

26.1 Introduction

Urinary oxalate plays a crucial role in urolithiasis, primarily due to the extremely low solubility of its calcium salt. This may lead to crystalluria, urolithiasis and nephrocalcinosis. The pathology of oxalate in humans can be divided into three principal groups:

1. Primary hyperoxaluria:
increased endogenous synthesis of oxalate
2. Secondary hyperoxaluria:
increased intestinal absorption of oxalate
increased ingestion of oxalate or its precursors
3. Hyperoxalemia:
decreased elimination in renal insufficiency.

Increased ingestion or intestinal uptake of oxalate usually poses as an acute or chronic intoxicating situation. Hyperoxalemia may also be subsequent to renal failure. These two pathophysiological situations will not be addressed in this chapter. However, guidelines are provided to differentiate enteric and secondary hyperoxaluria from primary hyperoxaluria (PH). The major source of human urinary oxalate is endogenous synthesis [1] from the single precursor, glyoxalate. This very reactive metabolite is most likely formed from glycolate, glycine, and hydroxyproline via 2-oxo-3-hydroxyglutarate. Older studies have ignored the metabolism of subcellular compartmentalization and the issue is still not absolutely clarified. The major site of glyoxylate production is the hepatic peroxisome. The enzyme responsible for the detoxification of glyoxylate to glycine is alanine:glyoxylate aminotransferase (AGT, EC 2.6.1.44). In humans, metabolically active AGT is present only in hepatic peroxisome [2]. The co-enzyme of the AGT is pyridoxal phosphate (Vitamin B6). Three enzymes are involved in the conversion of glyoxylate to oxalate. The flavoprotein glyoxylate oxidase and lactate dehydrogenase are (quantitatively) the main catalysts and xanthine oxidase, seemingly, a minor one in oxalate biogenesis. The impact of ascorbic acid on urinary oxalate excretion may have been widely overestimated under normal conditions, because of methodological problems related to oxalate mea-

surement. Recently, studies on oxalobacter formigenes colonization have demonstrated a potential, although not yet conclusive, role in decreasing renal oxalate excretion [3].

26.2 Nomenclature

| No. | Protein | Tissue distribution | Chromosome localisation | Disease (OMIM) |
|------|---|--|-------------------------|----------------|
| 26.1 | Alanine: glyoxylate aminotransferase Primary hyperoxaluria I | Liver (peroxisome) | 2q 37.3 | 259900 |
| 26.2 | Glyoxylate reductase Primary hyperoxaluria II | Liver (cytosol) Leukocytes, ubiquitous | 9cen | 260000 |

26.3 Metabolic Pathway

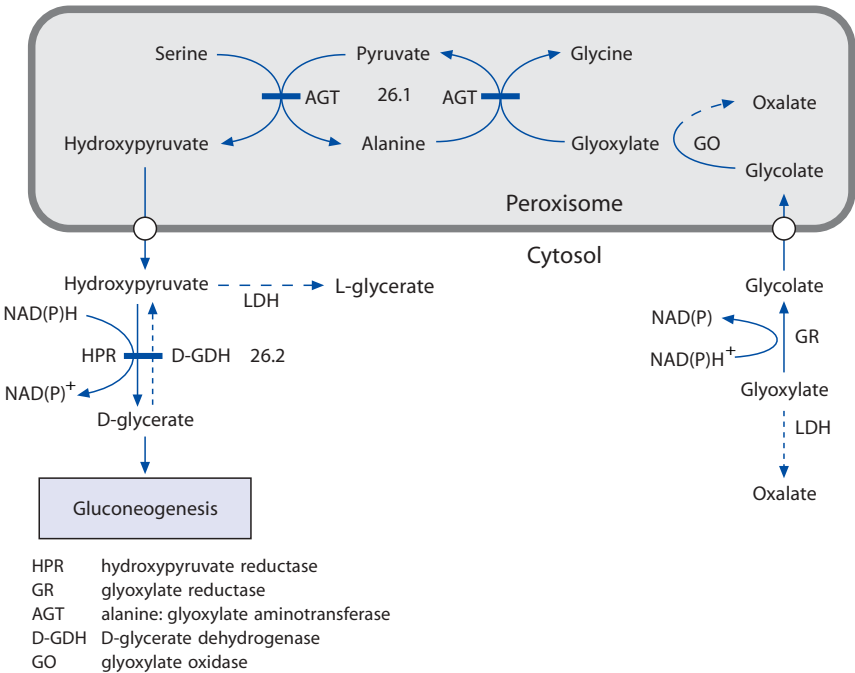


Fig. 26.1. Proposed pathways of oxalate and hydroxypyruvate metabolism in human liver [4]

26.4 Signs and Symptoms

Table 26.1. Primary hyperoxaluria type 1

| System | Signs/symptoms | Renal failure (all ages) | Neonate | Infant | Children | Adolescent | Adult |
|-----------------------|-------------------------------|-----------------------------|---------|--------|----------|------------|--------|
| Kidney | CaOx-nephrolithiasis | ± | ± | ± | + / ± | ++ / ± | ++ / ± |
| | Renal colic | ± | ± | ± | + / ± | ++ / ± | ++ / ± |
| | Nephrocalcinosis | +++ | ++ / + | ++ / + | ++ / + | + | + |
| | Renal failure | +++ | ± | ± | ± | ± | ± |
| | Urinary tract infection | ± | ± | ± | ± | ± | ± |
| | Hematuria | ± | ± | ± | ± | ± | ± |
| Eye | Retinopathy | ± | - | - | - | - | - |
| | Optic atrophy | ± | - | - | - | - | - |
| Bone | Bone in bone phenomenon | ++ | - | - | - | - | - |
| | Radiolucent metaphyseal bands | + | - | - | - | - | - |
| | Bone pain | ± | - | - | - | - | - |
| | Gout-like attacks | ± | - | - | - | - | - |
| | Pathological fractures | ± | - | - | - | - | - |
| Cardiovascular system | Cardiomyopathy | ± | - | - | - | - | - |
| | Heart block | ± | - | - | - | - | - |
| Nervous system | Peripheral polyneuropathy | ± | - | - | - | - | - |
| Skin | Livedo reticularis | ± | - | - | - | - | - |
| | Calcinosis cutis | ± | - | - | - | - | - |
| | Raynaud phenomenon | ± | - | - | - | - | - |
| | Gangrene | ± | - | - | - | - | - |
| Hematopoietic system | Pancytopenia | ++ / ± | - | - | - | - | - |
| Other | Failure to thrive | +++ | - | - | - | - | - |
| | Growth failure | ++ | - | - | - | - | - |
| Routine laboratory | Creatinine | ++ | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ |
| | Urea | ++ | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ |
| Special laboratory | Oxalate (U) | n-↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ |
| | Glycolate (U) | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ |
| | Oxalate (P) | ↑↑↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ | ↑-↑↑ |
| | Glycolate (P) | ↑-↑↑ | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ |

Table 26.2. Primary hyperoxaluria type 2

| System | Signs/symptoms | Renal failure (all ages) | Neonate | Infant | Children | Adolescent | Adult |
|-----------------------|-------------------------------|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Kidney | CaOx-nephrolithiasis | ± | ± | ± | +/ \pm | ++/ \pm | ++/ \pm |
| | Renal colic | ± | ± | ± | +/ \pm | ++/ \pm | ++/ \pm |
| | Nephrocalcinosis | ++ | + | + | + | + | + |
| | Renal failure | +++ | ± | ± | ± | ± | ± |
| | Urinary tract infection | ± | ± | ± | ± | ± | ± |
| | Hematuria | ± | ± | ± | ± | ± | ± |
| Eye | Retinopathy | ± | - | - | - | - | - |
| | Optic atrophy | ± | - | - | - | - | - |
| Bone | Bone in bone phenomenon | ++ | - | - | - | - | - |
| | Radiolucent metaphyseal bands | + | - | - | - | - | - |
| | Bone pain | ± | - | - | - | - | - |
| | Gout-like attacks | ± | - | - | - | - | - |
| | Pathological fractures | ± | - | - | - | - | - |
| | Cardiomyopathy | ± | - | - | - | - | - |
| Cardiovascular system | Heart block | ± | - | - | - | - | - |
| Nervous system | Peripheral polyneuropathy | ± | - | - | - | - | - |
| Skin | Livedo reticularis | ± | - | - | - | - | - |
| | Calcinosis cutis | ± | - | - | - | - | - |
| | Raynaud phenomenon | ± | - | - | - | - | - |
| | Gangrene | ± | - | - | - | - | - |
| Hematopoietic system | Pancytopenia | ++/ \pm | - | - | - | - | - |
| Other | Failure to thrive | +++ | - | - | - | - | - |
| | Growth failure | ++ | - | - | - | - | - |
| Routine laboratory | Creatinine | ++ | n- \uparrow | n- \uparrow | n- \uparrow | n- \uparrow | n- \uparrow |
| | Urea | ++ | n- \uparrow | n- \uparrow | n- \uparrow | n- \uparrow | n- \uparrow |
| Special laboratory | Oxalate (U) | n- \uparrow | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ |
| | Glycerate (U) | ? | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ |
| | Oxalate (P) | $\uparrow\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ | \uparrow - $\uparrow\uparrow$ |

26.5 Reference Values

| Metabolite | Age range [years] | Upper limit of normal |
|--------------------------------------|-------------------|-------------------------------------|
| Urinary oxalate (timed collection) | All ages | = 0.5 mmol/1.73 m ² /day |
| Urinary oxalate (spot urine) | | (mmol/mol creatinine) |
| | 1–6 months | 141–360 |
| | 7mo–2 | 61–162 |
| | 3–7 | 35–126 |
| | 8–16 | 19–76 |
| | > 16 | <73 |
| Glycolate | 1–6 months | 11–109 |
| | 7mo–25 | 22–139 |
| | 3–7 | 17–103 |
| | 8–16 | 18–92 |
| | > 16 | 6–80 |
| Urinary glycolate (timed collection) | Men | 0–1400 µmol/day |
| | Women | 91–1001 µmol/day |
| L-glycerate | 0–5 | 14–212 |
| | > 5 | 23–138 |
| Plasma oxalate | All ages | < 5 µmol/l |

26.6 Pathological Values/Differential Diagnosis

| Metabolite | Age range [years]/ specification | Result |
|------------------------------------|-------------------------------------|--|
| Urinary oxalate (timed collection) | All ages | > 0.5 mmol/1.73 m ² /day ^a |
| Urinary oxalate (spot urine) | Respective age | > Normal ^a |
| Urinary glycolate | All ages | PH1: normal – ↑ PH2: normal |
| Urinary L-glycerate | All ages | PH1: normal PH2: ↑ |
| Plasma oxalate | Normal GFR | 10–20 µmol/l |
| | GFR 10–50 | 20–60 µmol/l |
| | Pre-HD, CAPD | 80–250 µmol/l |

^a Occasionally normal values may occur intermittently, especially in pyridoxine-sensitive patients.

Daily oxalate excretion may turn normal in advanced renal failure. Oxalate/creatinine ratio will remain elevated.

26.7 Loading Tests

Not applicable.

26.8 Diagnostic Flow Chart

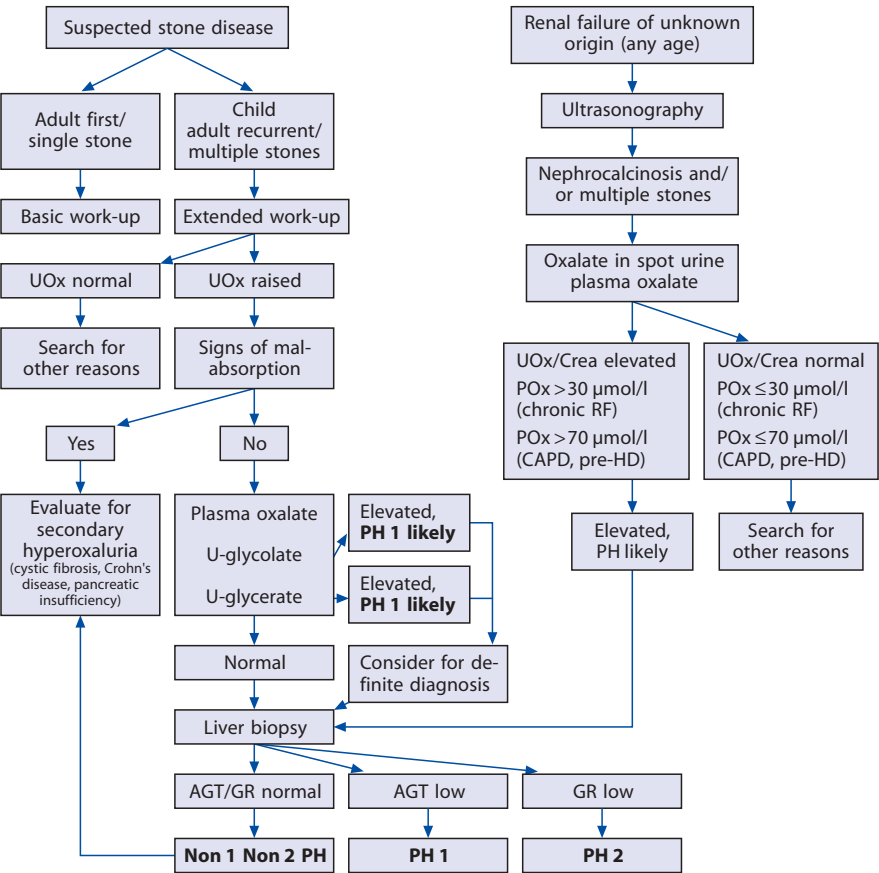


Fig. 26.2. Differential diagnosis of hyperoxalurias. *UOx*, urinary oxalate; *POx*, plasma oxalate; *RF*, renal failure; *CAPD*, continuous ambulatory peritoneal dialysis; *pre-HD*, pre-hemodialysis; *AGT*, alanine glyoxylate aminotransferase; *GR*, glyoxylate reductase

26.9 Specimen Collection

| Metabolite | Methods | Material | Handling | Pitfalls |
|------------|--------------------|--|---|--|
| Oxalate | Ion chromatography | Urine | Immediately acidify with 0.02 ml, 6 mol/l HCl/ml to pH < 3. Dilute 20-fold (with 0.3 mol/l boric acid) | 1. Excess alimentary oxalate or precursors (increased enteral uptake) |
| | Oxalate oxidase | Urine | Adjust to pH 5–7 Stable for 7 days at –20 °C | 2. Vitamin B6 deficiency 3. Chronic renal failure 4. Parental nutrition in prematures 5. Alkaline pH aids spontaneous formation of oxalate from ascorbate |
| | Ion chromatography | Blood, heparinized dialysate | Keep ice-cold after collection. Separate red cells and ultrafilter (cut-off: 10000 Da) 2 ml plasma on to 0.06 ml, 1 mol/l hydrochloric acid/ml. Dilute ultrafiltrate 1:1 with 0.3 mol/l boric acid. All steps at 4 °C. Store at –20 °C until analysis | 6. Precipitation of oxalate from urine sample before analysis |
| | Oxalate oxidase | Blood, heparinized | Centrifugate 5 ml for 10 min at 4 °C. Remove plasma; to 2.5 ml plasma add 0.125 ml of 6 mol/l hydrochloric acid and ultrafilter (cut-off: 10000 Da) by centrifugation at 4 °C and 2000 r.p.m. Store at –20 °C until analysis. | 7. Inadequate method or work-up procedure 8. The Sigma oxalate kit is not officially recommended by the manufacturer for measurement of oxalate in blood |
| Glycolate | | Urine, dialysate Blood, heparinized | Store and ship at –20 °C Centrifugate, store and ship at –20 °C | |
| Glycerate | | Urine | Store and ship at –20 °C | |

26.10 Prenatal Diagnosis

■ Prenatal Diagnosis of PH1

| Method | Comment | Timing (trimester) | Ref. |
|--|---|--------------------|------|
| Measurement of oxalate and glycolate in the amniotic fluid | Non-diagnostic | – | 1 |
| Fetal liver biopsy | Feasible, invasive, high risk | II | 1, 5 |
| Chorionic villous sampling | Requires definite index patient and informative family | I–II | 1, 5 |
| Amniocentesis (linkage analysis) | Genetic counseling is mandatory emphasizing the lack of genotype phenotype correlation in PH1 | II | |

26.11 DNA Analysis

26.1 PH1 (AGT deficiency) genomic sequencing feasible, but impractical due to high genomic variability, linkage analysis usually possible, if an index patient exists.

26.2 PH2 (GR deficiency) genomic sequencing feasible.

26.12 Initial Treatment (Management while Awaiting Results)

The sole route for oxalate excretion is the kidney. Thus increasing the urinary volume to the maximum possible is a major treatment goal. Additionally, with typical clinical symptoms, the administration of magnesium and citrate (0.1 g/kg/day in 4 divided doses) may prevent further crystallization. Any urinary obstruction due to calculi has to be treated as an emergency.

Once the diagnosis of PH1 is likely, testing for B6 sensitivity is essential. Approximately 30% of PH1 patients are responsive to B6 and adherence to the following protocol is recommended. It should be noted and stressed however, that there is no evidence that PH2 patients benefit from pyridoxine and that very high doses of pyridoxine has been reported to cause neurological abnormalities.

In general, the course of PH1 is probably more severe than that of PH2, but the variability for individual patients is high. Neither the time course nor the symptoms will differentiate between the two.

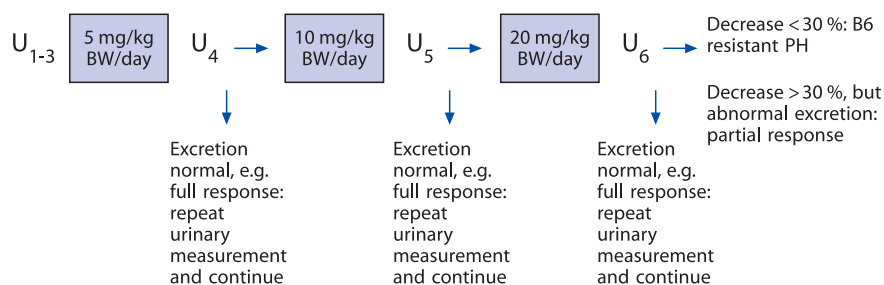


Fig. 26.3. Schematic overview for testing B6 responsiveness in PH1. U denotes timed urine collection

26.13 Summary

Primary hyperoxalurias are rare, but potentially life-threatening disorders. The lack of specific symptomatology makes diagnosis difficult. Nephrocalcinosis, primarily in the very young and later in those with renal failure, and recurrent nephrolithiasis in older patients are the key features of the disease. Involvement of other organs occurs with the development of renal failure. A proper diagnosis can be made by the measurements of urinary oxalate, glycolate and L-glycerate. An absolute diagnosis is possible only via a liver biopsy and with an estimation of the activity of the involved enzymes. A prenatal diagnosis is possible in PH1 using chorionic villous sampling and microsatellite markers. Conservative treatment can stabilize renal function in the vast majority of patients for many years, even decades.

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