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Urinary Oxalate in Primary Hyperoxaluria

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Primary Hyperoxaluria (PH)

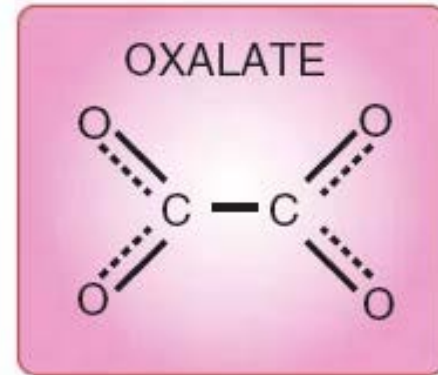
Genetic and Pathophysiologic Basis

Autosomal recessive inheritance

- Prevalence 1-3:10⁶
- Incidence rate 1:10⁵ births/yr

Endogenous oxalate synthesis in hepatocytes

- PH type 1: Peroxisomal AGT deficiency
- PH type 2: Cytosolic GRHPR deficiency



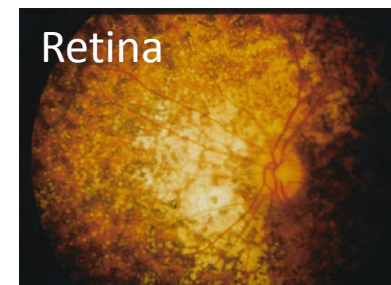
Pathology due to excessive production of endogenous oxalate, and excretion of this metabolic end product through the kidneys.

Disease Process a Consequence of Hyperoxaluria

- Damage to renal parenchymal cells
 - Oxalate toxicity
 - CaOx crystals
- Frequent nephrolithiasis
- Nephrocalcinosis
- Decline in renal function
- ESRD
- Systemic oxalosis
- Premature death

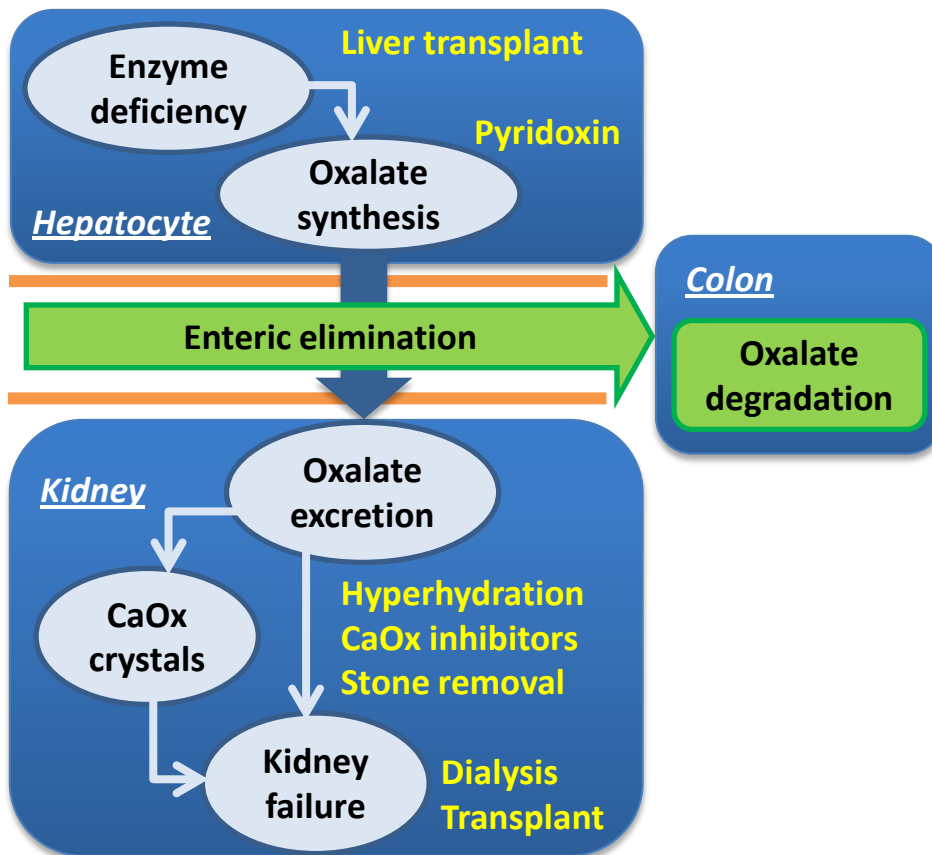


Systemic oxalosis



Current Therapeutic Strategies Aim at Lowering Urinary Oxalate

Reduce Urinary Oxalate and its Damage to the Kidneys

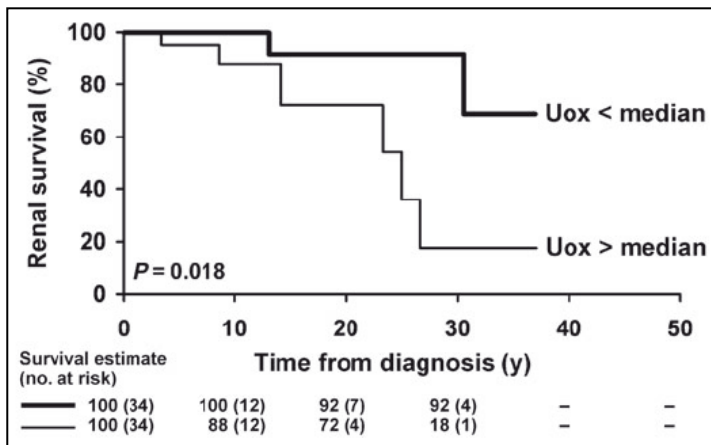


Enteric elimination of oxalate

- Colonic degradation of oxalate may provide a suitable trans-epithelial gradient for the enteric elimination of endogenous oxalate
- Mechanism confirmed in animal models
 - AGTX knock-out mice
 - Nephrectomized hyperoxaluric rats

Disease Progression Related to Urinary Oxalate

Renal survival influenced by the degree of hyperoxaluria



68 patients enrolled in IRPH had UOx measured at diagnosis, while renal function was maintained. Those with UOx of less than 1.2 mM/day had a 92% 20y renal survival after diagnosis, vs. 72% for those with UOx above this level. (Milliner 2006)

Disease progression reversed by liver transplantation

- Improved kidney graft survival with combined liver/kidney transplant vs. isolated kidney transplant. (Bergstrahl 2010)
- Renal deterioration is halted or even reversed by pre-emptive isolated liver transplantation in patients with residual renal function. (Brinkert 2009, Nolkemper 2000)

Analyzing Urinary Oxalate

Valid and reliable assays are well established and widely used in clinical practice

- Variability from sampling has been a bigger concern
 - 24h urine collections
 - Preservation of urine

Sampling compartment (urine) predicts disease compartment (kidney)

- Urinary oxalate is an end-product of metabolism that damages the kidneys

Supportive Data on Surrogate Endpoint

Endpoint confirmed in animal models

- AGTX knock-out mice
- Nephrectomized hyperoxaluric rats

Endpoint supported in patients

- PH type 1
- ESRD patients
- Infantile oxalosis

<i>Clinical Features Associated with Hyperoxalurias - Crossectional Data</i>		
Category	UOx (mM/day)	Clinical features
PH type 1	1.0 - 4.0	ESRD/Systemic Oxalosis
		Nephrocalcinosis
		Frequent nephrolithiasis
PH type 2	1.0 - 2.0	Renal damage
		Frequent nephrolithiasis
Post-bariatric surgery	0.8 - 1.2	Possible renal damage
		Recurrent nephrolithiasis
Idiopathic Hyperoxaluria	0.4 - 0.5	Preserved renal function
		Sporadic nephrolithiasis
Normal	0.1 - 0.4	

Urinary Oxalate in Primary Hyperoxaluria

Surrogate endpoint qualification

- ✓ Disease criteria
- ✓ Drug criteria
- ✓ Biomarker criteria
- ✓ Data criteria

Urinary oxalate was accepted as a surrogate endpoint

- Compelling reduction in UOx needed
- Trends in secondary endpoints reflecting clinical benefit needed
- Accelerated approval to be evaluated

References

- **Asplin JR, Coe FL.**
Hyperoxaluria in kidney stone formers treated with modern bariatric surgery.
J Urol. 2007 Feb;177(2):565-9.
- **Bergstralh EJ et al**
Transplantation outcomes in primary hyperoxaluria.
Am J Transplant. 2010 Nov;10(11):2493-501.
- **Brinkert F et al**
Transplantation procedures in children with primary hyperoxaluria type 1: outcome and longitudinal growth.
Transplantation 2009; 87:1415–1421.
- **Cochat P et al**
Primary hyperoxaluria type 1: strategy for organ transplantation.
Curr Opin Organ Transplant. 2010 Oct;15(5):590-3.
- **Fargue S et al**
Effect of conservative treatment on the renal outcome of children with primary hyperoxaluria type 1.
Kidney Int. 2009 Oct;76(7):767-73.
- **Grujic D et al**
Hyperoxaluria is reduced and nephrocalcinosis prevented with an oxalate-degrading enzyme in mice with hyperoxaluria.
Am J Nephrol. 2009;29(2):86-93.
- **Harambat J et al**
Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome.
Kidney Int. 2010 Mar;77(5):443-9.
- **Hatch M et al**
Oxalobacter sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion.
Kidney Int. 2006 Feb;69(4):691-8.
- **Hatch M et al**
Enteric oxalate elimination is induced and oxalate is normalized in a mouse model of primary hyperoxaluria following intestinal colonization with Oxalobacter.
Am J Physiol Gastrointest Liver Physiol. 2011 Mar;300(3):G461-9.
- **Hoppe B et al**
Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1.
Kidney Int. 2006 Oct;70(7):1305-11.
- **Hoppe B et al**
The primary hyperoxalurias.
Kidney Int. 2009 Jun;75(12):1264-71.
- **Hoppe B et al**
Efficacy and safety of Oxalobacter formigenes to reduce urinary oxalate in primary hyperoxaluria.
Nephrol Dial Transplant. 2011 Apr 2.
- **Hoppe B et al**
Reduction of plasma oxalate levels by oral application of Oxalobacter formigenes in 2 patients with infantile oxalosis.
Am J Kidney Dis. 2011 Sep;58(3):453-5.
- **Leumann E, Hoppe B**
The primary hyperoxalurias.
J Am Soc Nephrol. 2001 Sep;12(9):1986-93.
- **Milliner D**
Treatment of the primary hyperoxalurias: a new chapter.
Kidney Int. 2006 Oct;70(7):1198-200.
- **Sidhu H et al**
Rapid reversal of hyperoxaluria in a rat model after probiotic administration of Oxalobacter formigenes.
J Urol. 2001 Oct;166(4):1487-91.