	24.9	3.0	123
10/23/16	S20187718	102.5	2147	20.9	3.9	187
06/26/16	S19466608		2477			79
REFERENCE RANGE				male 18-24 female 15-20	<4	<140

Serial 24 hour urine collections reflect volume

- changes over time
- adequacy of urine collection
- amount of stone forming factors
- amount of stone inhibiting factors
- dietary intake
- urine super-saturations, pH

Conclusions for management of kidney stones & to protect bones

- Nephrolithiasis, low bone density are part of systemic disease syndromes along with metabolic syndrome, CVD and CKD
- 24 hr urines can help solve the mystery of pathogenic factors and dietary needs to support bones and reduce stone formation and help the patients
- 24 h urines do not show nutrition factors at the time of the kidney stone; some may have formed years ago; they are just a 24 hr snap-shot, do not show what happens on a daily basis or at particular times of the day
- Preventing recurrent kidney stones with diet requires understanding that **enough is good, more is not better**
- **Support the microbiome**
- Often, a combination of diet, fluids, and medication is required to achieve control of stone forming & inhibiting elements to prevent new stone formation and protect bone mass



Agudelo, Euro Urol Focus. 2024, 10: 902-905

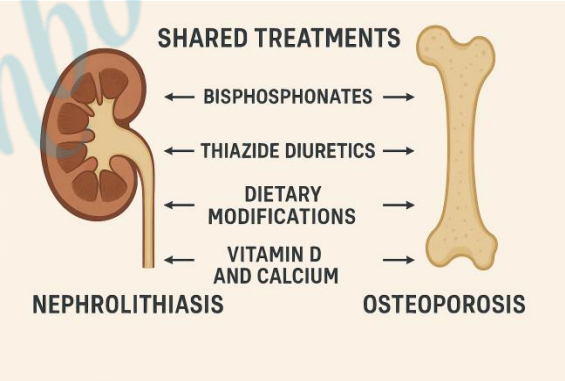
- Multidisciplinary clinics with **dietitian** can provide personalized nutrition as knowing **what to eat** is important but **how to** is more so.

Thank you - Questions?

Resources:

- LeBoff et al, Osteoporosis Int, 2022, 33:249-2102
- Rendina et al, International Journal of Medical Sciences, 2020, 21:8183-8200
- Ziemba et al, Investig Clin Urol, 2017; 58:299-306
- Vergatti et al, Archivio Italiano di Urologia, 2025; 97: 13870-13878;
- Cosmon, Osteoporosis Int 2014, 25: 2359

- **McMaster Textbook of Internal Medicine**
  Nephrolithiasis: Nephrolithiasis - Nephrology - Diseases – McMaster Textbook of Internal Medicine (empendium.com)



Podcasts

- Kidney stone passage prevention, dietitian's perspective https://www.backtable.com/shows/urology/articles/kidney-stone-management-passage-prevention-dieticians-perspective
- Canary in the Coal Mine- kidney stones https://www.vumedi.com/video/the-2024-collins-distinguished-lectureship-kidney-stones-canary-in-the-coal-mine/
- I ordered the urine stone profile, now what https://www.vumedi.com/video/i-ordered-the-urine-stone-profile-now-what/

❖ **Social Media:**
The Kidney Dietitian: www.thekidneydietician.org

Happy Eating!
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