Nephrolithiasis: a systemic disorder

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ABSTRACT BOOK

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CONTENTS

POSTERS

Heredity and Environment in Pathogenesis of Calcium Renal Stones

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Much evidence links idiopathic hypercalciuria (IH) to the pathogenesis of idiopathic calcium renal stones. Since 1936 clinical investigators have noted that idiopathic calcium stone formers (ICSF) excrete more calcium in their urine, on average, than non-stone forming people (11). The linkage is certainly not absolute. Not rarely one finds ICSF whose urine calcium excretion falls within the normal range. But, like hypertension and stroke, higher values are associated with disease. This association has long led clinicians to use measures against IH as prime treatments for ICSF. Fluids, of course, dilute all urine stone forming salts. Low calcium diets, perhaps an unfortunate choice, long dominated treatment. Thiazide diuretics and potassium alkali that both reduce urine calcium have been studied in reasonably high quality trials and found effective. Likewise, reduced diet sodium and protein can lower urine calcium and appear to reduce stones. Because of its centrality the causes and mechanisms of IH have been and are a main area of research in stone pathogenesis and treatment.

As to final cause, IH must be genetic being familial and successfully bred for in animals (37). Among first degree relatives of people with IH about half will have the trait. Children with calcium renal stones have urine calcium excretion rates about twice that of matched control children without stones or a family history of stones. The siblings of the stone forming children have calcium excretion rates midway between the stone formers and controls (5). The genes for IH are not known; the monogenic forms that have been identified account for only a tiny fraction of patients with the trait .

In multiple studies GI calcium absorption and serum calcitriol levels of IH have exceed normal controls. This supported low calcium diet as a treatment. Subsequent findings of reduced bone mineral density, however, suggested that vitamin D driven hyper-absorption of calcium

might not be the full mechanism (1). Fed a very low calcium diet for 9 days, IH subjects excrete more calcium than normal subjects, and frequently more than they ingest (13). A review of all published balance studies in IH demonstrate negative bone balances in IH calcium intakes that support neutral balances in controls. Administration of calcitriol to normal men duplicated these findings: Urine calcium rose, and bone balance became negative at diet calcium intakes sufficient for neutral balances without the calcitriol. Altogether the core traits of IH could reflect increased GI and bone, vitamin D effects (37).

The role of IH in stone pathogenesis awaited better understanding of how human stones form, which has only recently become clear. ICSF who form calcium oxalate (CaOx) stones with less than 50% calcium phosphate (CaP) admixture appear to form their stones as overgrowths on papillary interstitial apatite deposits (Randall's Plaque, RP) (32). The urothelium gives way over an RP deposit which a layer of urine molecules that include THP and osteopontin cover. Apatite crystals nucleate in this organic layer, are covered by another layer of organic molecules, and this process repeats to form a laminated ribbon of apatite crystals and urine molecules that eventually builds up the base of the nascent stone. Eventually CaOx crystals appear and ultimately predominate by presently unknown mechanisms (16).
The overgrowth process requires two driving forces - urine supersaturations (SS) - to nucleate the crystals, one for CaP and one for CaOx. Analysis of urine SS values under CRC conditions show that ICSF produce far higher CaP SS than normals eating the same diet, especially overnight, and this difference is due exclusively to IH, urine volume, phosphate excretions, and pH being no different. Also because of IH CaOx SS is higher, urine oxalate differences between ICSF and normals being insignificant with controlled diets (4).

Plaque is far more abundant on papillae of ICSF than normal, in the range of about 6% of surface being covered with it vs. <1% in normals. Plaque surface area has a weak positive correlation with urine calcium excretion, and inverse correlations with urine volume and pH (26). Plaque forms in the basement membranes of the thin

loops of Henle as multitudes of micro-spherules, each made of alternating lamina of apatite crystals and organic matrix (19). They fuse at their outer organic layers as they leave the basement membrane and enter the papillary interstitium, to form droplets of organic matrix with interior islands of apatite. These migrate between the tubules and vessels until they abut against the urothelium where we see them as white plaque deposits.

To foster nucleation in the thin loop basement membranes, ICSF must somehow raise CaP SS in the papillary interstitial space outside the loops, in the thin loop fluid, or both. Because calcium permeability of thin loop epithelium is notoriously low, movement of calcium from the lumen to the basement membrane will be slow and possibly offset by off-diffusion into the interstitium unless calcium concentration there is high. Our present theory is that interstitial and tubule fluid SS both are increased in at least some ICSF because of the physiology of IH (12).

Urine calcium could increase in IH because of increased filtered load, meaning a rise of serum calcium with meals, because of reduced tubule calcium reabsorption, or both. Professor Jack Lemann found that after a simple glucose load it was reduced tubule reabsorption not change in filtered load that raised urine calcium higher in IH than normals (28-30). Subsequently, Professor Elaine Worcester showed that the same was true after normal meals: Filtered loads of calcium did not increase; tubule reabsorption fell and that fall was the cause of higher urine calcium excretion (38; 39). Moreover, she showed that the proximal tubule (PT) could participate, reducing its reabsorption, especially after eating, in some, though not all IH ICSF (38).

Those IH who lower PT reabsorption with meals deliver more than normal amounts of calcium into their thin limbs, which could raise lumen SS there, and into their thick ascending limbs (TAHL) that reabsorb calcium without water mainly via passive trans-membrane potential driven paracellular diffusion and whose reabsorption rate is therefore strongly load dependent (24). The TAHL surround the vas recta bundles in the inner stripe of the outer medulla, so the calcium

they reabsorb can raise lumen calcium concentration in the descending vas recta that feed the capillaries surrounding the papillary thin limbs.

Thus, those IH patients with reduced PT calcium reabsorption could increase both thin limb lumen CaP SS and interstitial CaP SS surrounding the thin limb basement membranes; this would predict that plaque abundance will generally rise with urine calcium excretion. Because medullary TAHL transport is increased by vasopressin (22) and vasopressin is increased when urine volume is low, plaque will be predicted to vary inversely with urine volume. High sodium intakes raise urine calcium and also lower PT reabsorption of sodium and water (8), and because calcium reabsorption in PT is mainly passive and tracks with sodium and water reabsorption high sodium intake will increase delivery to TAHL (9). This, too, could link plaque abundance and urine calcium excretion. Acid loads from our contemporary diet also reduce PT reabsorption (34) (36), as well as calcium reabsorption elsewhere in the nephron (3), so acid urine pH would tend to associate with more plaque. Likewise, a more acid urine implies a higher rate of proton transport by inner medullary collecting ducts (IMCD) into the final urine, which must increase papillary interstitial bicarbonate concentration and pH, and therefore CaP SS.

Essentially, at least for a subset of cases, the high sodium and acid loading of modern diets could promote plaque and stones directly via their effects to amplify the genetic IH trait that would, given a low sodium and alkaline ash diet, appear very much more modest if even detectible. It is of note that common treatment include reduced sodium, moderation of diet protein, and potassium alkali supplements. Thiazides lower urine calcium partly via increase of DCT reabsorption, but increase of PT reabsorption has been shown in mice (27) and recently we have shown the same in people.

Some ICSF do not fit this picture. They have PT reabsorptions that overlap with normals yet are hypercalciuric. They have plaque. Presently we do not have enough data to understand how their IH links to plaque but suspect it must be via increased delivery to IMCD

with increased IMCD reabsorption of calcium into the papillary interstitium. This same mechanism should apply to those patients with reduced PT reabsorption, who would then have two rather than one mechanism for its formation and therefore might be expected to form more plaque. No data are available in this area. The nephron site for the normal PT IH patients must be TAHL or DCT. It is possible to differentiate these alternatives using furosemide blockade of TAHL but data are not as yet available. In rats bred for hypercalciuria it is TAHL that is abnormal, and has much reduced calcium reabsorption in vivo and in perfused tubule segments (35).

The proximate mechanisms for altered PT or TAHL reabsorption are presently unknown. High tissue vitamin D activity seems part of the IH phenotype, due to the well-known high calcitriol levels of IH and perhaps primary increase of VDR gene expression. In PT activation of VDR is known to reduce renin gene expression (31; 40). Renin, via A2, up-regulates NHE3 and therefore overall PT sodium and water reabsorption (25). By reducing local renin production increased VDR abundance and signaling could therefore reduce PT reabsorption. In TAHL the basolateral CaSR down regulates reabsorption of NaCl which must reduce calcium reabsorption (23); increased abundance from VDR up-regulation of VDR gene expression (2) could increase signaling by CaSR at any given level of serum calcium. Quite possibly genetic variability in VDR up-regulation, or VDR mediated changes in renin gene expression could lead to the IH phenotypes of reduced or normal PT reabsorption.

Yet another group of ICSF form stones in which CaP predominates, either as apatite or brushite, CaOx being a minor component of less than 50%. In these patients, plaque varies widely from abundant to no more than is found in normal people, and only a scattering of CaOx stones, usually very small grow on it. Instead the main papillary finding is plugging of IMCD and terminal ducts of Bellini (BD) with apatite crystals (20). The crystals appear to injure the epithelial cells, which are often damaged or even totally destroyed. The interstitium around plugged ducts is inflamed, and inflammation can be found

extending even into areas without plugging. Papillae are variably retracted and scarred, and dilated openings of BD frequent.

The IMCD and BD plugs show through the urothelium as yellow, well demarcated elongate structures sometimes called yellow plaque as opposed to the cloud-like irregular white deposits of RP. Not rarely, tiny nascent stones are found growing on the urinary end of plugs, but whether these overgrowths are the origins of clinical stones, or stones begin as nucleation in free solution remains an open question. This pattern of ductal plugging with papillary damage, essentially a crystal mediated papillary tubule-interstitial nephropathy is the rule in all systemic diseases that cause stones: Primary hyperparathyroidism (14), renal tubular acidosis (17), enteric hyperoxaluric states (21) including bariatric surgery, ileostomy (18), primary hyperoxaluria, and cystinuria (15). Put another way, the CaOx ICSF pattern of pristine papillae with only RP and CaOx stones growing on it seems unique to that specific clinical phenotype.

The only physiological mechanism for the apatite and brushite forms of ICSF found thus far is an increase of urine pH which raises CaP SS (33). IH is present as in CaOx ICSF, but the shift of pH shifts the balance of CaOx and CaP SS to favor the latter and that presumably is sufficient to promote both a change in stone type and precipitate IMCD and BD plugging. Why urine pH is high remains uncertain, but one clue is that the range of urine pH among normals includes the pH values found in CaP ICSF. Quite possibly, the wide range of normal urine pH is genetically determined, a matter that has not been tested experimentally, and the CaP ICSF may arise simply from IH and high normal pH coexisting in an individual.

All this makes clear how the change of diet from the evolutionary norm of low sodium and high potassium alkali would combine with genetic forms of hypercalciuria and perhaps genetically regulated urine pH to create the CaOx and CaP stone forming phenotypes. Likewise our present knowledge leads to reasonable speculation that the IH phenotypes could arise via variations, even tissue specific

variations in VDR and CaSR gene regulation, but gives no clue as to why IH should have arisen via genetic selection.

Because research is impossible without some starting hypothesis, we have attempted to propose one. Possibly, during our evolution in Africa, reduced PT reabsorption might have been helpful for potassium regulation. Given the very high potassium intakes we experienced as a species , high delivery from PT or TAHL could have increased potassium excretion by increasing delivery to the collecting ducts offering a survival advantage. On the other hand, the tubule physiology of IH would be maladaptive in reducing the efficiency of sodium conservation and especially water conservation; maximal water reabsorption requires low deliveries to the thin limbs.

One way to proceed is by comparing people whose genome is more like that during our African evolutionary period to those who evolved after the great migrations from Africa to Europe and Asia. In the one study comparing PT reabsorptions – using lithium clearances - of South African blacks to Belgium whites (6), the black subjects had markedly higher PT reabsorption, which did not respond well to increased diet sodium. With higher salt excretions, reflecting higher sodium intakes, blacks mainly reduced distal nephron sodium reabsorption, whites reduced PT reabsorption. Of note, tubule reabsorption was strongly hereditary within the many families this group studied. In another study, calcium excretion during Lasix TAHL blockade was lower in African Americans (AA) than whites, a finding most compatible with greater PT calcium reabsorption in AA than whites, and consistent with the Belgium study (10). Finally, in population studies of lithium clearances inter-individual variations were always much higher than intra-individual variations, even when effects of sodium intake were accounted for, meaning that PT reabsorption varies among otherwise normal people, presumably driven by genetic factors (7).

Given the forgoing we propose that IH did not originate in Africa, but after the northern migrations, a proposal which is compatible with the much lower urine calcium excretions of black people in the US and

their much lower frequency of stones compared to whites. What drove changes in reabsorption might have been less skin sunlight exposure in the colder northern latitudes that favored increases in VDR abundance or sensitivity and led to changes in tubule transport functions as a secondary byproduct of only modest evolutionary importance. When diet sodium was low, and diets contained significantly more potassium alkali from roots and tubers rather than the more neutral grains we began to produce no more than ten thousand years ago, in other words without the salt and acid loading of modernity, the IH phenotype would not exhibit impressive urine calcium excretions.

Likewise, high PT reabsorption, very valuable under low sodium conditions and in generally hot climates might have lost much of its adaptive value in the colder northern climates and maybe the higher sodium available near sea coasts so the 'cost' of reduced reabsorption was not enough to preserve high levels of reabsorption.

As the genes responsible for the common IH phenotype are identified, these matters can be addressed more directly. In the mean time we have available excellent methods for treatment, most of which, if one looks closely, merely act to reverse the effects of our peculiar and probably unhealthy sodium and acid loading diets.

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Epidemiology and Clinical Pathophysiology of Uric Acid Stones

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Abstract
Uric acid nephrolithiasis constitutes 8-10% of patients with kidney stone disease. The prevalence of uric acid nephrolithiasis has been recognized to be particularly higher in obese patients as well as certain ethnic backgrounds. A major pathophysiologic mechanism for the development of uric acid nephrolithiasis is unduly acidic urine. Typically a urinary pH below 5.5, the content of sparingly soluble uric acid, increases and facilitates the formation of uric acid stones. The underlying physiologic abnormality is dual and includes defective urinary ammonium excretion and increased acid production, which has been linked to metabolic syndrome and may be associated with fat accumulation in the kidneys. It is conceivable, with the increasing worldwide prevalence of obesity, that uric acid nephrolithiasis will become a major societal health burden.

Noninvasive differentiation of uric acid versus non-uric acid kidney stones

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Introduction. Identifying a patient's stones as being composed of uric acid allows proper planning for treatment that avoids unnecessary procedures and that properly addresses the unique metabolic concerns of this patient group. Uric acid stones are usually quite susceptible to fragmentation by shock wave lithotripsy, and these stones are the only type that has a high probability of being able to be removed by dissolution through alkali therapy. Thus, noninvasive differentiation of stone type from other types is valuable and recommended.

Plain films. The common kidney-ureter-bladder (KUB) radiograph can sometimes be used to identify uric acid stones, but studies show diagnostic accuracy to be less than 50%. Errors include missing the stone completely (when it is radiolucent) or confusion with calcium stones (when the uric acid stone contains some admixture of calcium salts). Combination of KUB with other modalities (ultrasound or computed tomography [CT]) has a potential for improving identification of uric acid stones. For example, a stone visible on ultrasound or CT but lucent on KUB might well be pure uric acid, but no studies on the reliability of this kind of comparison appear to be published.

Noncontrast CT. Imaging of stones by CT is the most specific and sensitive method for identifying the presence of calculi in the urinary system, and several studies have shown reasonable success in differentiating uric acid stones from other forms through the use of Hounsfield unit values, as the very low x-ray attenuation of uric acid makes it distinctive in many situations. However, this method is complicated by the presence of calcium salts (a frequent minor component in uric acid stones). Viewing of CT scans of stones using bone windows (to view CT-visible morphology within the stone) holds the possibility of being able to distinguish stones of uric acid that contain calcium salts, but this possibility has not yet been

explored clinically. Finally, images of smaller stones (<5 mm) are greatly affected by volume averaging effects, reducing the Hounsfield unit values of all small stones, and thus making distinction of uric acid even more difficult.

Dual-energy CT. Several manufacturers now make units that produce a CT scan that is produced using two different energies of x-ray, and the ratio of the attenuation values measured with the different energies provides a reliable way to distinguish uric acid stones from other types. Early clinical studies using this technology are just now emerging, and the results show promise at being able to correctly identify uric acid stones in patients. Refinement of technique in these systems may allow the identification of most types of stone mineral.

Summary. The noninvasive identification of uric acid stones in patients is valuable and recommended. Combinations of imaging modalities (such as a stone visible on ultrasound and lucent by KUB) may provide correct identification of uric acid stones, but presently the most accurate method appears to be the use of dual-energy CT.

Treatment of uric acid stones

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Uric acid nephrolithiasis accounts for 7% to 10% of stones subjected to analysis and the pathogenesis is incompletely understood.
Several urinary abnormalities predispose to formation of uric acid calculi: ***persistently low urinary pH***, ***low urinary volume***, and ***hyperuricosuria***.
Medical dissolution therapy is successful in a large number of cases and should be the initial treatment of patients except in cases where obstruction, azotemia, infection, or unremitting pain are present. Patient noncompliance or the intolerance of the prescribed medications are the typical causes for medical therapy failure

1. The critical role of ***low urinary pH*** can best be explained with fundamental acid-base chemistry: one nitrogen of the urate, when dissolving in water, can accept a free proton to form uric acid (Urate + H^+ Uric Acid). The acid dissociation constant (pKa) of this reaction is 5.5 and at a pH equal to the pKa, uric acid and urate exist in equal proportions. But in aqueous solutions at 37°C uric acid has a solubility constant of approximately 100 mg/L, whereas urate is 20 times more soluble so, if 1200 mg of urate were instilled into a 1L water solution at 37°C at a pH of 6.5, 1100 mg would remain in the soluble urate form. Thus, patients with normal uric acid excretion but a low urinary pH can develop uric acid stones, whereas those with a normal or higher urinary pH but excessive urate excretion will not.
Not only does pH need to be low to form uric acid stones, but it also must remain persistently low.
The goal of pH manipulation therapy is to maintain a urinary pH of 6.5 to 7.0. It is important that urinary pH is not maintained above this range because of the risk for developing calcium phosphate stones, and patients should monitor urine pH using a pH paper. **Potassium citrate** is the preferred agent: 15-30 mEq twice daily in adults will generally achieve the pH goal. Some patients present with diminished

renal function or high baseline serum potassium levels, or are intolerant of the possible gastrointestinal side effects of potassium citrate: **sodium bicarbonate** or sodium citrate, in absence of congestive heart failure or poorly controlled hypertension, are the preferred agents in this setting, with the former having also the advantage of limited cost. The usual adult dose of sodium bicarbonate is 650-1000 mg 3-4 times daily. Sodium bicarbonate powder, as available from supermarkets, is a very cost-effective option: one standard teaspoon contains approximately 5 g or 6 mEq of bicarbonate. Half to one teaspoonful in orange juice or lemonade is a palatable and cheap alternative to three to six capsules of sodium bicarbonate daily, although there is a risk of overuse resulting in alkalosis.

Because compliance is a major issue, expense convenience and palatability are all important and should result in individualization of therapy.

Acetazolamide, a carbonic anhydrase inhibitor that produces transient urinary alkalization, has been suggested as a method of overnight urinary alkalization to supplement daytime use of oral alkali. This has not been subjected to controlled trials and the drug is not recommended for routine use because it reduces citrate excretion and promotes calcium excretion.

In conclusion, the amount of alkali required to increase urine pH to over 6 varies between patients, dependent at least partly on diet. The normal urinary acid load is around 1 mEq/kg. Patients with chronic non-renal bicarbonate loss (chronic diarrhoea, ileostomy) require larger quantities. Usually a daily intake of about 1 mEq/kg body weight bicarbonate or citrate is required to dissolve stones; lower doses to transiently increase urine pH may be effective in preventing stone recurrence.

2. ***Decreased urinary output*****,** a marker of dehydration, is associated to an increase in the concentration of the urinary lithogenic solutes. The solubility of uric acid is limited, so high enough concentrations of urate may cause uric acid as well as monosodium urate precipitation; as a consequence, it is mandatory to maintain a **daily urinary output of at least 2L**, which is possible only with a vigorous hydration. After

meals, during physical activity, or at night-time, periods of high stone-forming potential, hydration has been also theorized to be important. Dipstick testing to assess specific gravity may be used to prompt compliance with fluid therapy in this cohort.

3. Almost all patients in whom uric acid calculi develop have persistently acidic urine while only a small fraction have ***hyperuricosuria,*** defined as 24-hour urinary uric acid exceeding 750 mg. Patients with hyperuricosuria but normal urinary pH also develop stones, although these are often mixed stones composed of calcium oxalate and urate; urate is many times more soluble than uric acid, but it is not infinitely so: at high enough concentrations monosodium urate precipitates and can cause calcium oxalate crystallization. Hyperuricosuria is most commonly caused by dietary excesses, though mutations in the URAT1 channel can cause congenital renal hypouricemic hyperuricosuria.
When hyperuricosuria is identified, its underlying cause should be addressed if possible. Uric acid is an end-product of the metabolism of endogenous and exogenous protein and purine nucleotides, so patients should first be counseled to **avoid foods rich in purine** such as red meat, fish, poultry, beer, and legumes. These foods increase the uric acid load to the kidneys; the digestion of animal protein also produces a transient metabolic acidosis that lowers urinary pH.
Patients not-responders to dietary changes or in symptomatic hyperuricemic conditions such as gout, hyperuricosuric calcium urolithiasis, and urate nephropathy, so requiring a fast reduction in uric acid burden, should be given 300-600 mg per day of **allopurinol**, a xanthine oxidase inhibitor which prevents the degradation of purines through xanthine to uric acid. There have been many reports of prophylaxis of uric acid lithiasis by allopurinol, although none of these were prospective randomized trials.

Metabolic syndrome
Deeper knowledge of the 'metabolic syndrome' highlights associations between uric acid stones and diabetes or glucose intolerance. Urate stone-formers could be screened for diabetes or glucose intolerance, or subjected to genetic studies. Moreover, as an

association has been demonstrated between high body weight and low urinary pH, weight loss could be suggested as a treatment for idiopathic uric acid nephrolithiasis in obese patients.

Surgical Management

A stone-removing procedure may be needed in patients who do not respond to dissolution therapy or have complicating features, such as urinary obstruction, sepsis, or unremitting pain. Uric acid stones are amenable to all modalities of lithotripsy. Three months after shockwave lithotripsy and postoperative pH manipulation therapy a stone –free rate of about 90% could be expected. Better success was observed with stones smaller than 20 mm and situated in the renal pelvis. The uric acid stones can also be removed effectively with ureteroscopy and Holmium laser lithotripsy or percutaneous nephrolithotomy and ultrasound lithotripsy. These are mainly assigned based on stone volume but other patient factors may influence treatment choices.

Calcium nephrolithiasis, gout and uric acid stones: how are they related?

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It has been known since many years that calcium stone disease can often be observed in gouty patients and that, mixed calcium (oxalate) and uric acid stones may occur in a small but significant fraction of stone forming patients.
The association between uric acid and calcium Nephrolithiasis should be viewed on different grounds:

1. are gouty patients specially prone to calcium stone disease?
2. uric acid and hyperuricosuria may act as a promoter for calcium stone formation?
3. is treatment of hyperuricemia and/or hyperuricosuria effective to prevent stone recurrence?

These points deserve distinct discussion.

1. Recent epidemiological data report that incidence of symptomatic Nephrolithiasis is about 16% in gouty patients, but increases to 34% if patients undergo CT scan. Compared to non gouty pts calcium oxalate stones were less frequent, but still about 45% of total vs 66% , whereas uric acid stones were 43% vs 18.2%. The prevalence of metabolic derangements was comparable between gouty and non-gouty, save for pH which was lower in the former. Interestingly, allopurinol therapy tended to reduce the above differences. Common underlying predisposing factors include resistance to insulin action and consequent changes in tubular function.
2. it has been reported that hyperuricosuria occurs at a higher than expected rate in patients with calcium stones. In our own experience 17.6% of men and 12.5% of women with Ca Stones had high uric acid excretion, defined as > 600 and > 700 mg/24h in females and males respectively. It has not been so far elucidated whether this association is merely casual or causative. It has been suggested that uric acid reduce the upper

limit of metastability and, therefore, the solubility of calcium oxalate.

3. allopurinol was shown to be effective in a controlled trial conducted on hyperuricosuric calcium stone formers. Gouty patients on treatment with allopurinol show a stone composition closer to non-gouty ones. Alkaline citrate salts are effective to prevent both calcium and uric acid stones, not only for their effect on citrate excretion, but also for the increase of urine pH.

In conclusion, the relationships between gout, uric acid and calcium Nephrolithiasis are still under investigation. Both gout and calcium stone disease have been associated with metabolic syndrome, insulin resistance, high consumption of fructose. It is therefore suggestive that, in a fraction of patients, western habits may be a common basis for these diseases.

Treatment of Calcium Nephrolithiasis in the Hyperuricosuric Patient

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Objective: Hyperuricosuria may be a risk factor for calcium oxalate (CaOx) stone formation. Febuxostat, a xanthine oxidoreductase inhibitor (XORI), may reduce the incidence of recurrent CaOx stones in hyperuricosuric calcium stone formers. We studied whether febuxostat, compared with allopurinol and placebo, would reduce 24-hr urinary uric acid (uUA) excretion and decrease diameter and number of existing stones.

Methods: In this 6-month, double-blind, multicenter, randomized, controlled trial, hyperuricosuric (>700 mg/d) subjects with a recent history of CaOx stones and ≥1 3-mm stone seen by multidetector computed tomography (MDCT) were randomized to receive daily febuxostat 80 mg, allopurinol 300 mg, or placebo. Primary endpoint was percent change from baseline to Month 6 in 24-hr uUA. The secondary endpoints included percent change from baseline to Month 6 in size of index stone and change from baseline in the mean number of stones.

Results: Of the 99 subjects enrolled, 86 completed the study. Key baseline characteristics were balanced. Febuxostat led to significantly greater reduction from baseline in uUA than either allopurinol (p=0.003) or placebo (p<0.001). Reductions in stone size and number with febuxostat were not statistically greater than allopurinol or placebo. There was no change in renal function across groups.

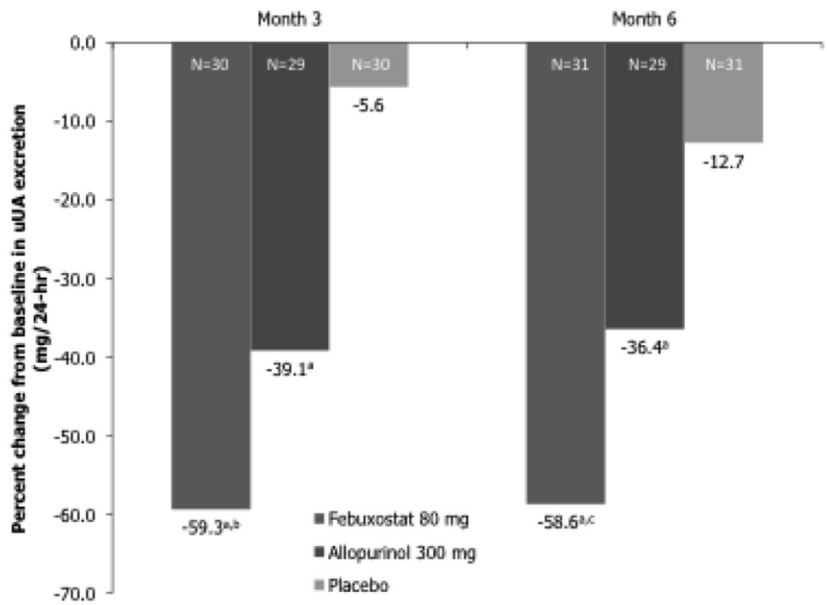

Figure: Percent change from baseline to Month 3 and to Month 6 in 24-hr urinary uric acid excretion. [a]$p<0.001$ vs placebo; [b]$p=0.008$ vs allopurinol; [c]$p=0.003$ vs allopurinol.

Conclusions: Febuxostat 80 mg lowered 24-hr uUA significantly more than allopurinol 300 mg in stone formers with hyperuricosuria. After 6 months of treatment neither XORI was associated with reduced stone number compared with placebo. Extended duration of febuxostat treatment leading to greater 24-hr uUA reductions compared with allopurinol may demonstrate improved prevention of CaOx stone recurrence.

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Genetics findings from the Global Urate Genetics Consortium

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Uric acid is a final breakdown product of purine oxidation in humans and present in the blood as urate. Hyperuricemia, elevated levels of serum urate, can cause gout, the most prevalent inflammatory arthritis in developed countries. Furthermore, increased levels of uric acid are associated with obesity, blood pressure and insulin resistance metabolic syndrome, type 2 diabetes and cardiovascular disease. The heritability of serum urate concentrations is estimated at 50% 70%. Eleven loci identified by previous genome-wide association studies (GWAS) only explain 5-6% of serum urate variance, suggesting that additional loci remain to be identified.

We performed a meta-analysis of GWAS on serum urate concentrations among 48 studies with more than 140,000 participants of European ancestry, and on gout among >70,000 individuals (2,115 cases) in the Global Urate Genetics Consortium (GUGC). Secondary analyses included, among others, stratification by sex, pathway analyses, and look-ups of the associated loci in individuals of other ancestries as well as with other urate-correlated traits. Replication was performed in 32,813 independent samples.

Altogether, we identified and replicated 28 genome-wide significant SNPs associated with serum urate concentrations, including 18 new loci. Nominal association with gout was found for 17 of the SNPs. Sex-specific effects were found for *SLC2A9* and *ABCG2*. Network analyses identified two novel genome-wide significant loci through protein-protein interactions. Effect sizes were similar among individuals of Indian ancestry, African Americans and Japanese individuals. There was no combined effect of an effect-size weighted genetic urate score on other outcomes after correction for multiple testing.

The genes implicated by our screen highlight the importance of metabolic control of urate production and excretion, and may have implications for the treatment and prevention of gout.

Familial Uric Acid Stones

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Main risk factors implied to uric acid stone formation are related to urinary pH< 5.5, increased urinary uric acid excretion, the presence of cavities of low urodinamic efficacy and deficit of crystallization inhibitors.
At low uric acid supersaturation, the thermodynamically stable anhydrous phase is generated. The calculus is formed through a mechanism of intergrown and primary agglomeration of crystals, generating compact structures. At high uric acid supersaturation, the kinetically favoured dehydrate phase is formed. Intergrown and secondary agglomeration of crystals takes place, generating fragile and porous structures.
It is well known that certain factors may increase the risk of uric acid stones. These factors are mainly related to hyperuricemia and hypouricemia but others related to diabetes also should be considered.

Hyperuricemia imply abnormally high urate blood concentrations (blood urate > 7 mg/L). Many factors can contribute to hyperuricemia: insulin resistance, hypertension, diet, use of diuretics, alcohol consumption (one of the most important) and genetics. The gene SLC2A9 encodes a protein that helps to transport uric acid in kidney (1). Several single nucleotide polymorphism of this gene have significant correlation with high blood uric acid.

Recently it has been described a familial hyperuricemic nephropaty (2, 3). It is a rare autosomal dominant disease. Uromodulin gene mutations encoding Tamm-Horsfall protein is responsible in less than half of families. At least two other genes have been implicated: TCF2 and the gene encoding rennin.

Hypouricemia is related to abnormally low urate blood concentrations (blood urate < 2.6 mg/dL) and is clearly associated to genetic alterations. It can be distinguished two types. Hypouricemia type 1 is

associated to mutation W258X in the uric acid transporter URAT1 encoded by SCL22A12 (4). The hypouricemia type 2 implies mutations of both SCL2A9 alleles related to the glucose transporter 9 (GLUT9), that cause this hypouricemia by their decreased urate reabsorption on both sides of the renal proximal tubule cells (5).

Urinary pH< 5.5 is undoubtedly the most important factor related to uric acid lithiasis. The links between diabetes and low urinary pH has been clearly established (6). Thus, insulin is important in ammoniagenesis and recent data indicates that insulin resistance is associated with impaired ammoniagenesis. In this case, there is less urine ammonia available to accept protons and pH is lower. Diabetes Type I is mainly genetic in origin (7) and diabetes Type II has an important genetic component (8), this demonstrating other clear correlation between genetics and uric acid urolithiasis.

In a group of 750 stone formers we identified a 0.3% with hypouricemia and a 12% with hyperuricemia (9). In the group of hyperuricemic patients we found a 71% that exhibited hyperuricuria but only a 24 % showed potentially lithogen risk associated to urinary uric acid (Uric acid > 600 mg/L). These 95 hyperuricemic patients produced: 12% calcium oxalate monohydrate papillary calculi, 21% calcium oxalate monohydrate no-papillary calculi, 30% calcium oxalate dehydrate calculi, 11% Calcium oxalate dehydrate/Hydroxyapatite calculi,4% struvite calculi, 12% uric acid calculi and 4% calcium oxalate monohydrate/ uric acid calculi. Thus, it is important to consider that apart from the uric acid stones, in urine uric acid can induce calcium oxalate crystal development through heterogeneous nucleation, forming typical mixed uric acid/ calcium oxalate stones but also apparently “pure” non-papillary calcium oxalate monohydrate stones in which only very sensitive methods (as HPLC) can detect uric acid in the “core” calculus. It is important to emphasize that hyperuricemia can induce sodium/potassium urate crystallization (as needles) in papillary tips. As a consequence of the caused injury, this can induce papillary calcium oxalate monohydrate calculi development. This could be a mechanism of stone formation directly linked to hyperuricemia, but still needs further research.

As main conclusions:

-Hyperuricemia is more frequently found compared with hypouricemia. The main gene implied in both cases is SLC2A9.

-Hyperuricemia is linked to uric acid stone formation but also related to development of other calcium stones.

-Hyperuricemia seems that clearly correlates with hyperuricuria (71%), but not with the potentially lithogen risk associated to urinary uric acid (24 %).

-The relation between hyperuricemia and calcium oxalate papillary calculi could be important and should be investigated.

-Due to the larger amount of possible genes implied in uric acid lithiasis (or related), is still difficult to evaluate the actual impact of genetics on such type of renal stones.

-The most important factor linked to uric lithiasis is urinary pH< 5.5 , nevertheless still is not clearly understood the genetic impact on such factor.

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Global Warming and Nephrolithiasis

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Objective

Changes in climate have been frequent during the Earth's 4500 million year existence.
There are numerous estimates of temperatures during the current Holocene epoch that started approximately 12,000 years ago following the last glacial period. During this epoch there were warmer and cooler periods, although the global mean surface temperatures over the last 25 years have been higher than any comparable period since AD 1600, and probably since AD 900. This climatic trend, named "global warming", seems to be caused primarily by human-induced emissions of "greenhouse" gases. There is a growing consensus that the 21st century will indeed see some 2 degrees C or more in additional warming. A secondary effect of global warming may be an increase in the prevalence rate of urinary calculi. The aim of this study was to review the papers evaluating the implications of global warming in the current epidemiology of nephrolithiasis.

Methods

The initial literature database used for the review was developed using PubMed. The database spanned the period from January 2003 through December 2012 and was limited to studies in the English language. Seventeen citations were extracted on the basis of the following key words: "(global warming) AND nephrolithiasis","(global warming) AND urinary calculi", "climate AND urinary calculi)
After the lecture of the abstracts 8 papers (6-13) were chosen to be included in the final analysis together with other 5 papers (1-5) selected as "milestones" by the Author.

Results

A body of literature confirms a possible role of heat and climate as significant risk factors for lithogenesis. Chronic dehydration associated to hot climate, hot occupation and low water intake is a

common cause of urolithiasis. Outdoor working in the tropics and austere desert environment with integration of hard physical work or militar duty strongly increase the risk of developing renal stones (1-3). Seasonal variation of the number of acute presentations of urinary calculi was frequently but not unanimously reported (4-5).Recently, in a nationwide population based study of patient visits to emergency departments in Taiwan the seasonal trends in the monthly urinary calculi attack rates revealed a peak in July to September, followed by a sharp decline in October (6). Urine volume, sodium, and pH are significantly lower during the Summer than in the Winter (7). Such seasonal changes are consistent with summertime increased physical activity and sweating. In some rural population of the tropics chronic dehydration may induce hypocitraturia associated to a state of potassium deficiency that is probably worsened in the hot season. The sexes differ in the seasonal timing of stone risk (7). Men show a Summer high risk for calcium oxalate and uric acid stone formation, while women show a early Winter high risk for calcium oxalate stone formation. Ambient temperature and hours of sunshine but not humidity were found to have a positive association with the stone colic attack rates (8). For each degree increase in temperature the number of stone episodes increased by 2.8% and for each 1-h increase in sunshine by 0.2%. Ambient temperature was related with Internet search volume activity for kidney stones that has the potential to serve as a surrogate for kidney stone incidence (9).
Estimates from computer models predicted up to a 10% increase in the prevalence rate in the next half century secondary to the effects of global warming, with a coinciding 25% increase in health-care expenditures (10-13).

Conclusions

A possible role of heat and climate as significant risk factors for lithogenesis is confirmed substantiating the risk of a further increase in the prevalence rate of renal stone disease due to global warming in association to worldwide changing of lifestyle and diet in the populations.

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Nutrigenomics and Nephrolithiasis

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Nutrigenomics and nutrigenetics respectively study the effects of a dietary treatment on gene expression and chromosomal stability and impact of an inherited trait on the response to a specific dietary treatment or to "functional food".
Nephrolithiasis, for its etiopathogenesis, could be an ideal model of study to prepare, through nutrigenetics and nutrigenomics, personalized and more effective, therapeutic and preventive strategies.
Nephrolithiasis etiopathogenesis is strongly related to the metabolism of specific electrolytes as calcium and phosphate and metabolites as citrate, urate and oxalate and therefore, the genes regulating them. Although numerous trials with controls have evaluated efficacy of diet, fluid, or supplement interventions for secondary prevention of nephrolithiasis, none of them, as so far, have included a relation with polymorphisms of candidate genes.
A key example for such nutrient-gene interactions is the impact that variation of the calcium sensing receptor (CaSR) gene might have. The G allele of the CaSR R990G polymorphism gives a gain of function to the receptor, decreasing the set point for ionized calcium concentration. This effect, in conjunction both with other candidate genes or with calcium intake levels, may have influence for predisposition to nephrolithiasis.
In addition to CaSR, other genes involved in the metabolism of calcium and citrate appear to be relevant in the process of nephrolithiasis, including vitamin D receptor, claudin 14 and the renal sodium-citrate cotransporter.
On the other hand, it has been referred that diet of stone formers is high in animal protein, salt, fructose, and poor of citrate. High and low intake of calcium are both referred to stone formation. Therefore, it could be interesting to study the influence of these and other macro and micro dietary factors on genome through epigenetic regulation of gene expression.

In conclusion, it may be a promising issue for future studies of nutrigenetics or nutrigenomics exploring nutrient effect on the association between genotypes and stones.

Nutrition and Renal Stones: Results from the large Epidemiological Studies

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Objective:
Information on the importance of a variety of risk factors for stone formation has increased substantially over the past several decades. This presentation will discuss the findings of the relation between dietary factors and nephrolithiasis from large epidemiological studies.

Methods:
Several large cohort studies have examined the association between diet and stone disease using a prospective analytic design. Specifically, information about dietary intake was assessed prior to the diagnosis of nephrolithiasis. Cohort studies that have provided valuable information on the relation between diet and stone disease include:

1. Nurses' Health Study—121,000 female nurses with ongoing follow-up since 1976; aged 30-55 years at baseline; information on lifestyle, medications and a variety of other factors collected by questionnaire every two years; diet information updated every four years using a food frequency questionnaire; incident cases of nephrolithiasis were identified by self-report and confirmed by supplementary questionnaire; medical records were obtained from a subset and demonstrated the self-reports were reliable.
2. Nurses' Health Study II—116,000 female nurses with ongoing follow-up since 1989; aged 25-42 at baseline; follow-up procedures similar to the Nurses' Health Study (see above).
3. Health Professionals Follow-Up Study—51,000 male health professionals with ongoing follow-up since 1986; aged 40-75 at baseline; follow-up procedures similar to the Nurses' Health Study (see above).

4. Women's Health Initiative Observational Cohort—93,000 women recruited in 1993; 5 years of follow-up; aged 50-79 at baseline; single dietary assessment at baseline; stone events self-reported with no validation study.
5. Cohort of Swedish Men—48 850 men recruited in 1997; aged 45 to 79 years at baseline; diet assessed at baseline; stone events identified using registry data.

Results:
Higher consumption of dietary factors that are associated with an reduced risk of nephrolithiasis include calcium, potassium, and phytate.
Higher consumption of dietary factors that are associated with an increased risk of nephrolithiasis include oxalate , fructose, calcium supplements and vitamin C supplements.
Overall, higher fluid intake is associated with a lower risk of nephrolithiasis. Types of beverages that are associated with reduced risk include caffeinated coffee, decaffeinated coffe, tea, beer, wine, and orange juice. Beverages associated with a higher risk include sugar-sweetened sodas and punch, and possibly grapefruit juice.
When examining dietary patterns, there is a strong and consistent inverse association between the DASH diet and risk of nephrolithiasis.

Conclusions:
Many dietary factors are associated with the risk of nephrolithiasis. Based on the available literature, dietary modification may be an important and effective option to prevent new stone formation.

The Association between Chronic Kidney Disease and Renal Stones

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Kidney stones are a frequent condition in the general population. Although generally considered to have a somewhat benign clinical course except for the risk of recurrence, several systemic conditions have been associated with kidney stones, including chronic kidney disease (CKD). It has been reported that the glomerular filtration rate of patients with kidney stones is on average 3.4 mL/min/1.73m^2 lower than those without stones. Other studies reported an increased risk of CKD in subjects with stones in the range of 27 to 67%. However, the study of the association between kidney stones and CKD is made difficult by the potential protective role of established CKD on the further development of stones caused by the reduced urinary excretion of calcium that accompanies CKD and by the fact that CKD is often asymptomatic in its initial stages. On the other hand, end-stage renal disease (ESRD) would be a better suited outcome to study the association: the prevalence of kidney stones among people with ESRD ranges from 3.6 to 8%. Given the high prevalence of kidney stones in the general population, however, these data do not necessarily mean that a causal link exists between kidney stones and ESRD. However, two recent prospective studies contributed to shed light on the issue, reporting a risk of ESRD in individuals with kidney stones more than twice higher than those without stones after controlling for risk factors for ESRD.

Arguably some forms of kidney stones carry a higher risk of CKD than others. A number of conditions known to cause nephrocalcinosis, such as primary hyperoxaluria, distal tubular acidosis and hyperparathyroidism, also cause kidney stones. Nephrocalcinosis lends itself well in explaining the irreversible and progressive renal damage observed in kidneys of patients with stones. Other conditions that increase the risk of renal impairment are infectious stones (especially in cases of incomplete stone removal), rare genetic forms

of kidney stones, conditions that increase the risk of urinary tract infections such as anatomic anomalies of the urinary tract or neurological bladder, and coexistence of other risk factors for CKD. The mechanisms by which kidney stones would impair kidney function remain to be fully elucidated; however, functional and structural changes secondary to flow obstruction and inflammatory activation due to infection may play a role, as well as direct damage of crystals on the tubular cell.

Chronic urate nephropathy - does it exist?

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The kidney apparently plays an important role in the genesis of hyperuricemia and gout, because genes coding for gout relate to transporters in the proximal tubule. There is some discussion whether elevated plasma uric acid is a pathogenetically irrelevant consequence of reduced renal function or whether it is actively contributing to progressive loss of renal function, thus providing a potential therapeutic target. Recent animal work shows that elevated uric acid causes proteinuria and glomerular and tubular injury which can be prevented by lowering uric acid, thus arguing for a causal role.
A number of recent studies documented that plasma uric acid concentration is a predictor of any type of chronic kidney disease, at least in males, and this has particularly also well been shown in primary kidney diseases, e.g. IgA-glomerulonephritis, nephropathy in type 1 and type 2 diabetes and many others. This conclusion is also supported by the finding that in primary chronic kidney disease plasma uric acid concentration is correlated with arteriolar hyalinosis and arteriolar wall thickening.
Classical urate nephropathy has today become extremely rare in Western countries.
Recent data suggest, however, but do not yet definitely prove, that in nongouty chronic kidney disease lowering of uric acid concentration retards progression of kidney disease; indirect evidence had shown that in CKD patients lowering uric acid using Losartan causes less deterioration of glomerular filtration; a recent small prospective controlled study in CKD showed that Allopurinol reduced albuminuria and increased GFR, and in addition even reduced CV-events. Allopurinol may cause Stevens-Johnsons-Syndrome in genetically predisposed CKD patients.

This is not the case with the xanthin oxidase inhibitor Febuxostat which has so far not caused adverse events and lowered urate more effectively in small cohorts of CKD, but information on its impact on progression of CKD is currently not available.

Uric Acid: A Multisystem Metabolic Disorder

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Uric acid urolithiasis is an example *par excellence* for a seemingly local urologic manifestation that transpires as a result of systemic disorders. The uric acid precipitation in urine is not due to hyperuricosuria but rather due to unduly low urine pH which results in titration of the relatively soluble urate to the highly insoluble uric acid. In pursuit of the origin of the low urine pH, one encounters multiple systemic defects in metabolism. Uric acid stone formers have an increased acid load to the kidney. Part of this is due to excessive dietary intake but independent from diet, they have an apparent increase in endogenous acid generation. The nature of this increase is multifactorial and not completely understood but the intestine is a likely origin. The kidney effectively excretes this increased acid load bringing the organism into acid-base balance and should not pose a problem. However, another defect exists in the kidney in the form of the inability to properly utilize ammonia to buffer urinary protons. This defect can be a result of fat infiltration of the kidney and is a manifestation of tubular lipotoxicity. This leaves the kidney with using alternative urinary buffers to carry protons in the urine which is acceptable form an acid-base point of view. However, one of these alternative buffer is urate which when titrated to uric acid, will precipitate and sets the stage for urolithiasis. Although uric acid stones is a local urologic disease to the practitioner, the origins of its pathophysiology spans a broad scope of defects in metabolism and is a true downstream target of the metabolic syndrome.

What's the Evidence of the Association between the Metabolic Syndrome and Nephrolithiasis?

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Metabolic syndrome (MetS) is a complex disorder defined by a cluster of clinical factors (i.e. central adiposity, disorders of glucose homeostasis, insulin resistance, dyslipidemia and hypertension) and associated with known cardiovascular risk factors like low-grade inflammation, endothelial dysfunction and atherosclerotic disease. MetS has been correlated with several renal diseases, including nephrolithiasis (NL). MetS and NL share similar pathogenetic and epidemiological characteristics: both are originated by the interaction between genetic, environmental and hormonal factors and appear to be strictly related in the adult population and in obese children and adolescents. Furthermore, epidemiological data indicate that MetS and NL show a worldwide increased prevalence and incidence in the last decades with a high level of morbidity and mortality if not adequately identified and treated. At the state of the knowledge, the bases of these associations are not completely understood. Potential pathogenetic links between MetS and NL include metabolic factors promoting insulin resistance as well as stone formation in urine, environmental factors as diet, oxidative stress and inflammation and molecular changes impacting the transport of some analytes in urine. An increased prevalence of urate stones has been described in stone formers with metabolic syndrome. However, the large majority of these patients form urinary calcium stones. Recurrent calcium stone formers with MetS show the onset of NL later in life, with less familial predisposition compared to patients without MetS. On free-diet, they show a peculiar biochemical profile compared to both stone formers without Mets and healthy controls. A seven days low-salt intake diet significantly reduce the urinary supersaturation of calcium-oxalate salts only in stone formers with MetS, confirming the significant influence of environmental (i.e. nutritional) factors in the pathogenesis of NL in this setting.

These data indicate that NL has to be considered a multifactorial systemic disorder needing a multidisciplinary approach for an adequate management.

Bariatric surgery and nephrolithiasis

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Surgical intervention has become an accepted therapeutic alternative for patients with medically complicated obesity. Prospective and retrospective studies report significant and sustained weight loss after bariatric surgery that is associated with improvement of many weight-related medical co-morbidities, and statistically-significant decreased overall mortality for surgically-treated as compared to medically-treated subjects. Although the Roux-en-Y Gastric bypass (**RYGB**), the most common bariatric surgery currently performed, is considered it an acceptably safe weight loss procedure, it is now known that this procedure is associated with calcium oxalate nephrolithiasis. The main risk factor appears to be hyperoxaluria, although low urine volume and citrate concentrations may contribute. The prevalence of these urinary risk factors appears to be fairly common amongst the total post-RYGB population, occurring in up to one half, although the risk of stone formation appears much less. A small number of patients have developed oxalate nephropathy and end-stage renal failure. In the majority, however, renal function appears to benefit with a decline in hyperfiltration and proteinuria that is proportional to the amount of weight loss. The etiology of the hyperoxaluria is unknown, but may be related to subtle and seemingly sub clinical fat malabsorption. Treatments typically used for enteric hyperoxaluria (low fiat low oxalate diet; calcium supplementation) are at least partially effective. Clearly, further study is needed to define better treatment options, and to identify those at risk for stone formation and, most importantly, those at risk for more serious complication of renal failure.

Metabolic Bone Disease in the Stone Former

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Hypercalciuria is the most frequent abnormality encountered in idiopathic calcium stone formers. Given that calcium is mainly stored in the skeleton, the question arises whether idiopathic hypercalciuria is the direct consequence of a skeletal abnormality, i.e is primarily a bone disease, whether idiopathic hypercalciuria is just a marker of a nephropathy leading to a renal leak of calcium with secondary negative calcium balance, skeletal abnormality and urine crystallization, or whether idiopathic hypercalciuria is the consequence of exaggerated ingestion, and/or absorption of calcium with secondary calcium accretion in the skeleton and calcium-phosphate deposition in soft tissues.
The purpose of this lecture is to dissect out the pros and cons of each of these scenarios.

Fasting hypercalciuria

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BACKGROUND:
Bone demineralization is frequent in renal-stone formers with idiopathic hypercalciuria, which comprises both fasting and absorptive hypercalciuria. Fasting hypercalciuria, after a calcium-free diet, may result either from a bone mineralization balance favoring catabolism or from a renal calcium leak. The latter situation is rare and is characterized by fasting hypercalciuria contrasting with a low fasting serum calcium level and secondarily elevated parathyroid hormone serum level. Renal calcium leak may result from genetic diseases or pharmacological compounds such as loop diuretics. By contrast, fasting hypercalciuria with normal level of serum calcium is frequent and may reflect primary abnormal bone remodeling. We analyzed the determinants of low bone mineral density (BMD) in 65 idiopathic hypercalciuric male renal stone formers, including bone mineral density and oral calcium test after a calcium-free diet. Thirty-five percent of men had osteopenia. Fasting hypercalciuria in this population appeared as the only biologic factor associated to low BMD. A fasting calcium/creatinine ratio above 0.25 mmol/mmol was associated with a 3.8-fold increase in the risk of low BMD, showing that impaired bone calcium metabolism results in demineralization. We recently analyzed the determinants of low BMD in pre- and post-menopausal female renal stone-formers. Fasting calcium/creatinine ratio was higher than in the male population but surprisingly did not correlate with BMD. These results suggest that, despite high bone calcium turnover, bone density alterations in female differ from male and may be related to matrix remodeling alterations. Overall, fasting hypercalciuria may be of help for clinicians to identify male patients at risk for low BMD but its significance in female remains uncertain.

Pathophysiology, Classification and Management of Renal Tubular Acidosis (RTA)

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(Note: **acidaemia** is blood pH<7.4; **acidosis** may be a compensated state with normal pH.)

RTA is a generic term that can be used to describe several disorders in which there is a failure of normal (and appropriate) renal acid excretion. Acid retention due to impaired renal function occurs in chronic renal failure (CKD), but in this setting the problem is a reduction in nephron number and less urinary buffer (*titratable acid* - less filtered phosphate - and *ammonium* - reduced proximal tubular capacity to synthesise ammonia) excretion, rather than a primary defect in renal tubular function and proton (H^+) secretion. In 'true' RTA there is usually a *hyperchloraemic normal anion gap acidosis* and (relatively) preserved GFR. Ammonium excretion may be decreased, but this reflects (probably) reduced conversion of NH_3 to NH_4^+, because of impaired H^+ secretion, rather than a decrease in ammonia synthesis (cf. CKD). (Indeed, when factored for GFR, ammonium excretion is NOT usually reduced.) In CKD the acidosis is usually of the *increased* anion gap type (due to retention of weak organic acids) and the GFR is significantly reduced.
A classification of RTA can be based on the main sites and mechanisms of renal tubular acid and base transport along the nephron. The PROXIMAL tubule is responsible for RECLAIMING filtered bicarbonate and generating 'new' bicarbonate as a by-product of ammonia/ammonium synthesis from glutamine. Impaired bicarbonate reabsorption is the hallmark of **proximal RTA** (type 2), but usually occurs as part of a renal **Fanconi syndrome** with characteristic 'tubular proteinuria', although there is a rare genetic form. The DISTAL tubule and COLLECTING DUCT are responsible for NET acid excretion, which is what is required to maintain normal acid-base balance - ~1 mmol H^+/kg on a typical Western diet. A characteristic feature of **distal RTA** (type 1 or classical), the more

commonly encountered form of RTA (at least in adults), and unlike proximal RTA, is a very low urinary citrate[1]. Nephrocalcinosis, renal stone disease, and bone loss are also more common in distal RTA than in proximal RTA. **Hypokalaemia** can occur in both types of RTA, but in the variant of distal RTA associated with **hyperkalaemia** (type 4) the problem is usually the result of reduced aldosterone secretion, or its action, as well as the effect of hyperkalaemia itself to suppress ammonia synthesis, a key urinary buffer in acidosis (see earlier). Clinically, type 1 distal RTA is often associated with **hypokalaemia**, and is seen in patients with **autoimmune disease** (most commonly Sjogren's syndrome), especially in those with hypergammaglobulinaemia.

Measuring urine pH alone will not diagnose RTA; although, if it is >5.5 in the setting of a systemic acidosis (bicarbonate <20 mmol/l), and a near normal GFR (and no urinary infection), it is certainly suggestive and worth following up. Beware of relying on urine dipstix pH; while broadly in line with laboratory-measured pH, it can be variable and misleading, especially in the presence of infection. The best confirmatory test is a urinary acidification test using oral NH_4Cl or furosemide with fludrocortisone (the F+F test), after which the urine pH should fall to <5.3. In proximal RTA, if the plasma bicarbonate concentration is low and the filtered bicarbonate load is reduced, urine pH can fall to <5.3, but not in distal RTA.

Treatment of RTA remains symptomatic, and is mainly with oral alkali, best given as potassium citrate or bicarbonate, especially if hypokalaemia is present. In hyperkalaemic distal RTA, treatment is of the underlying mineralocorticoid defect. Correcting the acidosis in RTA has more to do with maintaining growth in children and protecting bones in adults; it seems to have only a modest effect on the progression of nephrocalcinosis or renal stone disease.

[1] What distinguishes so-called 'complete' from 'incomplete' distal RTA (a distinction originally made by Professor Oliver Wrong) is a reduced plasma or serum bicarbonate concentration (<20 mmol/l) in the former and a near normal level in the latter.

As yet the recent genetic advances and insights in RTA have not translated into any new or more targeted therapies, but they have improved our understanding of renal acid-base transport mechanisms, and they have also highlighted the wider prevalence of RTA - 'presby-RTA' - and its complications, as well as its earlier recognition and treatment.

Rare diseases as a challenge for medicine and society

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William Harvey, as we can read in his famous letter to the Dutch physician John Vlackveld in 1757, had as one of the first the intuition that the study of rare diseases helps us to solve common diseases.
Patients with rare diseases are awaiting an answer to their needs. Traditionally, however, research on rare diseases has been limited by the idea that it was too difficult to do and too little rewarding in terms of return of profit. This attitude has actually changed during the last decade, because it was realized that research on rare diseases may help finding solutions valid also for common conditions. Indeed, while we all invoke translational research as the way to adapt results of laboratory studies into therapeutic interventions for patients, rare diseases often need the opposite path: we observe rare patients in the clinical practice, then we find out that they have a genetic defect, and finally we reproduce the defect in an animal model to extend the observation further beyond the clinic. In the process we also learn a lot about the physiology and the pathology and have insight into the mechanisms of common diseases. In other words, studying a rare condition may enlighten the path to other discoveries and to break the boundaries between disciplines and specialities to provide solutions for the sake of the patients.

The Association Between CKD and Renal Stones

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Renal stones are among the commonest maladies that affect human kidneys, and result from the interplay of genetics and environment on urine chemistry. In the modern era of shock wave lithotripsy and endourology, they seldom lead to loss of renal units because of bulky or obstructing stones, although they are still the primary etiology for 1-3 percent of end stage renal disease (ESRD) in the United States and Europe each year[1]. It has recently been appreciated that kidney stones may also contribute to risk for CKD, although the mechanisms are still unclear.

Vupputuriet. al. reported the association between CKD and history of stones in a case control study in the United States (US), comparing 548 patients with newly diagnosed CKD from diverse causes to 514 age, sex, and race matched controls. A history of kidney stones was reported significantly more often by the subjects with CKD than by controls (16.8 vs. 6.4% respectively, $p<0.001$)[2]. A similar association was found in Taiwan, where21,474 patients who received their first-time diagnosis of CKD between 2001 and 2009 were matched with controls for sex, age group, and index year. Using conditional logistic regression analyses they found that, compared with controls, the odds ratio of prior kidney stone for CKD patients was1.91 (95% CI 1.81 – 2.01, $p<0.001$) after adjusting for potential confounders[3]. An association between history of stones and CKD was found in the Third National Health and Nutrition Examination Survey, a cross-sectional study of the US population, but it was dependent onbody mass index (BMI)[4]. In subjects with BMI < $27 kg/m^2$, the median BMI of stone formers (SF) in this sample, history of stones did not increase the relative risk for decreased GFR. Among subjects with BMI $\geq$ 27,SF had a significantly increased risk of having Stage 2 (1.66-fold higher) or Stage 3 (1.87-fold higher) CKD (using the K/DOQI definitions for reduced renal function), after adjustment for age, gender, race, systolic blood pressure, diabetes,

smoking, cardiovascular disease and health insurance, compared to non-SF.

Several population-based cohort studies have assessed the risk of incident CKD or ESRD in SF. Using the Rochester Epidemiology Project (REP), which includes essentially all residents of Olmstead County, Minnesota, investigators at Mayo Clinic matchedall 4774 SF whose stone formation was diagnosed between 1986 through 2003 1:3 to 12,975control subjects[5]. After excluding those with prevalent CKD (which was significantly more common among SF than controls even after adjusting for comorbidities) the risk for incident CKD was assessed using Cox proportional hazardsmodels adjusted for age, gender, and comorbidities (hypertension, diabetes, obesity, dyslipidemia, gout, alcohol abuse,tobacco use, coronary artery disease, heart failure, cerebral infarct, and peripheral vascular disease). During a mean of 8.6 years of follow-up, SF were at increased risk for a clinical diagnosis of CKD (hazard ratio1.56; 95% CI 1.39 to 1.77). A second study, using a larger cohort drawn from the REP with mean follow-up of 7years, found an increased incidence of ESRD in SF as well (hazard ratio1.98;95% CI 1.13 to 3.45)[6]. Another group of investigators used the Alberta Kidney Disease Network databaseto assemble a cohort of over 3 million adults aged ≥18 years who resided in Alberta, Canada, between April 1997 and March 2009, and were followed for a median of 11 years[7]. Patients with pyelonephritis before or during follow up were excluded. Having at least one stone during the follow up period increased the risk of incident ESRD(adjusted hazard ratio 2.16; 95% CI 1.79 to 2.62) and CKD defined as eGFR<45 ml/min/1.73 m^2 or less (hazardratio 1.74; 95% CI 1.61 to 1.8), and the risk of these outcomes appeared to increase with the number of stone episodes. This study and at least one other find an increased risk for CKD among female SF compared with male SF[8].

In the study from the Mayo Clinic, SF with CKD were significantly more likely($p<0.05$) than SF without CKD to have had a history of diabetes (41.5% vs 17.0%), hypertension (71.7% vs49.1%), and frequent urinary tract infections (22.6% vs 6.6%), based on univariate analysis[9]. However, in the cohort studies the association between kidney stones and CKD/ESRD persists after adjustment for

these and other known cardiovascular risk factors[5;7] suggesting that the association is more than the co-occurrence of common diseases. Multiple pathways may be involved.

All symptomatic SF are subject to episodes of obstruction, and the potential need for urologic instrumentation or surgery, possibly on multiple occasions, which may result in some renal injury; we do not have data from cohort studies regarding the type and frequency of urologic stone removal procedures to judge their potential impact on renal function.When compared to non-SF with ESRD, SF who developed ESRD had an increased occurence of past hydronephrosis (44% versus 4%), recurrent urinary tract infections (26% versus 4%), and acquired single kidney (15% versus 3%)[6]. In addition, some urinary abnormalities may increase the risk both of stones and CKD; SF with ESRD were more likely to have neurogenic bladder (12% versus 1%), and ileal conduit (9% versus 0%)[6].

Deposition of mineral in the inner medullary collecting ducts is the rule in most stone forming states except for idiopathic calcium oxalate SF, and such deposition is associated with local scarring and fibrosis[10]. In some diseases, mineral deposition can lead to severe papillary deformity due to the large amount of mineral deposited, as in renal tubule acidosis[11]; in the hyperoxaluric states deposition of calcium oxalate may involve multiple tubule compartments, including the cortex[10]. Even in the absence of local crystal deposition, cortical scarring may be found[12]. In a study of potential kidney donors, those with a history of symptomatic stones had significantly higher urine albumin excretion than either non-SF or asymptomatic SF[13], potentially an indication of subtle cortical involvement.

Future studies are needed to clarify the pathways by which stones can increase the risk for CKD, and to determine whether treatment to prevent stone recurrence can also decrease the risk of CKD in SF.

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Tubular CaSR and lithogenesis

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The calcium sensing receptor (CaSR) is a member of the pheromone class of G-protein coupled receptors that is expressed in a variety of tissues throughout the body and has been identified to have a number of physiological effects including: modulation of fluid and electrolyte transport, regulation of calcium uptake, modulation of bone formation as well as cell proliferation and differentiation.
We have investigated the role the CaSR plays in proton secretion and fluid reabsorption in the rat and mouse proximal tubule by modulating luminal calcium concentration utilizing a combination of in vivo micropuncture in rats, and in vitro perfused mouse proximal tubules. We demonstrated that increased proton secretion and fluid reabsorption were CaSR dependent by using CaSR knockout mice and a calcimimetic agent that specifically targets CaSR. Therefore we postulate that the receptor, by increasing the amount of H^+ ion secretion in the proximal tubule, would induce Ca^{2+} in the lumen of the tubule to become ionized making it ready for absorption in the more distal portions of the nephron. It may also be that receptor activation and the concurrent NHE stimulation may lead to enhanced Ca^{2+} absorption through the paracellular pathway in the proximal tubule.

Therefore we speculate that the luminal CaSR along the proximal tubule acts as a modulator of both fluid and Ca^{2+} absorption, thus making it a key element to avoid Ca^{2+} precipitation along more distal segments of the nephron.

Extrarenal calcium-sensing receptor, hyperparathyroidism and lithogenesis

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Calcium-sensing receptor (CaSR) is a protein membrane, ubiquitously expressed in mammalian cells, that is a key factor for the control of serum calcium concentrations by parathyroid glands and kidney.
Studies in animals and humans suggest the CaSR involvement in calcium nephrolithiasis. The analysis of CaSR genotype distribution in stone formers showed that polymorphisms at the CaSR gene promoter 1 may may predispose to stones. These polymorphisms may decrease transcriptional activity and CaSR renal expression.
A decreased CaSR expression has been also evidenced in vascular walls of uremic patients and in calcified arteries of normal subjects. Experiments in cultured vascular muscle cells (VSMCs) undergone to calcifying stimuli demonstrated that CaSR activation with calcimimetic drugs antagonizes the deposition of calcium salts in culture medium. The process of calcification develops after VSMCs assume an osteoblast phenotype that enables VSMCs to synthesize proteins of the bone production, like alkaline phosphatase, osteopontin, RANKL, Runx2.
These observations suggest that calcium nephrolithiasis could be a renal variant of the soft tissue calcification that occurs in the hypertonic environment of renal papillae. Calcium-oxalate stones form on deposits of hydroxyapatite in the interstitium of renal papillae and defined as Randall'plaque. Mechanisms leading to the Randall's plaque are unknown and osteoblast differentiation of renal cells has not been demonstrated.
CaSR expression was found decreased in parathyroid adenomas from patients with primary hyperparathyroidism (PHPT) and was attributed to a flawed transcriptional activity of promoter 1. Polymorphisms at the CaSR gene promoter 1 were associated with calcium stones also in PHPT patients. PHPT patients carrying the minor alleles at promoter 1 polymorphisms also showed higher serum concentration of ionized

calcium. In addition to promoter 1 polymorphisms, also A990G polymorphism located at exon 7 of the CaSR gene was associated with stones in PHPT patients. PHPT patients carrying the minor 990G allele had higher urine calcium excretion and were more frequently stone formers than homozygous patients for 990A allele. The stone risk in PHPT patients carrying 990G allele and rarer allele at promoter 1 polymorphisms was higher than the sum of the stone risk induced in patients carrying minor allele at one of the two polymorphisms. Therefore A990G may predispose to stones by aggravating the already high calcium excretion of PHPT patients.

In conclusion, CaSR may predispose to calcium stones with two different and apparently opposite mechanisms. A defect of its activity may affect the renal cell response to calcification stimuli in idiopathic stone formers. A gain of its function may increase the calcium excretion and the risk of urine calcium salt precipitation in PHPT patients.

The nutritional evaluation, the Parma experience

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1. There is much evidence that inadequate nutrition has a direct effect on lithogenic risk factors and on the development of kidney stones. High animal protein diet increases urinary calcium, uric acid, oxalate, and phosphorus and decreases urinary citrate and pH, as an effect of a higher intake of purine and phosphorus and of the urinary acidification. Similar lithogenic changes have been reported with high carbohydrate and fat intake. Even salt intake, which is generally much higher than recommended in industrialized countries, represents a powerful factor that increases calciuria and lithogenic risk, in synergy with animal proteins. On the other hand, a low calcium intake was formerly thought to be protective against the onset of kidney stones, but nowadays is considered a risk factor, since it promotes the intestinal absorption of oxalate and encourages the onset of bad dietary habits, such as a high animal protein intake. A low consumption of fruit and vegetables, leading to an inadequate intake of anti-lithogenic factors such as potassium, magnesium and citrate, is considered a risk factor for kidney stone too, although there are some fruits (such as figs, prunes and raspberries) and vegetables (such as beets, spinach and tomatoes) which are the main dietary sources of oxalate. As a matter of fact, the oxalate excretion is poorly related to the dietary intake .
2. Furthermore, a low fluid intake is a heavy risk factor for the kidney stone onset, leading to a low urine volume and thus higher urinary concentration of lithogenic substances. All kind of drink share this beneficial effect, except few juices (such as apple juice and grapefruit juice), cola and some sport drinks, for their elevated content of oxalate and carbohydrates, such as fructose.
3. Although the relationship between diet and kidney stones has been investigated by a large number of studies, results from studies comparing stone formers and healthy controls dietary habits are

conflicting; moreover is unclear whether these supposed differences are important in the development and the progression of the disease.

4. Thence, in Parma area (Northern Italy), we analyzed through two different survey instruments (three-day dietary diary and food frequency questionnaire) the dietary habits of idiopathic calcium nephrolithiasis patients, comparing them with a healthy control group. The peculiarity of our research is the simultaneous use of two nutritional analysis tools in the same subjects: the bromatological food decomposition recorded by 3-day diary and the food frequency questionnaire. The assessment of dietary habits over an extended period of time is a more sensitive tool than the methodical collection of dietary intake for a short period. It is difficult to find in scientific literature a precise match between the experimental studies that have tested the effects of different foods/beverages in controlled conditions and the daily clinical practice. In fact, the dietary record by food diary has both advantages, such as the precise determination of the quantities of every food consumed and the possibility of a bromatological decomposition, and limits, such as Hawthorne effect, the short length of the record and the possibility of bias due to the software that determines the composition of different foods. Thus, we believe that using two different tools for recording eating habits is preferable to choosing one or another, as demonstrated by the absence of overlapping of these two methods. There may be some factors, known or unknown, that coexist in a single food and mask the effects of other nourishments. Therefore the risk of kidney stone is not simply due to a sum of stone promoters and inhibitors taken with diet, but it must consider many factors regarding the single individual (age, weight, height, sex, race, job) and his food habits (methods of cooking, type and frequency of meals, food choice and preservation, variety of diet). Unfortunately, these elements are not always simply to identify.

The urinary saturation evaluation: the LithoRisk2® software

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Urine supersaturation with lithogenic salts (***ß***) plays a pivotal role in the pathogenesis of stone formation in the urinary tract.
In clinical practice, some patients with nephrolithiasis have never passed stones, whereas others can not provide any reliable analysis of the passed ones. In this case, by means of the estimate of ***ß*** in urine of stone forming patients, the nephrologist may speculate on either the composition of stones (missed or retained) or the risk of disease relapse. During follow-up, the reduction of ***ß*** values compared to baseline suggests favourable effects of medical therapy on the individual risk of stone formation.

LithoRisk2® software is aimed at defining individual risk of stone formation in patients with nephrolithiasis, by providing an estimate of urine saturation in urine samples.

By this program, input variables are measurements of the main urinary anions and cations involved in stone formation, namely, calcium, magnesium, sodium, potassium, ammonium, pH, phosphate, citrate, oxalate, sulphate.

The output is urine saturation with calcium phosphate dihydrate (***ß*** brushite), calcium oxalate monohydrate (***ß*** CaOx), uric acid (***ß*** UA) and cystine (***ß*** Cys).

Sometimes, ammonium and sulphate are not available in routine laboratories. In this case, LithoRisk2® yields a reliable estimate of those missed determinations by means of a multiple regression analysis (based on the measured values of urea, creatinine and phosphate), thereby enabling to calculate ***ß*** CaOx and ***ß*** brushite.

Comparing ***ß*** CaOx and ***ß*** brushite obtained by using measured values of both ammonium and sulphate, with the predicted ones we found highly significant relationships between the two sets of

calculations, with $r^2 = 0.70$, $p < 0.0001$ for β CaOx and $r^2 = 0.98$, $p < 0.0001$ for β brushite.

In order to improve patient's awareness of its own metabolic risk, actual excretions of the main promoters and inhibitors of stone formation are represented graphically and related to an arbitrary normal range.

The program is available also in English version which can be easily downloaded from Internet.

DELTA 2012: software for the clinical and biochemical follow-up of renal stone forming patients

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The assessment of patients suffering from nephrolithiasis often involves collecting a considerable amount of information regarding the patient's medical history, chemistries and instrumental evaluation. Consultation and analysis of such information is complicated by the sheer quantity and by the lack of uniformity of the data. The lengthy follow-up which such patients often undergo increases the amount of informations to be handled even further. As a result, the type and quality of the technical support used to gather data is of crucial importance if these are to be easily consulted and compared.

DELTA 2012 is a database for the clinical and biochemical follow-up of renal stone forming patients. The software is made up of sections devoted to the physiological and pathological patient's medical history, dietary habits, risk factors, laboratory and instrumental evaluation, clinical evaluation, diagnostic conclusions and treatments prescribed. For each section of the program a sequence of *forms* shows the user how to enter data; *electronic keys* give easy access from one form to another to enter new data or correct existing data. The *fields* shown in the forms vary: 1) fields to be filled with data chosen from a series of predefined options 2) fields where data can be entered in numeric format and 3) fields which can be compiled writing freely in text or numerical format.

POSTERS

Blinded assessment of micro computed tomography accuracy in determining mineral composition in urinary calculi

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Clinical analysis of urinary stones is complicated by the wide variety of minerals found and the fact that the vast majority of stones are composed of more than one mineral. Micro computed tomography (micro CT) has recently been applied to urinary stones, and the technique shows promise as a non-destructive method for analyzing stones, but little testing has been done to validate the method. In this study, urinary stones were imaged by micro CT and compositions identified in a blinded manner, and then the same stones were analyzed by thin section and/or x-ray diffraction methods.

54 urinary stone specimens were scanned using a SkyScan 1172 system at 60 kV with a 0.5 mm Al filter, step size of 0.4 degree. Scans were reconstructed to a voxel size of 10-20 μm. Using these scans, the mineral content of each stone was identified. X-ray diffraction (XRD) and/or optical and scanning electron microscopy on thin sections were then carried out on the same specimens to determine the mineral and morphological compositions of stones. The XRD measurements were performed with microdiffractometer D/max RAPID Rigaku on whole samples (no need to powder the specimen).

The stone types were typical for Western countries, with 40 composed of calcium oxalate (CaOx), 6 uric acid and CaOx, 5 struvite, 2 apatite, and 1 stone a mixture of CaOx and ammonium urate. Of these 54 stones, micro CT analysis correctly identified the main minerals in 50 (93% accuracy). The 4 misses included 2 stones composed mainly of struvite, 1 stone with of mixed CaOx and ammonium urate, and 1 stone of mixed CaOx which had an unusual morphology. Micro CT also could not specify the form of CaOx (monohydrate or dihydrate) in 8 stones. However, micro CT also identified the presence of apatite in CaOx stones (by high x-ray

attenuation value, average of 3.9% apatite by volume) in 18 stones in which the apatite was not apparent by other methods.

Even in its present (early) development, micro CT provides accurate assessment of mineral composition in most urinary stones. In addition, micro CT also provides a more sensitive measure of the presence of apatite than does x-ray diffraction.

An Association between Kidney Stone Composition and Urinary Metabolic Disturbances in Children

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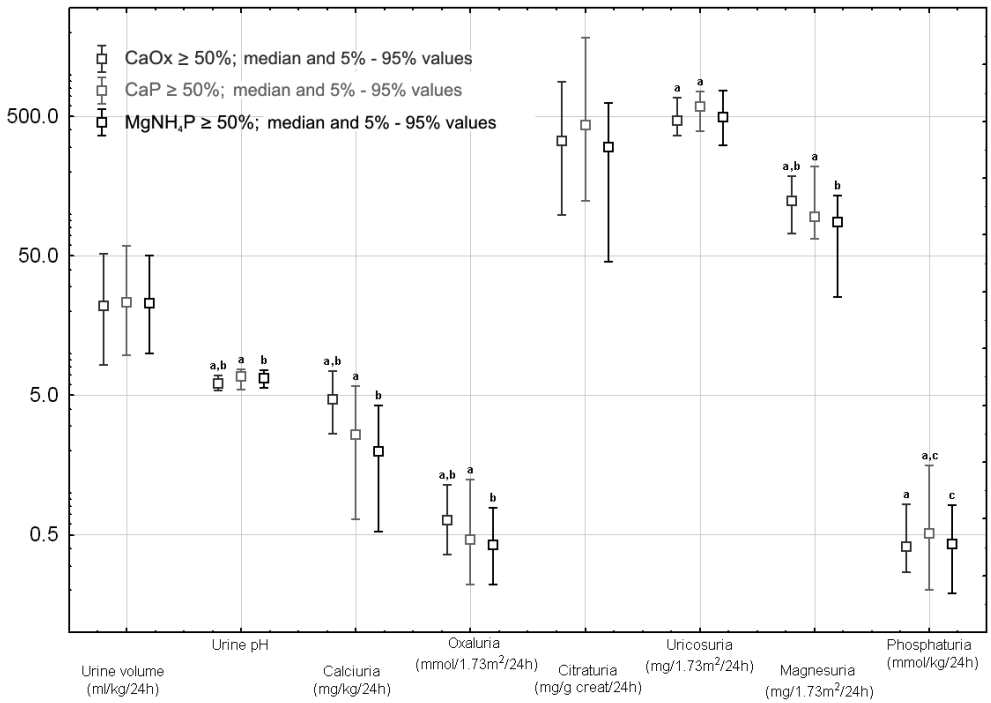
Abbreviations: CaOx - calcium oxalate, CaP - calcium phosphate, $MgNH_4P$ - struvite

Objective: To determine kidney stone composition in children and to correlate proportional stone fractions with urinary pH and accompanying metabolic urinary risk factors.

Subjects and methods: We studied 135 pediatric patients with upper urinary tract lithiasis in whom excreted stones were available for analyses. Composition of stones was analyzed using laboratory commercial test. A 24-h urine assessment included volume, pH and daily excretions of calcium, oxalate, uric acid, cystine, creatinine, phosphate, magnesium and citrate.

Results: The majority of kidney stones were mixed. Calcium oxalate was the major component of 73% stones, followed by struvite (13%) and calcium phosphate (9%). Uric acid was present in almost half of stones but in rudimentary amounts. The calcium oxalate content in calculi showed significant positive correlations with calciuria, oxaluria, magnesuria and acidification of urine. The percent content of struvite presented distinctly reverse relationships with regard to above urinary parameters. The calcium phosphate stone proportion revealed positive but not significant correlations with urine pH and phosphaturia and negative with calciuria.

Conclusions: The mixed composition of kidney stone in children may lead to difficulties in identification of the specific lithogenic factors and thus, urinary stone analysis in children should rather complement than replace urine metabolic evaluations.



Comparison of subgroups forming predominantly calcium oxalate, calcium phosphate and struvite stones (≥ 50 % of CaOx , CaP or $MgNH_4P$ in stone composition) are presented in figure.

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Body fat content and distribution as risk factors for nephrolithiasis

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Background and objective: The metabolic syndrome is associated with an increased risk of type 2 diabetes and cardiovascular disease. Higher total body fat and abdominal fat appear to have a more important influence than body weight in mediating this relationship, while higher fat content in lower extremities may be protective. Metabolic syndrome and obesity are also associated with a higher risk of uric acid nephrolithiasis, in part by lowering urine pH. However, it is not known whether higher body fat mass or abnormal fat distribution influence urine pH and uric acid stone risk. The primary objective of present study was to assess the influence of fat mass and distribution on urine pH and uric acid stone risk, and to examine the contribution of lean mass in this relationship.
Methods: In this cross-sectional study, non-stone forming men with a wide range of body weight, body fat and fat distribution collected a 24-hr urine while consuming a metabolic diet, and underwent a DXA scan to assess body composition and fat distribution. Urine pH and urine saturation with respect to uric acid (SI uric acid) were correlated with various measures of adiposity.
Results: Study subjects included 21 men (15 Caucasian, 4 African American, 1 Hispanic, 1 Asian) with a mean age of 52.1 years, mean weight of 86.0 Kg, mean total fat mass of 24.3 Kg, with mean truncal fat of 13.2 Kg and mean leg fat of 7.0 Kg. Mean 24-hr urine pH was 5.92, and mean SI uric acid was 0.85. 24-hr urine pH correlated inversely and significantly with total body weight (Spearman R= -0.45, p=0.039). The correlation of 24-hr urine pH with fat mass (R= -0.49, p=0.024) was stronger than with lean mass (R= -0.21, p=0.35). The correlation was also stronger with truncal fat (R= -0.52, p=0.017)

and trunk fat/leg fat (R= -0.58, p<0.01) than with leg fat (R= -0.13, p=0.55). After adjustment for % total body fat, the correlation between urine pH and leg fat mass becomes positive (R= +0.45, p=0.048). Similarly, the association between SI uric acid and fat mass (R=0.66, p=0.001) was stronger than with body weight (R=0.60, p=0.005) or lean mass (R=0.38, p=0.095). SI uric acid was also significantly correlated with truncal fat mass (R=0.69, p<0.001) and trunk fat/leg fat (R=0.72, p<0.001).

Conclusions: The association between 24-hr urine pH and SI uric acid and various measures of adiposity suggest that total body fat and truncal fat are stronger determinants of low urine pH and uric acid stone risk than total body weight and lean body weight. The positive correlation between leg fat mass and urine pH suggests that this fat compartment may protect against uric acid stone risk. Further studies are needed to confirm these findings in larger populations including women and stone formers.

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