# Hyperoxaluria

## Information Brochure for Patients with Primary Hyperoxaluria

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## Imprint

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# Introduction

This booklet in its third edition shall hopefully give patients, parents, or other caregivers the possibility to learn in more or less lay-term explanations about an ultra rare disease called PRIMARY HYPEROXALURIA.

This latest version now is updated with the current state of the art diagnostic and therapeutic information including new and future treatment options.

We hope, that we provide adequate information, however, if questions arose, or comments are popping up, you can contact us at **info@phhp-team.net**

We hope, you enjoy reading,

Bonn, November 2023,       *Cristina Martin-Higueras & Bernd Hoppe*

# 2

# Primary (and secondary) hyperoxaluria

# 2. Primary (and secondary) hyperoxaluria

An elevated excretion of oxalic acid/oxalate in urine is called hyperoxaluria. It is one of the main risk factors for recurring urolithiasis (= kidney stone disease, Figure 1a) or progressing nephrocalcinosis (= calcification of the kidneys ➜ deposition of calcium-oxalate crystals in the renal tissue, Figure 1b).

> **Hyperoxaluria =**
> **elevated risk for kidney stones and/or nephrocalcinosis**

Oxalic acid (oxalate) is an end product of the human metabolism and thus needs to be eliminated out of the body, which is mainly done by the kidneys. With increased excretion, oxalate in urine is increasingly bound to calcium. This results in small calcium-oxalate (CaOx) crystals at first, which are actually excreted unproblematic with a sufficient urine volume. Ultimately, however, especially with a low urine volume or with an excessively high oxalate excretion, bigger crystals built the basis for kidney stones or kidney calcification (nephrocalcinosis).

Approximately 10-15% of the adult population have at least one kidney stone passage in their lives. Kidney stones are rarer in children and adolescents, but they may occur at any age, even in infancy, and the prevalence is increasing. Calcium-oxalate is the most common component of kidney stones (75%). However, frequently, patients do not specifically consult for an explanation of a kidney stone passage, but rather because of other dominant symptoms:

- Blood (red, white blood cells) in urine
- Pain while passing urine
- Suspected urinary tract infection
- Pathologic ultrasound findings of kidneys and urinary tract
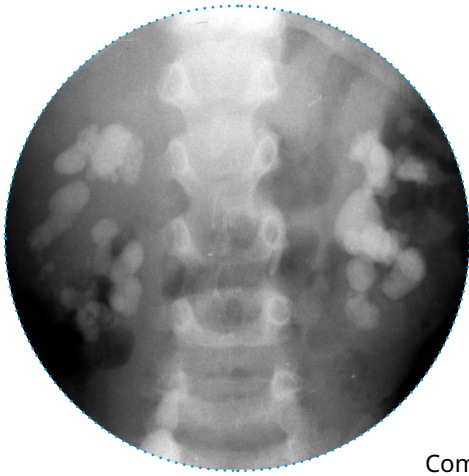
**Figure 1a:** Multiple kidney stones in plain abdominal X-ray



Computed tomography of a patient suffering from primary hyperoxaluria Type I (PH I)
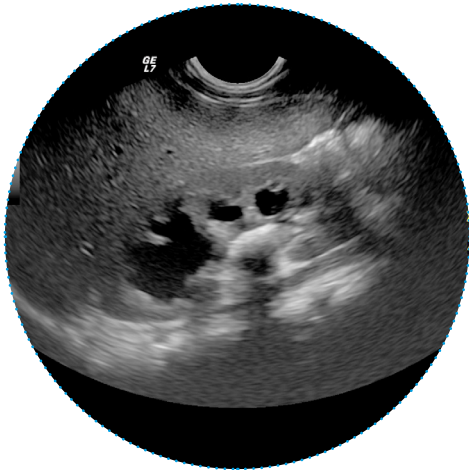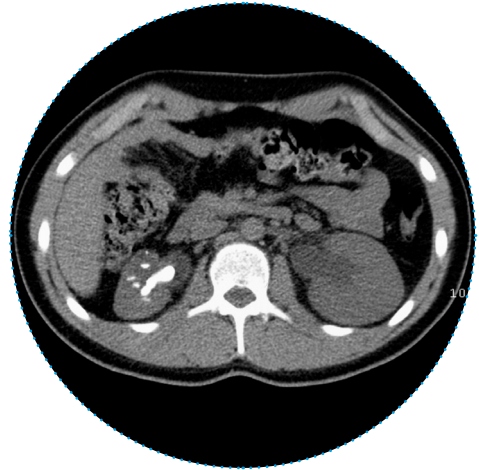


Ultrasound picture of an obstructive staghorn kidney stone in a patient suffering from PH type III.



**Figure 1b:** The ultrasound image shows a severe and diffuse calcification of the kidney in a 6-month-old patient suffering from PH I and acute kidney failure.
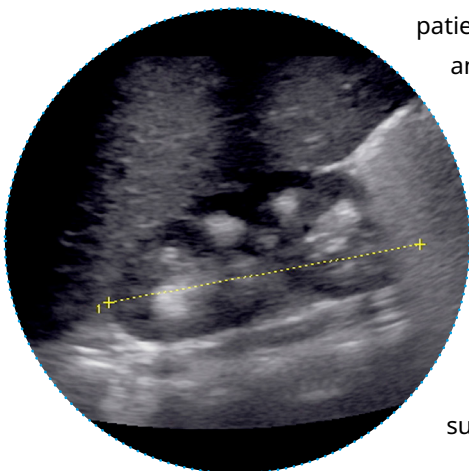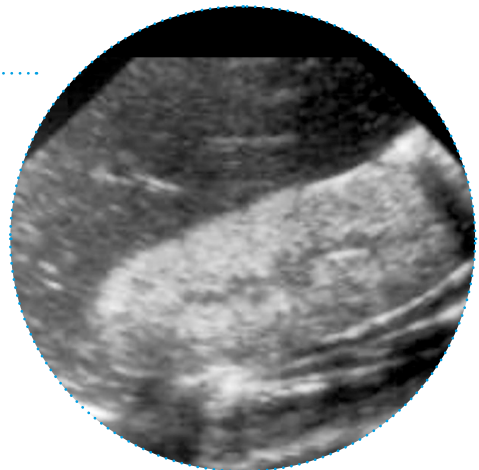


**Figure 1c:** Stage III medullary nephrocalcinosis in a 4-year-old patient suffering from PH I.

**Figure 2:** Typical first kidney stone in a patient suffering from primary hyperoxaluria,

Type I (top) or Type III (bottom):

- Bright in appearance
- Low content of organic material
- No core/edge structure
- Porous, often with large crystals
- Sometimes large crystals within a fine layer structure

**What causes the elevated excretion of oxalate in urine? Primary (congenital) are distinguished from secondary (acquired) hyperoxalurias.**

## 2.1. Primary hyperoxaluria

The three types of primary hyperoxaluria are extremely rare metabolic liver diseases, in which oxalate is overproduced based on three different enzymatic defects. In Germany, for example, only about 250 patients with any of the PH types are known. It is estimated that about 1-3 patients per one million population per country are affected. However, genomic studies calculate much more patients, thus it is to assume that the disease is underdiagnosed. This is supported by the fact that an increasing number of older patients are diagnosed only at renal failure or even after an unsuccessful isolated kidney transplantation. A postnatal screening study has just started in Germany to find proof of the true prevalence rates. As mentioned, three forms of primary (PH) are distinguished from secondary hyperoxaluria. The primary forms are autosomal-recessive inherited diseases. Autosomal-recessive means that the patient must have inherited a change in a specific gene in the chromosome component from both the mother and the father to finally be sick. The parents are (normally) not affected by the disease since they have one healthy and one altered allele. Chromosomes are structures containing genes and thus carrying our genetic information.

As a result of this, three enzyme defects lead way to an excessive amount of oxalate production in the liver in primary hyperoxaluria. Oxalate is later excreted in the urine as it is a waste product for the human body, whereas, for example, it is the main energy source for small bacteria populating the intestinal tract (*Oxalobacter formigenes*).

**Table 1:** Primary hyperoxaluria, Gene and gene product as well as brief description of the symptoms and frequency. UL = urolithiasis (urinary stones), NC = nephrocalcinosis (calcification of the kidneys), Ox = oxalate, LKTx = liver and kidney transplantation, iKTx = isolated kidney transplantation, VB6 = vitamin B6, HOG = Hydroxy-oxo-glutarate. DHG = Dihydroxy-glutarate, 4OHGlu = 4 Hydroxy-Glutamate, CKD = chronic kidney disease, ESRD = end stage renal disease

| Type | Gene/gene product/Locus | Clinic |
|------|------------------------|--------|
| **PH I** | *AGXT* <br> Alanine glyoxylate aminotransferase (*AGT*) 2q37.3 | MOST COMMON TYPE (70-80%) <br> Rec. UL and/or massive NC <br> urine/plasma: Ox + glycolate transplantation: LKTx, iKTx in VB6 sensitive patients |
| **PH II** | *GRHPR* <br> Glyoxylate reductase/ hydroxypyruvate reductase (*GRHPR*) 9q11 | LESS COMMON (< 10%) <br> Rec. UL, discrete NC <br> urine/plasma: Ox + glyceric acid transplantation: iKTx, in severe cases LKTx |
| **PH III** | *HOGA1* <br> 4-hydroxy-2-oxo-glutarate aldolase type 1 (*HOGA1*) 10q24.2 | INCREASING NUMBERS (> 10%) <br> Rec. UL, NC in about 10 % <br> Urine/plasma: Ox + HOG/DHG/4OHGlu <br> CKD in > 20 % of patients, ESRD also reported, transplantation ? |
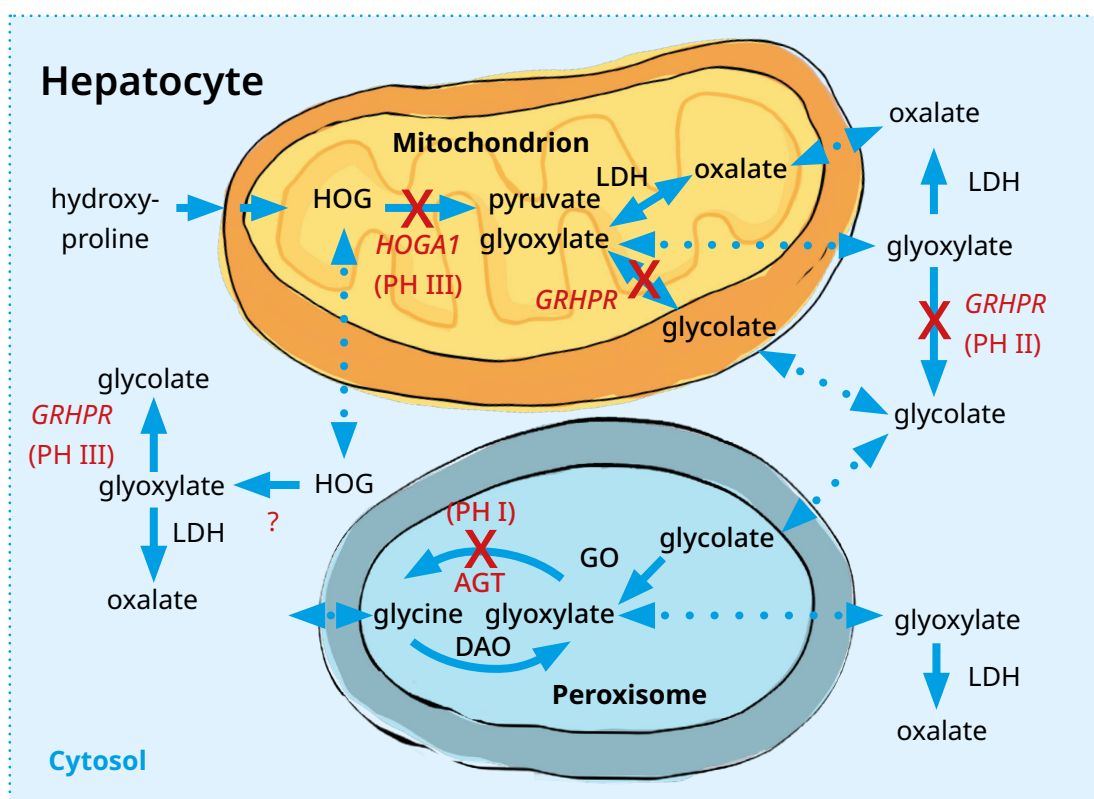
**Figure 3:** Primary reactions of the glyoxylate/oxalate metabolism in human liver cells. X indicates the enzymatic defect in PH I (alanine: glyoxylate aminotransferase (AGT), in PH II (glyoxylate reductase/hydroxypyruvate reductase (*GRHPR*), and 4 hydroxy-2-oxo-glutarate aldolase type 1 (*HOGA1*) in PH III. Glycolate oxidase (GO), D-amino-oxidase (DAO), lactate dehydrogenase A (LDHA), Diamino-oxidase (DAO) [modified according to Hoppe, Nephrologe 2015].

Hyperoxaluria and elevated excretion of glycolate in PH I, is caused by a lack of or missing activity or a wrong localization of the enzyme alanine: glyoxylate aminotransferase (AGT, *AGXT* gene on chromosome 2q37.3). AGT is usually present in the peroxisomes in the liver (**enzyme** = protein, which causes a chemical reaction, **peroxisome** = micro-body in the liver with detoxification function), but is then mislocalized into the mitochondria (= engine of the cell), where it cannot be active.

In PH II, a reduced activity of glyoxylate reductase leads to hyperoxaluria and increased urine excretion of L-Glyceric acid (*GRHPR* gene on chromosome 9p11). Since 2010, a third form of primary hyperoxaluria is known, which is due to a defect in the mitochondrial metabolism of hydroxyproline (Mitochondria = cell bodies, which can be described as a motor of a cell).

In PH III the enzyme 4 hydroxy-2-oxo-glutarate aldolase type 1(*HOGA1*) is defect, which leads to an elevated excretion of hydroxy-oxo-glutarate (HOG), di-hydroxy-oxo-glutarate (DHG) and 4-hydroxy-ketoglutamate (4OHGlu), apart from hyperoxaluria.

Extreme hyperoxaluria (> 1.0 mmol/1.73 m$^2$ body surface (BSA)/24 h, normal excretion < 0.5 mmol/1.73m$^2$/24 h) leads to recurrent kidney stone formation and/or progressive kidney calcification (= nephrocalcinosis or also called oxalosis) and thus to an increased risk of early kidney damage. In many patients with primary hyperoxaluria, the kidneys fail rapidly (= renal failure) and they become dialysis-dependent. This is especially true for patients with PH I, who have an almost 100% risk of permanent renal function impairment. In PH II, according to recent studies (OxalEurope Registry), it must be assumed that up to 50% of all patients develop renal impairment. In PH III, more recent registry studies revealed that about 20% of patients show reduced renal function and that patients can also experience end stage renal failure. Urinary oxalate excretion is similar in all PH types, with one exception, the PH I patients who are treated and are responsive to vitamin B6 medication have clearly lower levels. Plasma oxalate levels are also comparable within all PH forms, but again lower in those PH I patients with response to B6 medication. However, long-term follow-up data need to be further collected for PH III, as only a few adult patients are known and followed so far.

It is assumed today that not only the kidney stones or the nephrocalcinosis, but rather the high oxalate concentration in the kidney tubules (= the primary urine produced in the filtering unit „glomerulus" is concentrated in this tubule system, and the substances important for the body are reabsorbed) itself is the reason for the deterioration of the kidney function. In the kidneys, the deposition of oxalate crystals in the renal tissue results in an inflammatory reaction, which ends finally in scarring of the kidneys. But, frequent invasive kidney stone removing procedures may also contribute to the loss of renal function. Therefore, only problem making kidney stones should be removed by means of minimally invasive techniques.

In case of renal failure, the excessively produced oxalate is no longer eliminated by the kidneys, and therefore the blood oxalate value and blood saturation for calcium-oxalate (CaOx) is dramatically increasing. If blood is supersaturated for CaOx, crystals are deposited not only in the renal tissue but in almost all organs, such as in the bone (marrow) as well as in the heart or on the retina (eye).

This general deposition of calcium-oxalate is called **systemic oxalosis**. If systemic oxalosis occurs, primary hyperoxaluria becomes a multi-organ-illness, which furthermore shows a high morbidity and mortality.

Therefore, a timely diagnosis and prompt installment of treatment is needed in order to prevent early renal failure and subsequently systemic oxalosis, which can even be fatal. Unfortunately, the diagnosis is frequently made only several years after the first symptoms have appeared. Moreover, the latest data from both large PH registries of the Rare Kidney Stone Consortiums in the USA as well as of the European Hyperoxaluria Consortium (OxalEurope) show that still a significant amount of patients are only diagnosed in end stage renal failure, or even only after isolated kidney transplantation has failed.

## Clincial manifestations

**Systemic oxalosis**

| bone | kidney | skin/tooth | retina |
|------|--------|------------|--------|

**heart**
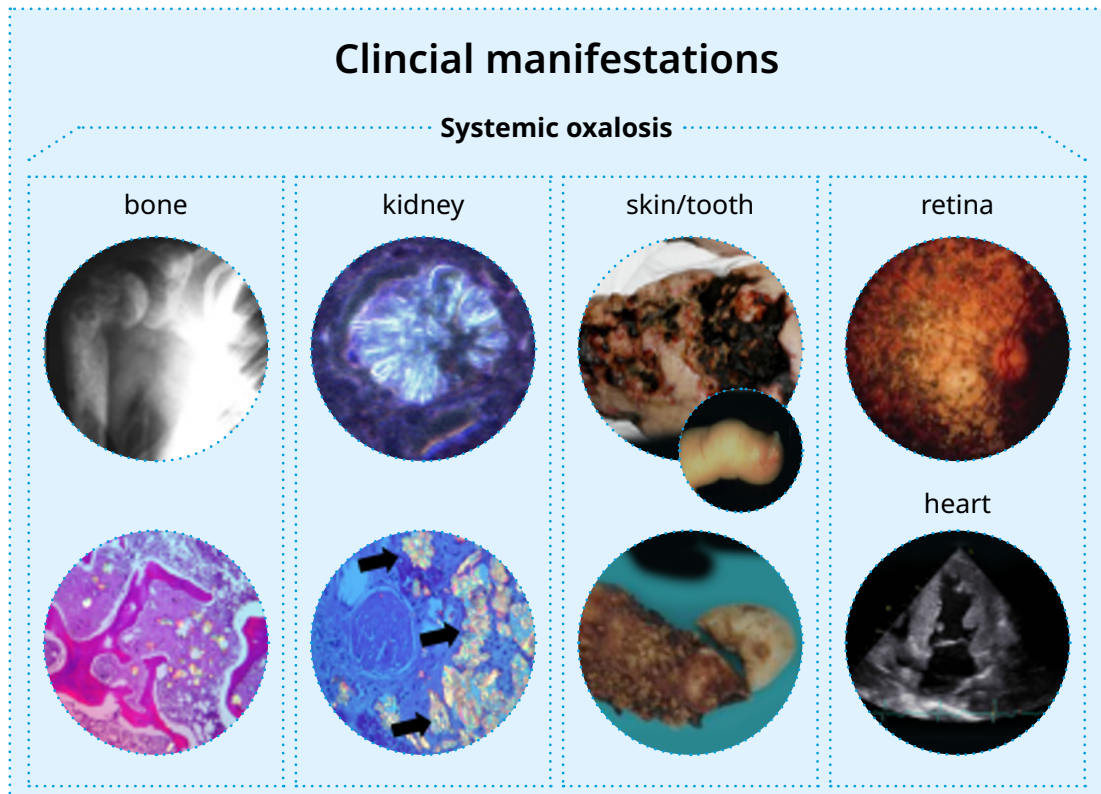
**Figure 4:** Systemic oxalosis = deposition of birefringent calcium-oxalate crystals in all body parts, such as in bone (here: shoulder joint as well as in the bone marrow biopsy), the kidney (in the renal tissue), in the skin or in the dental root, as well as on the retina and in the heart (from left top to right bottom).

Urinary oxalate excretion has to be determined already with the occurrence of a first kidney stone (in children), but also when kidney stones are suspected or if the ultrasound image or CT shows calcification of the kidneys (Figure 5), as well as in case of hematuria (= blood in urine). Oxalate must also be determined in patients with suspected recurrent urinary tract infections (UTI), treated with antibiotics, but without adequate signs of UTI, in patients with abnormal ultrasound findings, or in whom white (and/or red) blood cells are constantly found in urine. If hyperoxaluria is found, further diagnostic evaluation is absolutely necessary.
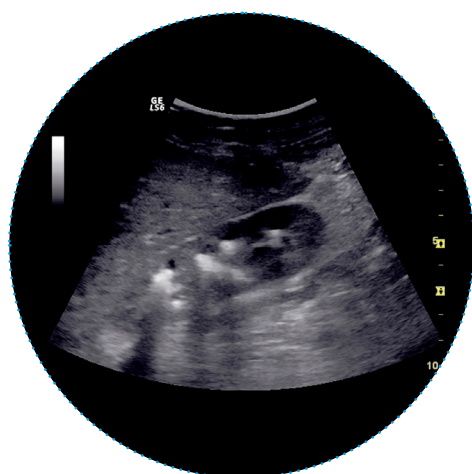
**Figure 5: a)** Ultrasound with a significant number of kidney stones,
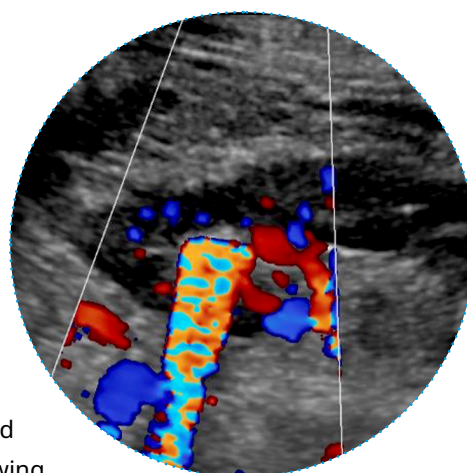


**b)** twinkling sign of a large kidney stone,
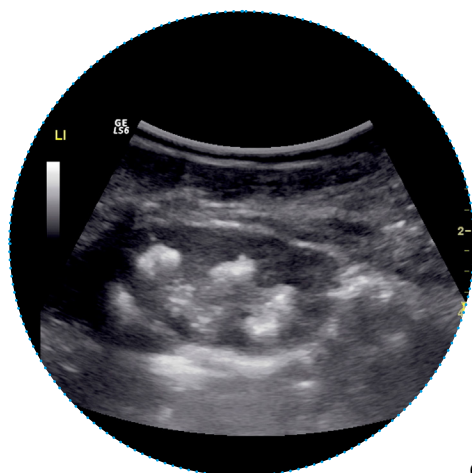


**c)** ultrasound image showing distinct nephrolithiasis and nephrocalcinosis,



**d)** computer tomograhy (CT) with staghorn stones in the renal pelvis on both sides (from a patient suffering from PH I).

PH I is quite heterogeneous, that is, the disease differs in its progress. Even siblings with the same mutations of the gene concerned (= mutations, genotype) may show a completely different progression of the disease (= phenotype). The infantile form of the disease can be particularly dramatic (= infantile oxalosis), which may already lead to early end stage renal failure. The disease is often noticed when recurring formation of kidney stones occurs or blood in urine is continuously recognized. Again: it is absolutely and extremely important to perform further evaluation in children with the first kidney stone and in adults with recurrent stones.

**A kidney stone is just the symptom of a disease,
but is not the disease itself!**

The removal of symptomatic kidney stones is rather simple, but regardless, finding the cause is eventually more important to the patient than the assurance that the next stone can easily be removed as well. The possibility nowadays to simply remove the stones may also apply to primary hyperoxaluria, but the kidney stone passages will eventually become increasingly frequent if the primary disease is not treated and thus become an agony. The kidneys will then be damaged both by the elevated excretion of oxalate in urine but also by the removal of stones. A further important mechanism of kidney damage is the permanent activation of an inflammatory reaction in the kidneys caused by the high oxalate concentration in the renal tubules and thus the absorption of oxalate into the renal tissue.

If the disease is left untreated, it may quickly lead to renal failure. This especially applies to patients suffering from PH I and less often in the other types of PH. However, we now also know, that patients with PH III develop end stage renal failure. Simply a significant loss of fluid, such as from diarrhea, may lead to an obvious deterioration of renal function. This means for example, that patients suffering from PH should receive an i.v. infusion earlier, than other patients in case of fluid loss. When traveling abroad, the patient should have an emergency card at hand, stating the diagnosis and describing the necessity of early intervention (**http://ph-europe.net/images/karte_eng.pdf**).

But even early and adequate treatment does not necessarily mean that the patient is not on risk to develop renal failure. The problem with renal failure is that no form of renal replacement therapy (= dialysis) can remove adequate quantities of oxalate from the body. Therefore, increasingly more calcium-oxalate crystals are deposited anywhere in the body and cause a multi-systemic disease called systemic oxalosis (= calcification in all possible parts of the body) (see Figure 4). Consequences up until recently: transplantation should be considered as early as possible. Above all, this should minimize the effect of systemic oxalosis. The longer the dialysis time prior to transplantation, the worse the course will be after transplantation (e.g. prompt recurrent calcium-oxalate deposition in the transplanted kidney).
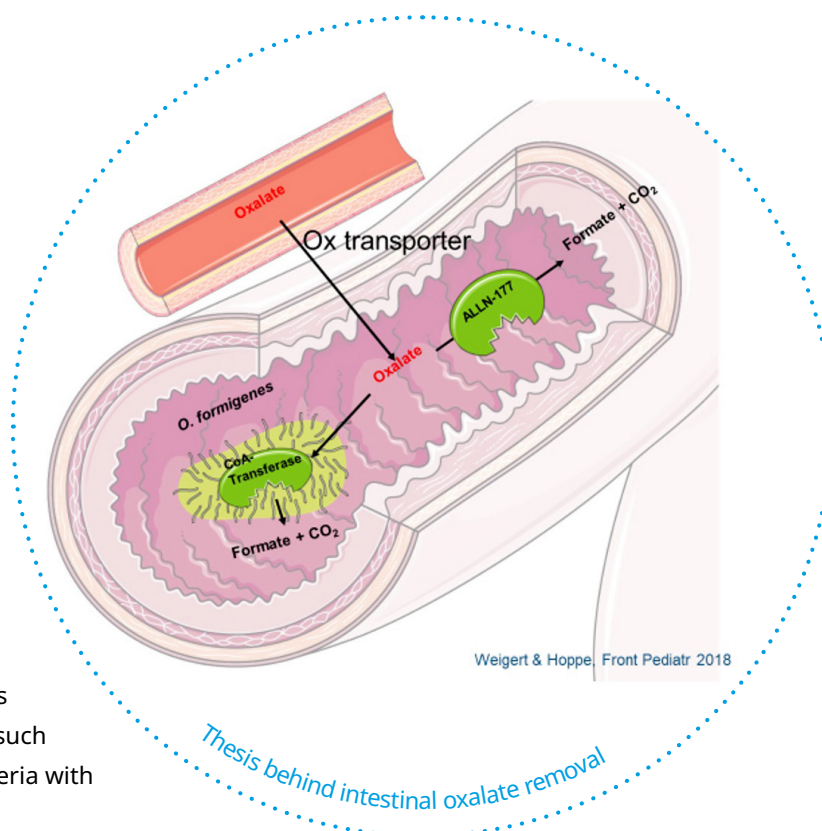
## 2.2. Secondary hyperoxaluria

Hyperoxaluria is said to be less severe in the secondary hyperoxalurias but it may also reach values > 1.0 mmol/1.73 m² body surface area/day and thus lead to recurrent formation of kidney stones or progressive calcification of the kidneys. Secondary hyperoxaluria is caused by an increased intake of oxalate by the intestine (enteric, e.g. in case of chronic inflammatory bowel diseases) or by an excessive intake of oxalate from the food (dietary).

It often occurs in chronic bowel diseases, especially in patients suffering from Crohn's disease or in patients after intestinal surgery (e.g. ileocecal resection). Here, calcium is bound to fatty acids instead of oxalate, therefore there is a greater quantity of free oxalate which is then absorbed. A regular administration of antibiotics can also lead to a lack of oxalate-degrading intestinal bacteria (e.g. Oxalobacher formigenes), and thus may cause alterations of the intestinal flora with an increased absorption of oxalate. An oxalate absorption test by way of a stable isotope ([$^{13}C_2$] oxalate) as well as a Microbiota analysis may provide further insight into the nature of secondary hyperoxaluria. However, the repeated examination of 24-h urine samples under different diets (normal diet, diet with a low and then high oxalate-rich content) is an easier procedure. This allows to distinguish well and particularly simple between primary and secondary hyperoxaluria on an outpatient basis.

For further information visit **www.EH-europe.net**

**Figure 6:** Possible intake and elimination of oxalate in the intestinal tract. The unbound food oxalate can be well absorbed by the oxalate transporters into the blood circulation. Oxalate then has to be eliminated by the kidneys. It can also be metabolized by oxalate-degrading bacteria in the intestinal tract, which can be basis for possible therapeutic options, such as the oral administration of bacteria with oxalate-degrading enzymes.

# 3

# Diagnostic Investigation

# 3. Diagnostic Investigation

To start early with an adequate therapy, diagnosis of primary hyperoxaluria as timely as possibly is of utmost necessity. The diagnostic investigation particularly includes urine and blood tests:

## 3.1. Urine and blood tests

### 3.1.1. Urine

The adequate diagnosis of a patient suffering from one of the currently known types of primary hyperoxaluria requires the analysis of the urinary excretion of oxalate as well as of glycolate in PH I, L-glyceric acid in PH II and hydroxy-oxo-glutarate (HOG), dihydroxy-glutarate (DHG), or 4-hydroxy-ketoglutamate (4OHGlu) when PH III is suspected. All this can be simultaneously determined routinely by means of ion and gas chromatography/mass spectrometry or other methods. Oxalate in urine can also be measured with an enzymatic method (oxalate oxidase, Sigma-Kit®). The urine or also plasma sample must be preserved with hydrochloric acid prior to analysis (different preservation methods per lab for blood samples).

Spot urine samples can be examined as well and is necessary in newborn or young children. However, more than one samples should be collected. In addition to the oxalate (and the other parameters of the glyoxylate metabolism), urine creatinine is determined and molar oxalate/creatinine ratios are then calculated and compared to normal values according to age (see table 2). Premature infants but also infants born at term might have the highest normal values (the ratios are even higher in formula than in breastfeeding), this has to be considered in interpretation of results.

The analysis of at least two to three 24-h urine collections for PH related metabolites but also for other stone-forming and stone-preventing substances (under different diets, normal food, food with low oxalate content and oxalate-rich food) should follow subsequently. This is necessary in order to have a good baseline parameter, as oxalate excretion may fluctuate also in the PH patient. With more baseline values a better follow up of oxalate excretion under therapy is possible. Also other treatment options (low citrate excretion ➤ citrate medication) can be considered. If the oxalate and glycolate excretion is significantly higher than 0.5 mmol/24 h normalized to 1.73 $m^2$ body surface (> 45 mg/24 h), there will usually be no doubt that PH I is the diagnosis, especially with a typical clinical course. The same applies to PH II and PH III if their specific metabolite profiles apart from the elevated oxalate excretion are found.

In approximately 25-30% of patients suffering from PH I, no elevated excretion of glycolate is found. We would therefore also additionally recommend to determine blood oxalate and glycolate in the blood (plasma).

**Table 2:** Normal values for urine or plasma values. The urine parameters are expressed as excretion per 1.73 $m^2$/24 h or molar creatinine ratios. Plasma values express the free oxalate or glycolate levels, total (free and protein bound) values are same for low levels, but increase more rapidly in renal failure. Normal values for DHG, 4-hydroxy-ketoglutamate and glyoxylate values are currently evaluated.

| **Plasma** | | |
|---|---|---|
| Oxalate in plasma | All age groups | < 6.3 ± 1.1 µmol/l (free oxalate) |
| Glycolate in plasma | All age groups | < 7.9 ± 2.4 µmol/l (assumed) |
| **24-h urine collection** | | |
| Oxalate in 24-h urine | All age groups | < 0.50 mmol/1.73 $m^2$/24h < 45 mg/1.73 $m^2$/24h |
| Glycolate in 24-h urine | All age groups | < 0.50 mmol/1.73 $m^2$/24h < 45 mg/1.73 $m^2$/24h |
| L-Glyceric acid in 24-h urine | All age groups | < 5 µmol/l |
| Hydroxy-oxo-glutarate in 24-h urine | All age groups | < 10 µmol//1.73 $m^2$/24h |
| **Controls/healthy persons:** | | |
| Oxalate/creatinine | 0–6 months 7–24 months 2–5 years 5–14 years > 14 years | < 325–360 mmol/mol < 132–174 mmol/mol < 98–101 mmol/mol < 70–82 mmol/mol < 40 mmol/mol |
| Glycolate/creatinine | 0–6 months 7–24 months 2–5 years 5–14 years > 14 years | < 363–425 mmol/mol < 245–293 mmol/mol < 191–229 mmol/mol < 166–186 mmol/mol < 99–125 mmol/mol |
| L-Glycerate/creatinine | 0–6 months 7–24 months 2–5 years 5–14 years > 14 years | < 14–205 mmol/mol < 14–205 mmol/mol < 14–205 mmol/mol < 23–138 mmol/mol < 138 mmol/mol |
| HOG/creatinine | All age groups | < 2.5 µmol/mmol |

## 3.1.2. Plasma (blood)

Analysis of oxalate, glycolate, glyceric acid and HOG/DHG in blood (plasma) should always be performed for follow up, but especially in case of impaired renal function. In this instance, the sample preparation and preservation is very important, since new oxalate will be quickly generated, such as via degradation of vitamin C, if the sample is incorrectly prepared. This results in incorrectly high values. Hence, the blood sample taken must be cooled directly and then acidified, just like the urine sample, however, in a more complex procedure (different routine in different labs).

Plasma oxalate can be measured by means of ion chromatography, gas chromatography. The plasma glycolate, glyceric acid and HOG (+ DHG and 4OHGlu) are principally determined by means of mass spectrometry. The normal values for plasma oxalate are between 1-6 µmol/l depending on the reference and laboratory method. In PH I, plasma oxalate values of > 10-20 µmol/l are measured in still good renal function. However, these values are already quickly increasing in the early stages of chronic renal failure and soon reach a level which leads to an oversaturation of the blood for calcium oxalate (see below). Patients in the final stage of renal failure show plasma oxalate values of > 60-110 µmol/l (free oxalate), which gives evidence on how long and how often a renal replacement therapy (= dialysis) has to be performed. The total (free + protein bound oxalate) plasma oxalate values are mostly higher by 30%.

The analysis of the other metabolites maybe interesting for diagnosis, but not all of them are easily determined. In our experience, glycolate is nicely measurable, however L-glyceric acid and also HOG, DHG or 4OHGlu are rarely findable. The glycolate concentration in blood gains further interest currently because of a new treatment option (see RNAi treatment).

In a patient suffering from renal failure requiring dialysis, the diagnosis of PH by means of urine analysis or by means of measuring plasma oxalate is not always safe. In all patients suffering from end stage renal failure (with or without PH), the plasma oxalate value is elevated. If the excretion of oxalate via the kidneys is significantly decreased in chronic but yet still compensated impairment of renal function, the urine examination is no longer a valid parameter. That means that increasingly less oxalate is filtered by the kidneys, and the plasma oxalate value is hence increasing. In patients suffering from PH, the plasma oxalate value is rapidly elevated, but here plasma glycolate must be determined as well and will show the proof of PH I.

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**Figure 7:** **Brief diagnostic algorithm in the hyperoxalurias**

| Urine/plasma: oxalate (primary) | Urine/plasma: oxalate (secondary) |
|---|---|
| • Glycolate | • $^{13}C_2$ oxalate absorption test |
| • L-glyceric acid | • 3 x 24-h urine with different diet |
| • HOG/DHG/4OHGlu |   (normal, low and high oxalate diet) |

### 3.1.3. Calcium oxalate saturation in urine and blood

The saturation for calcium oxalate (βCaOx) in urine and blood, can be calculated with computed programs and was reported as a further follow up parameter in patients with normal but also impaired renal function. It is calculated in absolute values and is elevated above 1 relative unit in blood, or age- and sex-specific values in urine. Of course, the urine must be supersaturated with regard to calcium-oxalate, however, there is one specific problem for computed methods: urine calcium excretion tends to be lowish, at least in PHI patients, as a lot of calcium is bound to oxalate already. This impacts the calculation in PH patients and provides rather lowish values, as compared to patients with idiopathic stone diseases and hyperoxaluria.

Calculation of ßCaOx in blood, however, is much more reliable and is correlated also to elevated Pox levels. Even in early stages of renal failure, the saturation for calcium-oxalate in blood can be elevated in patients suffering from PH. This specifically means that calcium oxalate crystals can be deposited anywhere in the body already early in the course of the disease, which leads to systemic oxalosis. This of course must be avoided by any means and shows once more that a timely diagnosis and initiation of therapy are of great importance. The problems of systemic deposition becomes obvious in end stage renal failure. In this case, for example, oxalate is deposited extensively in bone, or in the heart muscle, or on the retina in infants and young children.

A non-invasive imaging should be used to timely recognize systemic oxalate deposition. Special echocardiography examinations (= speckle echocardiography, the flexibility of the heart muscle is examined on different levels) as well as radiological measures, such as magnetic resonance imaging of the bone (MR), are used for this purpose. This allows to recognize early changes both in heart and in muscles as the most problematic "organs". All other imaging, e.g. X-ray or CT is using radiation or only is depicting pathologic changes late. Surprisingly, there is no true CaOx deposition in the liver, at which the huge amount of oxalate is produced. However, the liver are showing much more fibrosis or cirrhosis in the long term follow up, which needs more attention!

## 3.2. Liver biopsy

The diagnostic confirmation by means of liver biopsy was used before genetic testing became available. Now, only the latter is used and even the methods to determine liver specific AGT for example are no longer available in screening labs.

## 3.3. Genetic diagnosis

A clinical and biochemical-based diagnosis of PH I–III always requires confirmation by a definite test, which today is preferentially done by targeted or stepwise mutational analysis of the three causative genes: *AGXT*, *GRHPR*, and *HOGA1*. Genetic testing could

be considered the current gold standard for diagnosis since it provides fast and reliable distinction of the precise PH type. Exact genotype information has already become important as some mutations in the *AGXT* takes gene are more likely to respond to a specific medication (e.g. vitamin B6 treatment) and correlate with better long-term renal survival. Moreover, genotype data will become even more important with the personalized medicine approaches in the future. This is especially true, as now a new, but very expensive treatment option (currently only for PH I) is available (see treatment).

## 3.4.    Prenatal/prompt postnatal diagnosis

A prenatal (= before birth) diagnosis, when an index case is known within a family and with a serious infantile oxalosis can be important. The determination of oxalate in the amniotic fluid, however, is no adequate parameter for prenatal diagnosis. It is possible to measure also all metabolites of the glyoxylate metabolism, which are also important in urine for diagnosis, but the maternal metabolism is "cleaning" the blood of the fetus and thus wrongly low oxalate values in the amniotic fluid are measured. Also a liver biopsy of the fetus is of course regarded as an obsolete maneuver and hence, not undertaken.

A timely diagnosis is possible through a DNA analysis after chorionic villus sampling (extraction of membrane cavity cells), especially when known family members have previously been described. After a prenatal diagnosis, the genetic counselling of the parents based thereon must absolutely consider the heterogeneity of the disease progression. Even in identical mutations of the *AGXT* gene in siblings, completely different clinical follow ups may occur. One patient can present with infantile oxalosis, the other without only some stone up until late adulthood.

The genetic counselling of numerous families may be rather difficult based on these findings since a precise prediction of the progression of the disease is certainly not possible. Therefore, the question arises whether a prenatal examination still makes sense, if no secure statement is possible on the progression of the disease after birth. Moreover, it should be noted that the disease is now significantly better treatable (see below).

Prompt postnatal screening might therefore be a good idea, but not only in a family with index cases, it should be done in all newborns within their routine screening procedure, so that rapid treatment can be installed, like for all the other diseases included. This can prevent infantile oxalosis and should therefore be worth the effort!

In a case of PH within a family all other family members have to be examined, too. This does not only apply to the siblings, but also to the parents and grandparents. Sometimes surprising results are obtained, e.g. vertical (pseudo-dominant) inheritance with the parent generation also affected. The principle applies to all persons concerned, the earlier the diagnosis has been made, the better is the chance to prevent a deleterious deterioration of the disease.
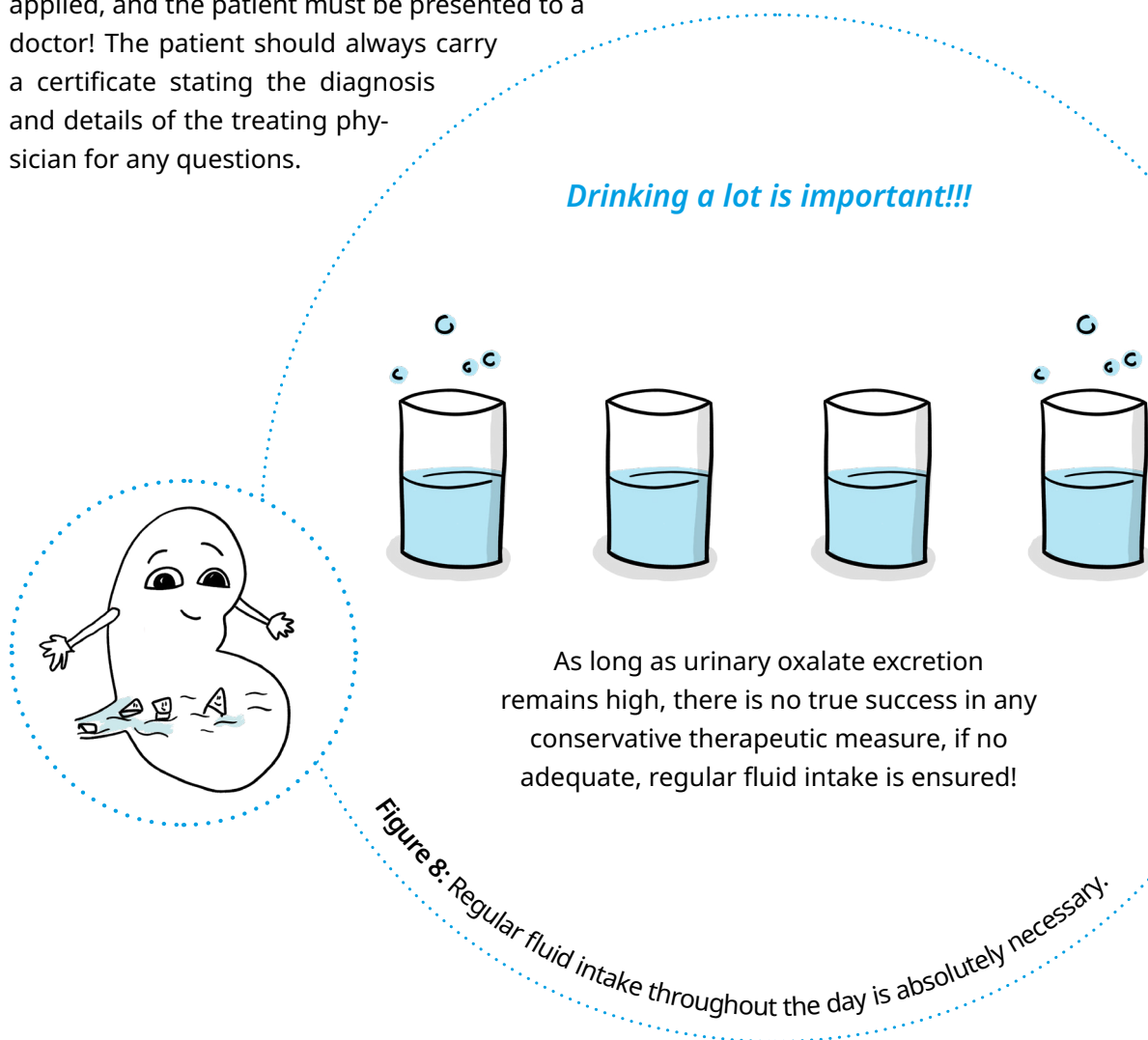
# 4

# Treatment

# 4. Treatment

## 4.1. Metaphylaxis

### 4.1.1. General

A daily fluid intake of > 2-3 L/m$^2$ body surface area per day is a first important parameter to improve the solubility of calcium oxalate by increasing the urine volume. Patients must be recalled frequently to adhere even to such a simple, but effective measure, since the majority was not used to drink such a quantity of liquid throughout the day.

In infants and children, a permanent gastric tube (PEG) might be considered in order to provide a sufficient quantity of liquid at night. In case of high fever, severe diarrhea or of fluid loss due to any other reason, a permanent intravenous drip must promptly be applied, and the patient must be presented to a doctor! The patient should always carry a certificate stating the diagnosis and details of the treating physician for any questions.

*Drinking a lot is important!!!*

As long as urinary oxalate excretion remains high, there is no true success in any conservative therapeutic measure, if no adequate, regular fluid intake is ensured!

Figure 8: Regular fluid intake throughout the day is absolutely necessary.

**Table 3:** Oxalate content in some exemplary food items. No particular dietary rules must be observed, just food products with a very high content of oxalic acid, such as spinach or rhubarb, should be avoided (Table 3). In patients suffering from primary hyperoxaluria, the absorption of oxalate from food products is lower than in healthy persons. This means that the proportion of oxalate from food sources is lower in urine. If a very rigid diet is recommended to the PH patient, compliance to the really important treatments will no longer be the best. We therefore go without a detailed dietary advice, and only point to a few food products with a problematic content of oxalate.

| Food | Oxalate content mg/100 g | | Oxalate content mg/100 g |
|---|---|---|---|
| **Fruits** | | **Breads** | |
| Bananas | 0.7 | Rye bread | 0.9 |
| Apples | 1.5 | White bread | 4.9–8.6 |
| Oranges | 6.2 | **Sweets** | |
| Strawberries | 15.8 | Marmalade (jam) | 4.5–10.8 |
| Gooseberries | 19.3 | Cocoa powder | 623 |
| **Vegetables** | | **Beverage** | |
| Asparagus (boiled) | 1.7 | Coffee | 1.0 |
| Sweet potatoes | 280–570 | Coffee powder | 57–230 |
| Beans (fresh) | 43.7 | Beer | 1.7 |
| Beetroot (boiled) | 96.8–121 | Wine | 3.1 |
| Spinach (boiled) | 356–780 | Tea (2 min.) | 7.0–10.8 |
| Rhubarb | 537 | Tealeaves | 375–1450 |

The regular intake of large quantities of vitamin C as one of the important precursors of oxalate must be avoided. Numerous cases of secondary hyperoxaluria are described, which have even led to maximum deposits of CaOx in the skin and in other tissues. In case of cystinuria, another congenital stone disease, vitamin C is, for whatever reason, therapeutically administered. In many cases, hyperoxaluria is induced with high quantities of vitamin C, which may absolutely be problematic.

The drug therapy of primary hyperoxaluria is based on several cornerstones, which are used depending on the treating center.

### 4.1.2. Pyridoxine = vitamin B6

Alanine:Glyxolate Aminotransferase (AGT), the defective enzyme in PH I, requires vitamin B6 as co-enzyme. In some patients, the daily administration of vitamin B6 (above all in patients where the AGT is in the wrong component of the liver cell) leads to a reduction, sometimes even to a complete normalization of the excretion of oxalate. Since even a tiny reduction of oxalate excretion represents a significant improvement, a therapeutic attempt in each patient with gradually increased B6 dosages from 5-20 mg/kg of body weight per day should be started. In some patients, even just a small amount (20 mg) suffices to reach an effect on the oxalate production and thus excretion, while in others, a maximum dosage is necessary. A therapeutic attempt includes an initial dose of 5 mg/kg body weight/day in two individual doses, followed by a urine analysis approximately 3-4 weeks after initiating the medication. This enables to prove an eventual therapeutic success, while the dosage can be adapted in steps of 5 mg/kg body weight/day if the decrease in oxalate excretion is not satisfactory. If no decrease of oxalate excretion has even been reached after reaching the final dosage, treatment is terminated in order to improve the patient's compliance with further treatment measures. Known side effects of the high-dose B6 therapy are paresthesia (= prickling) in hands and feet, and a distinct touch sensitivity. An increased restlessness in children was reported as well. Serum vitamin B6 levels, which should be clearly above the normal range, can be determined for therapeutic control!

Nowadays, the patients mutation is determining on whether or not a treatment with B6 is started. If it is really working, it is the cheapest and easiest medication to normalize or near normalize urinary and plasma oxalate levels. Even in patients with chronic or end stage renal disease treatment should be started in specific genotypes, e.g. when AGT is not in the right organelle of the liver cell. Patients can then, if sensitive, either ameliorate their kidney function (in CKD) or be transplanted by isolated kidney transplantation.

### 4.1.3. Alkaline citrate medication

The goal of the therapy with alkali citrates is to reduce the urinary calcium-oxalate saturation. Citrate forms soluble complexes with calcium, thus less calcium is available for binding to oxalate and urine shows a lower saturation for CaOx. In the liver, citrate is converted to bicarbonate and thus leads to an alkaline metabolic state (higher pH value in blood and urine), while more citrate is secreted with urine (not needed to keep blood pH in a good range).

In a pilot study and a long-term study in patients suffering from primary hyperoxaluria under alkali citrate therapy, this medication enabled stabilization of renal function, a reduction of the rate of kidney stone passage and/or a lesser degree of renal calcification. The dosage of alkali citrate is 0.1-0.15 g/kg body weight per day (0.3-0.5 mmol/kg) of a sodium and/or potassium citrate-containing preparation. In the majority of patients, who have well cooperated over an observation period of several years, above all the re-

nal function remained stable or even improved. The best control parameters for the less compliant patients eventually are the clinic (sharp increase in kidney stone passages), a reduced urinary citrate excretion, or an acidic pH value of the urine.
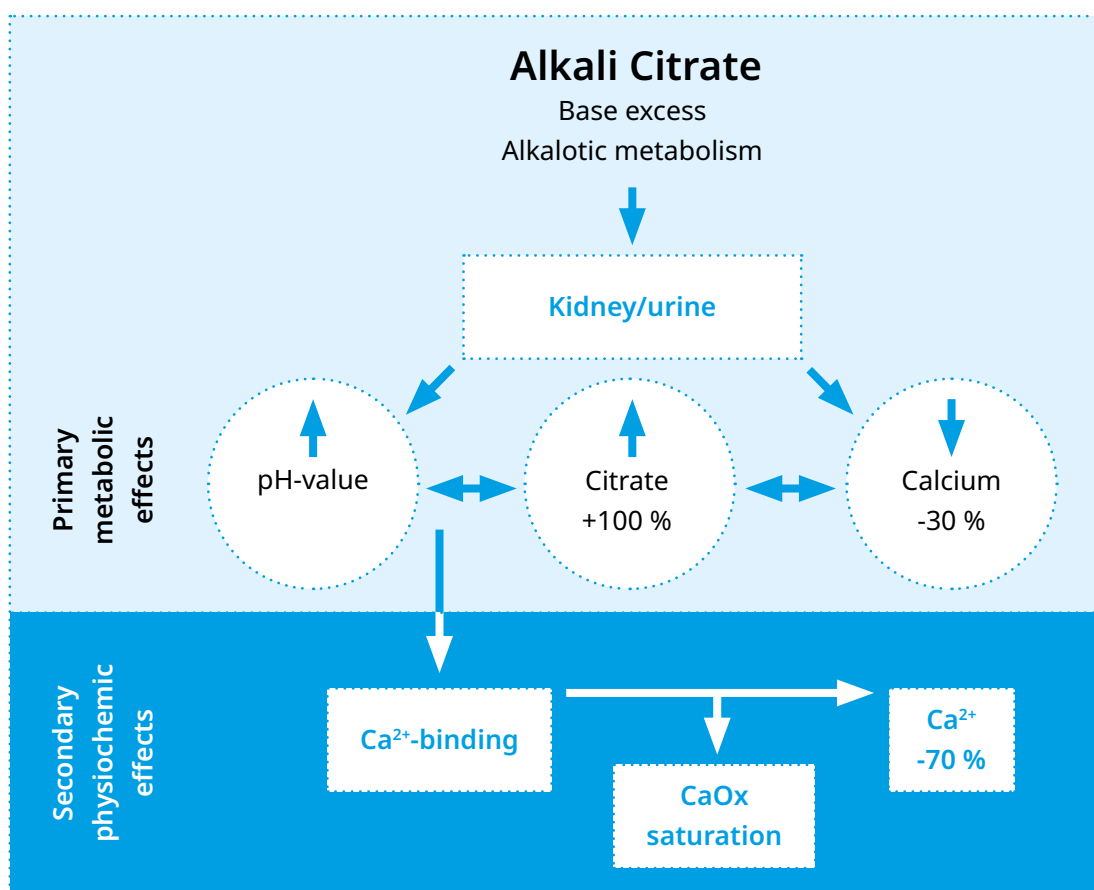


**Figure 9:** Way of action of treatment with alkaline citrate.

## 4.1.4. Other inhibitors of calcium oxalate crystallization

In its effectiveness, orthophosphate is also comparable to alkali citrate. Also, the administration of magnesium is recommended. Both substances lead to a good inhibition of calcium-oxalate crystallization. For example, in patients suffering from recurring kidney stone passages, a favorable effect of magnesium on urine saturation of CaOx has been noted.

## 4.1.5. New and future therapies

A new therapeutic approach is RNA interference (RNAi) therapeutics. This approach works at the level of messenger RNA (mRNA) translation. Synthetic small double-stranded RNA molecules (small interfering RNA, siRNA) bind to a cytoplasmic protein complex (RNA-induced silencing complex, RISC), which high-specifically degrades the targeted mRNA and thus prevents translation into the corresponding protein. This renders placing false information at the site that normally produces an enzymatic protein involved

in oxalate metabolism (in the liver). If this is not produced, oxalate production in the liver can be significantly reduced or even completely blocked.
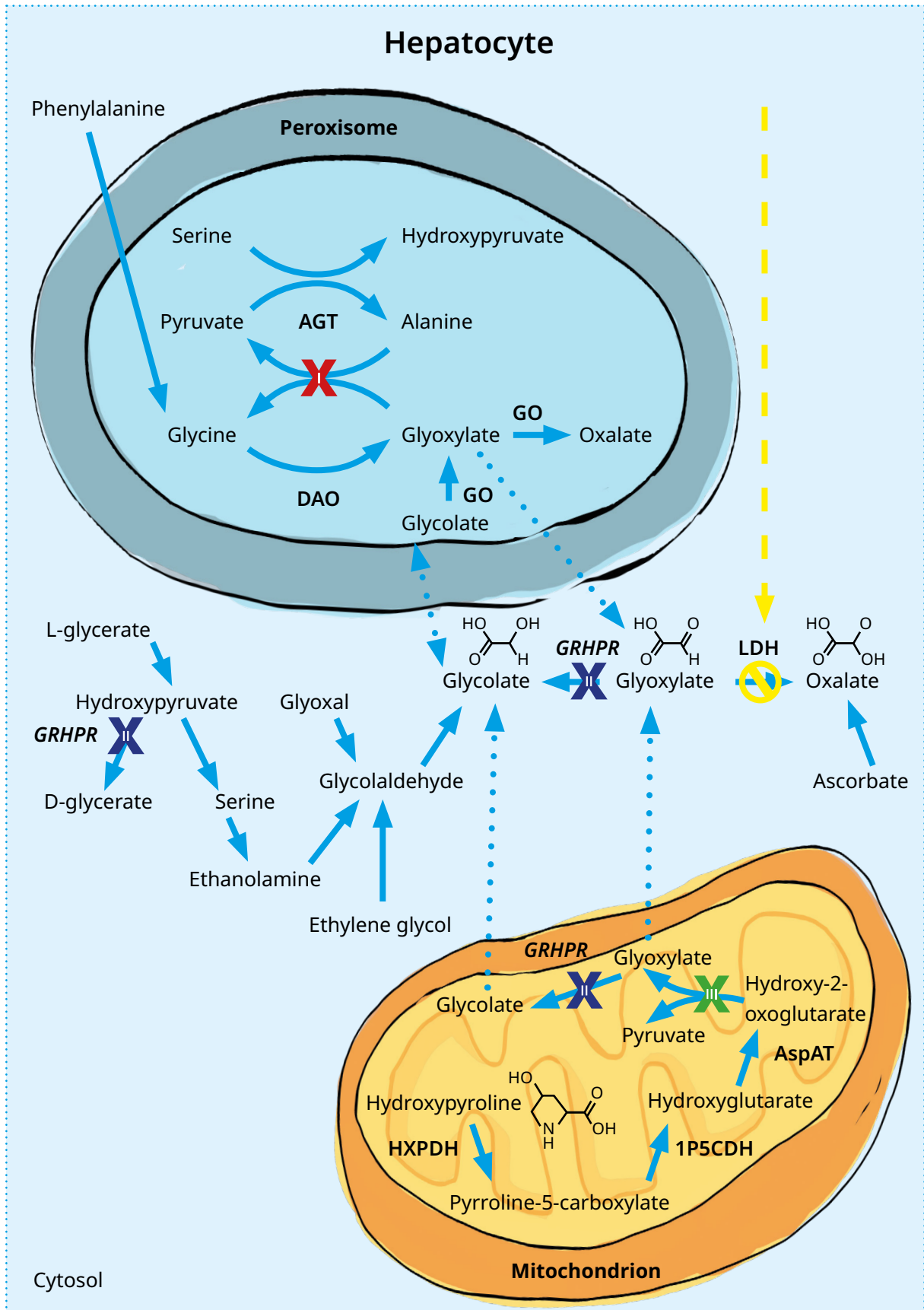
**In other words**, the RNAi medication temporarily blocks a specific enzyme of the glyoxylate/oxalate metabolism, which reduces endogenous oxalate production and thus either oxalate excretion in urine (in stable kidney function), or plasma (blood) oxalate in patients on dialysis. A first RNAi drug, Oxlumo® (Lumasiran, Alnylam Pharmaceuticals, USA), has now been approved and can be prescribed since January 2021 in some European countries (Austria, France, Germany, Switzerland, Spain, Luxembourg, Poland and Bulgaria, as well as in Russia, Israel, Qatar and the USA).

Oxlumo® targets the mRNA of glycolate oxidase (GO) and thus prevents its translation in patients with PH I. This reduces the production of glyoxylate (i.e. the precursor to oxalate) and thus also the oxalate production. Subcutaneous administration of Oxlumo® in healthy volunteers, was able to block about 80 % of the corresponding mRNA without relevant side effects. In PH I patients, urinary oxalate excretion was reduced by an average of 68 %. Due to the therapeutical mechanism, patients showed an increase in urinary glycolate excretion or blood glycolate concentration, however, it is currently considered a harmless substance for the body. At present, in countries where Oxlumo® has not yet received final approval by medical agencies, treatment can be requested from Alnylam.
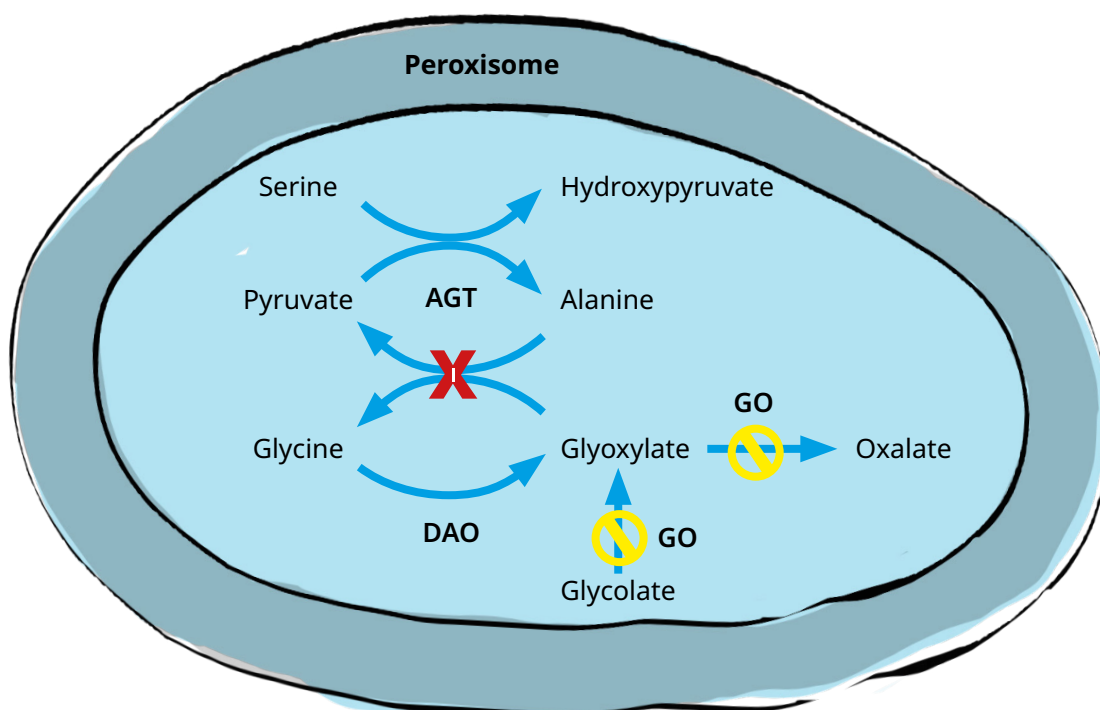


Another RNAi medication, Nedosiran® (Dicerna Pharmaceuticals, USA, a subsidiary of NovoNordisk) interferes with the final step towards oxalate production, the translation of liver-specific lactate dehydrogenase A (LDHA), preventing the conversion of glyoxylate to oxalate in all three types of PH.

# Hepatocyte

**Peroxisome**

Phenylalanine

Serine → Hydroxypyruvate

Pyruvate **AGT** Alanine

Glycine → Glyoxylate **GO** → Oxalate

**DAO**

**GO** ← Glycolate

L-glycerate

Hydroxypyruvate

**GRHPR**

D-glycerate ← Serine

Glyoxal

Glycolaldehyde

Ethanolamine

Ethylene glycol

Glycolate **GRHPR** Glyoxylate **LDH** Oxalate

Ascorbate

**Mitochondrion**

**GRHPR** Glyoxylate ← Hydroxy-2-oxoglutarate

Glycolate Pyruvate

**AspAT**

Hydroxypyroline Hydroxyglutarate

**HXPDH** **1P5CDH**

Pyrroline-5-carboxylate

Cytosol

Also this medication (Rivfloza®) is now approved for treatment of PH I. In the pivotal study, a significant decrease in urinary oxalate excretion, comparable to that of Oxlumo®, was found in PH I patients, however, there was no clear result in patients with PH II. Reason for that needs to be evaluated further. Results for a pilot study in PH III patients are showing a decline of urinary oxalate excretion, but this is currently evaluated in a more profound study setting.

Of course, it is reasonable to discuss on whether every PH I patient should be treated with RNAi medication. There is fundamental evidence, that the completely responsive vitamin B6 treated PH I patient has no need of further treatment, at least those with stable kidney function. For those patients, being only partly responsive or without change in urinary oxalate excretion, personalized evaluation is necessary. In patients with chronic kidney failure and in those being on dialysis vitamin B6 sensitivity can also be defined (lower blood oxalate and glycolate levels), so there may also be no need for RNAi medication in responsive patients. In all others, however, treatment with RNAi should be started asap.

But, especially in patients on dialysis we need to be careful in data interpretation. Plasma (blood) oxalate may not be the best treatment response surrogate, as it may remain high, based on the dissolution of the systemically deposited oxalate. Therefore, imaging procedures should also be performed to evaluate the amelioration of the situation and to finally decide on whether liver transplantation can be avoided, because RNAi (or vitamin B6) works adequately. However, in any case, please contact your primary physician to discuss possibility of treatment in your own case, or that of your child.

The chronic inflammation of the kidney caused by CaOx crystals is also the object of current research. It was recently found that the „Inflammasone" is an important component in the inflammation process. This is a protein complex within the cytosol of the macrophages, which is secreted after activation and then triggers the enzyme caspase-1. This later activates the cytokine IL-1ß and IL-18. This attracts more macrophages and lymphocytes, which support the inflammation process, and which leads to the formation of granulomas and eventually to renal fibrosis. Translated, this means that oxalate crystals being absorbed into the renal tissue, are starting an inflammation process, which then later leads to chronic injury and thus to scarring of the kidneys. CRID-3, a substance suppressing this inflammatory reaction, significantly retarded the progression in mice developing such a scarring of the kidneys due to an oxalate-rich feed.

Before the CaOx crystals can enter the renal tissue, they are bound on the surface of the small renal tubuli. The TNF (tumor necrosis factor) receptor seems to be contributing to this, since the animals do not develop any CaOx deposit without this receptor (double knock out animals examinations have shown that). In the mouse model, the TNF receptor blocker R-7050 delayed the progression of nephrocalcinosis (calcification of the kidneys) and thus also the scarring of the kidneys.

As a curative approach gene therapy or also the new CRIPS/Cas Method are currently evaluated. In gene therapy SVac vectors (vector = transport vehicle), a recombinant vector of macaques polyoma virus SV40, transports healthy information of the gene affected to the liver. This is safe for humans, since the virus cannot multiply itself and causes no immune response. In the animal model, it was shown that intravenously applied SVac led to an expression of the desired gene in the liver. Since the genes affected by PH are more or less liver-specific, this could indeed be a curative approach for the patients. In the CRISPR/Cas Method, a defect information is replaced by a healthy one (Figure 10, modified from Weigert et al, Expert Opinion in Emerging Drugs, Volume 23, Issue 4, 2018). There are many more developments currently adding some more interesting ideas, or even already phase 1 studies. Small molecule treatments, orally, for example, or pluripotent stem cell approaches, may here be mentioned. Maybe at the next edition of this brochure we will add some more information.

However, all intestinal medications, being it oxalate degrading bacteria, or oxalate degrading enzyme preparation so far failed to proof their effectiveness in PH. They may, however, be a possible add on medication next to RNAi (or after transplantation) in those patients with severe systemic oxalosis.
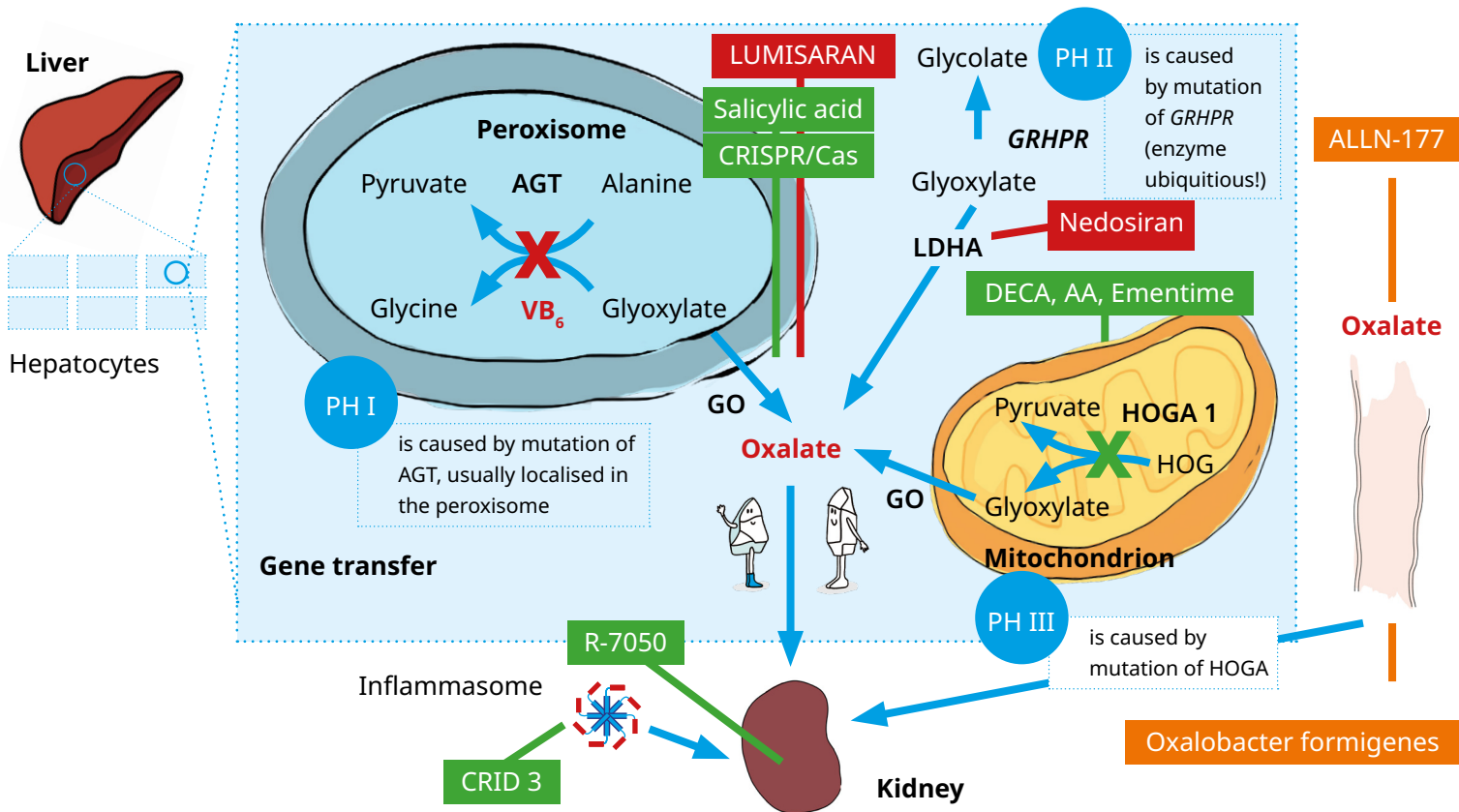


Figure 10: Overview of the underlying pathomechanismns of PH I-III and schematic representation of possible new therapeutics for the primary hyperoxalurias. PH I results from a mutation of the *AGXT* gene (encoding for alanine:glyoxylate aminotransferase, PH II from a mutation in the *GRHPR* gene (for glyoxylate reductase/hydroxypyruvate reductase), and PH III from a mutation in the

*HOGA1* gene (4-hydroxy-2-oxoglutarate aldolase 1). Every subtype leads to an accumulation of oxalate, which has to be eliminated by the kidney. The possible treatment alternatives (red: established therapy, here vitamin $B_6$ and RNAi), orange: treatment in clinical study, green: future treatment option): 1) lumisaran (Oxlumo) a RNAi medication, suppresses glycolate oxidase (GO), less oxalate is being produced, 2) Nedosiran, a further RNAi medication, blocks liver-specific lactate dehydrogenase A (LDHA), which also leads to a reduced oxalate production, 3) ALLN-177 is a recombinant microbial enzymatic oxalate decarboxylase, which degrades oxalate in the intestines, 4) O. formigenes is an anaerobic bacterium, which uses oxalate as it source of energy; it degrades oxalate in the intestine and activates an intestinal oxalate transporter, which leads to an active secretion of bloodoxalate into the intestinal lumen, 5) CRID-3 inhibits the pathway of NLRP3-inflammasome, which prevents the development of renal fibrosis, 6) R-7050, a TNF receptor blocker, prevents the adhesion of calcium oxalate crystals in the proximal tubule, 7) DECA, amino oxy acetic acid and Emetine prevent the entering of AGT into mitochondria, 8) molecules derived from salicylic acid, which also inhibit the GO enzyme, 9) CRISPR/Cas-reducing glyoxylate production by GO gene editing, 10) AVV vectors, SVac vectors by functional gene expression into the liver.

## 4.2.  Treatment of kidney stone passage

The recurrent passage of urinary stones represents a major problem of primary hyperoxaluria. A stone blocking the urinary tract, e.g. a stone in the ureter, makes a surgical procedure necessary, which should be as minimal as possible. However, a stone removal by surgery should only be considered for obstructive stones or in case of a massive stone burden in the kidney(s) and frequent painful kidney stone passage as well as in case of a secondary infected stones. Kidney stones, which are not blocking or asymptomatic, can be left in situ.
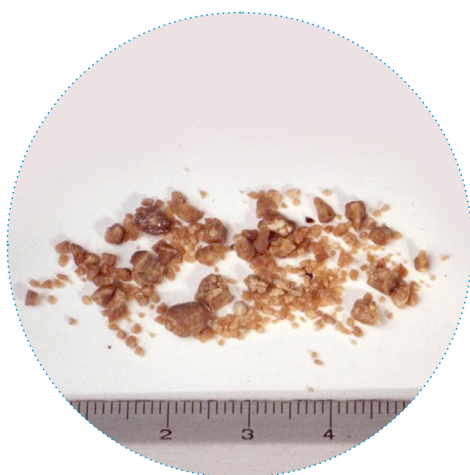


**Figure 11:** Stone granules after crushing by shock waves of a staghorn calculus in the left renal pelvis in a 9-year-old girl suffering from primary hyperoxaluria Type I (loss of renal function after ESWL).

**Figure 12:** Computer tomography of a staghorn calculus in the left renal pelvis in a 16-year-old patient suffering from PH I. The staghorn calculus had developed within a very short time due to mal compliance regarding medication. The staghorn stone was surgically removed.
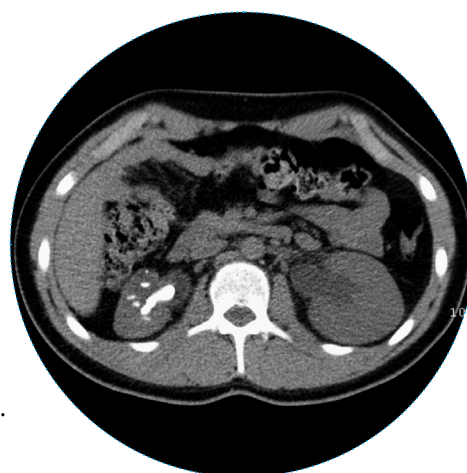
## Acute therapy

In an acute situation, adequate analgesia is required until and even after the diagnosis is confirmed by imaging. In case of persistent symptoms („status colicus"), the insertion of a ureteral splint or percutaneous nephrostomy (catheter placed in the kidney from outside) for decompression or primary stone removal – if technically reasonable and possible – is necessary. In cases of high-grade obstruction with consecutive urinary retention in the kidney and/or increasing retention values (postrenal failure), very prompt urinary drainage is indicated. In case of infection and urinary stasis and/or sepsis (fever, leukocytosis, CRP increase), emergency urinary drainage is required [6]. Secondary – after treatment of the infection/sepsis – stone removal is performed.

## Stone therapy

Active stone removal is indicated for symptomatic stones, staghorn stones, stones that are clearly increasing in size, and infectious stones. This should be performed in centers with equipment suitable also for children and appropriate expertise (extracorporeal shock wave lithotripsy = ESWL, percutaneous nephrololithotomy = PCNL, mini-PCNL, ureterorenoscopy = URS, retrograde intrarenal „surgery" = RIRS and open stone removal).

## Spontaneous stone clearance/Medical Expulsion Therapy (MET)

The majority of smaller stones (<5-7mm) pass spontaneously. After acute therapy for colic, Medical Expulsion Therapy (MET) can also be used successfully in children and adolescents, for example with tamsulosin.

## Interventional stone therapy

The choice of the therapeutic procedure must take into account the stone size and shape, the number and localization of the stone mass, and the anatomy of (the child's) urinary tract. In principle, all current procedures for invasive stone treatment can be used. ESWL here is not the best procedure in the PHs, although the overall higher success rate in children may justify an attempt at therapy. This better success rate is partly due to the increased transport capacity of the child's ureter for stone fragments. Larger stones up to staghorn stones can be treated successfully in this way. However, even in children and adolescents, stone clearance rates decrease with increasing stone size. The need for general anesthesia depends, among other things, on age, stone localization, and also the lithotripter used.

In PH, however, patients with nephrocalcinosis sessions appear to be at increased risk of impaired renal function. Therefore, ESWL maybe used as preparative procedure, e.g. to crack a stone, which was not passable by a ureteroscope, but otherwise should be avoided.

The availability of miniaturized instruments (mini-PCNL, ultra-mini-PCNL or micro-PCNL) has led to a significant increase in the use of endoscopic techniques in children and ado-

lescents. Not only PCNL but also URS has been shown to be relatively safe and effective in children. In addition to semirigid URS devices, flexible uretero-renoscopes for endoscopic stone repair and RIRS are increasingly used with good success rates at acceptable complication rates in specialized centers.

Today, an indication for an open surgical procedure is rarely given, e.g., when the correction of an anatomic anomaly underlying the stone formation is performed simultaneously, especially in very young children with complex anomalies. An open procedure may also be necessary in cases of orthopedic limitation of positioning due to pronounced malformations.

## 4.3. Dialysis

No form of renal replacement therapy is able to remove a sufficient amount of oxalate. This means, the blood oxalate value rises, which induces an increased blood saturation for calcium oxalate and rather quickly an oversaturation of blood with corresponding CaOx crystal deposits in all tissues. Both in adults and children, the removal (clearance) of oxalic acid is better with hemodialysis (HD) as compared to peritoneal dialysis (PD), with ~ 115 ml/min. x 1.73m2 body surface through HD as to just ~5-8 ml/min. for PD. In adults, the clearance values for peritoneal dialysis are lower by 50% than in children (4.0 +/- 0.5 ml/Min.). The better clearance in children is explained by the larger peritoneal surface in comparison to body surface area.

The weekly rate of elimination of oxalic acid is equal in both dialysis methods (standard therapy 3 x 5 h hemodialysis and ambulatory peritoneal dialysis with 2.3% glucose solution, filling quantity of 40 ml/kgKG and 4 bag changes daily). About 6-9 mmol oxalate are eliminated weekly in patients suffering from PH I. Thus the weekly rate of elimination of both renal replacement therapies is clearly below the endogenous production of oxalate of approximately 4-7 mmol per day. In patients suffering from PH II, there seems to be a better elimination rate of oxalic acid, the average rate of elimination is at 1.1 mmol oxalate/24 h (0.8 mmol/24 h for L-glyceric acid) in ambulatory peritoneal dialysis, in comparison to just 0.3 mmol oxalate/24 h in (adult) patients suffering from PH I.

For the surgical preparation of patients for transplantation procedures (see below), oxalate should be removed as much as possible from the body so to keep the systemic oxalate burden as low as possible. For this, hemodialysis frequency has to be increased to 6 x 3-4 h/week or more in order to remove as much as possible oxalic acid from the body prior to transplantation. A combination of hemodialysis and peritoneal dialysis can also be considered at this time. However, only an insufficient amount of oxalate is still removed, so that more and more oxalate is deposited into the tissue.

> **For that reason, time from start of dialysis
> should be short until transplantation!**

## 4.4.   Transplantation

Liver transplantation cures the enzyme defect in PH I and hence, sequential or combined liver/kidney transplantation and pre-emptive liver transplantation are possible procedures. Combined liver/kidney transplantation is the method of choice, especially in end stage kidney failure and in patients being vitamin unresponsive without severe systemic oxalosis. Pre-emptive liver transplantation may be an option in a patient with a more rapid decline in kidney function, but timing of that procedure is difficult and sequential kidney transplantation may later be necessary. In patients with infantile oxalosis, sequential liver/kidney transplantation, based on anatomical reasons (e.g. small size, inadequate vessels for anastomosis), but also based on severe systemic oxalosis, should be considered to avoid prompt recurrence of oxalosis within the kidney graft. Isolated kidney transplantation might be considered in elderly patients with late onset of kidney failure and/or with a $VB_6$-sensitive genotype. This procedure was recently described to be then equivalent in terms of long-term outcome as compared to the combined transplantation procedures. Hence, personalized decisions on transplantation procedures are necessary, even more now, considering the new pharmacological options.

In PH II isolated kidney transplantation is the transplant method of choice. Although the current follow-up of the tiny group of PH II patients being transplanted is good, patients with oxalate-related graft dysfunction or problematic follow-up, which make a subsequent liver transplantation necessary, are described. In patients with PH III no data on transplantation procedures are currently available.

**A transplantation in a patient suffering from primary hyperoxaluria should only be performed in a center that really specializes in this disease.**

## 4.5.   Conclusion

The excretion of urinary oxalate should be analyzed in each patient with a kidney stone or a calcification of the kidneys. If hyperoxaluria is found, the analysis of all other parameters of the glyoxylate pathway should follow to distinguish primary from secondary, but also the specific type of the primary hyperoxaluria. Timely diagnosis of a patient suffering from primary hyperoxaluria can nowadays prevent a problematic clinical course.

Keep the diagnosis in mind in all patients with (recurrent) calcium oxalate kidney stones or with severe nephrocalcinosis!

**An early diagnosis of primary hyperoxaluria is mandatory!**

## 4.6. Self-support groups, centers

Well organized patient support groups have been in established in Europe (**www.ph-europe.net**), but also locally in Germany (**www.PH-Selbsthilfe.org**), in the Netherlands, in Spain (**https://asociacionaphes.wordpress.com/**) and in the USA (**www.ohf.org**). All websites have significant information in the country specific language, but in six different languages at PH Europe!



and

In Europe, a group of scientists have joined the European Hyperoxaluria Consortium (**www.oxalEurope.com**). Apart from a European database, the biggest worldwide, there are joint research projects.

**O** | **X** | **A** | **L** | E | U | R | O | P | E

In the USA, above all, the Hyperoxaluria Center of the rare kidney stone consortium is worth mentioning (**http://www.mayoclinic.org/nephrology-rst/hyperoxaluriacenter.html**). They also have a patient database, which is jointly organized by the OHF.

# Glossary

**Alkalosis**
Elevated pH value in blood and urine

**Autosomal recessive**
The chromosome the patient had been transferred from both the mother and the father must possess the same change in a specific gene to be affected

**Clearance**
Removal of a substance through the kidneys or through the dialysis machine

**Chorionic villus sampling**
Extraction of membrane cavity cells

**Chromosomes**
Structures containing genes and thus genetic information.

**Colonialization**
Population

**Compound heterozygote**
Two different mutations on both chromosomes

**Dialysis**
Renal replacement therapy

**Enzyme**
A protein driving a chemical reaction.

**ESWL**
Abbreviation for extracorporeal shock wave lithotrypsis =

crushing of stones by means of ultrasound waves from the outside Genetic information on a chromosome

**Gene**
Genetic information on a chromosome

**Genotype**
Certain mutations on a gene determining the disease

**Hematuria**
Blood in urine

**Hemodialysis**
Dialysis

**Hepatocytes transplantation**
Transfusion of liver cells into the large hepatic vein

**Heterozygous**
Only one mutation on one chromosome

**Homozygous**
One same mutation on both chromosomes each

**Hyperoxaluria**
Increased oxalate secretion in urine

**Intestinal oxalate absorption**
Oxalate absorption in the intestine

**Liver biopsy**
Tissue extraction from the liver

to gain material (microscopic analysis, analysis of enzyme defects)

**Metaphylaxis**
Treatment (particularly aftercare check-up and aftercare therapies)

**Nephrocalcinosis**
Calcification of the kidneys that is, deposit of calcium oxalate crystals in renal tissue

**Peroxisom/emitochondrion**
Individual components of the liver cell

**Phenotype**
Progression of a disease/appearance

**Polymorphisms**
Occurrence of a gene variant in a certain population

**Polymorphisms and microsatellite**
Helpful parameter for the analysis of mutations on special genes

**Prenatal**
Before birth

**Systemic oxalosis**
oxalate deposits in all body tissue

**Urolithiasis**
Kidney stone disease