Hyperoxaluria – A Major Metabolic Risk for Kidney Stone Disease

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ABSTRACT

Hyperoxaluria is a clinically relevant metabolic entity that portends a high morbidity burden. Primarily manifesting as kidney stone disease and chronic kidney disease, advanced hyperoxaluria can also affect major organs, including the brain, heart, liver, bone, and the skin. It is categorized based on etiology into primary and secondary hyperoxaluria. Pathology is attributed to excess de novo oxalate production in the former and multifactorial exogenous oxalate absorption or excess intake of its precursors in the latter. Diagnosis often involves demonstrating elevated urinary oxalate levels, especially in patients with normal kidney function. Here in this review, we will perform an in-depth discussion of various causes of hyperoxaluria and describe treatment options. In view of the significant morbidity burden associated with hyperoxaluria, patients could benefit from heightened clinician awareness to aid in the timely diagnosis and management of this condition.

KEYWORDS: hyperoxaluria, kidney stones, nephrolithiasis, chronic kidney disease

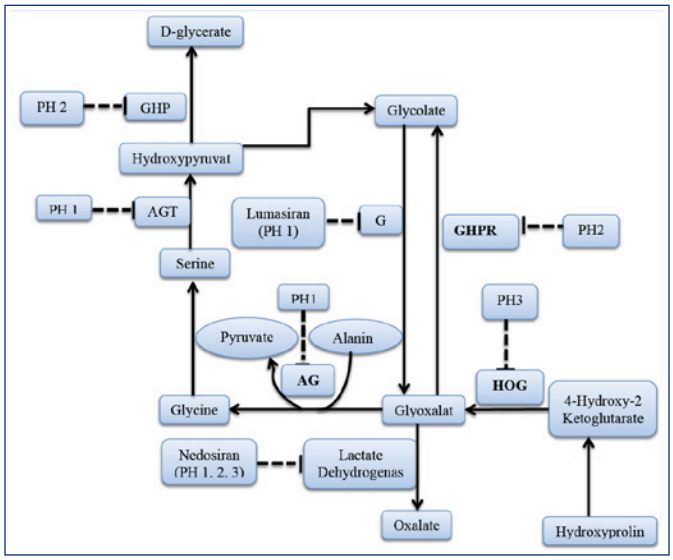
INTRODUCTION

Kidney stone disease poses a growing clinical problem with its prevalence rate reaching 8.8% according to a large U.S. population survey in the late 2000s.[1] Of these, calcium oxalate stones account for the vast majority, contributing to 70–80% of all kidney stone events.[2,3] Hyperoxaluria, a clinical condition associated with excess urinary oxalate excretion is commonly encountered and is seen in 25–45% of stone formers.[4] Broadly it is subdivided into primary hyperoxaluria characterized by excess endogenous oxalate production and secondary hyperoxaluria which could be a result of excess intake of oxalate rich foods or oxalate precursors such as ethylene glycol, or reduced gut colonization of oxalate metabolizing bacteria. As a disease entity, hyperoxaluria carries a high morbidity burden among patients affected with significantly increased utilization of health services.[5-7] We therefore seek to highlight in this review the role of hyperoxaluria in kidney stone formation, disease pathophysiology, clinical presentation and management.

OXALATE PHYSIOLOGY/METABOLISM

Widely found in plant-derived foods consumed by humans, oxalate is the ionic form of oxalic acid.[8–10] Humans gain oxalate through two mechanisms. One is through the endogenous production of oxalate in the liver which is particularly amplified in enzymatic deficiency states that limit glyoxylate metabolism as illustrated in **Figure 1**.[11,12] Secondly, oxalate can be obtained through intestinal absorption after ingestion of oxalate rich foods such as spinach, rhubarb, nuts, plums, chocolate, beetroots, soybean and strawberries.[8,10]

Figure 1. Summary of oxalate metabolism including defects seen in Primary Hyperoxaliuria and targets for therapeutic molecules.
PH 1 – Primary Hyperoxaliuria Type 1, **PH 2** – Primary Hyperoxaliuria Type 2, **PH 3** – Primary Hyperoxaliuria Type 3, **AGT** – Alanine Glyoxylate Aminotransferase, **GHPR** – Glyoxylate Hydroxy-Pyruvate Reductase, **HOGA** – 4-hydroxy 2-oxoglutarate aldolase, **GO** – Glycolate oxidase.



Estimates of the average daily oxalate intake in the western population are highly variable and range anywhere between 44 and 351 mg/day. In fact, daily oxalate intake may even exceed 1000 mg/day when oxalate-rich foods are consumed. However, the fraction of dietary oxalate absorbed in the gut is highly variable. It is influenced by the amount of oxalate binding cations, such as calcium and magnesium, especially in diseases causing fat malabsorption, and the presence of

gut commensal bacteria with oxalate-degrading activity.[13]

On the other hand, clearance of oxalate from the body is primarily through kidney by glomerular filtration and tubular secretion. In patients with normal kidney function, increased levels of plasma oxalate will lead to increased filtration and tubular secretion of oxalate. More specifically, in the proximal renal tubules, secretion of oxalate is mediated by the SLC26 transport proteins located on both apical and basolateral sides of tubular cells. SLC26A1 is critical in oxalate extraction from peritubular capillaries on the basolateral side. While on the apical surface, the SLC26A6 transport protein mediates oxalate secretion into the urinary space. Similarly, the SLC26A6 transport protein seems to play a key role in the secretion of oxalate in the intestines, but its significance remains unknown.[14,15] As such, renal impairment contributes greatly to the increase in plasma oxalate levels. Clinically, hyperoxaluria is often defined as urinary concentrations of oxalate above 40 mg/24hr and is associated with significant risk of developing kidney stones.[16] Despite its clear clinical significance, there seems to be no known beneficial effect of oxalate in the human body.

OXALATE ON KIDNEY STONE RISK

In the urinary space, oxalate has been shown to bind calcium, sodium, potassium and magnesium. While most of these are soluble in water, calcium oxalate has a particularly low super-saturation threshold of 5mg/L in urine at physiological pH, therefore is more likely to result in crystal formation.[17,18] While hyperoxaluria portends a huge risk for kidney stones, it doesn't guarantee stone formation. Development of urolithiasis is dependent on other factors, most prominent being the level of urinary citrate which acts as an inhibitor of calcium stones. It forms a more soluble complex with calcium in the urinary space and further inhibits the crystallization of calcium oxalate stones.[19] In the absence of adequate inhibition, calcium oxalate stone formation starts with a process known as nucleation, followed by crystal growth and agglomeration as stone materials travel down the urinary space.[17]

While both primary and secondary hyperoxaluria lead to the formation of kidney stones, a key distinction to note is that primary hyperoxaluria is commonly associated with pure calcium oxalate monohydrate crystals while secondary hyperoxaluria presents with either pure calcium oxalate dehydrate or mixed (monohydrate and dihydrate) crystals in urine.[20] With recurrent formation of kidney stones and nephrocalcinosis, impairment of kidney function slowly develops due to kidney parenchyma inflammation and fibrosis.[21] This leads to a decrease in glomerular filtration rate (GFR) that further impairs plasma oxalate clearance. Consequently, the excess oxalate is deposited in other body organs resulting in systemic oxalosis as the GFR drops to less than 30–45 mL/min/1.73 m^2. Some of the organs involved include the brain, heart, bone and skin resulting in cerebrovascular accidents, cardiomyopathy, fractures and non-healing skin ulcers among other presentations.[22] However, this is not the case in secondary hyperoxaluria where systemic oxalosis has not been described.

PRIMARY HYPEROXALURIA

Primary hyperoxaluria (PH) is a clinical entity characterized by increased urinary concentration of oxalate secondary to abnormal endogenous hepatic production. It remains a rare disease with an estimated worldwide prevalence of less than 3 per 1,000,000.[23] Current evidence describes three distinct types of primary hyperoxaluria; Type 1, 2 and 3. While all are inherited in an autosomal recessive fashion, primary hyperoxaluria type 1 (PH1) is the most common form of PH. It accounts for up to 80% of cases of PH.[24] Excess oxalate production results from the shunting of glyoxylate metabolism away from the physiological route of glycine and pyruvate production. This is due to either deficiency or a defect in the vitamin B6-related Alanine Glyoxylate Aminotransferase (AGT) enzyme located in the peroxisome first described by Danpure and Jennings in 1986. Additionally, PH1 with AGT defect attributed to a genetic mutation on the AXGT gene on chromosome 2 is phenotypically the severest form of PH with early disease onset, followed by a progressive course leading to end-stage renal disease.[25,26]

PH type 2 which is less common, accounts for approximately 10% of patients with primary hyperoxaluria and is somewhat less aggressive clinically compared to PH1.[27] Characterized by increased oxalate production due to a defect in the hepatic cytosolic Glyoxylate Hydroxy-Pyruvate Reductase (GHPR) enzyme, PH2 also has disease onset in childhood. More specifically, a genetic mutation in the GHPR gene on chromosome 10 has been implicated.[28] Finally, PH3 which is the least common form of PH also represents the mildest subtype with a reduced incidence of end-stage renal disease. A genetic mutation in the HOGA1 gene on chromosome 9 encoding the 4-hydroxy 2-oxoglutarate aldolase hepatic mitochondrial enzyme results in a deficiency of the enzyme. Consequently, 4-hydroxy 2-oxoglutarate metabolism is diverted into the oxalate pathway leading to excess endogenous production.[29,30] **Figure 1** summarizes hepatic oxalate metabolism highlighting enzyme defects in primary hyperoxaluria and their respective therapeutic targets.[31]

SECONDARY HYPEROXALURIA

Secondary hyperoxaluria presents a complex metabolic disorder with several known etiologies. Causes can be broadly categorized as follows, enteric hyperoxaluria which mainly comprise fat malabsorption states, excess intake of oxalate precursors like ethylene glycol, and disturbed gut microbiota.

Enteric hyperoxaluria

Enteric hyperoxaluria represents a subset of secondary hyperoxaluria whose pathophysiology centers around the abnormal handling of oxalate in the gut. Causes under this group are numerous. One relatively common cause is fat malabsorption as a result of various gastrointestinal pathologies such as exocrine pancreatic insufficiency and inflammatory bowel disease. Secondly, diverting surgical procedures such as bariatric surgery, jejunoileal bypass, Roux-en-Y gastric bypass and biliopancreatic diversion result in a lack of or limited bile interaction with fat due to the anatomic alterations. Also implicated in enteric hyperoxaluria is Orlistat – a potent pancreatic enzyme inhibitor prescribed for weight loss. The described disease states have a final common mechanism leading to the development of hyperoxaluria. Often, this involves excess fatty acid delivery to the colon, which in turn binds to calcium. Free oxalate is subsequently absorbed through the gut into the bloodstream.[32,33]

Excess intake of oxalate precursors

Oxalate precursors are quickly absorbed into the bloodstream and thereafter broken down into oxalic acid. One particularly important substance is ethylene glycol. Ingested either accidentally or deliberately, Ethylene glycol is quickly absorbed from the gut and metabolized in the liver into glycol aldehyde by the enzyme alcohol dehydrogenase. Through multiple enzymatic reactions, glycol aldehyde is converted to oxalic acid. High plasma oxalate levels lead to the formation and deposition of calcium oxalate crystals in various body tissues. Renal manifestations, often seen around 48 hours after ingestion, are characterized by calcium oxalate deposition within the renal tubules and other tissues.[34,35]

Vitamin C, which is also known as L-ascorbic acid can be broken down into oxalate especially when ingested in large amounts. High-dose vitamin C, (>1g per day) has been associated with an increase in the risk of stone formation as demonstrated in a prospective study done by Taylor et al.[36-38] Mostly absorbed in the jejunum and ileum, vitamin C is a potent antioxidant in the human body. It is usually metabolized in the liver, where it is initially converted to dehydroascorbic acid (DHA). Through further non-enzymatic reactions, DHA can be metabolized to diketogluconic acid and eventually oxalic acid. Despite the strong evidence to support vitamin C breakdown to oxalic acid, the relationship is far from linear with exact conditions precipitating vitamin C metabolism to oxalate remain unclear.[39]

Altered gut microbiota

Oxalobacter formigenes, an anaerobic gram negative rod that forms part of the normal flora in the colon largely depends on oxalate for carbon dioxide and energy needs.[40] In humans, several bacteria forming the normal flora have been shown to break down oxalate in the gut. However, *Oxalobacter* is the key player in oxalate homeostasis, handling approximately 70 to 100 grams of ingested oxalate daily.[41,42] In normal physiologic states, the net outcome of colonic *Oxalobacter* colonization is a reduction of oxalate absorption. However, several conditions can reduce *Oxalobacter* colonies in the gut resulting in increased oxalate absorption. For example, obesity is associated with reduced *Oxalobacter* colonies, possibly due to systemic inflammation. Furthermore, *Oxalobacter formigenes* has been shown to be particularly sensitive to antibiotics such as tetracyclines, macrolides and fluoroquinolones. As expected, the use of these antibiotics can lead to reduced colonies as well.

DIAGNOSIS

Diagnosis of both primary and secondary hyperoxaluria is a multistep process based on clinical presentation, biochemical testing, imaging and histology as appropriate. Being a relatively rare disease, strong clinical suspicion should always be entertained. Clinicians should keep hyperoxaluria in the differential when patients present with kidney stones at an early age or have either symptomatic (based on symptomatic stone passage or surgery on an asymptomatic kidney stone) or radiographic recurrent (based on new stone formation or evidence of significant previous stone growth) stones during adulthood. Unique to secondary hyperoxaluria, stone formers often present with chronic diarrhea, inflammatory bowel disease, obesity, bowel resection, prolonged antibiotic use, or had recent ingestion of ethylene glycol.

In such scenarios, a 24-hour urine collection for stone risk assessment should be ordered. This is preferably done in the outpatient setting when stone formers are on their regular home diet. Testing is then performed for parameters such as urine volume, pH, calcium, oxalate, uric acid, phosphate, citrate, ammonium, magnesium, sulfate, sodium, potassium and creatinine. All these parameters combined with stone composition analysis help in teasing out the cause of urolithiasis and guide treatment.[43]

More specifically, 24-hour urine oxalate levels above 40mg are usually concerning for hyperoxaluria. For accuracy purposes, two separate measurements are recommended with appropriate adjustments for body surface area. Often, patients with primary or secondary hyperoxaluria will have 24-hour urinary oxalate levels exceeding 88mg/1.73m^2 compared to an expected normal of less than 40mg/1.73m^2. If primary hyperoxaluria is suspected, subsequent testing of urine glycolate and glycerate may give pointers towards PH1 and PH2 respectively based on underlying disease pathophysiology. These tests are, however, not highly sensitive and don't exclude disease presence.

Often, genetic tests are used to diagnose primary hyperoxaluria definitively. The presence of AGXT, GHPR and HOGA1 gene mutations are used to diagnose PH1, PH2 and PH3 respectively. As is the case with most genetic testing, recommended samples include saliva, a buccal swab, or a

blood sample. Testing should also be offered to relatives of index patients with primary hyperoxaluria. While non-invasive genetic testing offers a diagnosis in most cases, results can sometimes be inconclusive even as clinical suspicion remains high. As such a liver biopsy can be undertaken in these cases to obtain definitive data on specific diagnosis.[44,45] In patients with impaired kidney function and declining GFR, urine oxalate excretion can be deceivingly low. Therefore, a serum oxalate level becomes necessary. Values above 30 umol/L are typically seen in patients with hyperoxaliuria.[44] Testing for secondary hyperoxaluria may include stool *Oxalobacter formigenes* PCR, and 13-C oxalate absorption test.[46,47] However, anecdotal evidence suggests that these tests are rarely utilized in clinical practice.

TREATMENT

General supportive treatment

Several measures are recommended to help reduce kidney stone recurrences. Foremost, adequate hydration ensures enough urine output to reduce calcium oxalate supersaturation. Based on this, liberal fluid intake to achieve a urine output of at least 2 liters is frequently encouraged.[48] Further treatment recommendations are usually based on the 24-hour urine biochemical testing. Some key parameters relevant to the management of patients with hyperoxaluria include urine pH, sulfate, citrate, calcium, sodium and potassium. The goal is to optimize urine citrate content, alkalize urine and reduce the amount of urine calcium. Also of note is that thiazide diuretics could have a role in patients with co-existing hypercalciuria. This is even with recently published clinical trial data not showing benefit in reducing stone recurrence on the background of previous supportive evidence.[49] We believe that clinicians will still need to assess on a case-by-case basis which patients to offer this treatment and appropriate dosage to be used.

Definitive treatment

Primary Hyperoxaluria

In addition to general supportive measures, insights into the pathophysiology of primary hyperoxaluria have led to not only the development of new therapeutics but also the repurposing of others to treat patients with PH. Most of the data available seems to involve patients with PH1.[50,51]

Pyridoxine is perhaps the oldest molecule available for the treatment of PH1. Used at higher doses than usual, it acts by stabilizing the vitamin B6-dependent AGT enzyme thereby enhancing its activity.[50] Despite this strong pathophysiological basis for use, it only has a therapeutic effect in 30% of patients with PH1 implying further genotype differences in PH1 patients that determine pyridoxine therapy response. Similarly, urinary oxalate reduction of 30% is seen in pyridoxine responders.[50,52] In some instances, sustained therapeutic effect can delay further invasive treatment such as liver transplants for years.

More recently, newer novel therapies have emerged as the go-to options in the treatment of PH1. Lumasiran, an RNA interference molecule targeting glycolate oxidase has been shown to reduce endogenous oxalate production and subsequently urinary oxalate.[51] Dual approved by the US FDA and European Medicines Association (EMA), Lumasiran has shown significant efficacy in 24-hour urinary oxalate excretion reduction in children and adults.[53] Additionally, efficacy among patients with advanced chronic kidney disease has been demonstrated in the ILLUMINATE-C trial. Injections of the drug are administered subcutaneously three-monthly. Further, no significant adverse reactions were reported in the Lumasiran trials with current data reporting skin reactions as the main side effect to look out for.[54] Despite strong data to support use currently in PH1, there remains a need to collect prospective long-term data to answer questions on sustained efficacy and how reductions in 24-hour urinary oxalate impact long-term clinical outcomes.

Also in the pipeline is another RNAi molecule – Nedosiran. It targets the LDH-A enzyme to decrease endogenous oxalate production. So far, promising data from early phase studies show the drug's safety and efficacy in the reduction of 24-hour urinary oxalate excretion in all types of primary hyperoxaliuria.[55,56] Results from currently ongoing PHYOX trials will shed more light on Nedosiran's efficacy in different age groups and GFR stage.[57–59] Finally other promising non-RNAi therapies under investigation include targeted gene therapy and Stiripentol, a repurposed FDA-approved therapy for Dravet syndrome.[60,61]

Secondary Hyperoxaluria

Treatment in secondary hyperoxaluria centers on the management of underlying medical condition and dietary interventions. While dietary oxalate modifications are not aggressively pursued in primary hyperoxaluria since intestinal oxalate absorption is not the main driver of hyperoxaluria, they are crucial in the management of patients with secondary hyperoxaluria. Limiting oxalate-rich foods helps reduce the amount of oxalate absorption in the gut. Furthermore, dietary calcium intake should be optimized so that enough calcium is available in the gut to bind free oxalate, further reducing oxalate absorption. Additional dietary calcium supplementation is yet to be shown to be beneficial in prevention of calcium oxalate stones. Another potential target in this particular patient population is the altered gut microbiome with reduced Oxalobacter colonies. Interventions include oral probiotic supplementation or fecal transplant of Oxalobacter formigenes. While this is promising, one challenge encountered is non-persistence of colonies after supplementation, and large scale randomized trials are needed to establish its efficacy in reducing oxalate absorption from the gut and stone prevention.[62]

CONCLUSION

In conclusion, hyperoxaluria poses a major risk for calcium kidney stone disease. Its clinical outcomes hinge upon timely diagnosis and early initiation of effective treatment. Primary hyperoxaluria type 1 remains the most severe form of PH.[31] Often, it is associated with earlier onset of disease and rapid progression to ESRD. Luckily, novel therapies based on disease pathophysiology continue to offer hope for patients and their care providers. A high clinical suspicion coupled with appropriate testing and treatment could potentially help avert long term end organ damage from the disease.

References

1. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of Kidney Stones in the United States. Eur Urol. 2012;62(1):160. PMID: 22498635
2. Zhang D, Li S, Zhang Z, et al. Urinary stone composition analysis and clinical characterization of 1520 patients in central China. Scientific Reports 2021 11:1. 2021;11(1):1-8. PMID: 33742013
3. Ivanovski O, Drüeke TB. A new era in the treatment of calcium oxalate stones? Kidney Int. 2013;83(6):998-1000. PMID: 23728004
4. Spradling K, Vernez SL, Khoyliar C, et al. Prevalence of Hyperoxaluria in Urinary Stone Formers: Chronological and Geographical Trends and a Literature Review. J Endourol. 2016;30(4):469-475. PMID: 26738689
5. Wang X, Danese D, Brown T, et al. Primary Hyperoxaluria Type 1 Disease Manifestations and Healthcare Utilization: A Multi-Country, Online, Chart Review Study. Front Med (Lausanne). 2021;8:1636. PMID: 34616753
6. Garrelfs SF, Rumsby G, Peters-Sengers H, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney Int. 2019;96(6):1389-1399. PMID: 31685312
7. de Freitas HM, Danese D, Hubig L, Lloyd A, Lombardelli S. Estimating health state utilities in primary hyperoxaluria type 1: a valuation study. J Med Econ. 2023;26(1):386-393. PMID: 36852648
8. Mitchell T, Kumar P, Reddy T, et al. Dietary oxalate and kidney stone formation. Am J Physiol Renal Physiol. 2019;316(3):F409. PMID: 30566003
9. Asplin JR. Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin North Am. 2002;31(4):927-949. PMID: 12474639
10. Noonan SC, Savage GP. Oxalate content of foods and its effect on humans. Asia Pac J Clin Nutr. 1999;8(1):64-74. PMID: 24393738
11. Holmes RP, Assimos DG. Glyoxylate synthesis, and its modulation and influence on oxalate synthesis. J Urol. 1998;160(5):1617-1624. PMID: 9783918
12. Farinelli MP, Richardson KE. Oxalate synthesis from [14C1]glycollate and [14C1]glyoxylate in the hepatectomized rat. Biochim Biophys Acta. 1983;757(1):8-14. PMID: 6838909
13. Robijn S, Hoppe B, Vervaet BA, D'Haese PC, Verhulst A. Hyperoxaluria: A gut-kidney axis. Kidney Int. 2011;80(11):1146-1158. PMID: 21866092
14. Sindić A, Chang MH, Mount DB, Romero MF. Renal physiology of SLC26 anion exchangers. Curr Opin Nephrol Hypertens. 2007;16(5):484-490. PMID: 17693766
15. Mount DB, Romero MF. The SLC26 gene family of multifunctional anion exchangers. Pflugers Arch. 2004;447(5):710-721. PMID: 12759755
16. Leslie SW, Sajjad H, Bashir K. 24-Hour Urine Testing for Nephrolithiasis: Interpretation Guideline. StatPearls. Published online January 4, 2023. Accessed May 6, 2023. https://www.ncbi.nlm.nih.gov/books/NBK482448/ PMID: 29494055
17. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. Nat Rev Dis Primers. 2016;2:16008. PMID: 27188687
18. Streit J, Tran-Ho L, Chemie EKM für, 1998. Solubility of the three calcium oxalate hydrates in sodium chloride solutionsand urine-like liquors. elibrary.ru. Accessed May 6, 2023. https://elibrary.ru/item.asp?id=1049201
19. Kok DJ, Papapoulos SE, Bijvoet OLM. Excessive crystal agglomeration with low citrate excretion in recurrent stone-formers. Lancet. 1986;1(8489):1056-1058. PMID: 2871335
20. Daudon M, Bader CA, Jungers P. Urinary calculi: review of classification methods and correlations with etiology. Scanning Microsc. 1993;7(3):1081-1106. PMID: 8146609
21. Zisman AL, Evan AP, Coe FL, Worcester EM. Do kidney stone formers have a kidney disease? Kidney Int. 2015;88(6):1240-1249. PMID: 26376133
22. Tantbirojn P, Kittikowit W, Kingwattanakul P. Primary Hyperoxaluria. Int J Nephrol. 2011;2011(8):1669-1672. PMID: 17927001
23. Hopp K, Cogal AG, Bergstralh EJ, et al. Phenotype-Genotype correlations and estimated carrier frequencies of primary hyperoxaluria. Journal of the American Society of Nephrology. 2015;26(10):2559-2570. PMID: 25644115
24. Lieske JC, Monico CG, Holmes WS, et al. International registry for primary hyperoxaluria. Am J Nephrol. 2005;25(3):290-296. PMID: 15961949
25. Fargue S, Acquaviva Bourdain C. Primary hyperoxaluria type 1: pathophysiology and genetics. Clin Kidney J. 2022;15(Supplement_1):i4-i8. PMID: 35592619
26. Danpure CJ, Jennings PR. Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett. 1986;201(1):20-34. PMID: 3709805
27. Milliner DS, Wilson DM, Smith LH. Phenotypic expression of primary hyperoxaluria: Comparative features of types I and II. Kidney Int. 2001;59(1):31-36. PMID: 11135054
28. Cramer SD, Ferree PM, Lin K, Milliner DS, Holmes RP. The gene encoding hydroxypyruvate reductase (GRHPR) is mutated in patients with primary hyperoxaluria type II. Hum Mol Genet. 1999;8(11):2063-2069. PMID: 10484776
29. Singh P, Viehman JK, Mehta RA, et al. Clinical characterization of primary hyperoxaluria type 3 in comparison with types 1 and 2. Nephrology Dialysis Transplantation. 2022;37(5):869. PMID: 33543760
30. Belostotsky R, Seboun E, Idelson GH, et al. Mutations in DHDPSL Are Responsible For Primary Hyperoxaluria Type III. Am J Hum Genet. 2010;87(3):392. PMID: 20797690
31. Bhasin B, Ürekli HM, Atta MG. Primary and secondary hyperoxaluria: Understanding the enigma. World J Nephrol. 2015;4(2):235. PMID: 25949937
32. de Martines DGL, Gianotten S, Wetzels JFM, van der Meijden WAG. Secondary hyperoxaluria due to pancreatic insufficiency. Netherlands Journal of Medicine. 2019;77(8):287-292. PMID: 31814577
33. Solomon LR, Nixon AC, Ogden L, Nair B. Orlistat-induced oxalate nephropathy: An under-recognised cause of chronic kidney disease. BMJ Case Rep. 2017;2017:1-6. PMID: 29133578
34. Pomara C, Fiore C, D'Errico S, Riezzo I, Fineschi V. Calcium oxalate crystals in acute ethylene glycol poisoning: A confocal laser scanning microscope study in a fatal case. Clin Toxicol. 2008;46(4):322-324. PMID: 18363130
35. Chen YH, Liu HP, Chen HY, et al. Ethylene glycol induces calcium oxalate crystal deposition in Malpighian tubules: A Drosophila model for nephrolithiasis/urolithiasis. Kidney Int. 2011;80(4):369-377. PMID: 21451462

36. Fletcher RH. The risk of taking ascorbic acid. JAMA Intern Med. 2013;173(5):375-394. PMID: 23381657
37. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: New insights after 14 years of follow-up. Journal of the American Society of Nephrology. 2004;15(12):3225-3232. PMID: 15579526
38. Thomas LDK, Elinder CG, Tiselius HG, Wolk A, Åkesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. JAMA Intern Med. 2013;173(5):386-388. PMID: 23381591
39. Simpson GLW, Ortwerth BJ. The non-oxidative degradation of ascorbic acid at physiological conditions. Biochim Biophys Acta. 2000;1501(1):12-24. PMID: 10727845
40. Stewart CS, Duncan SH, Cave DR. Oxalobacter formigenes and its role in oxalate metabolism in the human gut. FEMS Microbiol Lett. 2004;230(1):1-7. PMID: 14734158
41. Mittal RD, Kumar R. Gut-inhabiting bacterium Oxalobacter formigenes: role in calcium oxalate urolithiasis. J Endourol. 2004;18(5):418-424. PMID: 15253809
42. Miller AW, Dearing D. The metabolic and ecological interactions of oxalate-degrading bacteria in the mammalian gut. Pathogens. 2013;2(4):636-652. PMID: 25437337
43. Maalouf NM. Approach to the adult kidney stone former. Clin Rev Bone Miner Metab. 2012;10(1):38-49. PMID: 22654574
44. Milliner DS. The Primary Hyperoxalurias: An Algorithm for Diagnosis. Am J Nephrol. 2005;25(2):154-160. PMID: 15855742
45. Hoppe B, Beck BB, Milliner DS. The Primary Hyperoxalurias. Kidney Int. 2009;75(12):1264. PMID: 19225556
46. Voss S, Hesse A, Zimmermann DJ, Sauerbruch T, von Unruh GE. Intestinal Oxalate Absorption is Higher in Idiopathic Calcium Oxalate Stone Formers Than in Healthy Controls: Measurements With the [13C2]Oxalate Absorption Test. Journal of Urology. 2006;175(5):1711-1715. PMID: 16600737
47. Von Unruh GE, Voss S, Hesse A. Experience with the [13C2]oxalate absorption test. Isotopes Environ Health Stud. 2000;36(1):11-20. PMID: 11022322
48. Prezioso D, Strazzullo P, Lotti T, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. Arch Ital Urol Androl. 2015;87(2):105-120. PMID: 26150027
49. Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence. New England Journal of Medicine. 2023;388(9):781-791. PMID: 36856614
50. Gibbs DA, Watts RW. The Action of Pyridoxine in Primary Hyperoxaluria. Clin Sci. 1970;38(2):277-286. PMID: 5416155
51. Liebow A, Li X, Racie T, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. Journal of the American Society of Nephrology. 2017;28(2):494-503. PMID: 27432743
52. Watts RWE, Veall N, Purkiss P, Mansell MA, Haywood EF. The effect of Pyridoxine on Oxalate Dynamics in three Cases of Primary Hyperoxaluria (with Glycollic Aciduria). Clin Sci. 1985;69(1):87-90. PMID: 4064559
53. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. New England Journal of Medicine. 2021;384(13):1216-1226. PMID: 33789010
54. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial. American Journal of Kidney Diseases. 2023;81(2):145-155.e1. PMID: 35843439
55. Hoppe B, Koch A, Cochat P, et al. Safety, pharmacodynamics, and exposure-response modeling results from a first-in-human phase 1 study of nedosiran (PHYOX1) in primary hyperoxaluria. Kidney Int. 2022;101(3):626-634. PMID: 34481803
56. Goldfarb DS, Lieske JC, Groothoff J, et al. Nedosiran in primary hyperoxaluria subtype 3: results from a phase I, single-dose study (PHYOX4). Urolithiasis. 2023;51(1):1-9. PMID: 37118061
57. Natural History of Patients With PH3 and a History of Stone Events - Full Text View - ClinicalTrials.gov. Accessed June 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04542590
58. Nedosiran in Pediatric Patients From Birth to 11 Years of Age With PH and Relatively Intact Renal Function - Full Text View - ClinicalTrials.gov. Accessed June 16, 2023. https://clinicaltrials.gov/ct2/show/NCT05001269?term=05001269&draw=2&rank=1
59. Safety & Efficacy of DCR-PHXC in Patients With PH1/2 and ESRD - Full Text View - ClinicalTrials.gov. Accessed June 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04580420
60. Le Dudal M, Huguet L, Perez J, et al. Stiripentol protects against calcium oxalate nephrolithiasis and ethylene glycol poisoning. J Clin Invest. 2019;129(6):2571-2577. PMID: 30946030
61. Estève J, Blouin JM, Lalanne M, et al. Targeted gene therapy in human-induced pluripotent stem cells from a patient with primary hyperoxaluria type 1 using CRISPR/Cas9 technology. Biochem Biophys Res Commun. 2019;517(4):677-683. PMID: 31402115
62. Hoppe B, Beck B, Gatter N, et al. Oxalobacter formigenes: A potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70(7):1305-1311. PMID: 16850020

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Conflict of Interest

Authors declare that they have no competing interests

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