Amorphous phosphates

Amorphous phosphates are the name given to a granular precipitate containing calcium and phosphate in an alkaline urine. Calcium phosphate crystals, regrouped under the term apatite, have mineralogical names that differ according to their chemical composition. The CaH2PO4 (2H2O) is called Brushite, the calcium hydroxyl phosphate is called hydroxyl-apatite, the calcium bicarbonate phosphate is called Dahlite or carbonate-apatite.

The main cause of this crystalluria is the alkaline pH that decreases the solubility of the calcium phosphate and entails a precipitation of the former. The alkaline pH can be caused by the diet (vegetarian, rich in phosphates) but can also represent a pathological situation. Usually, the presence of these crystals is non significant. The distinction between amorphous urates and amorphous phosphates is often made on the urinary pH basis. With a simple examination of the centrifuge pellet, the precipitate of calcium phosphate is white, while that amorphous urate is pink.

Triple phosphates (Magnesium ammonium phosphates)
(Struvite)

Triple phosphates are found in urines whose pH is superior to 6.5. The former crystallize in the orthorhombic system. The crystal is slightly birefringent and often shows a polarization color. The classic shape is the pyramid that reminds a coffin lid. The crystalluria is usually polymorphous.

The primary factor to the triple phosphate crystals formation is the ammonia concentration. Alkalanisation of a urine specimen with ammonia generates triple phosphates while Alkalanisation with sodium hydroxide does not. A normal freshly voided specimen contains little free ammonia; this substance is mainly generated by urea splitting bacteria. Triple phosphates are usually associated with

bacterial growth. With a first-morning fresh specimen, triple phosphates can indicate urinary tract infection. Otherwise, triple phosphates are of little clinical value.

Clinical significance

Except for the cystine crystals and a few others, the majority of crystals found in the urinary sediment are of limited clinical value. It is tempting to associate crystals with a risk of urolithiasis, but the majority of patients with a crystalluria does not have and will not develop kidney stones. Many benign situations can provoke crystal formation.
In the majority of cases, the crystals found in urine are not present in the freshly voided specimen. Alkalization and refrigeration are promoters of crystals formation.

Drug crystals are sometimes found in urine. In most cases, these findings are of little clinical value except, if the sediment's picture indicates a possible renal obstruction. Crystal casts are pathognomonic of this situation.

Some think that giving much time to the identification of unusual crystals is not worthwhile.

Crystals related to urolithiasis are, except for cysteine, usual and easy to identify. Calcium is found in 80 to 95% of kidney stones, mostly as oxalate or phosphate crystals. Many stones are not homogeneous. Some have a nucleus of a different composition from the surrounding matrix. The following table shows stones composition listed by occurrence.

Urolithiase composition and occurrence	
Type	**Occurence in %**
Calcium oxalate Whewellite (mono-hydrate) Weddellite (di-hydrate)	70

Calcium phosphate Hydroxyl-apatite Carbonate-apatite Calcium hydrogen phosphate (Brushite) Tri-calcium phosphate (Whitlockite)	10
Triple phosphates (Magnesium ammonium phosphate) (Struvite)	5 to 10
Uric acid	<5
Cystine	1

In many cases, the presence of crystals is a pest to the microscopic examination.

The elimination of these crystals can be made by gently heating the specimen at 37°C. To attain complete dissolution, it is preferable to heat the whole specimen. Once decanted, it is often impossible to dissolve the bulk in the small remaining volume.

It is possible to dissolve the obscuring crystals by adjusting the pH. Phosphates can be dissolved by adding a drop or two of 2% acetic acid. Amorphous urates can be dissolved by adding an alkali like a 2% ammonia solution. But heating is by far a preferred method. It is not wise to solve a urate problem by creating a phosphate precipitation.

Causes of crystal formation

It is impossible to dissolve the quantity of calcium, phosphate, and oxalate eliminated in a 24-hours urine specimen into 1 to 2 liters of water. It is therefore necessary to conclude that substances inhibiting the crystallization are present. Known inhibitors of urinary crystallization are pyrophosphate, citrate, magnesium, and certain macromolecules. The Tamm-Horsfall protein is believed to be an important calcium oxalate inhibitor. This role is thought to be due to the sialic acid residue of the protein. While the fully sialated protein is an inhibitor, the sialic residues lacking protein is a crystallization promoter.

Urine is a supersaturated solution of calcium, phosphate and oxalate in equilibria.

Crystal formation can be caused:

- *By an augmentation of concentration beyond the super-saturation capacity.* This situation is mostly the result of a decreased dilution like in a case of insufficient water intake. The situation could also be caused by a high elimination.
- *By a decreased super-saturation capacity.* This situation could be caused by a decrease in inhibitors concentration, a neutralization of these inhibitors, by some electrolytes, or a by pH change.
- *By the presence of crystals with a promoter effect on the crystallization of another species.* Crystallization of calcium oxalate promoted by amorphous urates is a good example of this phenomenon. This situation is thought to be the result of a competition for the inhibitor site of Tamm-Horsfall protein. Urates and calcium oxalates adhering to mucus is a frequent observation.

Some crystals are found exclusively in acid urine, others are found exclusively in alkaline urine.

Amorphous crystals are often identified on the basis of the urine pH. In an acid specimen, urates are reported, in an alkaline specimen, amorphous phosphates are reported. This simplification should be used with care. Amorphous phosphates and triple phosphates are sometimes observed in slightly acid specimens. (pH 6.5)

The usual crystals found in urine

Alkaline pH	**Acid pH**
Amorphous phosphates	Amorphous urates
Triple phosphates	Uric acid
Ammonium biurates	Calcium oxalates
Calcium phosphates	
Calcium carbonates	Cystine

Specific clinical conditions that explain Urolithiase formation can also explain a persistent crystalluria.

Hypercalciuria

Increased urinary calcium elimination can result in a crystalluria, mostly as calcium oxalates. The superior limit for the calciuria is 75 mmol/d under a 250 mmol/d diet.

Hypercalciuria can be caused by:

- an increase of the fraction of the diet absorbed.
- a renal loss with a secondary increase in intestinal absorption.
- an excessive bone resorption.
- a primary hyperparathyroidia.
- a combination of the previous causes.

Hyperoxaluria

Calcium oxalate is probably the crystal that one meets the most frequently in urinary sediment. In the majority of cases, the presence of these crystals is without any clinical meaning. According to Conyers, only 10 to 15% of the urinary oxalate is directly related to the diet. The majority of the urinary oxalates are produced by the metabolism (glyoxilic acid cycle). It seems that even light hyperoxaluria is, after the decreased urinary volume, the most significant factor in the recurrent calcium oxalate urolithiasis.

In some cases, the crystallization of the calcium oxalate is massive and catastrophic. A typical example of the oxalate clinical catastrophe is the cases of ethylene glycol poisoning. In this situation, one can find oxalate crystals in the patient's tissues. The toxicity syndrome affects organs like the liver, the kidney, and the brain and is accompanied by a metabolic acidosis. Naturally, the oxalate crystalluria is massive, and is predominated by the ovoid crystals (Whewellite) forming microlithes.

Calcium oxalate casts are highly significant. These imply that the oxalate crystals were already formed when the urine was at its maximum dilution.

Conyers has reported other substances that can lead to oxalosis. Some of these substances are used as glucose substitutes in parental alimentation.

Other causes of hyperoxaluria are:

- Primary hyperoxaluria (a rare genetic disease).
- Pyridoxine deficiency (vit B6).
- Increased intestinal absorption of oxalates.

Fatty acids are competing with oxalate for the intestinal calcium. In fat malabsorption, the increase of unabsorbed fatty acids mobilizes the calcium leaving the oxalate, free to be absorbed. *Intestinal calcium limits the absorption of oxalate.*

Hyperuricosuria and calcium oxalates

An increased elimination of urate is most frequently caused by a high purine diet. Over production, can also be a cause of hyperuricosuria. With a urinary pH greater than 5.5, amorphous urates will be the major crystal form. Below 5.5, uric acid crystals are observed.

It is not rare to observe calcium oxalate crystals with amorphous urate in the same urinary sediment. Urate crystals seem to have an enhancer effect on the calcium oxalate crystal formation. A possible explanation is that urates and oxalates are competing for the litho-inhibitor macromolecules.

Hypocitraturia

The chelating effect of citrate is known to reduce the saturation in calcium salt. Also, the soluble chelating calcium complex seems to have an inhibiting effect on crystal formation. One can therefore expect an increase in crystals formation, and even urolithiasis in conditions leading to hypocitraturia.

Hypocitraturia is seen in conditions like in:

- Renal tubular acidosis, especially of the distal type. (RTA type I)
- Chronic diarrhea.
- Excessive animal protein intakes.

Many bacteria infecting the urinary tract reduce the citrate concentration.

5% of the hypocitraturia are of unknown causes.

Uric acid

Approximately 66 to 75% of the uric acid is eliminated by the urine. The quantity to eliminate depends mostly on the diet (meat). In increased uricosuria, values > 4.5 mmol/d are observed.

Uric acid crystals are formed when the urinary pH is <5.5 since the ph of uric acid is 5.5.

Uric acid crystalluria is mainly due to a poor dilution volume at an acid pH, or due to an over production. In the majority of cases, this finding is of little clinical value and represents a pinpoint situation.

Acid pH

Some conditions, like chronic diarrhea, can be responsible for uric acid urolithiasis. Many of these patients will also have calcium stones.

Over production

Uric acid stones are seen in cases of gout, myeloproliferative syndrome, glycogenosis and neoplasms.

Cystinuria

Cystine crystals are found in urine of almost exclusively patients with a genetic disease giving impairment with the tubular reabsorption of

the basic aminoacid: lysine, arginine, ornithine and cystine. This disease is called cystinuria. For a few patients with cystinuria, stones will develop. The urolithiasis is highly dependent of the urinary pH and water intake. Cystine is less soluble at a pH lower than 5.0 (saturation 300 mg/l); saturation is of 500 mg/l at a pH of 7.4.

Infection

Infection with urea splitting bacteria (ex: proteus species) leads to a production of ammonia an alkalinization of the urine. The produced ammonia generates magnesium ammonium phosphate crystals, also called triple phosphates. The mineralogical name of triple phosphate is Struvite. Triple phosphates are usually found with amorphous phosphates, owing to their low solubility at alkaline pH.

Crystalline structures

Solid substances are divided in two large groups, amorphous substances and crystalline substances. Crystals have defined geometrical shapes while amorphous substances have not. More, crystals have a precise melting point, while amorphous substances have a melting point that spreads over an interval of temperature. In crystallography, one speaks of planes, axes, and angles to describe their shape. Crystals, while preserving their primary shape, have a very variable size, but the ratios and angles between the faces and between the sides, are constant.