Inborn errors of metabolism presenting with kidney stones: clinical aspects

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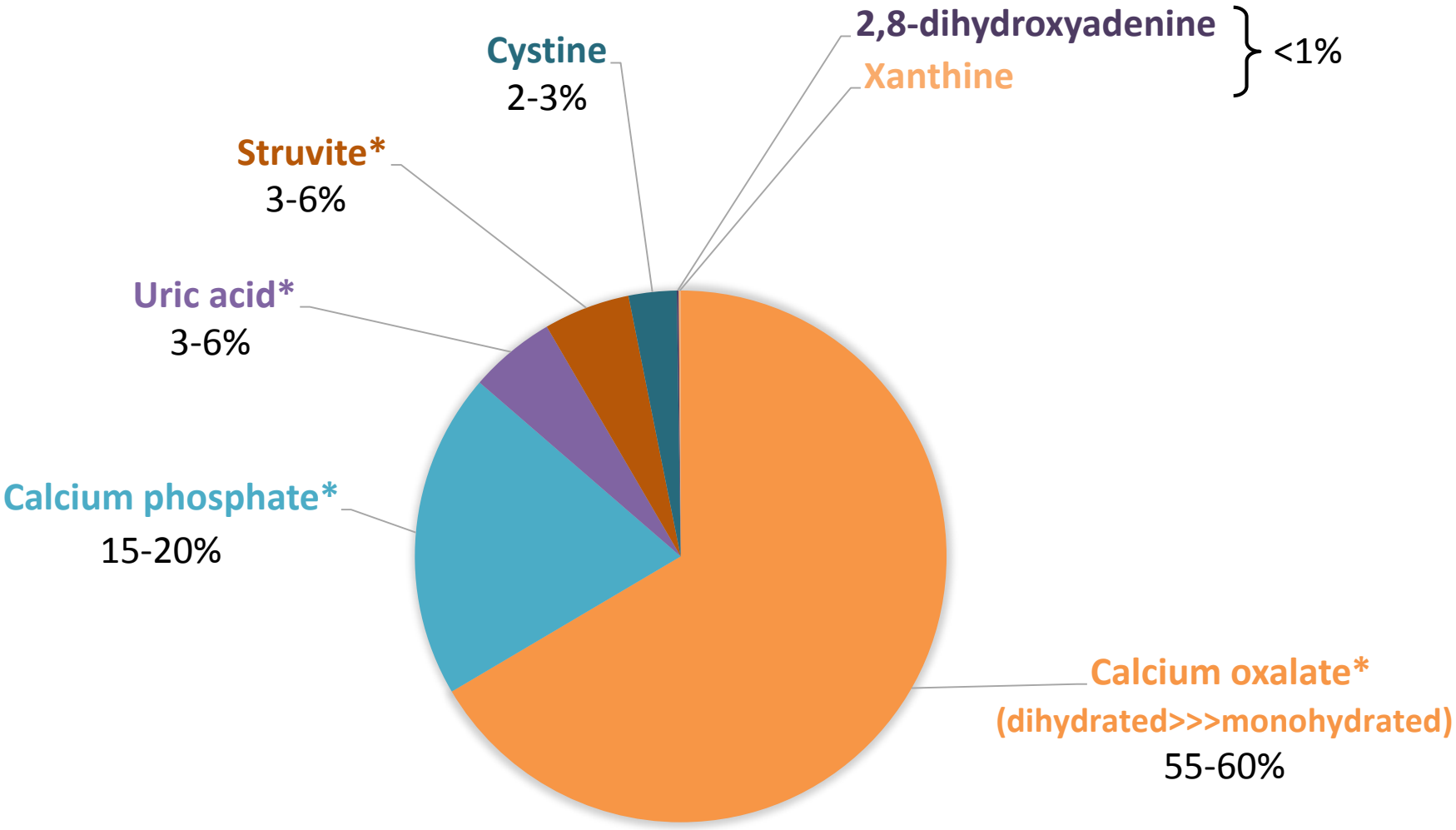
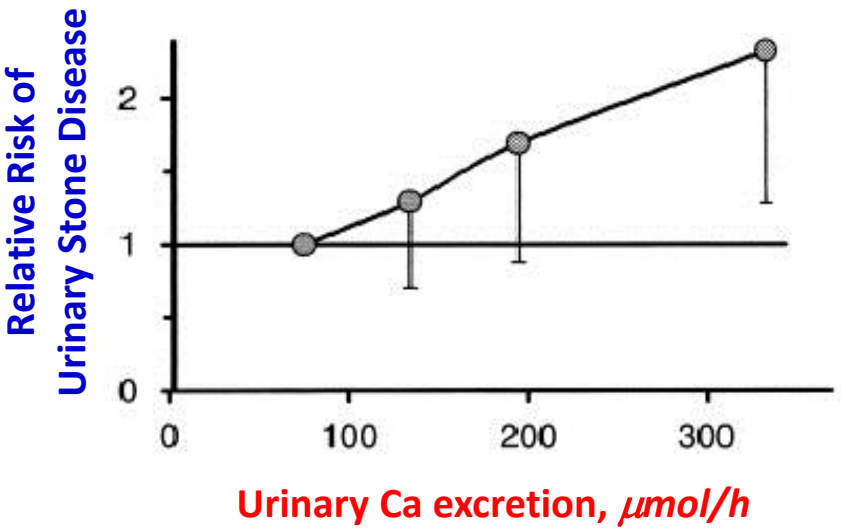
Bambino Gesù
OSPEDALE PEDIATRICO

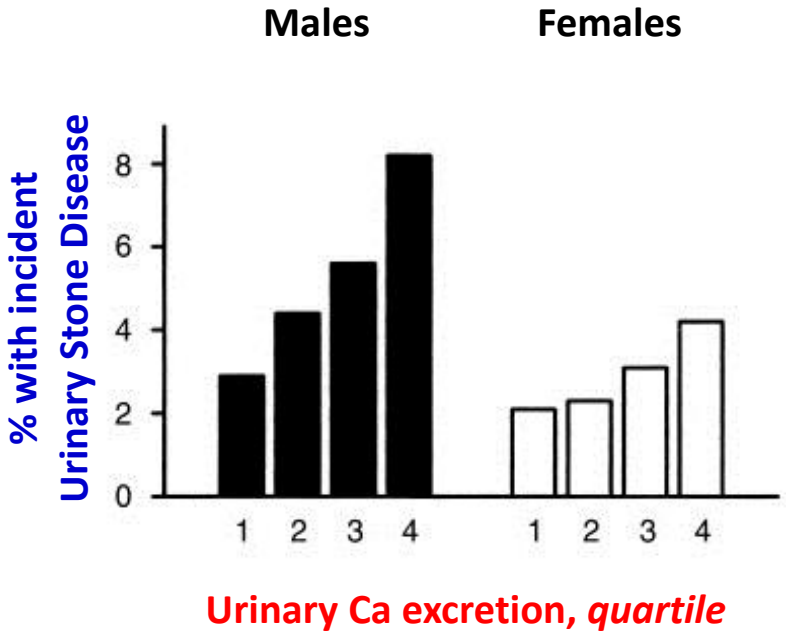
Pediatric renal stones in the western hemisphere



(*) ~65% major component and ~35% principal component

Cross-sectional / prospective data from the Gubbio study

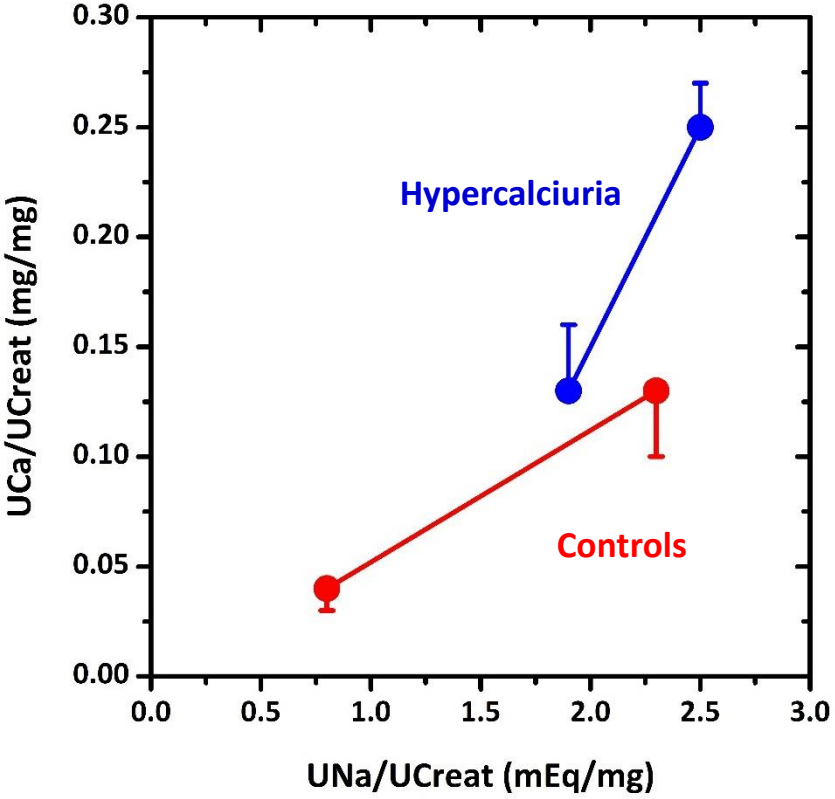




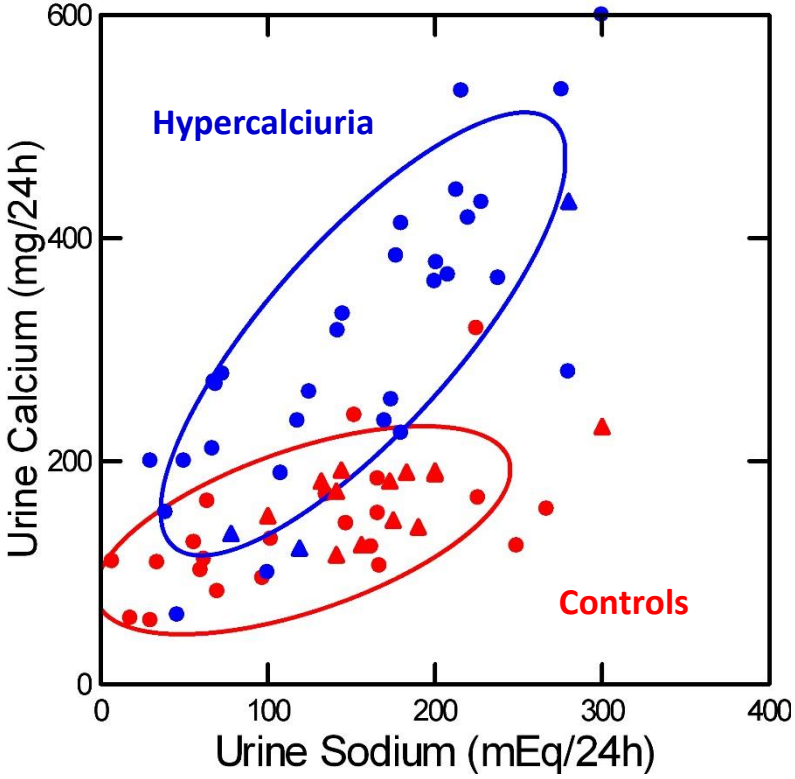
Cirillo et al, Kidney Int 63:2200-2206 (2003)

UNa vs Uca

CHILDREN



ADULTS



F.Emma, unpublished data

http://kidneystones.uchicago.edu/

Hereditary diseases causing calcium-based nephrolithiasis and/or nephrocalcinosis

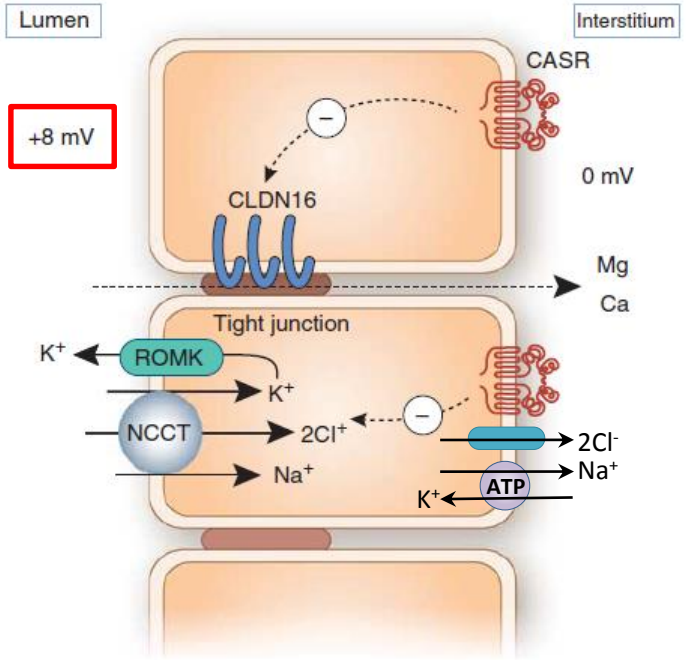


Figure 3 | Claudins are transmembrane proteins and important components of the tight junctions where they are connected with ZO-1 protein and actin of the cytoskeleton to regulate the paracellular permeability to water and ions and preserve cell polarity. Claudin 16 (CLDN16) is detected in cells of the ascending limb. Its variants may change tight junction permeability and paracellular reabsorption of divalent cations driven by the electric gradient maintained by potassium-channel (ROMK) and sodium-chloride cotransport (NCCT). The calcium-sensing receptor (CASR) inhibits the expression of claudin 16 in tight junctions and the activity of NCCT, thus decreasing the paracellular reabsorption of calcium and magnesium. Claudin 14 is located in cells of the distal convoluted tubule and its role is as yet unclear.

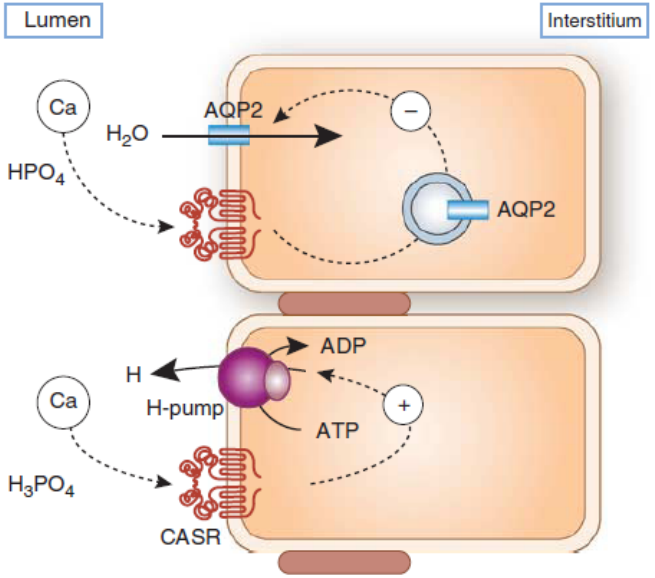


Figure 1 | When the concentration of calcium increases in the tubular fluid, two counterbalancing mechanisms are activated by the calcium-sensing receptor (CASR) in the distal tubule. Here, CASR stimulates proton excretion by H-pump in intercalated cells and decreases water reabsorption by the reduction of aquaporin 2 (AQP2) expression on the apical membrane. As a consequence, urine dilution and acidification protect against calcium-phosphate salt precipitation within the tubular lumen. It is noteworthy that CASR is not a regulator of urine pH or osmolality, but may have a local effect on tubular handling of protons and water. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Vezzoli et al, Kidney International (2011) 80, 587–593

Hereditary diseases causing calcium-based nephrolithiasis and/or nephrocalcinosis

	Gene	Locus/ inheritance mode	Protein	Cellular defect	Tubular defect	Disorder	Ref.
Dent	*CLCN5*	Xp11.22 X-linked recessive	Chloride channel 5 on the endosome membrane	Impaired acidification of the endosome fluid in proximal tubular cells.	Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure.	Dent's syndrome	Cho *et al.*[6] and Scheinman *et al.*[7]
	OCRL1	Xq26.1 X-linked recessive	Phosphatidylinositol 4,5-bisphosphate 5-phosphatase	Accumulation of phosphatidylinositol 4,5-bisphosphate in proximal cells, followed by actin polymerization, and tight and aderens junction defects.	Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure. Hydrophthalmia, cataract, mental retardation.	Dent's syndrome 2 Lowe syndrome	Cho *et al.*[6]
Claudin mutations	*CLDN16*	3q27 Autosomal dominant	Claudin 16	Alteration of tight junction ion selectivity in the thick ascending limb of Henle loop.	Urinary loss of magnesium and calcium, nephrocalcinosis, and progressive kidney failure in homozygotes. Heterozygotes may produce kidney stones.	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Muller *et al.*[8]
	CLDN19	1p34.2 Autosomal dominant	Claudin 19	Alteration of tight junction ion selectivity in the thick ascending limb of Henle loop.	Renal wasting of magnesium and calcium, nephrocalcinosis and progressive kidney failure in homozygotes. Macular colobomata, myopia, and nystagmus.	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular impairment	Konrad *et al.*[9]
RTA	*ATP6N1B*	7q33-q34 Autosomal recessive	β-Subunit ATP6N1B of the H-pump	Defect of the proton secretion and urine acidification in the α-intercalated cells of the collecting duct.	Hypokalemic hyperchloremic acidosis with nephrocalcinosis and kidney stones.	Distal tubular acidosis	Smith *et al.*[10]
	ATP6B1	2cen-q13 Autosomal recessive	Subunit ATP6B1 of the H-pump	Defect of the proton secretion and urine acidification in the α-intercalated cells of the collecting duct.	Hypokalemic hyperchloremic acidosis with nephrocalcinosis and kidney stones. Neural deafness.	Distal tubular acidosis with progressive neural deafness	Karet *et al.*[11]
	SLC4A1	17q21-q22 Autosomal dominant	Anion exchanger	Decreased bicarbonate reabsorption at the basolateral membrane of the α-intercalated cells of the collecting duct.	Hypokalemic hyperchloremic acidosis, nephrocalcinosis and kidney stones. Kidney stones and incomplete tubular acidosis in heterozygotes.	Distal tubular acidosis	Bruce *et al.*[12]
Hyperphosphaturia	*SLC34A3*	9q34 Autosomal recessive	NPT2c sodium-phosphate cotransporter	Reduced phosphate reabsorption and increased calcitriol synthesis in the proximal tubular cells.	Severe rickets and kidney stones caused by renal loss of phosphate, hypophosphatemia, and hypercalciuria.	Hypophosphatemic rickets with hypercalciuria	Bergwitz *et al.*[13] and Tencza *et al.*[14]
Bartter	*CASR*	3q13.3-q21 Autosomal dominant	Calcium-sensing receptor (activating mutations)	Inhibition of calcium reabsorption in the ascending limb of Henle loop.	Hypercalciuria and hypocalcemia. Hyperphosphatemia and hypophosphaturia. Renal hypopotassemia if very potent effect of the mutation.	Autosomal-dominant hypoparathyroidism Bartter syndrome type 5	Pearce *et al.*[15]
	SLC12A1	15q15-q21.1 Autosomal recessive	NKCC2 sodium-potassium-chloride transporter	Decreased sodium, potassium and chloride reabsorption in the ascending limb of Henle loop.	Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.	Bartter syndrome type 1	Puricelli *et al.*[16]
	KCNJ1	11q24 Autosomal recessive	ROMK1 potassium channel	Decreased sodium, potassium and chloride reabsorption in the ascending limb of Henle loop.	Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.	Bartter syndrome type 2	Puricelli *et al.*[16]

Gene mutations cause phenotypic alterations at protein, cellular, and body level that are described in the table. All these mutations cause a protein loss-of-function with the exception of *CASR* gene mutations that cause nephrolithiasis in the presence of activating mutations.

Vezzoli et al, Kidney International (2011) 80, 587–593

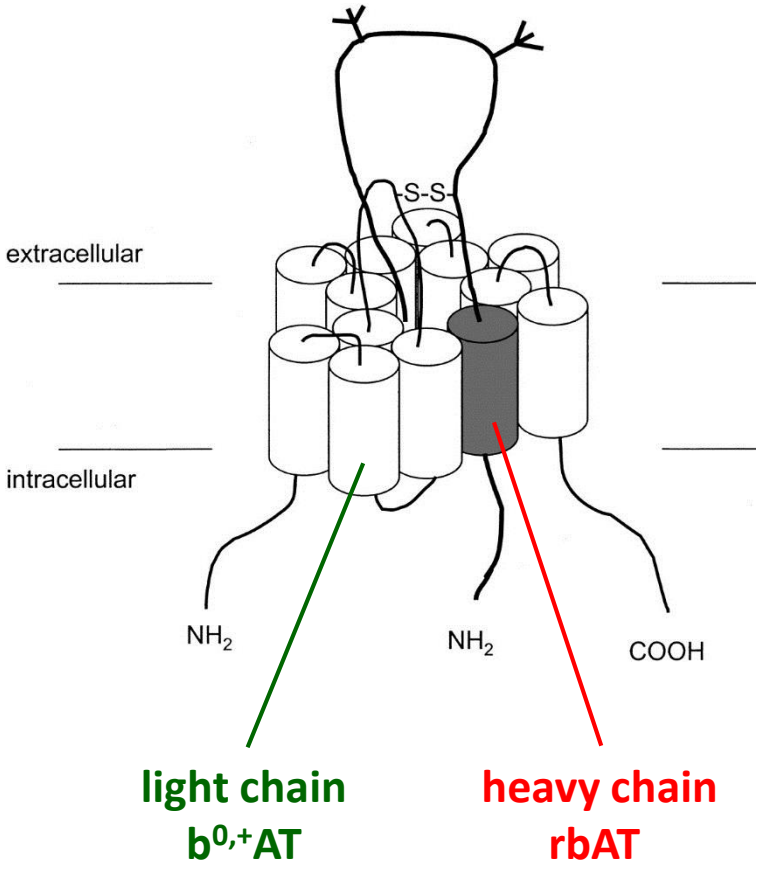
Underlying diseases causing renal stones

Structure	Disease
PO_4-NH_3-Mg (struvite)	UTI
Calcium phosphate	**Hypercalciuria**
Calcium oxalate, dihydrated	
Calcium oxalate, monohydrated	Hyperoxaluria
Cystine	Cystinuria
Uric acid	Purine synthesis disorder
2,8-dihydroxyadenine	APRT deficiency
Xanthine	Xanthinuria

Courtesy Pierre Cochat

Cystinuria

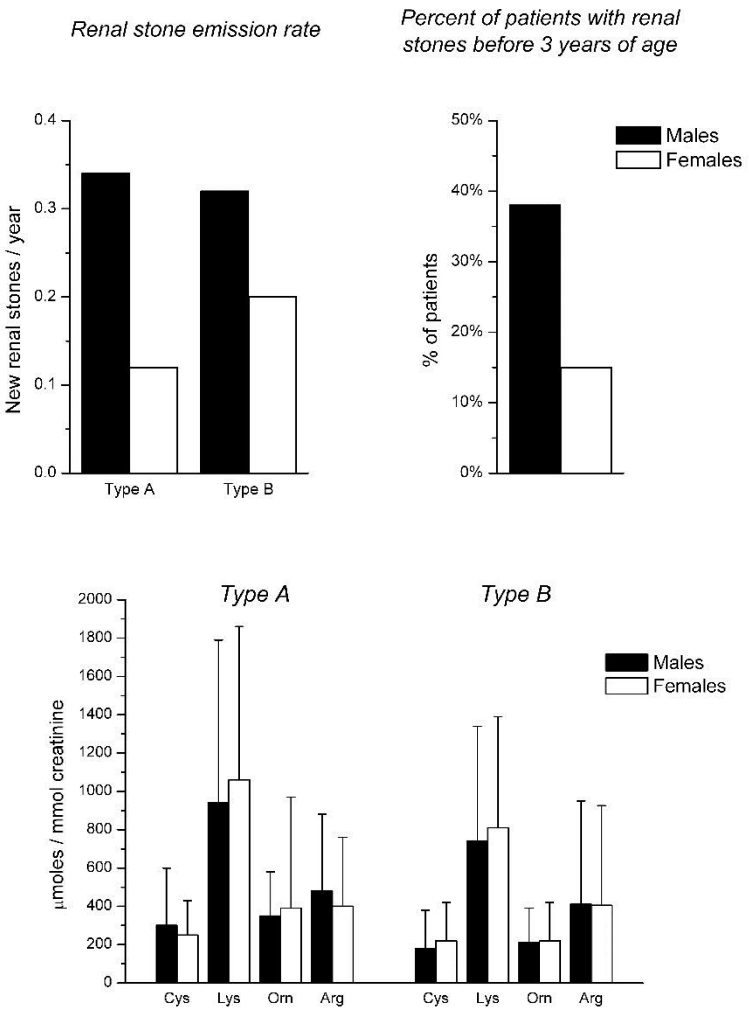
Historical classification	Type I	Type II	Type III
Aminoaciduria heterozygous	N	↑↑	↑
Plasma cystine after oral load	↑↑	↑↑	N
Chromosome	2	19	19
Gene	*SLC3A1*	*SLC7A9*	*SLC7A9*
Protein	rBAT	$B^{0,+}AT$	$B^{0,+}AT$
Gene-based classification	Type A	Type B	



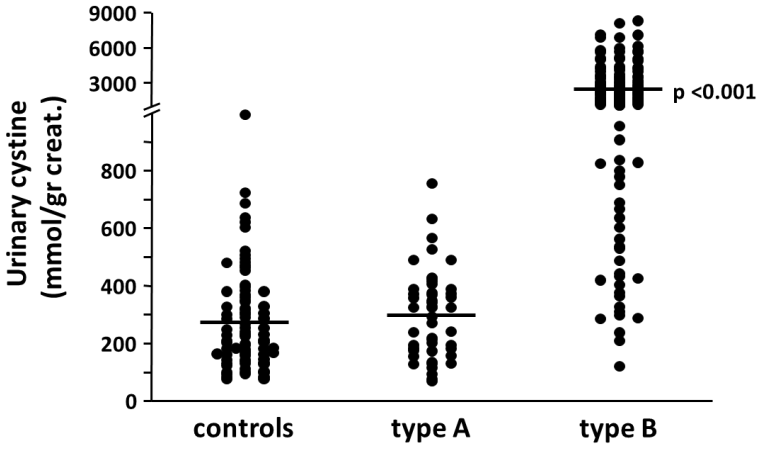
Wagner et al. Am J Physiol Cell Physiol 2001;281:C1077-C1093

Cystinuria

Gender effect

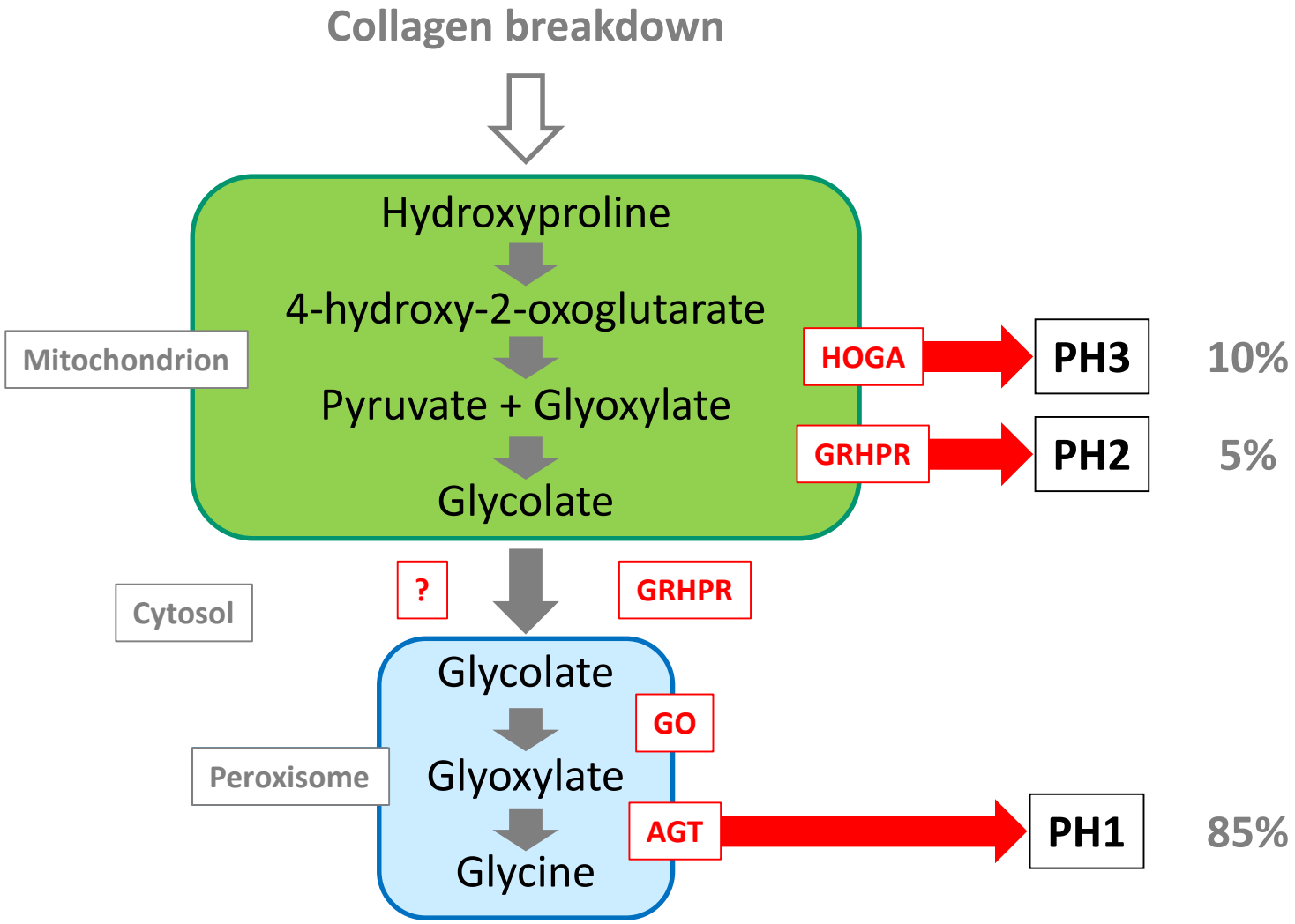


Heterozygous carriers



Dello Strologo, JASN 2002

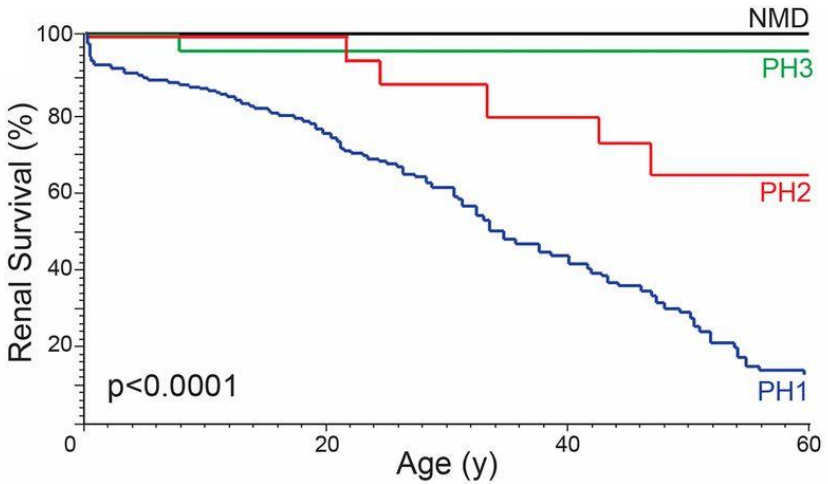
Glyoxylate metabolism in the hepatocyte



Courtesy Pierre Cochat

Genotype-phenotype correlations

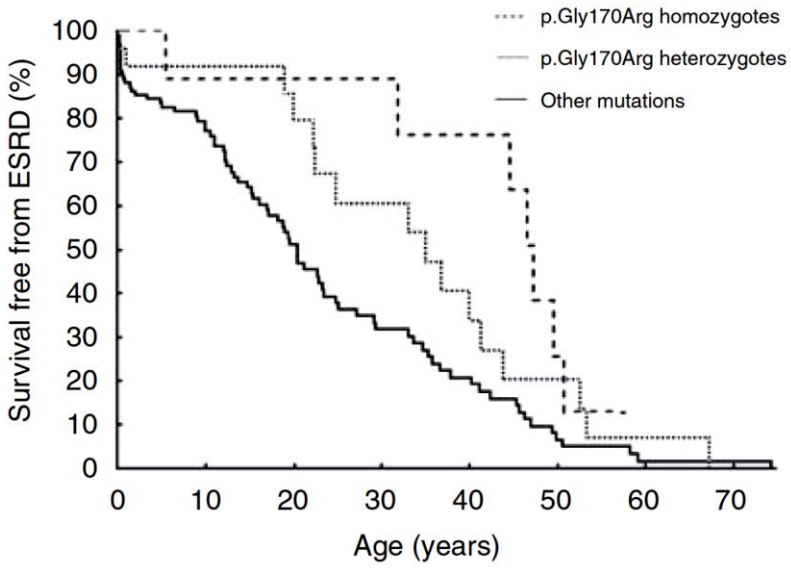
PH1-PH2-PH3



PH1	76% (129)	43% (49)	12% (7)
PH2	100% (18)	82% (11)	66% (4)
PH3	96% (12)	96% (8)	96% (4)
NMD	100% (14)	100% (12)	100% (7)

Hoppe, JASN 2015

PH1



Age	10	20	30	40	50
Survival free from ESRD (no. at risk)					
Homozygous	90% (8)	90% (8)	90% (8)	78% (7)	22% (2)
Heterozygous	91% (18)	85% (14)	60% (9)	33% (5)	20% (3)
Others	78% (69)	52% (31)	31% (18)	22% (12)	7% (4)

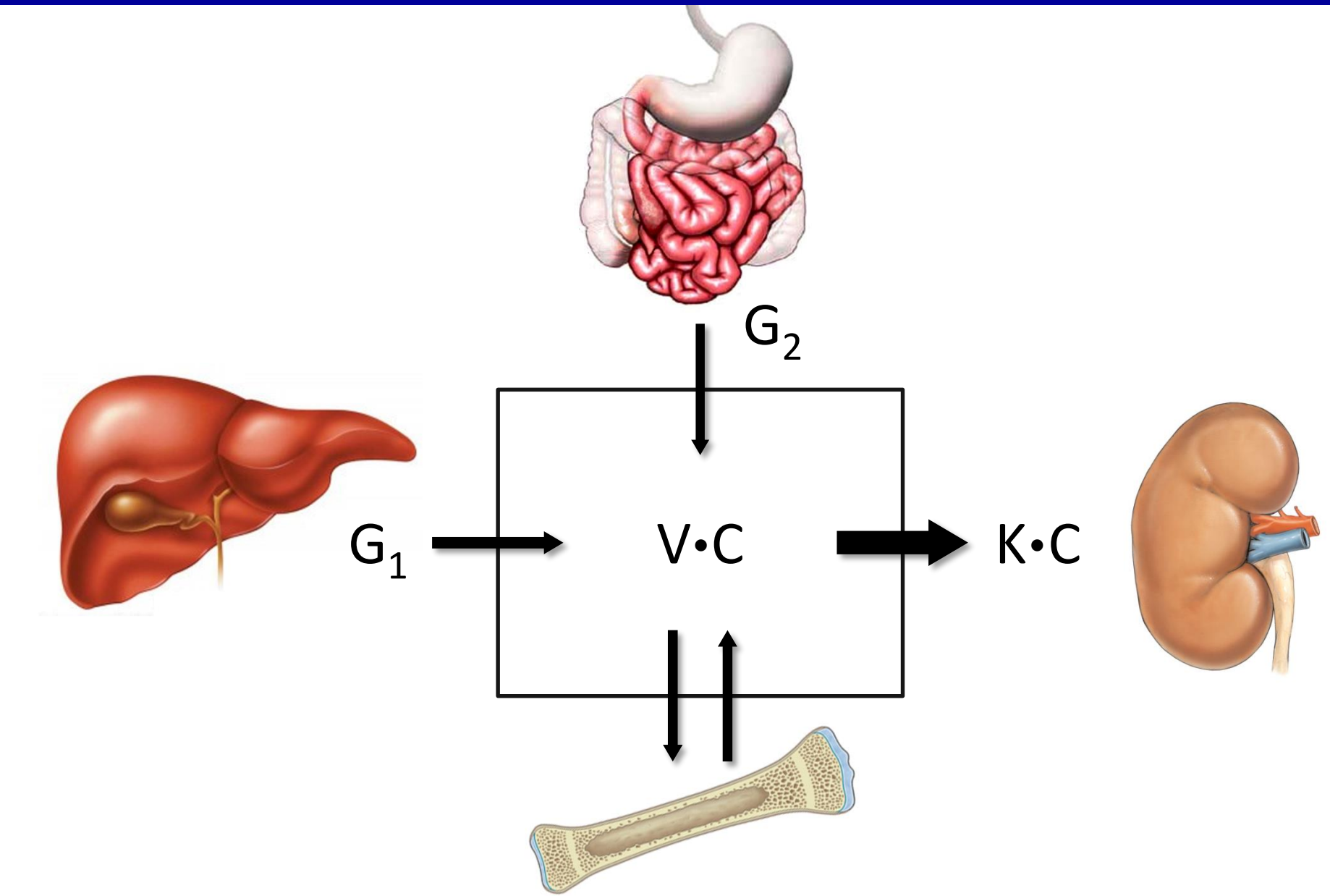
Harambat, Kidney Int 2010

PH1 diagnosis

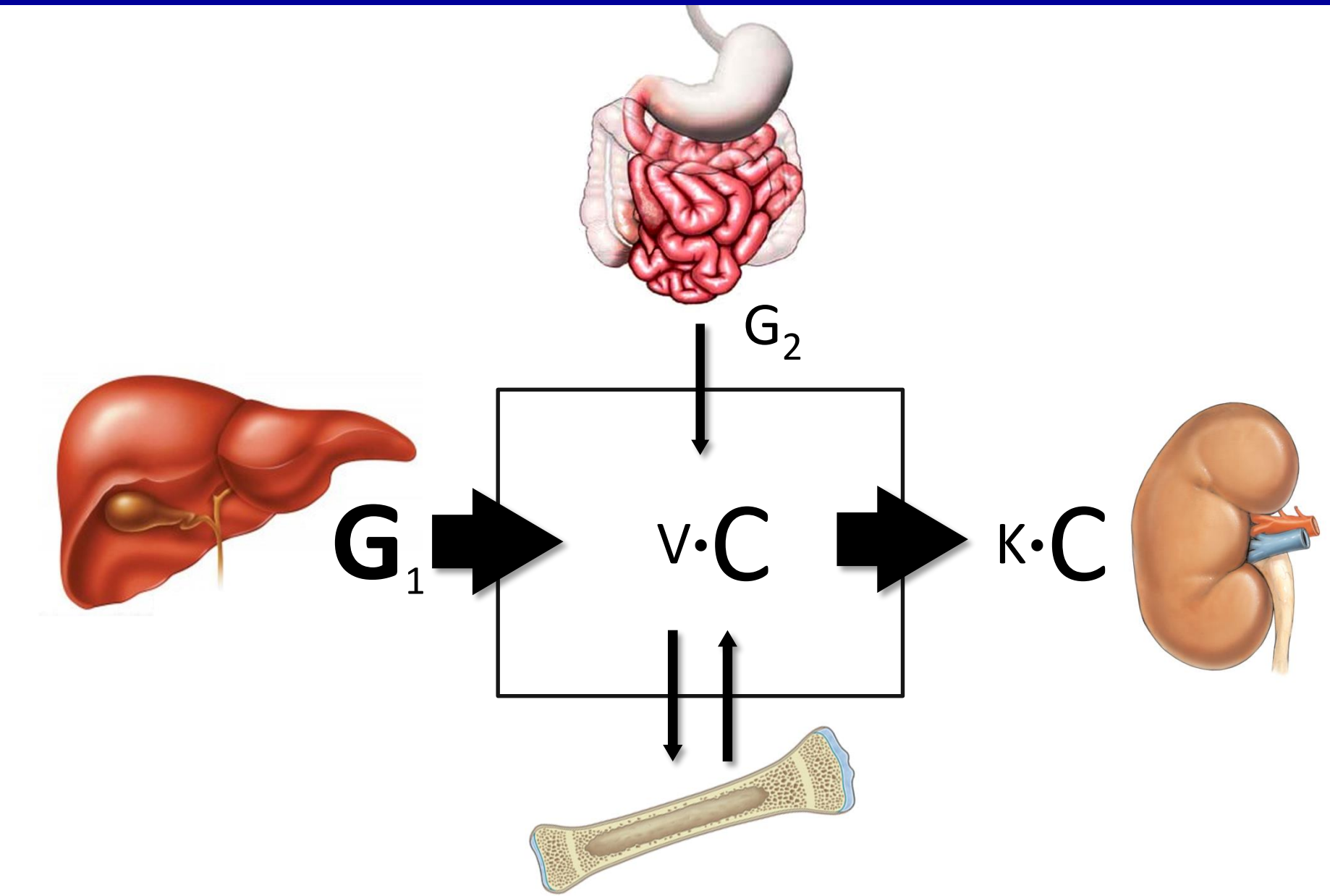
Infantile form	35%
Recurrent stones with progressive CKD	20%
Late onset during adulthood	15%
Pedigree screening	15%
Diagnosis after recurrence on a kidney transplant	10%

Courtesy Pierre Cochat

Oxalate mass balance



Oxalate mass balance

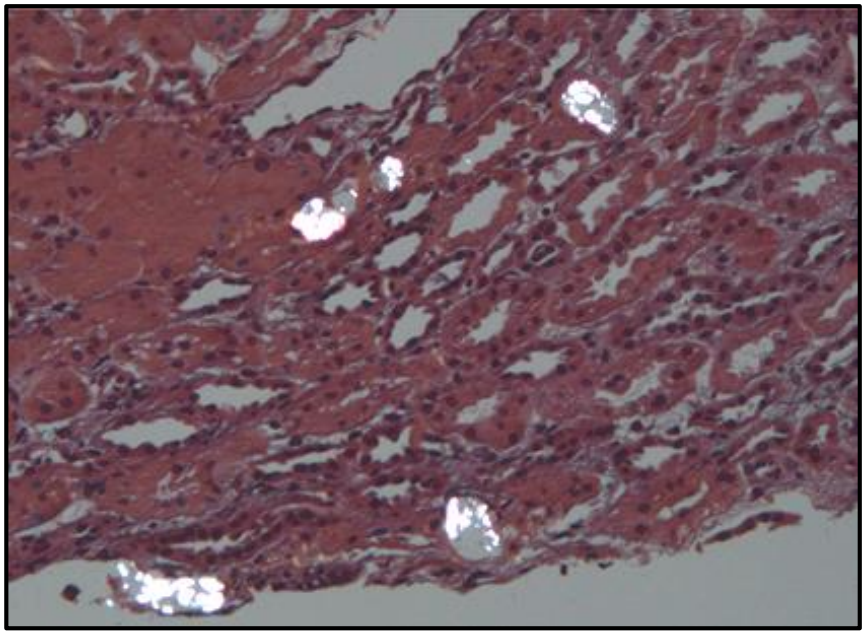


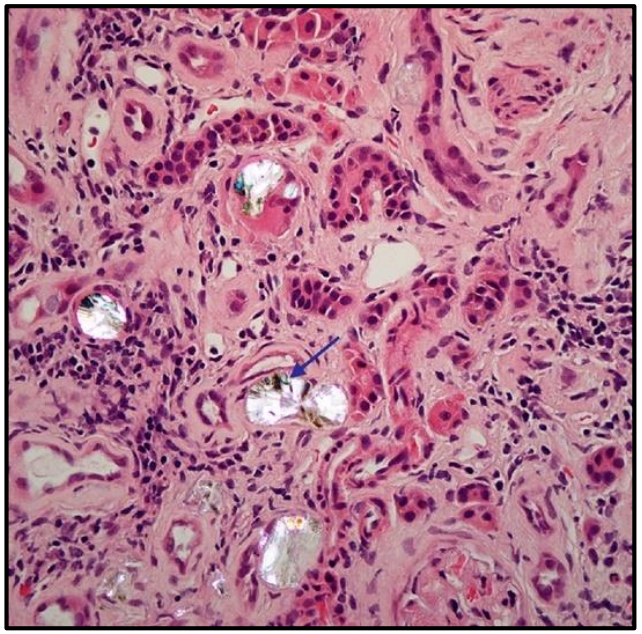
Oxalate nephropathy

- **Conditions that promote renal calcium oxalate crystals precipitation:**
  - **low tubular flow rate (low GFR)**
  - **high oxalate concentration in the tubular lumen**
  - **pre-existing tubular damage**

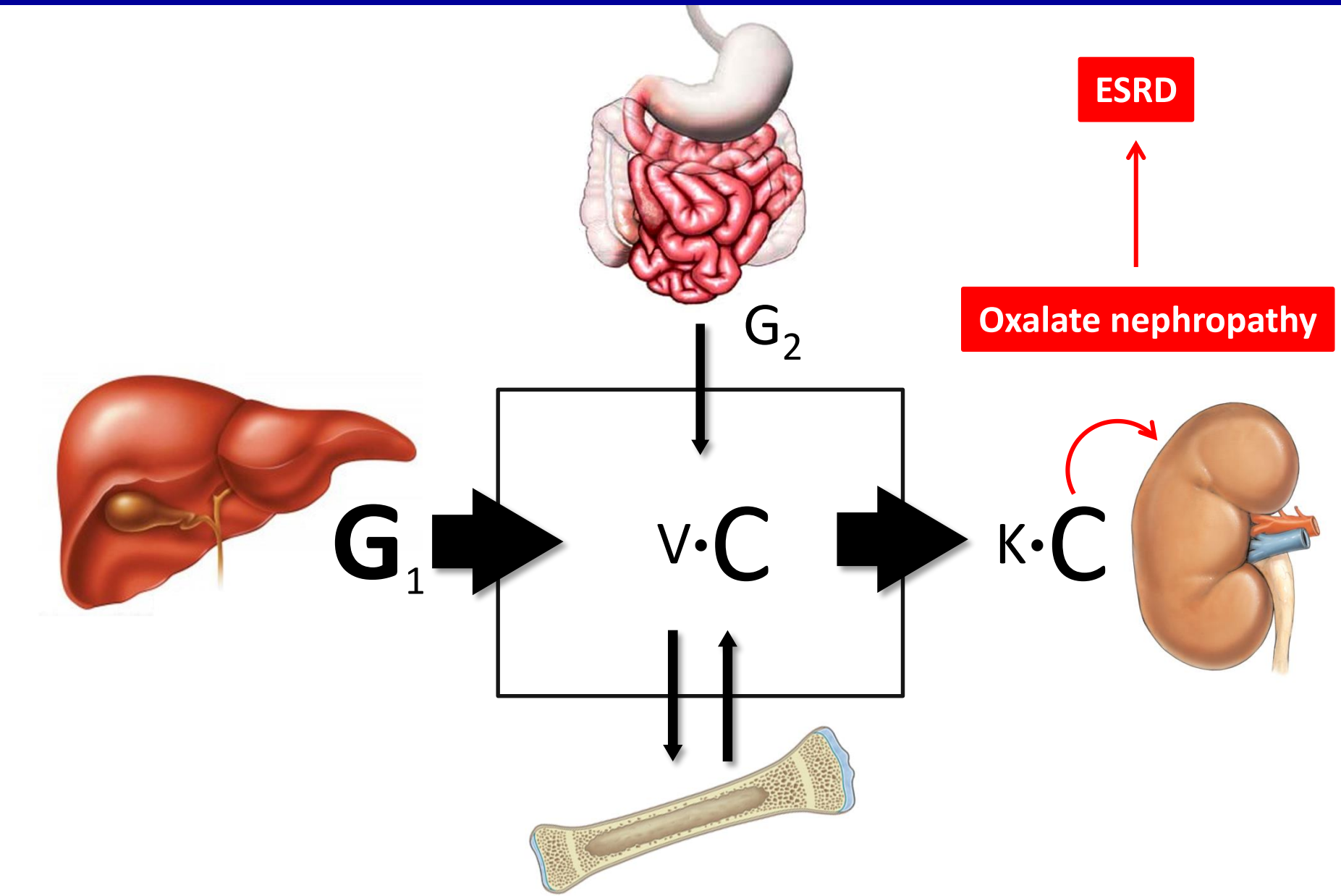
  (early hours after renal transplantation are at very high risk of precipitation!!!)

- **Once calcium oxalate crystals precipitate, they cause chronic interstitial inflammation and irreversible damage.**

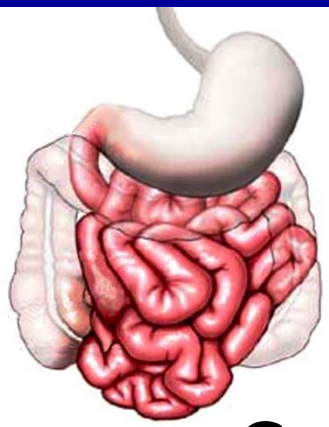




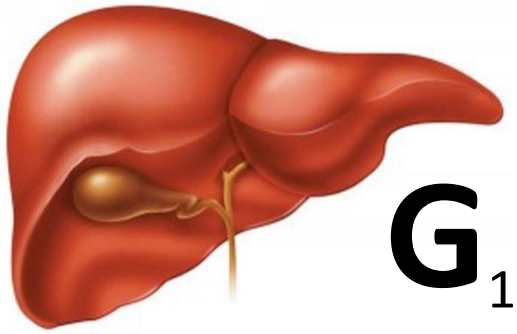
Oxalate mass balance



Oxalate mass balance



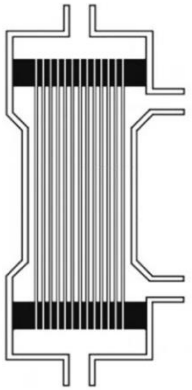
G_2

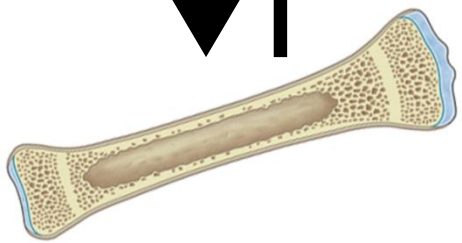


G_1

$V \cdot C$

$K \cdot C$

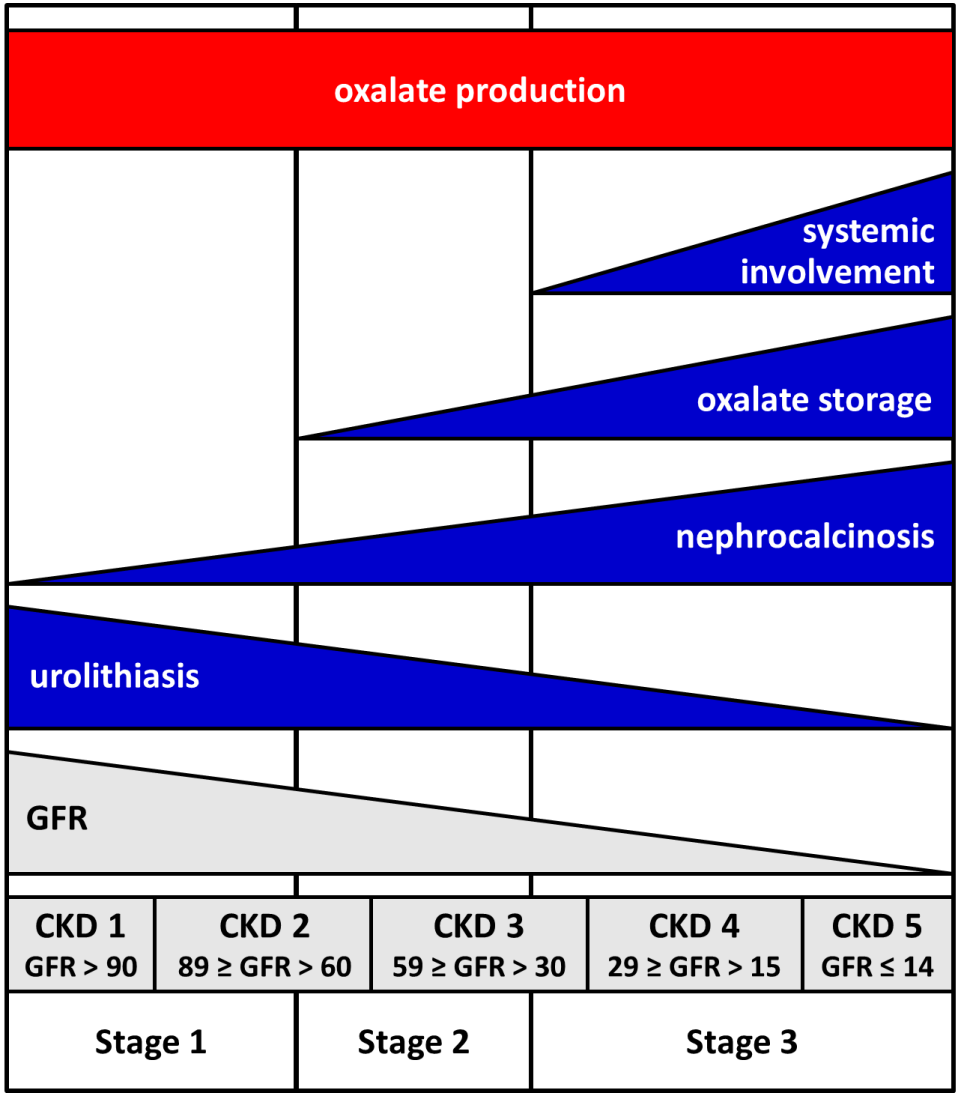




Systemic oxalosis

- bones
- heart
- peripheral nerves
- joints
- skin, soft tissues, retina…

PH1 disease progression



Adapted from Cochat et al, Pediatric Nephrology 7th edition, 2015

Conservative management

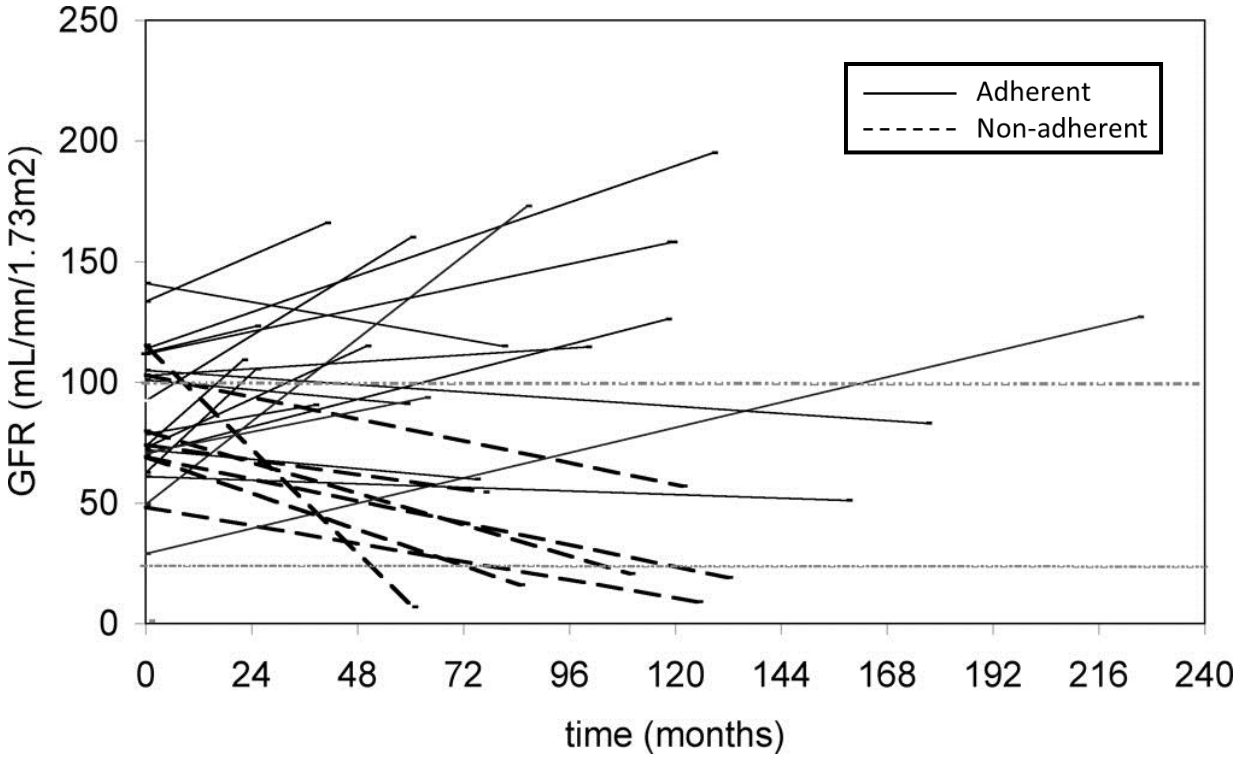
- **High fluid intake (> 3000 ml/m^2/24h)**
- **Potassium citrate**
- **Try pyridoxine**
  - 5-20 mg/Kg/d
  - G170R and P152L mutations
  - goal: Uox reduction >30%
- **Orthophosphate (?)**
- **Hydrochlorothiazide (?)**
- **Low oxalate diet has limited benefit**
  (>90% of plasma oxalate is secondary to the liver overproduction)

Early diagnosis is essential

Two sisters with PH1 (AGT Gly170Arg mutation)

- **Lucia**
  diagnosed at 2.5 years with creatinine 1.4 mg/dl
  now, aged 13, creatinine 2.7 mg/dl
- **Giulia**
  diagnosed at birth
  medical treatment started immediately
  NGT for 6 months to guarantee large fluid intake
  now, age 8, creatinine 0.47 mg/dl

Compliance is essential



Fargue Kidney Int 2009

Primary hyperoxaluria: ESPN/ERA-EDTA Registry

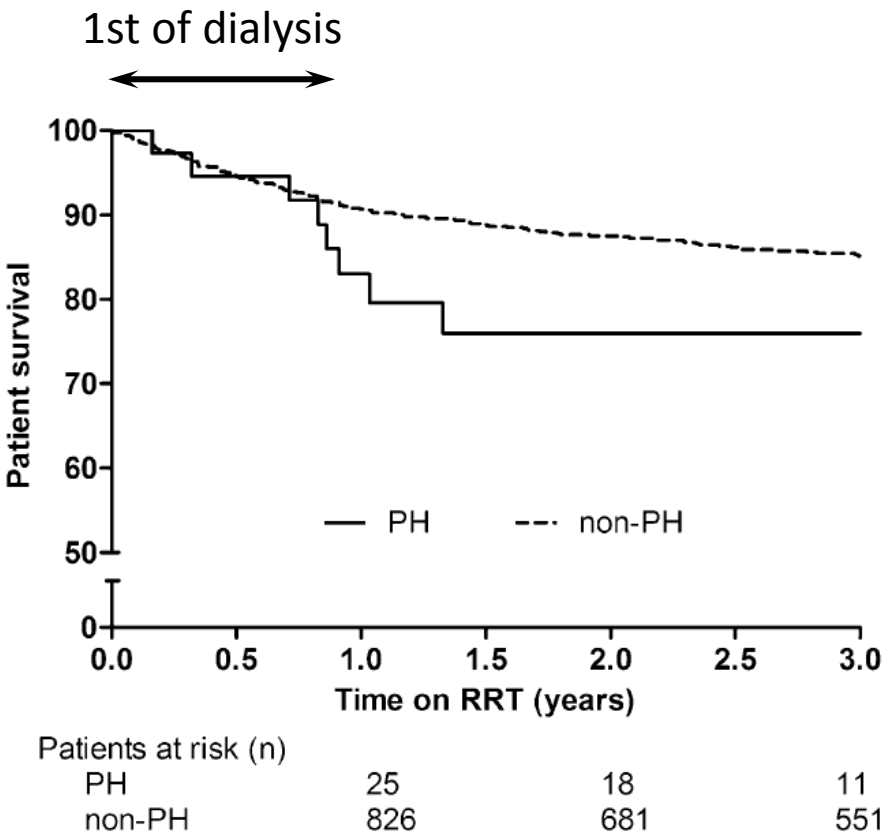


Figure 3. | Unadjusted 3-year survival on RRT in children aged <2 years for PH patients versus non-PH patients (log-rank *P*=0.03). RRT, renal replacement therapy; PH, primary hyperoxaluria.

Harambat et al, Clin J Am Soc Nephrol, 2012

Oxalate accumulation on dialysis

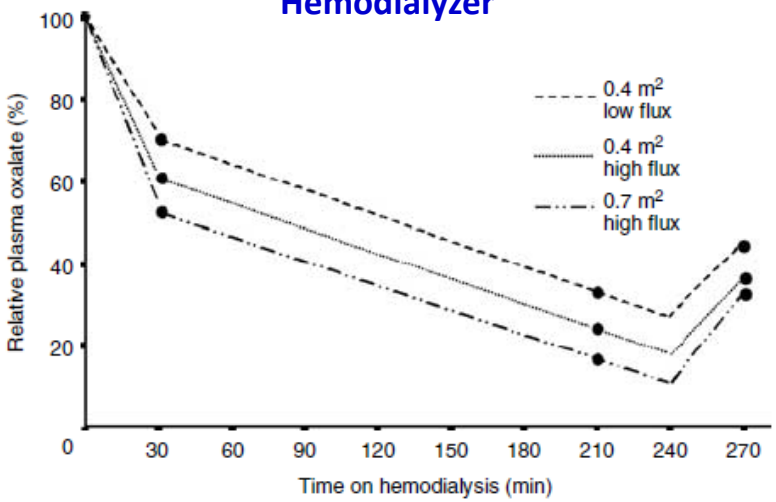
Oxalate generation : 4-7 mmol/1.73 m^2/24h

Removal by conventional dialysis : 1-2 mmol/1.73 m^2/24h

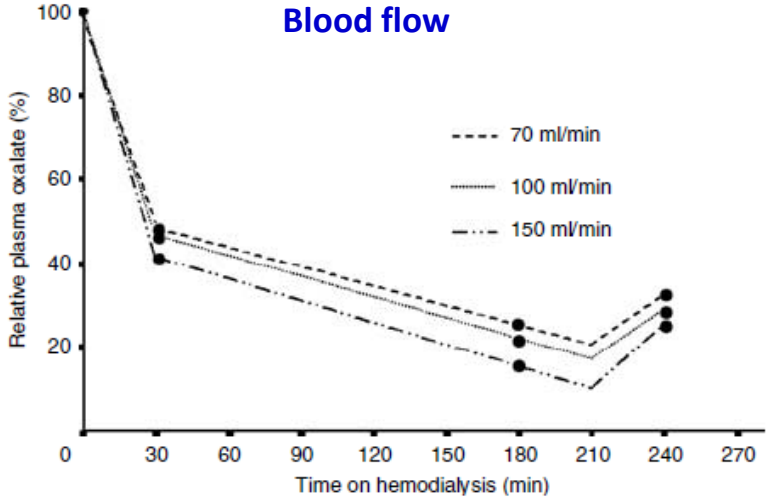
Cochat et al, Ped Nephrolol, 2006

Maximizing dialysis

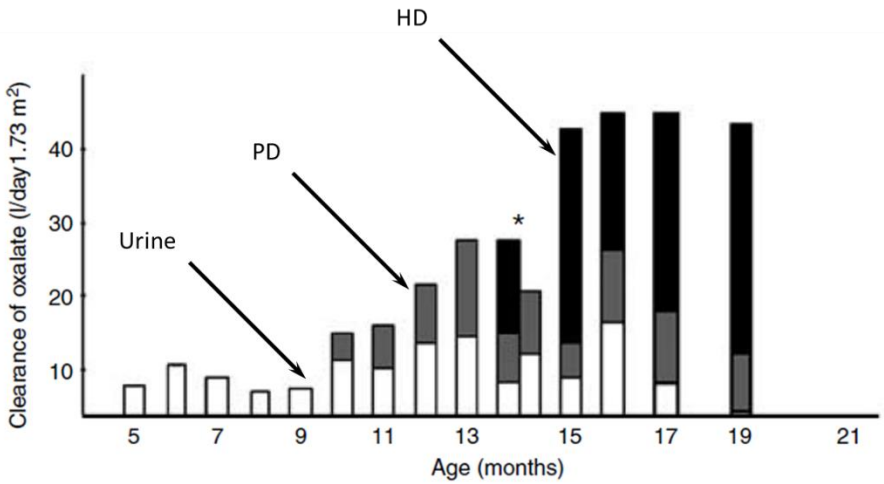
Hemodialyzer



Blood flow



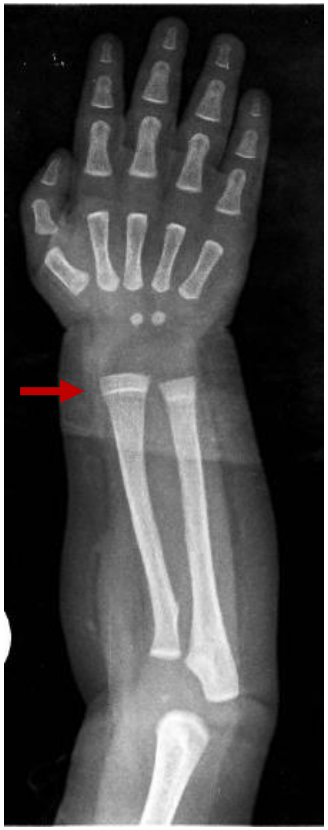
HD + PD



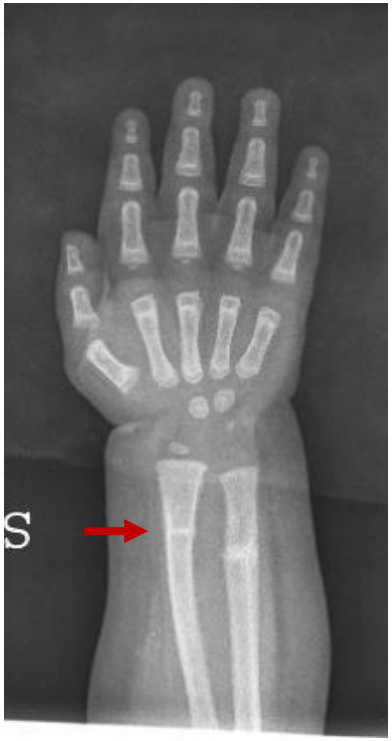
Illies et al, Kidney Int, 2006

Intensive dialysis can limit oxalate deposition

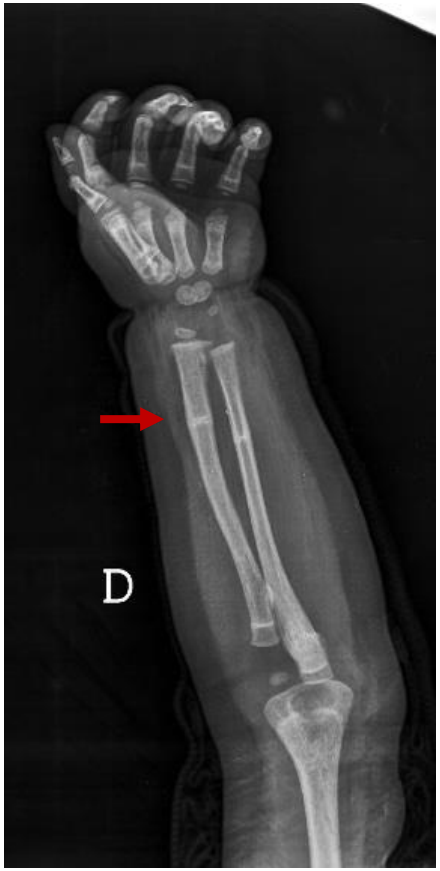
Migration of a single translucent band



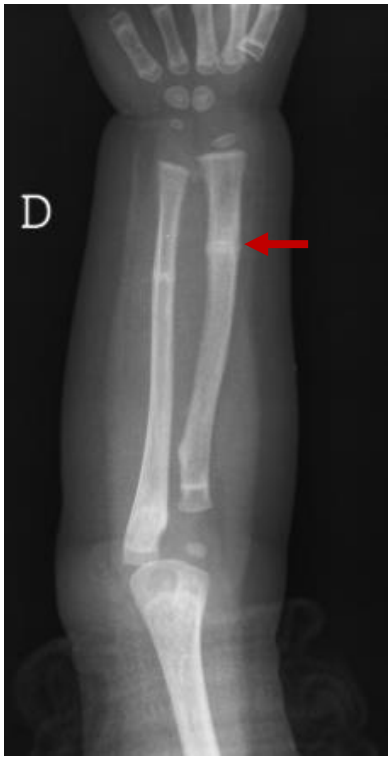
6 months



12 months



16 months



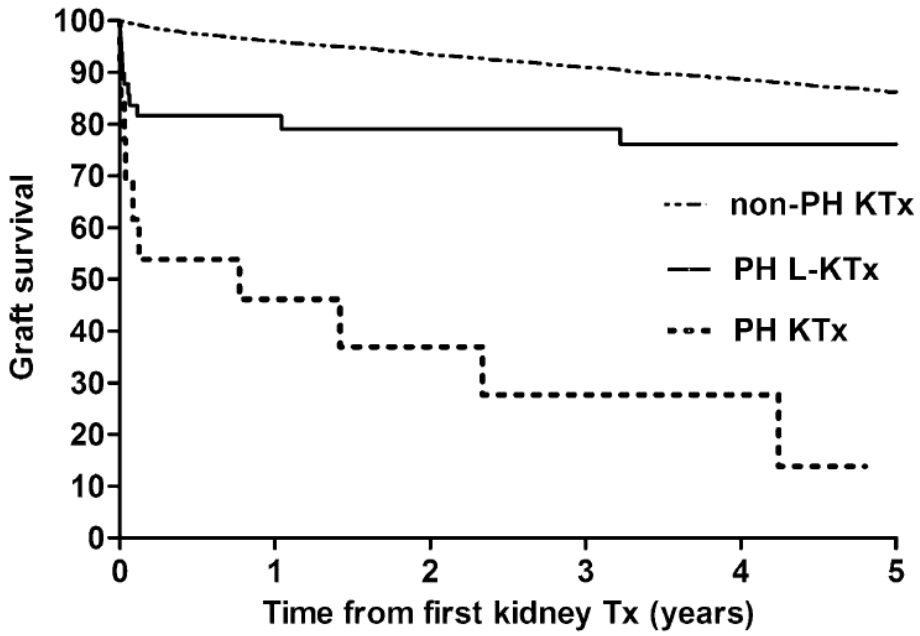
18 months

Even intensive dialysis cannot completely prevent oxalate depositions

Patient age, body weight HD setting, blood flow	Plasma Oxalate, µmol/l	Mass Removal, µmol	Generation Rate, µmol/l/h	Distribution Volume, L (% of BW)	Tissue Deposition, µmol/24h/kg	Oxalate clearance, l/week/1.73 m^2
6 months, 5.0 kg daily CVVHD, Qb 40 ml/min	PreHD: 205 PostHD: 31	644	10.0	2.84 (56.8)	**5**	228
8 months, 6.5 kg daily CVVHD, Qb 50 ml/min	PreHD: 178 PostHD: 41	615	9.14	3.68 (56.7)	**19**	167
30 months, 12.3 kg HDx6/week, Qb 110 ml/min	PreHD: 102 PostHD: 28	812	4.81	8.28 (67%)	**12**	185

Calculations based on Marangella 1992 and Yamauchi 2001

Primary hyperoxaluria: ESPN/ERA-EDTA Registry

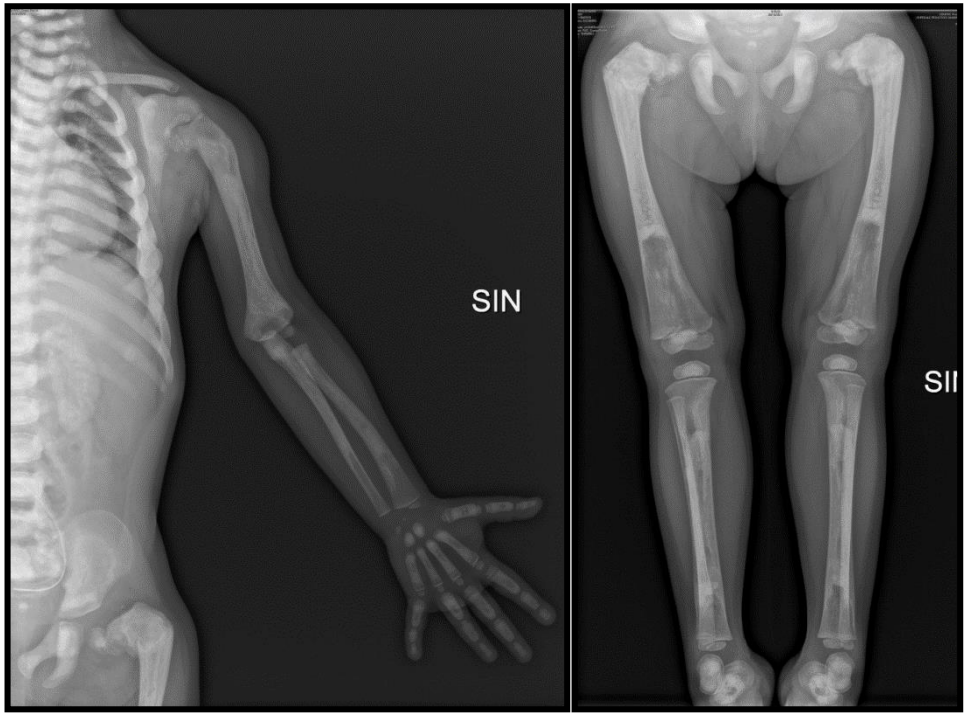


Patients at risk (n)					
PH L-KTx	33	30	29	22	19
PH KTx	7	5	3	3	1
non-PH	4510	3716	3042	2525	2013

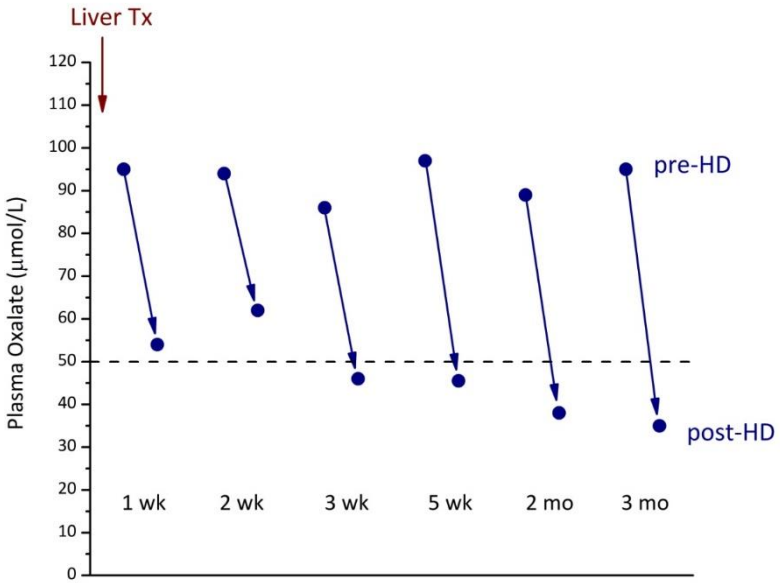
Harambat et al, Clin J Am Soc Nephrol, 2012

Prolonged dialysis causes extensive oxalate depositions

Oxalate accumulation after 3 years of PD



Oxalate levels after isolated liver Tx



Pre-emptive liver transplantation

Pre-emptive liver transplantation for PH-I arrests renal function deterioration

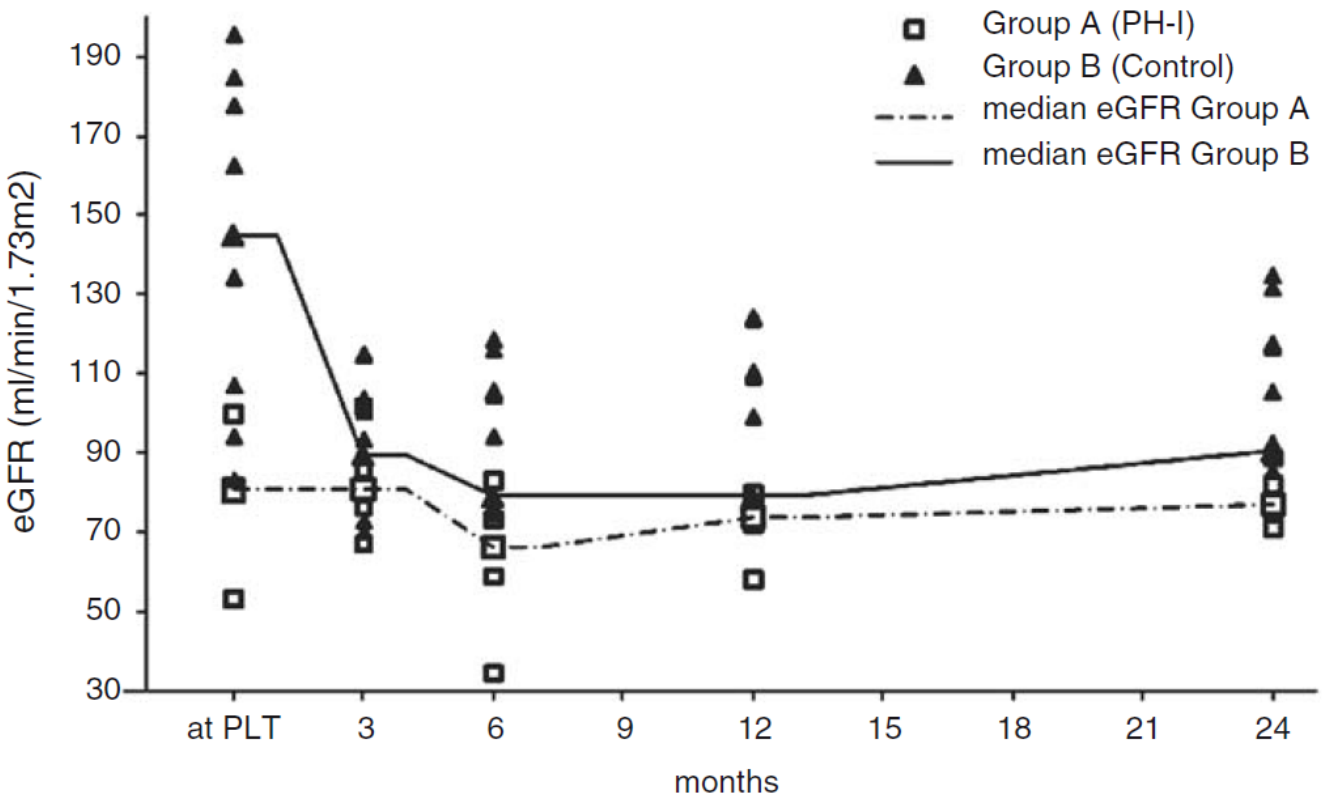


Fig. 1. Renal function of patients in both groups at the time of isolated liver transplant and at regular intervals post-transplant.

Perera et al, Nephrol Dial Transpl, 2010

Transplant strategy

Tx strategy	Simultaneous liver + kidney	Sequential liver–kidney	Isolated kidney	Isolated liver
CKD Stage 3b (30 < GFR < 45)				**Expert opinion**
CKD Stage 4 (15 < GFR < 29)	++		**Gly170Arg? Phe152Ile?**	
CKD Stage 5 (GFR < 15)		+++	**Gly170Arg? Phe152Ile?**	
Infantile form (ESRD < 2 years)		+++		
HD strategy	**During and after Tx according to POx and GFR**	**Standard HD following liver Tx aiming at POx < 20 µmol/L**	**During and after Tx**	**Sometimes during Tx**

Adapted from Cochat et al, Pediatric Nephrology 7th edition, 2015

Thank you!