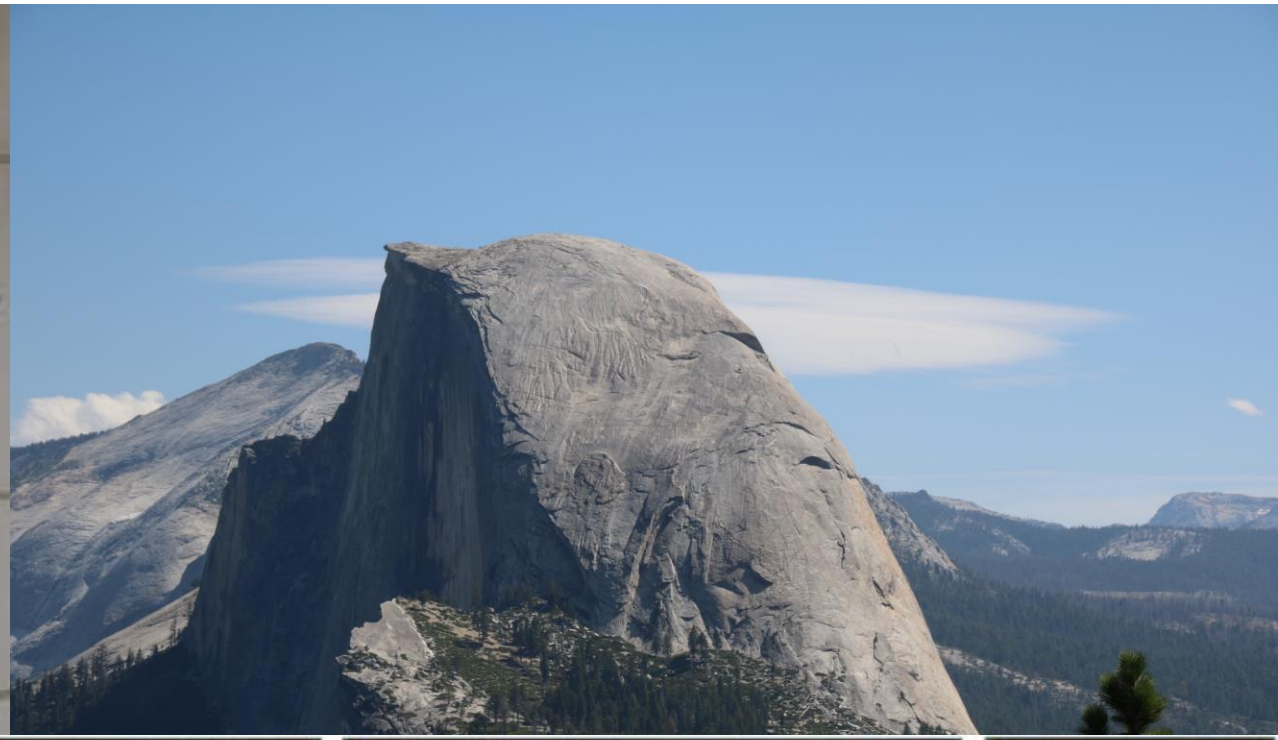
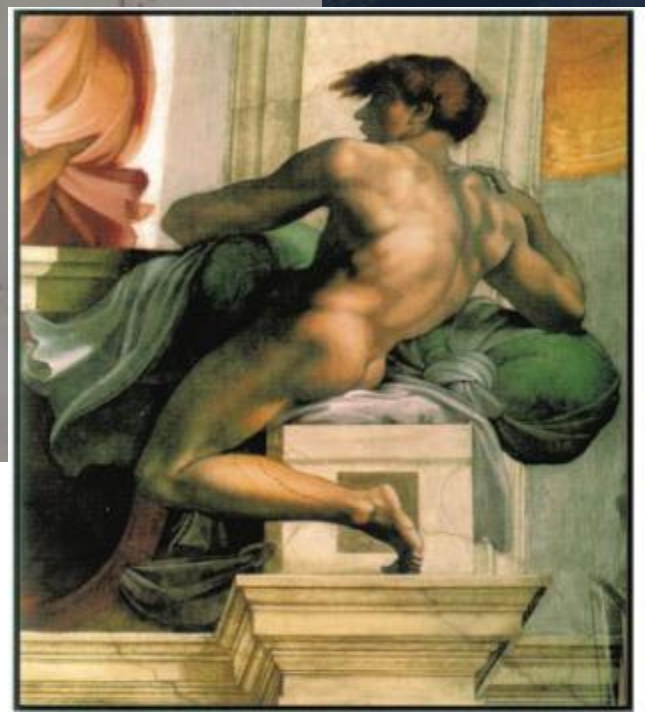
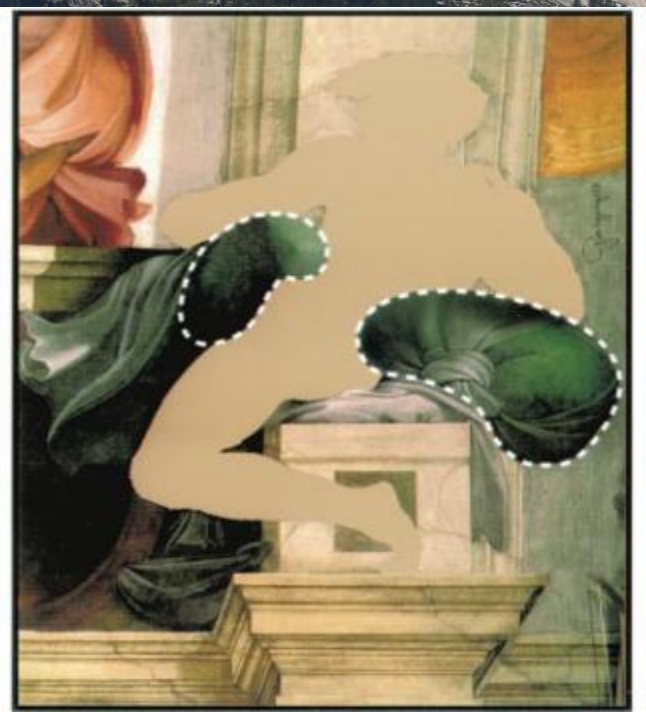


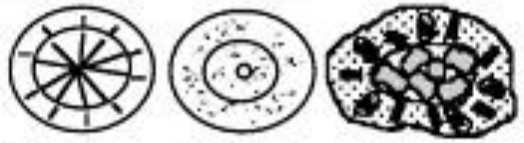




Arjan van der Tol, nefrologie UZG

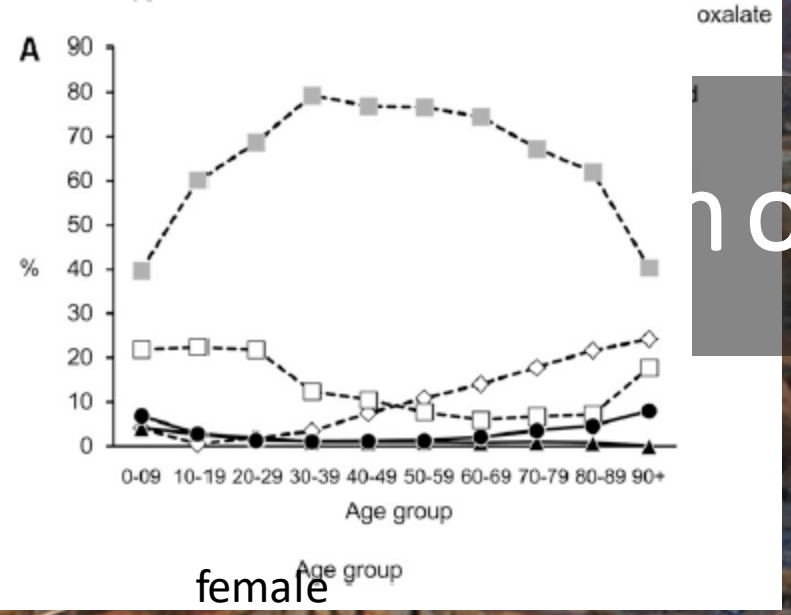
Urolithiasis

- 10%: life time prevalence (increasing)
- 5% of patients who have US or CT: Asymptomatic incidental stones
- 10-30% of asymptomatic stone will develop symptoms or undergo a procedure < 5 yr
- 26% of first symptomatic stone will recurrence < 5 yr
- Stone analysis & blood sample in all first stone
- Metabolic evaluation: early onset, fam history, recurrent stones, brushite, uric acid, solitary kidney, underlying diseases (obesity, CF, Crohn,..)

Type and main component	%
Calcium oxalate monohydrate papillary calculi 	12.9
Calcium oxalate monohydrate unattached calculi (formed in renal cavities) 	16.4
Calcium oxalate dihydrate unattached calculi 	33.8
Calcium oxalate dihydrate/ hydroxyapatite mixed unattached calculi 	11.2
Hydroxyapatite unattached calculi 	7.1
Struvite infectious calculi	4.1
Brushite unattached calculi 	0.6
Uric acid unattached calculi 	8.2
Calcium oxalate/uric acid mixed calculi	2.6
Cystine unattached calculi	1.1
Unfrequent calculi	1.9

F Grases. 2002 Clinica Chimica Acta 322: 29-36

n of gender and age with stone type



female

male

JC Lieske 2014 CJASN 9:2141-6

JC Lieske CJASN 9:2141-6 2014

Underlying determining factors…

- Calciumoxalate: hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria
- Calciumphosphate (brushite, hydroxyapatite, carbonate apatite): hypercalciuria, hypocitraturia, high urinary pH
- Stuvite: UTI, high urinary pH
- Uric acid: low urinary pH, MS, DM
- Cystine, xantine, 2,8 dihydoxyadenine: genetic

Treatment

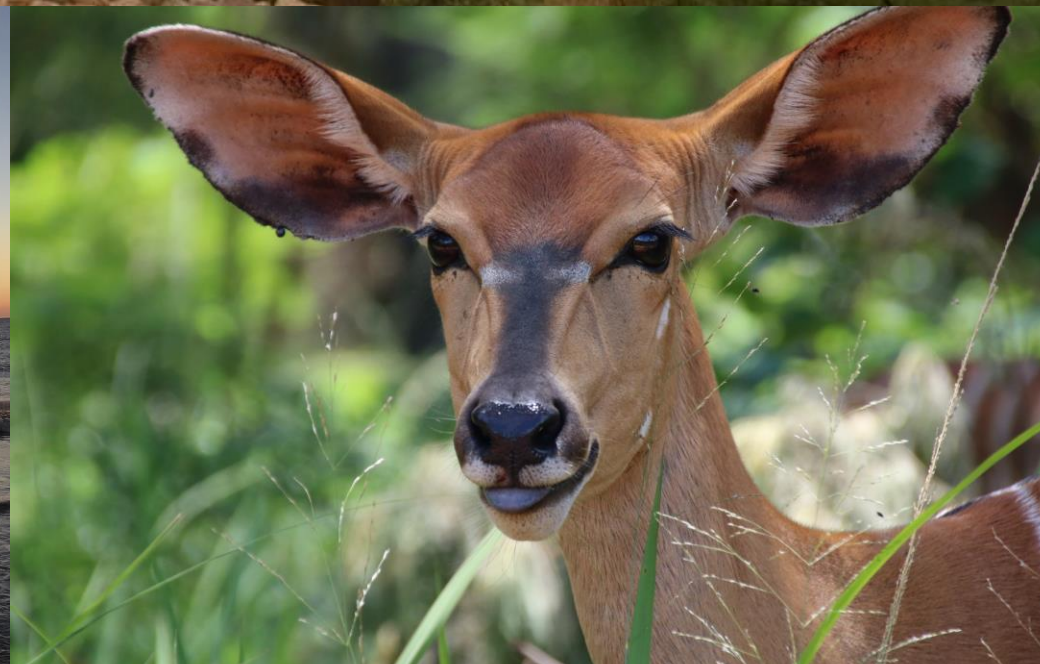


TABLE 3. *Values of urine volume and relative supersaturation of lithogenous salts during the baseline and followup interval in groups 1 and 2*

	Baseline	Followup Interval (Yrs.)				
		1	2	3	4	5
Vol. (ml./24 hrs.):						
Group 1	1,068 ± 240	2,127 ± 546 p < 0.0001	2,261 ± 575 p < 0.0001	2,611 ± 683 p < 0.0001	2,654 ± 587 p < 0.0001	2,621 ± 443 p < 0.0001
Group 2	1,008 ± 231	1,258 ± 292	1,183 ± 271	1,032 ± 256	1,005 ± 183	1,014 ± 195
Calcium oxalate, relative supersaturation:						
Group 1	10.1 ± 4.9	5.2 ± 3.2 p < 0.0001	4.4 ± 2.9 p < 0.0001	4.0 ± 2.4 p < 0.0001	3.5 ± 2.0 p < 0.0001	2.6 ± 0.8 p < 0.0001
Group 2	11.2 ± 5.3	8.1 ± 5.2	9.5 ± 5.2	10.2 ± 4.7	10.2 ± 3.3	9.9 ± 3.4
Brushite, relative supersaturation:						
Group 1	1.6 ± 1.24	0.97 ± 0.99	0.84 ± 0.72 p < 0.001	0.65 ± 0.58 p < 0.0001	0.54 ± 0.36 p < 0.0001	0.48 ± 0.24 p < 0.0001
Group 2	1.82 ± 1.67	1.22 ± 1.06	1.33 ± 1.16	1.60 ± 1.14	1.60 ± 0.90	1.58 ± 0.99
Uric acid, relative supersaturation:						
Group 1	3.48 ± 2.95	1.72 ± 1.49 p < 0.001	1.29 ± 1.19	1.15 ± 0.93	0.80 ± 0.52	0.60 ± 0.35
Group 2	3.64 ± 3.08	2.66 ± 2.3				

Control values of the relative supersaturations in 101 healthy controls were 5.87 ± acid.

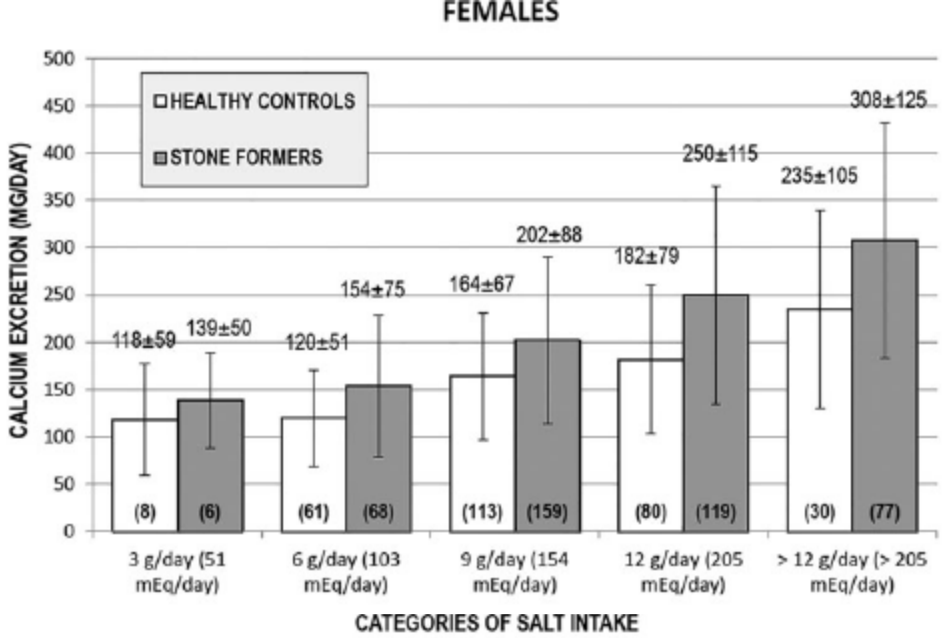
TABLE 4. *Urinary stone risk profile during the baseline period in calcium stone patients with and without relapse in groups 1 and 2*

	Group 1			Group 2		
	No Relapse (87 pts.)		Relapse (12 pts.)	No Relapse (73 pts.)		Relapse (27 pts.)
Vol. (ml./24 hrs.)	1,051 ± 232		1,191 ± 275	987 ± 242		1,064 ± 189
Creatinine (mg./24 hrs.)	1,450 ± 308		1,623 ± 397	1,419 ± 407		1,584 ± 365
Urea (gm./24 hrs.)	22.8 ± 7.9		24.4 ± 9.8	23.3 ± 7.2		23.7 ± 6.7
Sodium (mmol./24 hrs.)	156 ± 53		175 ± 43	158 ± 49		175 ± 69
Potassium (mmol./24 hrs.)	47 ± 14		45 ± 12	46 ± 15		50 ± 16
Calcium (mg./24 hrs.)	233 ± 100	p = 0.005	326 ± 140	249 ± 107	p = 0.01	313 ± 113
Phosphorus (mg./24 hrs.)	705 ± 220		708 ± 331	673 ± 273		661 ± 201
Magnesium (mg./24 hrs.)	84 ± 31		96 ± 35	86 ± 32		94 ± 35
Chloride (mmol./24 hrs.)	159 ± 55		173 ± 36	153 ± 51		177 ± 63
Uric acid (mg./24 hrs.)	579 ± 162		659 ± 294	565 ± 189		591 ± 264
Citrate (mg./24 hrs.)	517 ± 212		478 ± 173	529 ± 262		532 ± 255
Oxalate (mg./24 hrs.)	28.5 ± 8.8		30.1 ± 13.9	28.1 ± 10.1		30.2 ± 11.6
Sulfate (mmol./24 hrs.)	19.8 ± 5.1		24.6 ± 8.4	20.2 ± 5.6		21 ± 7.3
Ammonium (mmol./24 hrs.)	35 ± 10		38 ± 12	34 ± 13		36 ± 11
pH (24 hrs.)	5.92 ± 0.48		5.80 ± 0.53	5.91 ± 0.54		5.88 ± 0.42
Relative supersaturation:						
Calcium oxalate	10.1 ± 4.9		10.9 ± 5.0	10.9 ± 5.1		12.2 ± 5.9
Brushite	1.56 ± 1.15		1.88 ± 1.81	1.81 ± 1.58		1.85 ± 1.93
Uric acid	3.38 ± 2.93		4.24 ± 3.08	3.82 ± 3.38		3.16 ± 2.03

Borghi JU 1996

Hypercalciuria

- Def: >4mg/kg/day (>0.1 mmol/kg/day) in normal 24-h urine sample
- Kidney stones, nephrocalcinosis, CKD and osteoporosis
- Etiology:
  1. Increased filtered load? (hypercalcemia)
  2. Dietary (salt intake)
  3. Absorptive (GI)
  4. Resorptive (bone)
  5. Renal leak



associated with
pecially in stone formers

Ticinesi, 2014, NDT

Salt reduction is important in SF

- Kidney stone formers
  - ↓100 mmol Na/d → Urinary calcium ↓ 2 mmol/d
- Non-stone formers
  - ↓100 mmol Na/d → Urinary calcium ↓ 1 mmol/d

Salt intake → hypervolumia → sodium and calcium reabsorption ↓ (Ca handling depends on Na)

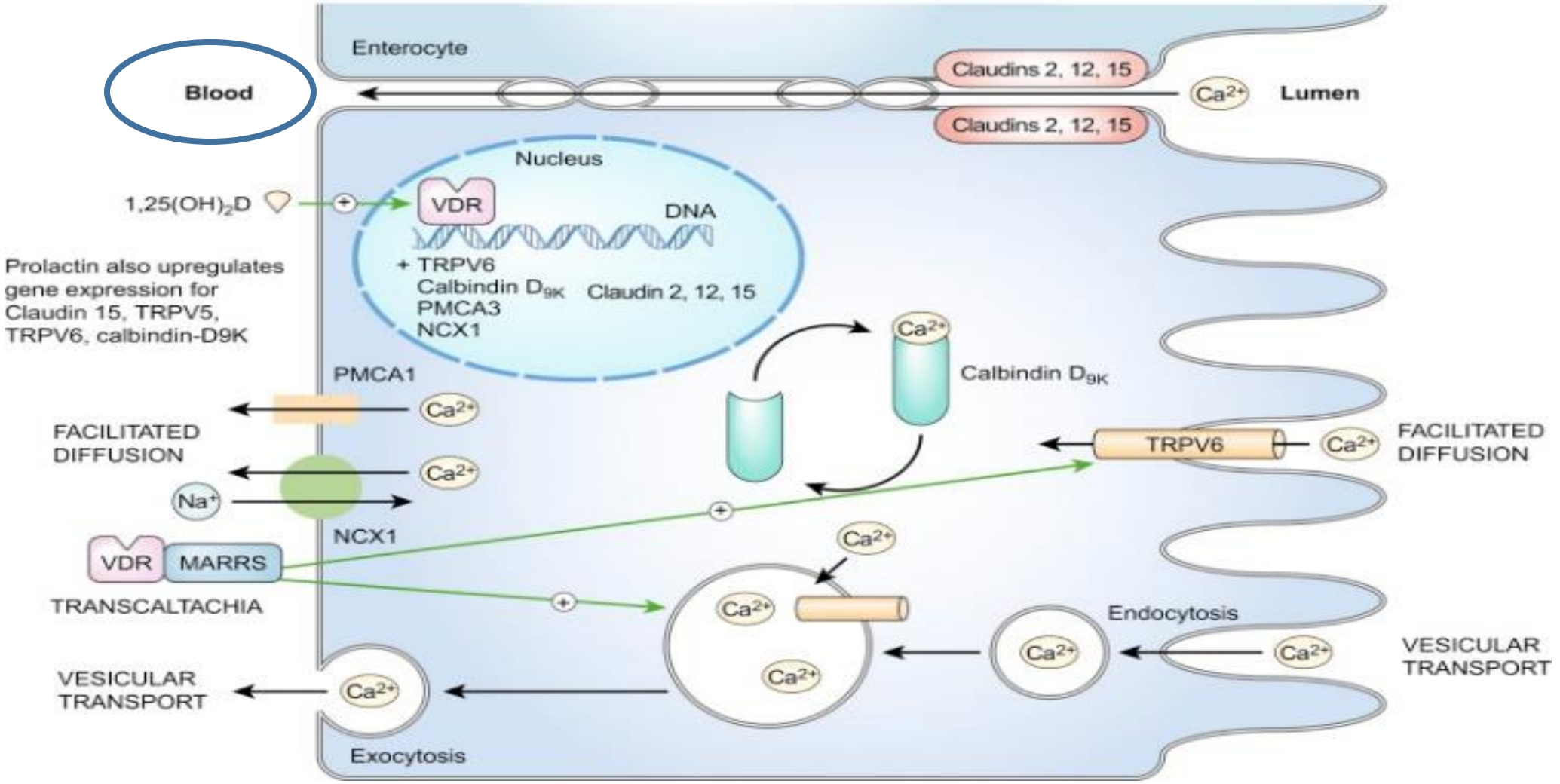
High protein intake is associated with hypercalciuria

- Unknown mechanism
- High protein intake (Atkins diet) is associated with lower urinary pH, high net acid excretion, low urinary citrate and hypercalciuria (Reddy, 2000, AJKD)
  - Potassiumcitrate neutralized the acid load (increased urinary citrate) delivered by high protein diet but did not reduced hypercalciuria (Maalouf, 2011, J Clin End Met)

Absorptive hypercalciuria

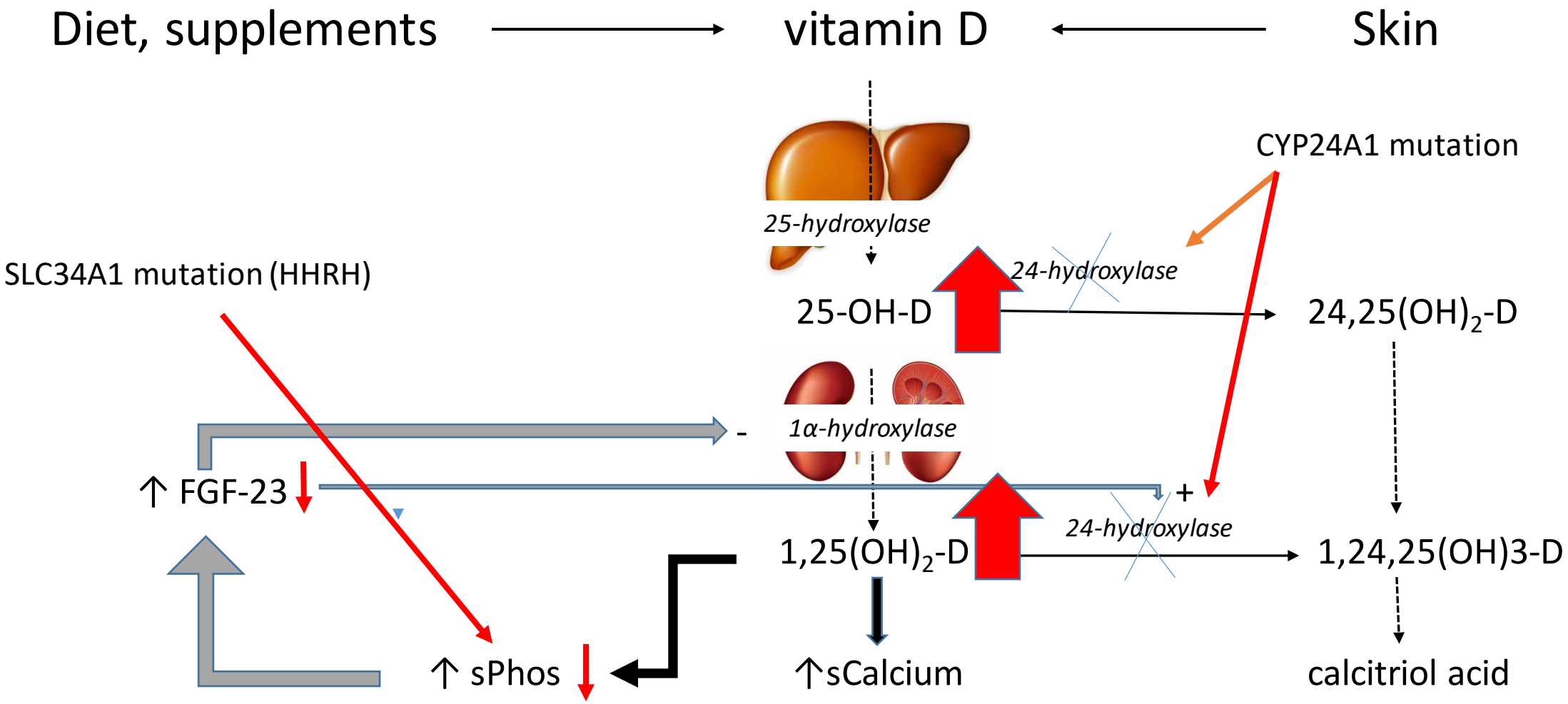
- Def: increase of urinary Ca/creatinine ratio (>0.5 mmol/mol) after a calcium load, low PTH, high calcitriol
- Intestinal calcitriol activation (active Ca absorption via TRPV6)
  - Idiopathic or hypervitaminosis D (iatrogenic, sarcoidosis or genetic)
  - Homozygous mutations in the CYP24A1 (nefrocalcinosis) or SLC34A1/A3 (low phosphatemia: Hereditary Hypophosphatemic Rickets with Hypercalciuria)

Calcium reabsorption in the GUT



G Diaz de Barbozam WJG 2015, vol 21 issue 23

Vit D metabolism



Resorptive hypercalciuria

- Def: fasting urinary calcium/creatinine ratio > 0.4mmol/mmol and increase in bone markers and low BMD
- Etiology
  - PHP
  - HHRH
  - Immobilization
  - Chronic alcoholism
  - Coeliac disease
  - Corticoidtherapy
  - menopause

Renal hypercalciuria

- Def (hard): normal of low calcium levels, high urinary fasting calcium/creatine ratio and normal-high PTH (proteinuria, metabolic acidosis, hypomagnesemia)
- Etiology
  - Idiopathic
  - Tubular acidosis
  - HHRH (SCL34A1/A3, NHERF1)
  - Cacchi-Ricci
  - FHHNC syndrome (CLDN16/19)
  - Dent/Lowe disease (CLCN5/OCRL1)
  - Bartter syndrome (NKCC2, ROMK, CLCNKB, Barttine, CaSR)

Treatment hypercalciuria

- Thiazide (side effects hypoNa, hypoK, hypotension, hyperglycemia and dyslipidemia) (Thiazide 25-50mg or indapamide 2,5mg od)
  - Mainly effective by salt restriction (Ca-Na reabsorption)
- Potassium citrate 5gr in 1 or 1,5L water daily
  - Decreasing intestinal calcium absorption, increasing calcium reabsorption distal tubuli and decreasing bone resorption.

Vitamin D supplementation in vit D deficiency

- 1 year randomized placebo-controlled trial of vit D dose (400-4800 IU/d) in 163 postmenopausal women (calcium intake 1200mg/d in all groups)

- Hypercalciuria (>300mg/d) occurs in 30.6%
- Hypercalcemia (>10.2 mg/dl) occurs in 8.8%
- Hypercalcemia and hypercalciuria not related to vit D dose!

Gallagher JC, Menopause 2014

Calcium/vit D intake and urolithiasis

RCT

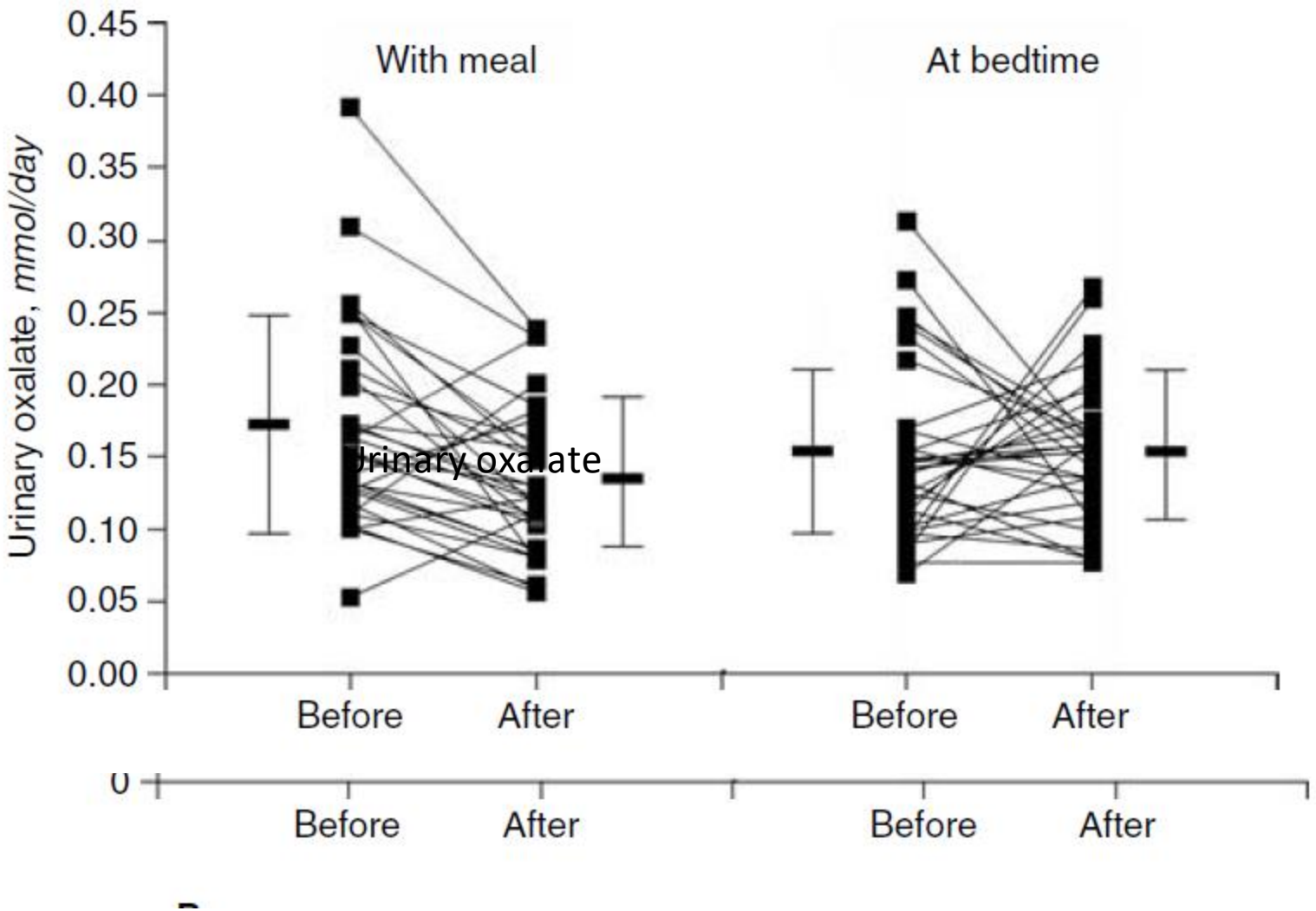
- WHI 36,282 postmenopausal women with baseline calcium intake 1100mg Ca
- 1gr CaCO/400IU vit D versus Placebo
- Urolithiasis RR 1.19 (1.02-1.34 during 7 years FU)

Wallace RB, Am J Clin Nutr, 2011

Observational study

- NHS 91,731 nurses age 34-59: 884 stones in 12 years of follow up
- Risk for urolithiasis:
  - 1.2 (1.01-1.41) with supplemental 1000mg calciumcarbonate
  - 0.65 (0.50-0.83) with high dietary calcium intake

Curhan GC AIM 1997



h meals vs.
: bedtime

Urinary calcium

Domrongkitchaiporn, KI 2004

Conclusions

Calcium supplements

- Dietary Ca = safe (lower sCa, uCa, oxalate binding)
- Prefer calciumcitrate (oxalate binding, provides citrate)
- Mealtime = better (oxalate binding)

Vit D repletion

- Daily and not monthly
- Cave in some stone formers (not in sarcoidosis and CYP24A1 mutations): metabolic bilan

Hypocitraturia

Def: <320 mg/day
etiology:
Acid-base balance: RTA, diarrhae/malabsorption/renal failure
Diet: animal proteins, salt, low fruit/veg
Medication: acetozolamide, amiloride, topiramate
Genetic (VDR polymorphism)
Hypokalemia

Treatment: K-citrate

Hyperuricosuria

Def: >800 mg/day in men, >750mg women

Etiology

- Purine intake
- Production (gout, MXD, neoplasia)
- ua metabolism & reabsorption

Treatment

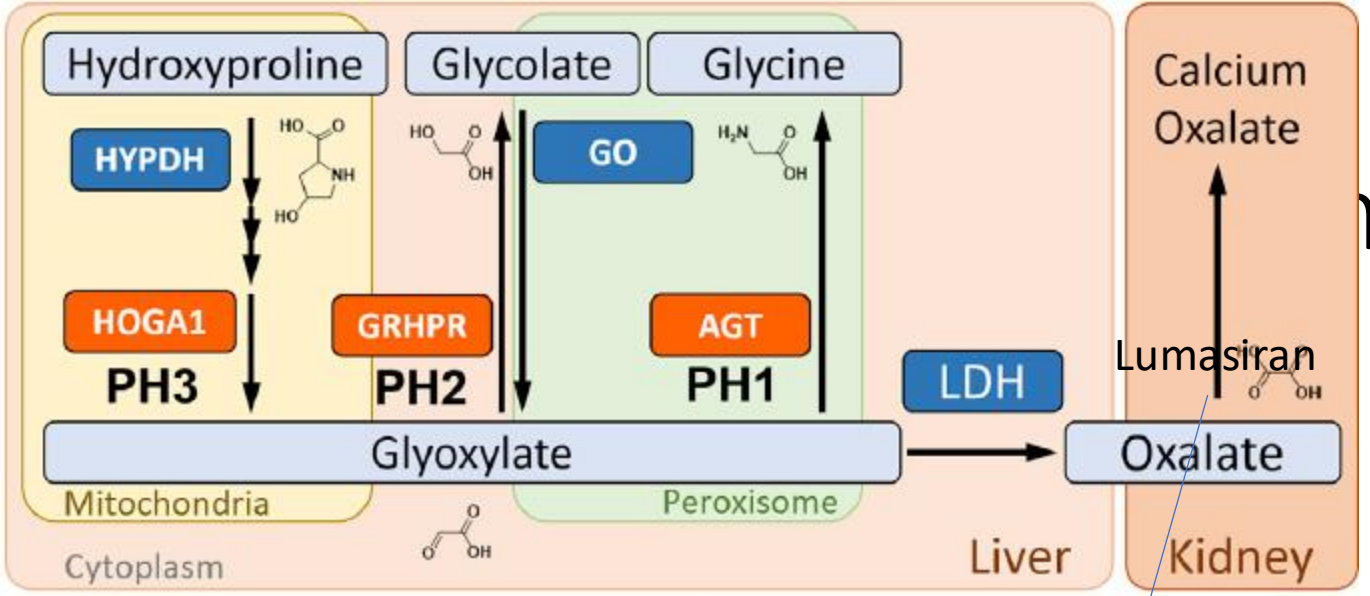
- Xanthine oxidase inhibitor

Hyperoxaluria

Def: >27 mg/L or >45 mg/day

Etiology

- Endogenous oxalate production (genetic)
- Intestinal (increased absorption)
- Dietary (oxalate rich food and precursors)



mall interfering RNA

Lumasiran

Nedosiran

Lai 2018 Molecular therapy

Safety, pharmacodynamics, and exposure-response modeling results from a first-in-human phase 1 study of nedosiran (PHYOX1) in primary hyperoxaluria.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Group A: Healthy participants (blinded) — N=25

Randomized to:

1 of 5 *sequential* dose (mg/kg) cohorts

0.3 → 1.5 → 3.0 → 6.0 → 12.0

n=5/cohort

n=3 nedosiran
n=2 placebo

Single-dose injection (**Day 0**) ●·····► EOS (**Day 29**)

Group B: Patients with PH1/PH2 (open-label) — N=18

Randomized to:

1 of 3 *sequential* nedosiran dose (mg/kg) cohorts

1.5 → 3.0 → 6.0

PH1: n=15
PH2: n=3

24-hour Uox ≥0.7 mmol

Single-dose injection (**Day 0**) ●·····► EOS (**Day 57**)

Primary Study Objective:

Safety/tolerability

Secondary Study Objectives:

Pharmacokinetics/pharmacodynamics

Nedosiran Safety

Injection-site reactions most common AE

13.3%	**27.8%**
Group A (2/15)	**Group B** (5/18)

No severe ISRs

No dose-related trends

No dose-limiting toxicity

No withdrawals

Nedosiran PD

Baseline → **55%** *Day 57 (EOS)*

Mean maximum reduction in 24-hour Uox excretion
(Range: 22%–100%)

67%

reached normal (n=6) or near-normal (n=6) 24-hour Uox excretion

Nedosiran PK/PD data

Exposure-Response Model

Optimal dosage

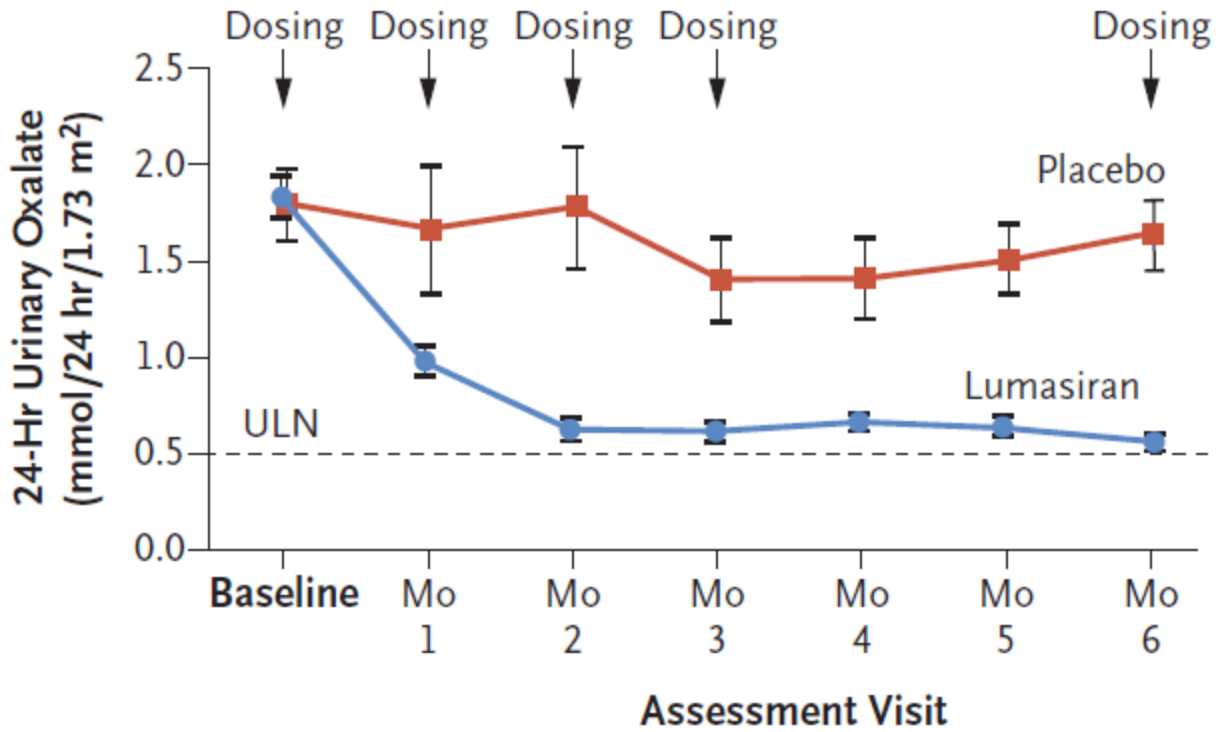
Once-monthly **Nedosiran 160 mg**
(free acid)

Fewest fluctuations in Uox response

CONCLUSION: Single-dose nedosiran demonstrated acceptable safety and evidence of a pharmacodynamic effect in PH1 and PH2 patients

Hoppe, et al, 2021

B 24-Hour Urinary Oxalate Excretion over Time



No. of Patients

Placebo	13	13	12	13	13	13	13
Lumasiran	26	24	26	24	23	25	25

peutic for Primary ype 1

M.D., Sally A. Hulton, M.D.,

NEJM 2021, 384, 1216-20

Increased intestinal oxalate absorption

- Malabsorption syndrome
  - IBD (Crohn disease & ulcerative colitis)
  - Chronic pancreatitis (CF)
  - Iatrogenic: RT, pancreas resection, bowel resection, bypass

  - Treatment:
  - Calciumcitrate
  - ALLN177-302 URIROX-2: Reloxaliase (recombinant oxalase decarboxylase E)
    - oxaluria > 50 mg/day
- Decreased colonisation of O. formigenses (macrolides, tetracyclines, rifampicine and metronidazole)(CF)

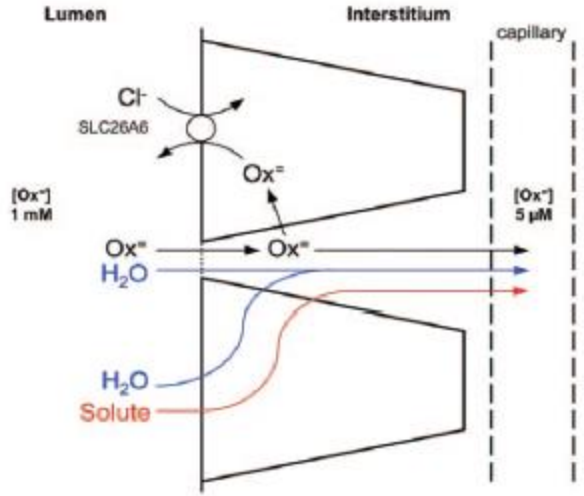


Figure 9. Proposed model of epithelial oxalate transport. Oxalate absorption is largely passive and paracellular across the tight junction. Oxalate then is back-secreted by a transcellular route requiring apical membrane SLC26A6.

d intestinal oxalate secretion (CF)

Felix Knauf 2011 JASN

High oxalate food

- Fruit: figs, raspberries, dates
- Vegetables: spinach, beans, beets, okra
- Whole grain products
- All nuts
- chocolate
- Black tea
- Vit C tablets!

VOEDINGSDRIEHOEK

VLAAMS INSTITUUT GEZOND LEVEN

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Target Treatment of calciumoxalate lithiasis

Hypercalciuria	• Thiazide/Kcitrate
Hypocitraturia	• Kcitrate/diet/etiology
Hyperuricosuria	• Diet/Allopurinol
Hyperoxaluria	• Diet/New agents?