OXALATE NEPHROPATHY

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KOCHI

ACADEMIC CORDINATOR -ECNG

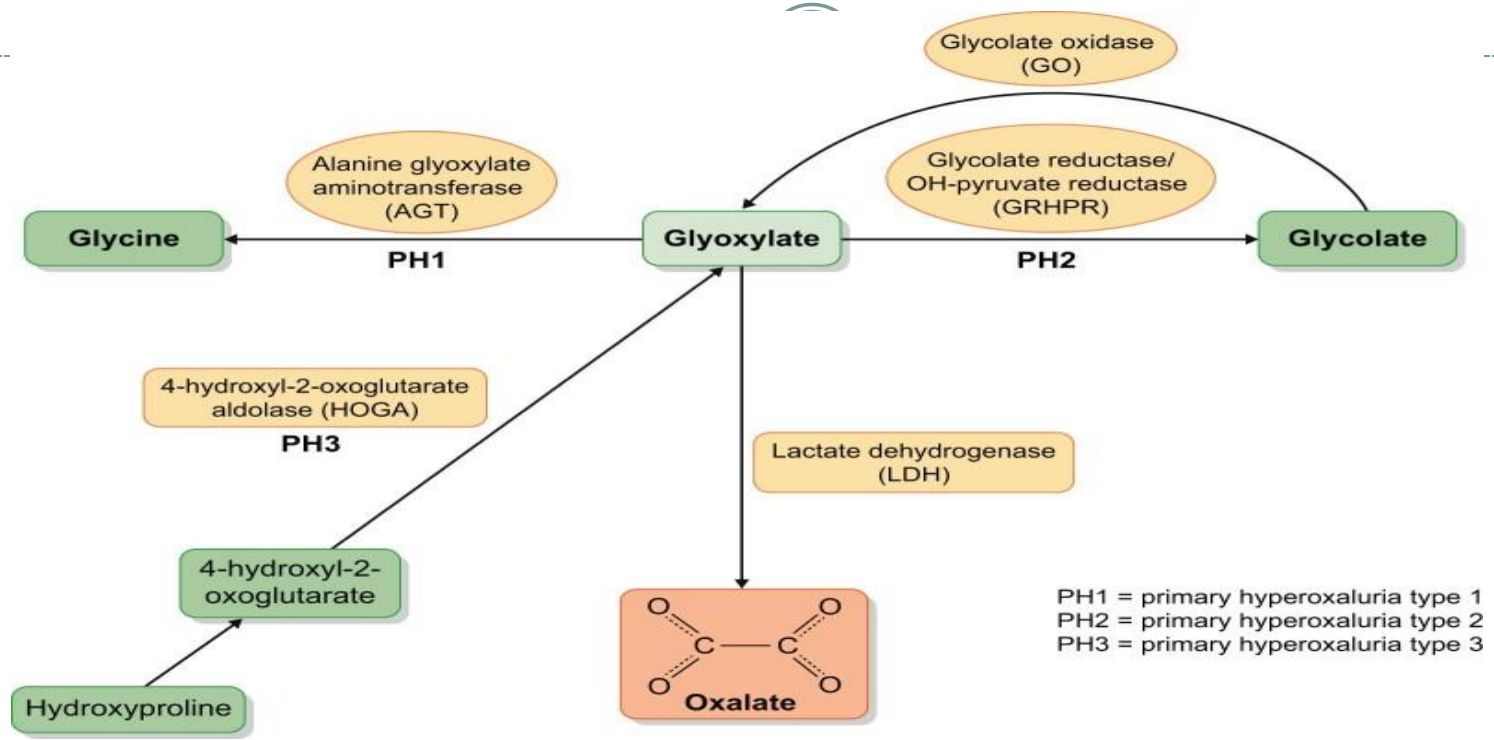
INTRODUCTION

Definition of Oxalate Nephropathy :-

- **1.**Progressive kidney disease.
- **2.**Deposition of calcium oxalate crystals (birefringent on polarized light) within tubular epithelial cells, tubular lumens, and less frequently in the interstitium, associated with tubular injury and interstitial nephritis.
- **3.**Exclusion of other causes of kidney disease (apart from nonspecific microvascular lesions and/or diabetes-associated glomerular lesions).
- **4.**Ideally, a hyperoxaluria enabling-condition should be identified.

- Hyperoxaluria - defined as 24-h urine oxalate of >40–45 mg/day.
- The urinary oxalate excretion tends to be higher in Primary hyperoxaluria >88 mg/day as opposed to 44–70 mg/day in enteric hyperoxaluria.
- The average age that symptoms appear is 5 years old.
- About 50% of children will experience kidney failure by age 15. About 80% will experience kidney failure by age 30.

PRIMARY HYPEROXALURIA



Primary hyperoxaluria types 1 and 2, associated with peroxisomal AGT and cytosolic GRHPR deficiency respectively, result in accumulation of glyoxylate, which is converted to oxalate by LDH.

Primary hyperoxaluria 3 is caused by a defect in HOGA in mitochondria.

Causes of Secondary Hyperoxaluria and Oxalate Nephropathy

Increased intestinal oxalate absorption:-

- Chronic pancreatitis , Pancreatectomy.
- Use of orlistat (lipase inhibitor).
- Roux-en-Y gastric bypass , Small bowel resection.
- Crohn's disease , Celiac disease.
- Cystic fibrosis.
- Use of somatostatin analogue.

Increased dietary oxalate or precursor intake

- Rhubarb, *Averrhoa carambola* (star fruit), *Averrhoa bilimbi*, tea, nuts, "juicing" Vitamin C, ethylene glycol, methoxyflurane, naftidrofuryl oxalate.

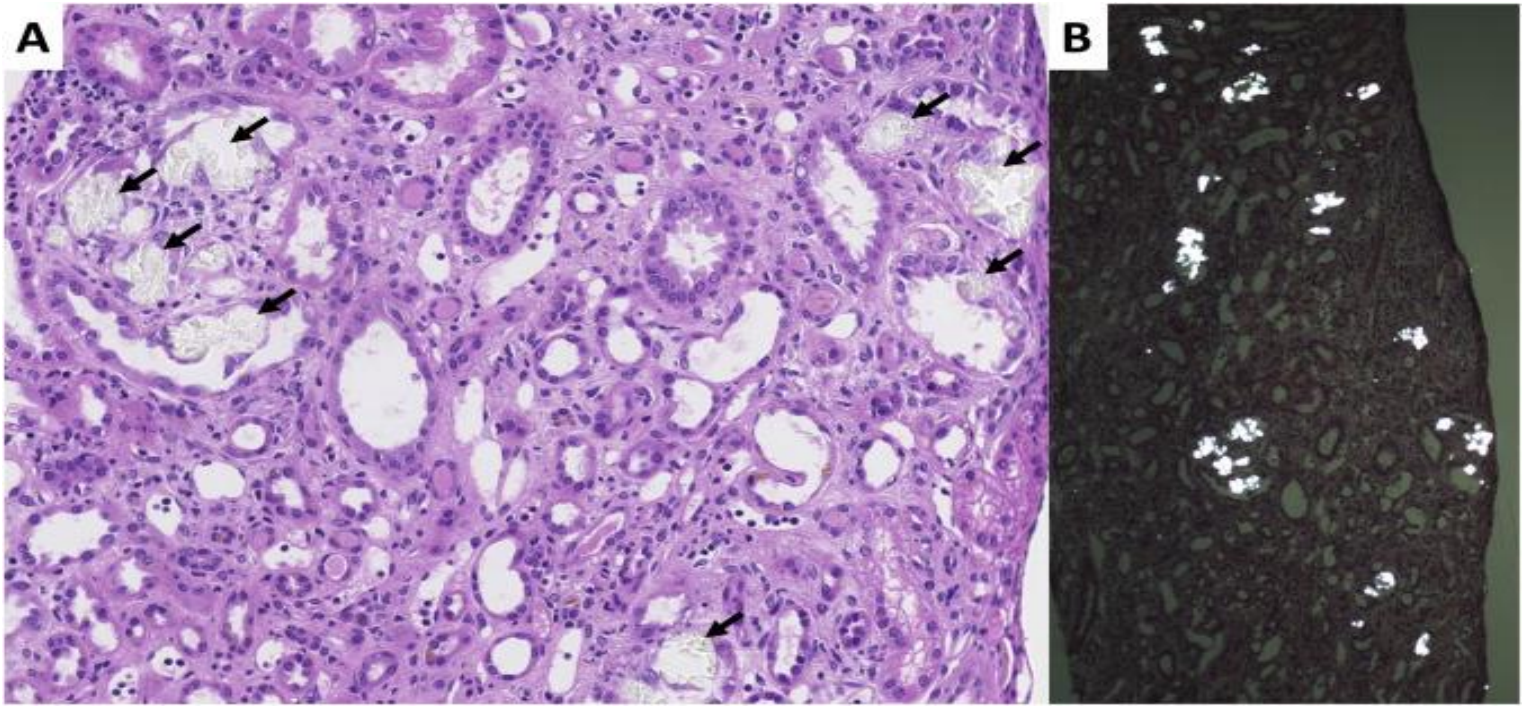
Decreased intestinal bacterial oxalate degradation

- Antibiotic use.

Others

- Obesity, genetic variations in oxalate transporters?[a]

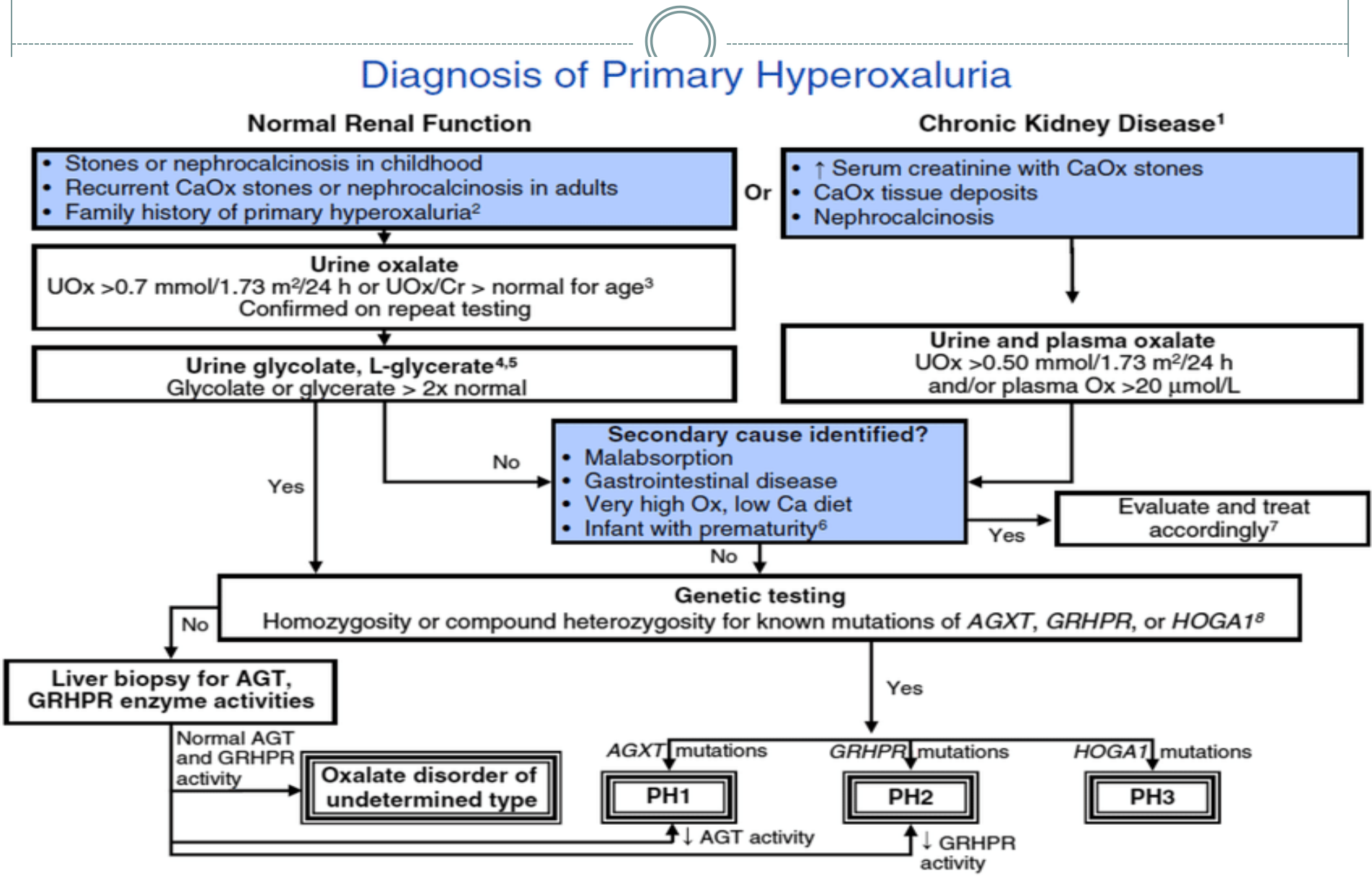
OXALATE NEPHROPATHY



(A) Intratubular translucent polyhedral or rhomboid crystals (black arrows) on light microscopy (hematoxylin and eosin stain, original magnification, ×20).

(B) Crystals shown as birefringent under polarized light (original magnification, ×5). Biopsy also shows acute tubular injury and mild interstitial inflammation.

DIAGNOSTIC ALGORITHM



TREATMENT OF OXALATE NEPHROPATHY

Treatment	Rationale	Supporting evidence
High fluid intake (urine output >2-3 L/d)	Reduces urine calcium oxalate supersaturation.	Reduces stone formation.
Low-oxalate diet	Reduces bioavailability of intestinal oxalate.	Reduces urinary oxalate excretion in small-sized studies; caveat: comparisons were based on a low-oxalate diet compared to a very-high-oxalate diet.
Low-fat diet	Reduces intestinal oxalate absorption (by increasing bioavailability of intestinal calcium).	Reduces urinary oxalate excretion in small studies.
Normal-calcium diet	Avoid low-calcium diets, which lead to more free intestinal oxalate.	Reduces urinary oxalate excretion in small-sized studies.
Calcium supplements	Reduce bioavailability of intestinal oxalate and its absorption.	Reduces urinary oxalate excretion but may lead to hypercalciuria. Calcium citrate may be more bioavailable than calcium carbonate.
Cholestyramine	Binds intestinal bile acids, reduces diarrhea, and binds oxalate in vitro.	Studies show contradicting results.
Oxalobacter formigenes administration	Increases intestinal oxalate degradation.	Reduces urinary oxalate excretion in rat model and plasma oxalate levels in dialysis patients with primary hyperoxaluria (phase 2 study).
Oxalate decarboxylase	Degrades intestinal oxalate.	Reduces urinary oxalate excretion in rat model and in phase 3 pilot study in humans.
NLRP3-specific inflammasome inhibitor	Reduces crystal-induced kidney damage.	Reduces calcium-oxalate crystal-induced kidney fibrosis in mouse model.

TRANSPLANT

- Combined liver and kidney transplant is the mainstay of treatment in primary hyperoxaluria.
- Sequential liver followed by kidney transplant in patients with less severe renal disease.
- Recurrence of oxalate deposition in the graft due to secondary hyperoxaluria needs continuous monitoring and medical management with early loss of graft.

Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1, Results From a Phase III Clinical Trial

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- Primary Hyperoxaluria Type 1
- Age ≥6 years
- eGFR ≥30 mL/min/1.73 m^2
- 6-month double-blind placebo controlled period followed by an extension period

UOx, Urinary Oxalate; ULN, upper limit of normal

EXTENSION PERIOD (Month 36)

	Mean 24-hour UOx reduction from baseline	% of patients who reached 24-hour UOx excretion ≤1.5 x ULN
Lumasiran/ lumasiran group (n=24) *36 months of lumasiran*	63%	76%
Placebo/ lumasiran group (n=13) *30 months of lumasiran*	58%	92%

eGFR remained stable and medullary nephrocalcinosis remained stable or improved

The most common lumasiran-related adverse events were mild, transient injection-site reactions

KI REPORTS
Kidney International Reports

Saland J et al, 2024

Visual abstract by:
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Conclusion In patients with primary hyperoxaluria type 1, longer-term lumasiran treatment led to sustained reduction in urinary oxalate excretion, with an acceptable safety profile and encouraging clinical outcomes.

Multicenter Long-term Real World Data on Treatment with Lumasiran in Patients With Primary Hyperoxaluria Type 1

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Methods and cohort

- Multicenter
- 33 genetically proven PH1, 13 on dialysis
- 14 adults, 14 females
- Age at starting treatment: 2day-59yrs
- Lumasiran treatment 6-27m (med 18)*

*** Lumasiran dosing:**

1) <10Kg= Loading: 6mg/kg monthly for 3 doses; Then 3mg/Kg once monthly (Begin after 1m of loading)
2) 10-20Kg= Loading: 6mg/Kg monthly for 3 doses; Then 6mg/Kg quarterly (Begin after 1m of loading)
3) >20Kg= Loading: 3mg/Kg monthly for 3 doses; Then 3mg/Kg quarterly (Begin after 1m of loading)

Findings

Results are expressed as Mean (SD)

Patients with preserved kidney function

	At baseline	At 3 months	At 12 months	At 18 months
Mean urine oxalate (mmol/1.73m²/d)	1.88 (0.8)	0.73 (0.26)**	0.72 (0.3)**	0.65 (0.2)**
Mean urine glycolate (mmol/1.73m²/d)	2.13 (2.3)	3.54 (1.3)**	5.09 (2.6)**	5.88 (5.7)**
Mean plasma oxalate (mmol/1.73m²/d)	10.65 (4.0)	6.96 (4.1)	9.31 (3.6)	9.9 (3.6)
Mean plasma glycolate (mmol/1.73m²/d)	67.21 (88.2)	85.43 (46.8)	315.8 (302.8)**	240.9 (174)**
Mean eGFR (ml/min/1.73m²)	70.6 (25.5)	Vitamin B6		74.1 (27.7)
	71.3 (18.8)	Non Vitamin B6		86.4 (25.4)

** means significantly different as compared to baseline

Dialysis patients

Mean plasma oxalate (mmol/1.73m²/d)	78.0 (40.2)	37.2 (16.9)**	43.1 (16.3)	59.3 (23.8)
Mean plasma glycolate (mmol/1.73m²/d)	197.2 (220)	337.4 (294)**	443.3 (638)	259.5 (271)

KI REPORTS
Kidney International Reports

Martin-Higueras C et al. 2023

Visual abstract by:
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Conclusion Lumasiran treatment is safe and efficient. Not all patients with preserved kidney function experienced satisfactory reduction of urinary oxalate excretion in quarterly dosing. On whether or not a dosage (interval) adjustment is advisable needs clarification. In dialysis, lack of plasma oxalate reduction may relate to dissolving systemic oxalate deposits.