Inborn errors of metabolism presenting with kidney stones: clinical aspects

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Pediatric renal stones in the western hemisphere

- Calcium oxalate*: 55-60%
- Calcium phosphate*: 15-20%
- Uric acid*: 3-6%
- Struvite*: 3-6%
- Cystine: 2-3%
- 2,8-dihydroxyadenine
- Xanthine

(*) ~65% major component and ~35% principal component
Cross-sectional / prospective data from the Gubbio study

Relative Risk of Urinary Stone Disease

Urinary Ca excretion, $\mu$mol/h

% with incident Urinary Stone Disease

Males

Females

Urinary Ca excretion, quartile

UNa vs Uca

**CHILDREN**

**ADULTS**

Hypercalciuria

Controls

F. Emma, unpublished data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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus/inheritance mode</th>
<th>Protein</th>
<th>Cellular defect</th>
<th>Tubular defect</th>
<th>Disorder</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLCN5</td>
<td>Xp11.22 X-linked recessive</td>
<td>Chloride channel 5 on the endosome membrane</td>
<td>Impaired acidification of the endosome fluid in proximal tubular cells.</td>
<td>Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure.</td>
<td>Dent’s syndrome</td>
<td>Cho et al.² and Scheiman et al.⁷</td>
</tr>
<tr>
<td>OCR1</td>
<td>Xq26.1 X-linked recessive</td>
<td>Phosphatidylinositol 4,5-bisphosphate 5-phosphatase</td>
<td>Accumulation of phosphatidylinositol 4,5-bisphosphate in proximal cells, followed by actin polymericization, and tight and adherens junction defects.</td>
<td>Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure.</td>
<td>Lowe syndrome</td>
<td>Cho et al.⁶</td>
</tr>
<tr>
<td>CLDN16</td>
<td>3q27 Autosomal dominant</td>
<td>Claudin 16</td>
<td>Alteration of tight junction ion selectivity in the thick ascending limb of Henle loop.</td>
<td>Urinary loss of magnesium and calcium, nephrocalcinosis, and progressive kidney failure in homozygotes. Heterozygotes may produce kidney stones.</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis</td>
<td>Muller et al.⁸</td>
</tr>
<tr>
<td>CLDN19</td>
<td>1p34.2 Autosomal dominant</td>
<td>Claudin 19</td>
<td>Alteration of tight junction ion selectivity in the thick ascending limb of Henle loop.</td>
<td>Renal wasting of magnesium and calcium, nephrocalcinosis and progressive kidney failure in homozygotes. Macular coloboma, myopia, and myotonia.</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular impairment</td>
<td>Konrad et al.⁹</td>
</tr>
<tr>
<td>ATP6B1</td>
<td>7q33-q34 Autosomal recessive</td>
<td>Subunit ATP6B1 of the H-pump</td>
<td>Defect of the proton secretion and urine acidiﬁcation in the α-intercalated cells of the collecting duct.</td>
<td>Hypokalemic hyperchloremic acidosis with nephrocalcinosis and kidney stones.</td>
<td>Distal tubular acidosis</td>
<td>Smith et al.¹⁰</td>
</tr>
<tr>
<td>SLC4A7</td>
<td>17q21-q22 Autosomal dominant</td>
<td>Anion exchanger</td>
<td>Decreased bicarbonate reabsorption at the basolateral membrane of the α-intercalated cells of the collecting duct.</td>
<td>Hypokalemic hyperchloremic acidosis, nephrocalcinosis, and kidney stones. Kidney stones and incomplete tubular acidosis in homozygotes.</td>
<td>Distal tubular acidosis</td>
<td>Bruce et al.¹²</td>
</tr>
<tr>
<td>SLC34A3</td>
<td>9q34 Autosomal recessive</td>
<td>NPT2c sodium-phosphate cotransporter</td>
<td>Reduced phosphate reabsorption and increased calcium synthesis in the proximal tubular cells.</td>
<td>Severe rickets and kidney stones caused by renal loss of phosphate, hypophosphatemia, and hypercalciuria.</td>
<td>Hyperphosphatemic rickets with nephrocalcinosis and hypercalciuria.</td>
<td>Bergwitz et al.¹³ and Tencza et al.¹⁴</td>
</tr>
<tr>
<td>CASR</td>
<td>3q13.3-q21 Autosomal dominant</td>
<td>Calcium-sensing receptor (activating mutations)</td>
<td>Inhibition of calcium reabsorption in the ascending limb of Henle loop.</td>
<td>Hypercalciuria and hypocalciemia. Autosomal-dominant hypoparathyroidism.</td>
<td>Hyperparathyroidism and hypophosphatemia. Renal hypopotassemia if potent effect of the mutation.</td>
<td>Pearce et al.¹⁵</td>
</tr>
<tr>
<td>SLC12A1</td>
<td>15q15-q22 Autosomal recessive</td>
<td>NKCC2 sodium-potassium-chloride transporter</td>
<td>Decreased sodium, potassium and chloride reabsorption in the ascending limb of Henle loop.</td>
<td>Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.</td>
<td>Bartter syndrome type 5</td>
<td>Puricelli et al.¹⁶</td>
</tr>
<tr>
<td>KCNJ1</td>
<td>11q24 Autosomal recessive</td>
<td>ROMK1 potassium channel</td>
<td>Decreased sodium, potassium and chloride reabsorption in the ascending limb of Henle loop.</td>
<td>Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.</td>
<td>Bartter syndrome type 2</td>
<td>Puricelli et al.¹⁶</td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Structure</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO$_4$-NH$_3$-Mg (struvite)</td>
<td>UTI</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Calcium oxalate, dihydrated</td>
<td></td>
</tr>
<tr>
<td>Calcium oxalate, monohydrated</td>
<td>Hyperoxaluria</td>
</tr>
<tr>
<td>Cystine</td>
<td>Cystinuria</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Purine synthesis disorder</td>
</tr>
<tr>
<td>2,8-dihydroxyadenine</td>
<td>APRT deficiency</td>
</tr>
<tr>
<td>Xanthine</td>
<td>Xanthinuria</td>
</tr>
</tbody>
</table>
# Cystinuria

## Historical classification

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminoaciduria heterozygous</strong></td>
<td>N</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Plasma cystine after oral load</strong></td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>N</td>
</tr>
<tr>
<td><strong>Chromosome</strong></td>
<td>2</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td><em>SLC3A1</em></td>
<td><em>SLC7A9</em></td>
<td><em>SLC7A9</em></td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>rBAT</td>
<td>B(^{0,+})AT</td>
<td>B(^{0,+})AT</td>
</tr>
</tbody>
</table>

## Gene-based classification

<table>
<thead>
<tr>
<th></th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
</table>

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**Diagram:**

- **extracellular**
- **intracellular**
- **light chain:** b\(^{0,+}\)AT
- **heavy chain:** rbAT
Cystinuria

Gender effect

Renal stone emission rate

Percent of patients with renal stones before 3 years of age

Heterozygous carriers

Urinary cystine (mmol/gram creat.)

Dello Strologo, JASN 2002
Glyoxylate metabolism in the hepatocyte

Collagen breakdown

Hydroxyproline → 4-hydroxy-2-oxoglutarate → Pyruvate + Glyoxylate → Glycolate

Mitochondrion

Peroxisome

Cytosol

Peroxisome

GRHPR → PH1 85%

AGT → GO

GRHPR → PH2 5%

HOGA → PH3 10%

Courtesy Pierre Cochat
Genotype-phenotype correlations

**PH1-PH2-PH3**

- PH1: 76% (129)
- PH2: 100% (18)
- PH3: 96% (12)
- NMD: 100% (14)

Survival free from ESRD (%)

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

p<0.0001
**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%
Oxalate mass balance
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

ESRD
Oxalate nephropathy

![Diagram showing the process of oxalate mass balance with liver, intestine, and kidney illustrations.](image-url)
Oxalate mass balance

- 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/m²/24h)
- 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)
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

![Graph showing GFR (mL/min/1.73m²) over time (months) for adherent and non-adherent patients. The graph illustrates the decline in GFR for non-adherent patients compared to adherent patients.](image)
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.
Oxalate accumulation on dialysis

Oxalate generation: 4-7 mmol/1.73 m²/24h

Removal by conventional dialysis: 1-2 mmol/1.73 m²/24h
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

<table>
<thead>
<tr>
<th>Patient age, body weight</th>
<th>Plasma Oxalate, μmol/l</th>
<th>Mass Removal, μmol</th>
<th>Generation Rate, μmol/l/h</th>
<th>Distribution Volume, L (% of BW)</th>
<th>Tissue Deposition, μmol/24h/kg</th>
<th>Oxalate clearance, l/week/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months, 5.0 kg daily CVVHD, Qb 40 ml/min</td>
<td>PreHD: 205</td>
<td>644</td>
<td>10.0</td>
<td>2.84 (56.8)</td>
<td>5</td>
<td>228</td>
</tr>
<tr>
<td>8 months, 6.5 kg daily CVVHD, Qb 50 ml/min</td>
<td>PreHD: 178</td>
<td>615</td>
<td>9.14</td>
<td>3.68 (56.7)</td>
<td>19</td>
<td>167</td>
</tr>
<tr>
<td>30 months, 12.3 kg HDx6/week, Qb 110 ml/min</td>
<td>PreHD: 102</td>
<td>812</td>
<td>4.81</td>
<td>8.28 (67%)</td>
<td>12</td>
<td>185</td>
</tr>
</tbody>
</table>

Calculations based on Marangella 1992 and Yamauchi 2001
Primary hyperoxaluria: ESPN/ERA-EDTA Registry

![Graph showing graft survival over time for different groups: non-PH KTx, PH L-KTx, PH KTx.]

Patients at risk (n)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH L-KTx</td>
<td>33</td>
<td>30</td>
<td>29</td>
<td>22</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>PH KTx</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>non-PH</td>
<td>4510</td>
<td>3716</td>
<td>3042</td>
<td>2525</td>
<td>2013</td>
<td></td>
</tr>
</tbody>
</table>

Prolonged dialysis causes extensive oxalate depositions.

Oxalate accumulation after 3 years of PD

Oxalate levels after isolated liver Tx
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.
### Transplant strategy

<table>
<thead>
<tr>
<th>Tx strategy</th>
<th>Simultaneous liver + kidney</th>
<th>Sequential liver–kidney</th>
<th>Isolated kidney</th>
<th>Isolated liver</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CKD Stage 3b</strong> (30 &lt; GFR &lt; 45)</td>
<td>Red</td>
<td></td>
<td>Yellow</td>
<td><strong>Expert opinion</strong></td>
</tr>
<tr>
<td><strong>CKD Stage 4</strong> (15 &lt; GFR &lt; 29)</td>
<td>++</td>
<td>Yellow</td>
<td>Gly170Arg? Phe152Ile?</td>
<td><strong>Expert opinion</strong></td>
</tr>
<tr>
<td><strong>CKD Stage 5</strong> (GFR &lt; 15)</td>
<td>Green</td>
<td>+++</td>
<td>Gly170Arg? Phe152Ile?</td>
<td><strong>Expert opinion</strong></td>
</tr>
<tr>
<td><strong>Infantile form</strong> (ESRD &lt; 2 years)</td>
<td>Green</td>
<td>+++</td>
<td></td>
<td><strong>Expert opinion</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HD strategy</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During and after Tx according to POx and GFR</strong></td>
<td><strong>Standard HD following liver Tx aiming at POx &lt; 20 μmol/L</strong></td>
<td><strong>During and after Tx</strong></td>
<td><strong>Sometimes during Tx</strong></td>
<td></td>
</tr>
</tbody>
</table>

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