Urolithiasis

Clinical Biochemistry

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Incidence of urolithiasis

In affluent countries, urolithiasis is a major cause of morbidity in individuals, with considerable socioeconomic costs for health care and productivity in the community. Renal stones may cause renal damage, often progressive, renal tests then show deterioration.

Several studies (USA and FRG) have shown that **men** have a l0% to 12% chance of experiencing an attack of renal colic or the passage of a stone at least once during their lifetime. The incidence in **women** is increasing, and, according to one survey, is already between one-third and one-half that of men in affluent countries.

Calcium urolithiasis - **more than 80 %**

Calcium oxalate

Calcium phosphates – secondary origin mostly

Uric acid / urate lithiasis – **about 10 - 15 %**

Cystine stones – less than 1 %,

very rare xanthine or 2,8-dihydroxyadenine stones

Formation of renal stones

Physicochemical principals govern the formation, and are relevant to the chioce of treatment aimed at preventing progression or recurrence.
The solubility of a salt depends on the product of the activities of its constituent ions. Frequently, the **solubility product in urine is exceeded** (supersaturated solution) without the formation of a stone, provided there is no "seeding", nucleation. "**Seeding**" promotes crystal formation in relation of particles present in urine, such as debris or bacteria. Formation of stones may be prevented by inhibiting substances (**inhibitors of lithogenesis**) that are normally present in the urine.

Formation of renal stones results from interaction of three factors:

1 – increased urinary **concentration of lithogenic components**,
2 – presence of "**seeding centres**", and
3 – reduction in the **concentration of inhibitors of lithogenesis**.

Urinary tract infection, inadequate fluid intake as well as stasis of urine support stone formation.

Risk factors in stone formation and inhibitors of lithogenesis

1 Past history of a patient

- Family occurrence of urolithiasis.
- Inadequate fluid intake, people living or working in hot conditions are liable to become dehydrated.
- Sedentary occupations.
- Age: peak occurrence in men 40-50 years, in women aged 16-30 years and post-menopausal.
- Cystinuria (cystine stones occur mostly in the age of 10-20).
- Diet: high consumption of animal protein, milk, and dairy products, mineral waters rich in calcium, spinach, rhubarb, chocolate, cocoa, black tea, alcohol.
- Long-term administration of, for example, laxatives, vitamin D, ascorbate (vitamin C) in high doses.
- Diseases: hyperuricaemic syndrome, diabetes, renal and urinary tract diseases (infections above all), renal tubular acidosis, hyperparathyroidism and some other endocrinopathies, enteropathies and intestinal resections, malignancies (metastases, radiotherapy, cytostatics), oxalosis, haematuria.

2 Biochemical factors

A Lithogenic components

Calcium - Hypercalciuria (enhanced intestinal absorption of Ca, decrease in calcium reabsorption in renal tubules, stimulated bone resorption) is the cause of increased Ca-oxalate or Ca-phosphate saturation in the urine.

Uric acid - In hyperuricosuria higher concentrations of undissociated uric acid (less soluble than urate anion) supports crystallization of Ca-oxalate.

Oxalates - Hyperoxaluria is caused most oft by an increase in intestinal absorption of oxalate.

Sodium ions - High intake of NaCl results in high urinary Na^+ concentration that supports excretion of Ca^{2+} and so formation of Ca-oxalate as well as monosodium-urate renal stones.

Phosphates - Diet rich in meat products results in high excretion of phosphates that facilitates saturation of Ca-phosphate in the urine.

Sulfates - High urinary concentration of sulfate is usually the consequence of diet rich in proteins (amino acids methionine and cysteine are acidifying components) – and a cause of low urinary concentration of citrate.

Urinary pH - Long-term pH values < 5.5 cause high ratio of undissociated molecules of uric acid, long-term pH values > 7.0 (namely in renal tubular acidosis support precipitation of calcium phosphates.

Cystine - In cystinuria, cystine renal stones are formed very oft (very low solubility of cystine, namely in acidic urine.

B Inhibitors of crystallization

Inhibitors of crystallization decrease saturation of the urine by lithogenic substances and keep them dissolved.

Magnesium ions

Mg^{2+} ions bind oxalate anions in part in the form of Mg^{2+}-chelate and reduce so saturation with Ca-oxalate.

Low concentration of Mg^{2+} may be induced by some diuretics (eg., amiloride).

Citrate

Low concentration of citrate in the urine may be a consequence of metabolic acidosis, renal failure, exacting physical work, hyperoxaluria, urinary tract infections, ibntestinal malabsorption, diarrhoea, high protein intake, and therapy with thiazide diuretics.

Lack of citrate in the urine disables formation of soluble Ca^{2+}-chelates binding free Ca^{2+}, the activity of which increases.

Sufficient fluid intake

Urinary concentration of all lithogenic components decreases significantly if the daily volume of urine exceeds 2 l / d.

Metabolic risk factors in renal stone formation

Hypercalciuria

(urinary excretion > 7.5 mmol / d in men, > 6.2 mmol / d in women
or urinary concentration U-Ca > 10 mmol / l)

– **primary hyperparathyroidism** (with hypercalcaemia),

– **idiopathic** hypercalciurias (at normal calcaemia), obviously inherited (dominant autosomal) defects:

hyperabsorptive type – increased intestinal absorption of Ca^{2+} (postprandial hypercalcaemia and hypercalciuria occur; in fasting individuals, calciuria may be lower than normal).

renal type – the failure in renal reabsorption of Ca^{2+} (type 1 and 2) or reabsorption of phosphate anions (type 3 – the renal phosphate leak).

Hyperoxaluria

(urinary oxalate excretion over 500 μmol/d, i.e. > 45 mg/d)

– hyperabsorptive

dietary – high intake of oxalate (spinach, rhubarb, cacao, chocolate), long-term high intake of animal proteins

intestinal – occurs very oft in different malabsorptions: Ca^{2+} are bound preferentially with anions other than oxalate (fatty acids, phosphates) or Ca^{2+} are absorbed intensively (hypervitaminosis D, hyperparathyroidism) so that more oxalate unbound to Ca^{2+} is absorbed (and not eliminated in the faeces as Ca-oxalate).

– metabolic

primary hyperoxaluria is a rare inherited defect due to insufficient decomposition of glycine, overproduction of oxalate may cause a serious renal failure or liver injury, even in childhood (sometimes kidney or liver transplantation is inevitable)

intake of oxalate precursors – megadoses of ascorbate, earlier xylitol, maybe also an anaesthetic ethoxyflurane, ethylene glycol

Mineralogical names

Renal stone	Mineralogical name	Chemical formula
Calcium oxalate – monohydrate – dihydrate	 **whewellite** **weddellite**	 $Ca(COO)_2.H_2O$ $Ca(COO)_2.2H_2O$
Uric acid and urates amorphous uric acid crystalline dihydrate of uric acid monosodium urate monohydrate ammonium hydrogen urate	(uricite)	 $C_5H_4N_4O_3$ $C_5H_4N_4O_3.2H_2O$ $NaHC_5H_2O_3N_4.H_2O$ $NH_4HC_5H_2O_3N$
Calcium phosphates hydroxylapatite – tricalcium phosphate calcium hydrogen phosphate dihydrate	 **apatite** **whitlockite** **brushite**	 $Ca_{10}(PO_4)_6(OH)_2$ $Ca_3(PO_4)_2$ $CaHPO_4.2H_2O$
Infectious origine carbonateapatite magnesium ammonium phosphate hexahydrate (triple phosphate)	 **dahlite** **struvite**	 $Ca_{10}(PO_4CO_3OH)_3(OH)_2$ $MgNH_4(PO_4)_2.6H_2O$
Organic origine cystine xanthine fibrin artefacts		 $(SCH_2CH(NH_2)COOH)_2$ $C_5H_4N_4O_2$

The most common causes of some renal stones

Type of stone	*Metabolic cause or relevant factor*
Calcium oxalate	Primary hyperparathyroidism Idiopathic hypercalciuria Low citrate concentration in urine Primary hyperoxaluria Hyperuricaciduria
Calcium phosphate	Renal tubular acidosis
Urate stones	Acidic urine Hyperuricaciduria
Struvite stones	Urinary tract infection (fall in $[H^+]$, microorganisms producing urease)
Cystine stones	Cystinuria (diaminoaciduria)

Biochemical investigations in urolithiasis

Risk values of lithogenic compounds

Calcium

dU-Ca	> 6.25 mmol / d (children > 0.10 mmol / kg)
U-Ca / creatinine	> 0.592
S-Ca	> 2.65 mmol / l
P-Ca^{2+}	> 1.32 mmol / l

Oxalate

dU-oxalate	> 0.46 mmol / d
U-oxalate /creatinine	> 0 030

Ions Na^+

U-Na^+	> 200 mmol / l

Uric acid

dU-urate	> 4.16 mmol / d
U-urate / creatinine	> 0.30
S-urate	> 415 µmol / l in men
	> 365 µmol / l in women

Phosphate

dU-P_i > 35.5 mmol / d (increase in meat diet)

Sulfate (high intake of Met and Cys is proton-productive, low concentration of citrate in acidic urines)

dU-sulfate > 30 mmol / d

pH

low urinary pH (< 5.5) increases precipitation of unionized uric acid

high urinary pH (> 7.0) supports precipitation of Ca-phosphates

Cystine (low solubility in acidic urine)

dU-cystine > 1.66 mmol / d

Risk values of lithogenesis inhibitors

Ions Mg^{2+}

dU-Mg	< 2.47 mmol / d
U-Mg / creatinine	< 0.020
U-Ca / Mg	> 2.0
U- $\frac{[Ca] \times [oxalate]}{[Mg] \times [creatinine]}$	> 0.050

Citrate

(low citrate concentration increases concentration of free Ca^{2+})

dU-citrate	< 1.67 mmol / d

Urine volume < 2 000 ml / d

Example of low-calcium, low-oxalate, and low-salt diet

	ALLOWABLE	NOT ALLOWED
Beverages	unsweetened soft drinks, coffee, table waters	**milk** and **dairy products**, yoghurt, **mineral waters**, cocoa, **strong tea**
Bread	rye bread, unsalted rolls	wheat and salted bread
Starchy eatables	pastries, potatoes	chipped potatoes
Candies	without milk	**chocolate**,,ice cream
Cheese	none	**cheese**
Fruit, fruit juice	fresh, bottled, tinned	concentrated fruit products, grapes
Vegetables	restricted amount, carrot, tomato	spinach, rhubarb, sauerkraut, young peas, green pods, parsley
Soups	low-salt or unsalted	salted, vegetable, and cheese soups
Fat	vegetable butter (without milk), margarine	cheese salads, acidic custards
Meat products	only 2 portions of meat daily, fish, poultry	roast or grilled meat, pork, luncheon meat, smoked goods, pizza
Other	low-salt extracts	Na-**glutamate**, soya sauce, olives, mineral supplements, supplementation with **vitamin C and D**

Long-term limitation calcium intake is acceptable only in hyperabsorptive type of calciuria – it enhances oxaluria!.