

KIDNEY STONES: Causes and Prevention

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MEDICINE AND SCIENCE AS STORIES

Medicine

Medicine is made of stories, each one a person with illness from a disease. In any life, we have more than one such, most, fortunately, if not trivial at least limited. So it is in my practice of medicine. I will argue the general premise in science that stones arise from inheritance and the lives we lead, this latter being mainly diet and hydration but also innumerable oddities of behavior. But how a physician can make the scientific premise work toward successful stone prevention, is personal.

I have [written about it before](#). My focus was on my life as a professor, who has time enough for long patient visits and a financial setting in which billing for time and a practice limited to stone prevention are reasonable options. But I included a case, a real person as illustration.

Here I am more ambitious. I will share my techniques, how I enact the premise with individual patients, not by illustration but in general. I have, usually, 50 - 60 minutes to spend with a new patient, and from those minutes I need to understand disease in the context of a life lived. I think patients may find this illuminating. A few of my colleagues may enjoy a brief and passing interest, or amusement.

Science

The world we know, the one we can see and live in, arose from and arises from causes we can only infer. This is true for the stars in the heavens, the ocean seas, the tectonic plates we live over, and the diseases, including kidney stones.

My view, after a lifetime of thought, is that stones arise from a failure of compromises forced on humans throughout their evolution. Perfectly normal metabolic systems inevitably produce some risk of crystal formation in the kidneys, and in general evolution has favored a balance of risks that minimize stones. But in some people, because of inheritance or habits, or even accident and chance, workable compromise is breached, crystals form excessively, and they become stone formers.

I have told this story already, [most completely in my large website](#). The problem is that when told in extenso, whether in a book or website, or massive review, the story line becomes buried in details, like English History if we go too far into the Kings and Queens, and their unenviable wars and intrigues. This book is meant to give the story itself, and use the site for the details as one desires to read about them.

MY PRACTICE OF STONE PREVENTION

Kidney Stones in Life

What I Want from A Visit

I make a map of stone events, with their surgeries, overlaid by major life contours - other diseases, work, marriage, children, food, and whatever else seems important. Often, what has most promoted stones shows up clearly and offers things I can do. I try to get the crystal composition of stones as best possible, often sketchy at first.

I overlay on that map treatments that have been tried for prevention and major known associates of stones like high blood pressure and bone disease. I add in the family stone history and bone disease as well. As best I can, my written report is that map, to the extent words will convey it reasonably well in a reasonable length.

How I Get What I Need

That is my goal. Below is how I collect material in my practice, and the general order of my work. I write my note as we speak. As I write patients often correct themselves, or get in a detail or so. At the end I ask them if they think I have made a reasonable map of their life in relation to stones.

I try to get the map made in the first 30 minutes of an initial visit, so there is time to review lab findings and plan treatment. But I am not adverse to running longer and scheduling a second visit. Stones are chronic, prevention is utterly dependent on what patients choose to enact, so time spent in fashioning the right treatment program is not time wasted.

The Unique Importance of Conversation

You might think a list or questionnaire would be ideal for my purposes, but I have not found that so. I used many questionnaires, over five decades, not a few made by experts. All proved too cold, too narrowing, too explicit when compared to conversation. When everything is conversation, when I can follow as lightly as those old fashioned phonograph needles that once brought music to life from grooved vinyl, then I will capture what I need. Patients will know that is true, and be less unwilling to consider what I suggest.

Is this uniquely personal act of transcription not a large portion of what people pay me to do for them? Does it not reside in the very soul of medicine?

Making of the Map

How Many Stones, and When

I find it best to locate the first stone and the last, then fill in those between. Dates to a year or so work well to start with. How many falls into three grades - single, or first time stones, so many stones no one can count them anymore (more than 10 episodes) and the commonplace 2-10 episodes.

At the beginning I do not attempt to separate new stones from passage or removal of prior stones, merely to get the groundwork of symptomatic stone disease in the life at hand. But I do separate pain attacks from stones. Many times crystal passage causes a semblance of stone passage, and stones that do not pass can cause repeated pain attacks.

When I need to I count new stone episodes more exactly. [That is hard to do and I detail it here.](#)

Morbidity

For the whole of the episodes, how much morbidity? I count shock wave treatments, ureteroscopies, and percutaneous nephrolithotomies. Hospitalizations matter, sepsis, and terrible things like loss of a kidney or other surgical complications. What happened to the person? Just isolated brief episodes, or loss of work time, or jobs, or pregnancies.

Stone formers are abnormally prone to [hypertension](#), [bone disease](#), [cardiovascular disease](#) and - as noted - [pregnancy issues](#). [Kidney disease is also associated with stone forming.](#)

What

[What were stones made of?](#) This can take time beyond a visit. Here, perhaps, computer medical records may make a difference - I have found some stone analyses here and there searching in our hospital but mainly other hospitals. Sometimes patients have to ask their personal physicians, so the knowledge is much delayed. But it is crucial. How can you prevent crystals if you do not know what they are?

Prevention Efforts

What was offered and used to prevent the stones, and when? With the skeleton of the stone events in place, can you see any benefits from what was offered and used long enough to have some chance at improving matters.

Family History of Stones

I ask about father, mother, sisters, brothers and children. Patients sometimes offer grandparents and uncles/aunts. I do ask how many there are of each - even parents, sometimes there is no father or mother, or no one knows their health.

You might say this is decorative, but not I. Sometimes the type of stone can be guessed, outcomes for kidney or bone disease, diagnoses made, treatments used and what happened.

Other Diseases and Events

Diabetes, prolonged immobility, major surgeries, obesity, pregnancy - all are examples of conditions that predispose to stone formation. Essentially any consequential diagnosed disease or surgical event might matter, so I sketch them into the timeline of the stones. Perhaps more common and as important, people begin and end extreme diets, exercise plans, travel, training programs, lifestyle modifications and any of these could play a role.

Work

I find a large fraction of stone causes in work and the education that prepares for it. There is no sense in detailing this part as it is unique to everyone. Usually the most dramatic factors are travel for work - flying most of all, or long car trips. But especially in the early years work can involve very long hours, exposure to temperature extremes, time pressures. Education likewise - time pressures, work/study programs, high level sports - all these can be factors.

Major Life Events

Marriage, divorce, children, deaths, illness in the family, all these.

Food

I need to know present meals to interpret the all important 24 hour urine studies that underlie stone prevention. But prior diet is crucial - was there a yearslong oxalate binge? Fad diet, weight loss diets, odd diets, very low calcium diet, use of diet supplements. This topic is vast and every patient will have their own oddnesses.

Integration and Prevention

If I have a good map, and proper testing from serum and 24 hour urine, I can make up a reasonable case for how stones formed and what to do about them. This is what physicians do, and there is not sense to writing about it here, before we consider the scientific underpinnings of stone formation which follow.

When we have that, it will seem reasonably apparent how integration can take place.

STONES ARE FAMILIAL AND PRESUMABLY INHERITED

Familial Risk of Kidney Stones

Although evidence from multigenic studies remains scanty to the present time, kidney stones are remarkably [familial](#). This recent study from Sweden has special value in that data are countrywide and spousal data are available to control for diet, habits and the like. Their parental population was 8.09, the offspring 8.85 million, and incidence rates per 100,000 patient years for stone disease 90.5 and 94.2 for parents and offspring. The standardized incidence ratio (rate in offspring of stone formers vs. non stone formers) was 1.94 (1.62-1.96 95% CI). Spousal ratios were insignificant. A myriad of family studies all make the same point: kidney stone formation is strongly familial.

Monogenic Traits

Common practice includes treatment of [cystinuria](#) and [primary hyperoxaluria](#). A wide range of other [mendelian single gene abnormalities](#) can raise urine calcium or oxalate, overloading urine with stone forming salts. Inherited renal tubular acidosis raises urine pH and lowers urine citrate, which will promote calcium phosphate crystallizations. Disorders of purine metabolism can lead to increases in urine 2.8 dihydroxyadenine or xanthine, or remarkable excesses of uric acid - all reviewed in the above reference. Taken together, these are a scant tiny minority of stone patients, however instructive about the range of natural experiments. One presumes these kinds of gene mutations have arisen throughout human evolution, those with severe disease died, but carrier heterozygotes did not thus preserving the disorders.

Multigenic Factors

[Genetic variants](#) of the vitamin D receptor (VDR) and urokinase genes appear to have strong effects on risk of kidney stones in general populations. This massive meta analysis culled out these associations as the only seemingly reliable among many scattered through the literature. Whether or not they will be of use in predicting new stone onset remains an open issue, and their significance likewise.

STONES ARE AN PERSISTING EVOLUTIONARY DISADVANTAGE

They Must Reduce Reproductive Fitness

I think few would argue that kidney stones have been anything but a great disadvantage during evolution of humans. [Pain](#), [obstruction](#), infection, [bleeding](#), all these would greatly reduce the reproductive potential of an individual living in the absence of effective surgery, pain management, and means for controlling infection - as a hunter gatherer, for example. At least in modern times, stone forming adversely affects [pregnancy](#) and probably always has done so. One notices that stones are far less common among [children](#) than adults, and the average [age of onset, around 35](#) or so, well past the middle of reproductive years. Even so, they would tip the balance against those who form them. Despite all this, stone passage has been described into antiquity. [Rhazes wrote of them in the 900s](#), [Hippocrates in the 400s BC](#), and famously in a mummy. They have accompanied humans, apparently, despite all their disadvantages.

The Causes of Stones May Well Have Conferred Advantages

As we explore the way stones form, their persistence throughout evolutionary time will seem most probably a result of conflicting outcomes. In the broadest sense stone crystals reflect an [imbalance](#) between the amounts of stone forming materials the kidneys must remove daily, and the amount of water available to dissolve them, as in a salt pond whose seawater is let to evaporate.

For example, urine losses of calcium, oxalate, and phosphate, the three most important components of contemporary stones, urine pH, and urine citrate - the only fully documented inhibitor of stone formation - all reflect metabolic pathways that have their own purposes. Likewise, for water balance. It reflects water availability, non renal losses, and behavior.

Taken in ensemble these six factors can lead to stones - a disadvantage during evolution. But on the other hand, the processes they reflect also affect evolutionary fitness. So all may be compromise - the most beneficial settings for the metabolic processes and water balance versus the risk of stones from water loss inadequate to losses of stone forming materials.

My story is about that compromise.

THE EFFICIENT CAUSE OF STONES IS SUPERSATURATION

Without crystals stones can be nothing but aggregates of proteins, and though such 'soft' stones can occur they are more oddity than mainstream medical problem. So crystals are necessary to make consequential stones, and crystals form according to well established physical laws that transcend biology and lie outside the world of living things.

The Constituents of Crystals are Prone to Wander - Like Bees

The constituents of any crystal bathed in water, if you could see them, resemble honey bees around their hive. Endless comings and goings, lighting on the crystal surface and flying away. It is random motion, related to temperature, in our case 37°C. If the water is still, it will fill with our bees until the number lighting on the surface matches the number flying away. That point of stable crystal mass we call solubility. Like the hive, crystals are attractive to their visitors, who tend to loiter there. That is why crystals form in the first place. A few by chance find each other attractive, make a tiny colony, and others, lighting upon them randomly, loiter so the colony grows.

Should some of the water evaporate, the bees have less space to fly in, and will by chance find the crystal surface more often until enough of them attach to the crystal so those leaving and those entering balance once again. Should you add water, the opposite, and the colony shrinks as more leave than arrive.

The Constituents of Crystals Attract Each Other - Like Dancers

They are not really like bees. They are binary, charged, one negative, one positive, and opposites attract one another. Calcium, an atom, has 2 positive charges. Oxalate, a famous stone constituent, has 2 negative charges. Phosphate, the same, negative times two. So the proper image is not, perhaps, a hive but a dance, of men and women, who prefer to join for a while then part.

Not any kind of dance, but a folk dance, or formal ball dance where couples aggregate into patterns. The music plays, a few dancers begin, according to the rules of the dance, others add and leave, the mass of dancers being the mass of our crystal. They are not arranged like a lump of clay, but in a pattern, often of alternating sexes, once again determined by what people can do with themselves and the underlying rules or laws of the dance. So are the components of a crystal arranged in a pattern according to the laws of crystal structure.

I should not be totally focused on the binary. Sometimes molecules form crystals with themselves - uric acid for example. They are like the beautiful 'Women's Dance' I saw once at an orthodox Jewish wedding. Men, too. My grandfather's generation danced the Kazatsky, Polish or Russian, where the men display their balance, and athleticism. But if you look closely at uric acid crystals, or cystine crystals, you will find hidden attractions that draw them to each other, like to like, so they are a variation on the more obviously polar partners. [As an example, the nitrogens and oxygens link for uric acid.](#)

Saturation Quantifies Crystal Forming Propensity

Atoms and molecules cannot choose to dance or not but combine in thrall to unchanging laws of the universe, and the nature of those laws and their application to crystals were worked out long ago, by mathematicians and physicists and chemists. Their work culminates in the idea of saturation, a single expression that sums up the tendency for crystals, and therefore stones, to form, or dissolve, or grow.

That expression is called saturation. There is that point at which the constituents of a crystal enter and leave the crystal at the same rates, so the crystal will not grow or shrink. Called saturation, it is the axis around which all crystallizations pivot. Above saturation, supersaturation, crystals must grow, and if not present will tend to form. Below saturation, underaturation, crystals cannot form and will shrink if present.

Let me be perfectly clear. Saturation governs crystallization everywhere in the universe. In water systems as much as in molten metals. Biology produces innumerable molecules that can bind to crystal constituents so they are not free to crystallize. They can attach to crystals and disrupt their growth, or even cause them to come apart. Because living organisms can modify the rates of crystal formation and dissolution saturation is not *sufficient* to produce crystals, and therefore stones. But supersaturation is *necessary* for crystal formation, and undersaturation for crystal dissolution, and therefore degree of saturation exerts an inevitable control over stone formation.

Supersaturation In Stone Disease

How We Measure It

For all the image making, supersaturation is easily measured in urine usually as [calculated from a number of individual complexes](#) - eg. oxalate with calcium, with magnesium, with potassium etc, calcium with citrate, a crucial binding material. The article shows other ways it is measured but none are important for patient care.

What Affects Supersaturation

Exactly what you would expect. It is the relative amounts of the main stone forming materials vs. the amount of water - urine volume - to dissolve them. [For calcium oxalate, the most common stone crystal](#), it is the amounts of calcium and oxalate lost in urine vs. the amount of citrate (to bind calcium so it cannot make calcium oxalate) and the amount of urine lost in that same period.

Of course, that is to say the concentrations of calcium, citrate, and oxalate. But I mean to state it in relative rates of delivery out of the kidney. Calcium and oxalate losses are regulated independently of each other, and water loss is regulated independently and more rapidly. During a meal, urine losses of the former two will surely rise, but water loss may not - forget to drink, for example, eat outside on a hot day, and urine flow may fall.

On the other hand, the relative rates of calcium and citrate are independent of urine volume or oxalate, and they determine how well citrate can bind calcium so it cannot combine with oxalate.

For [calcium phosphate crystals](#), the same, except urine pH matters a lot as it determines whether urine phosphate will have its needed 2 charged sites. Depending on the foods eaten, urine may be acid - lower calcium phosphate saturation, or rise, the opposite.

For [uric acid](#), which makes stones, urine pH and losses of uric acid and water control saturation. Of these, urine pH is overwhelmingly important, volume next, and uric acid excretion least.

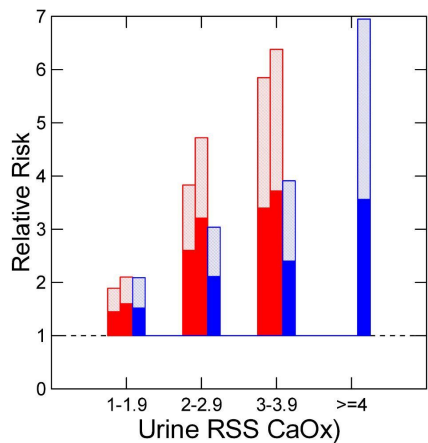
Saturation is Produced by Concentration Products

To a crystal, the concentration of calcium is by itself meaningless. Calcium atoms can add on to the surface of a crystal but cannot make more crystal without a corresponding oxalate or phosphate molecule, and the same for oxalate or phosphate taken individually. More crystal means calcium and oxalate come in reasonably equal amounts, for they will invariably leave in that manner. So the effect of a given calcium contraction on crystal mass is proportional to the concentration of its opposite number - oxalate or phosphate, depending on the crystal.

The only reason saturation is hard to determine is that calcium, phosphate, oxalate, citrate, all make multiple complexes in water so the actual amount of unbound, and therefore available crystal component requires one consider all known complexes [and solve for them simultaneously using a computer.](#)

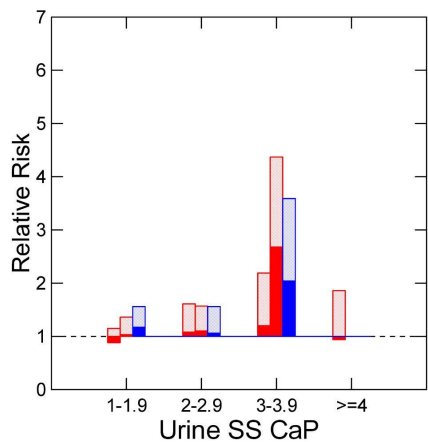
Supersaturation Predicts New Stone Onset

In the graph, the three cohorts are plotted as before. Calcium oxalate supersaturation is



in the upper panel. Through an arbitrary and, looking backward, unfortunate choice, the real values were divided by the mean value from a group of about 50 normal people so sort of make an index in which normal was set to 1. [To get the real value you have to mentally multiply these values by about 3.3.](#) So above 3.3 risk rises to about 2 fold, and thereafter rises steadily up to 7 fold, in men.

Calcium phosphate supersaturations, shown in the lower panel of the graph, are not altered, and the graph makes clear that risk begins above 1. Thereafter, risk does not rise smoothly, but rather peaks in one sector, 3-3.9 and is not even available above 4 except in one female cohort.



This is not surprising. Calcium phosphate crystallization is complex and begins with early crystal phases. In urine the main early phase is [brushite, a very soluble and rather unstable](#) crystal. Oxalate molecules can pull the calcium out of brushite to make calcium oxalate, or brushite can convert into the much more insoluble crystal called hydroxyapatite - which is the crystal of bone. As a result, brushite is itself rather uncommon as a kidney stone crystal.

But calcium oxalate requires a much higher supersaturation to produce itself than it requires if brushite comes first and provides convenient calcium atoms for oxalate to bind. So brushite is to calcium oxalate crystals like tinder to oak. The same, although for different reasons, for

the hydroxyapatite crystals we usually find in calcium phosphate stones.

A purist might say this experiment is unnecessary because supersaturation is the single force that drives crystal formation, but that is not true. Biological products can so modify solution chemistry, as I already noted, that supersaturation is necessary but not sufficient for stone

formation. That it indeed predicts risk of becoming a stone former means it is at least to some extent sufficient, and therefore of tremendous clinical value - to predict more stones, and to guide stone prevention.

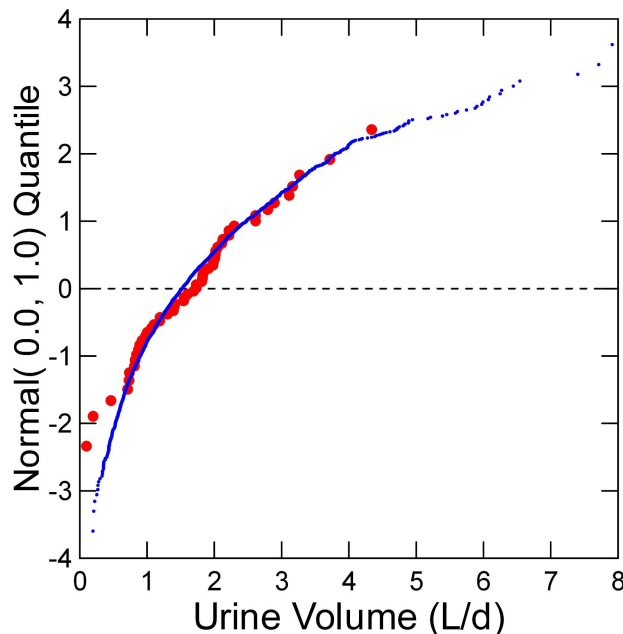
SUPERSATURATION IS, TO ME, THE CENTRAL FOCUS OF STONE DISEASE

Many biological processes influence supersaturation. The most obvious ones are urine losses of calcium, oxalate and citrate, urine pH, and of course urine volume flow. Each is controlled by its own biological system, and there are powerful interactions with diet. Because we influence supersaturation only by adjusting these influences, it can be easy to lose track of the main cause of stones, the supersaturations themselves. That is invariably regrettable.

What follows in my story is the subplots, water balance, and balance of calcium, oxalate, citrate, pH, and more. Each is a world of science and medicine. That is why stone prevention seems formidable. I suspect that the persistence of stones throughout our evolution has something to do with the settings for each of these individual contributors to saturation, for each can influence the general fitness of the individual as well as propensity to form stones.

I imagine not everyone will share my view, which is well founded but perhaps more personal than I might think. That should not worry me, nor disturb those who read this. Science is a story about presumed causes. Mine is no better than anyone else's who has thought about the matter. So I offer supersaturation centered story without concern, until such time it is falsified by new experiments.

WATER BALANCE



Urine Volume

You would think that stone formers had lower urine volume than non stone forming people, but that is not true so far as I can tell.

Each of the blue dots is a 24 hour urine from a stone forming patient, whereas the red dots are from normal people. The vertical axis is the 'normal' function, so normally distributed points would be straight lines. The mean is at zero - dashed line.

Urine volume is not so normally distributed, the low and high 'tails' are less common than one expects. In the middle, between about 1.5

and 3 liters of urine a day the data are straight. So it is more uncommon to be above 3 liters or below 1.5 liters a day than one might expect from the main group of points.

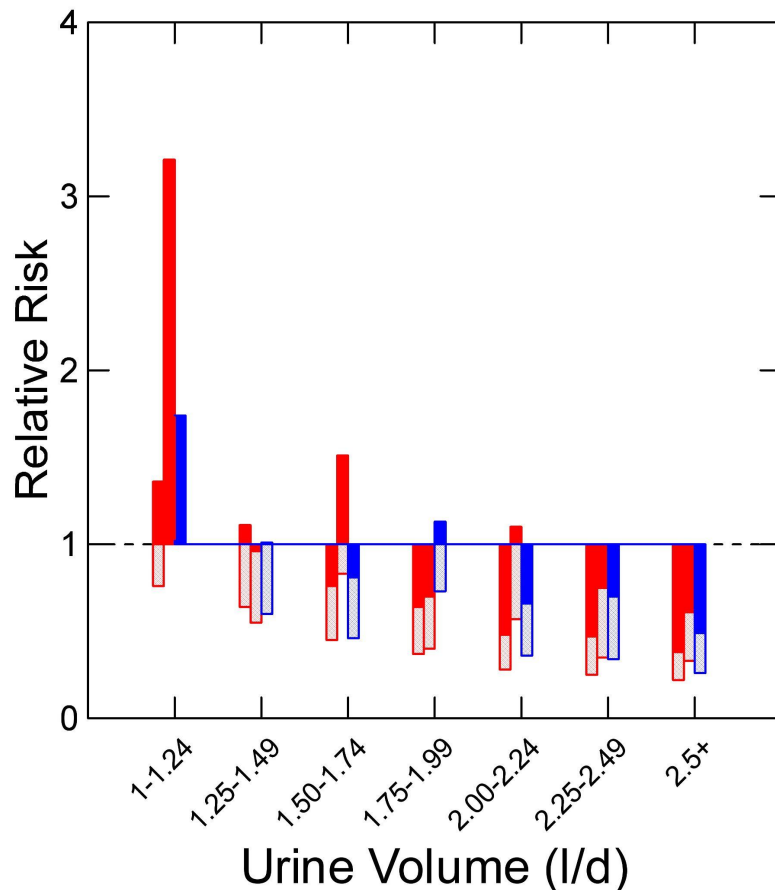
All this to one side, there is no basis here for saying stone disease is from low urine volume as a general rule, but some stone formers do have very low urine volumes that certainly could concentrate their stone forming materials.

All these data are from adults, but [children are the same](#). Urine volume is no lower in children who form stones than in their siblings or in children with no stones and no family history of stones.

Low Volume Raises Risk of Stones

On the other hand, those normal people who become stone formers during years of observation have lower urine volumes than those who do not become stone formers.

In three cohorts, 2 women (red) followed by questionnaires over decades, some people became



stone formers. Most, of course, did not. Those who did and a random sample of those who did not collected 24 hour urine samples for this study. As best one could, the controls - no stones - were matched in age and other traits to the ones who began forming stones.

On the vertical axis is the relative risk of being a new onset stone former for people whose 24 hour urine volume was in each of 7 groupings.

The dashed line at 1 divides the urine volumes as lowering risk (below the line) or raising it. The top of the bars above 1 and the bottom of the bars below 1 are at the mean - average - risk increase or reduction. The other end of the bar is the 95% confidence limit in the other

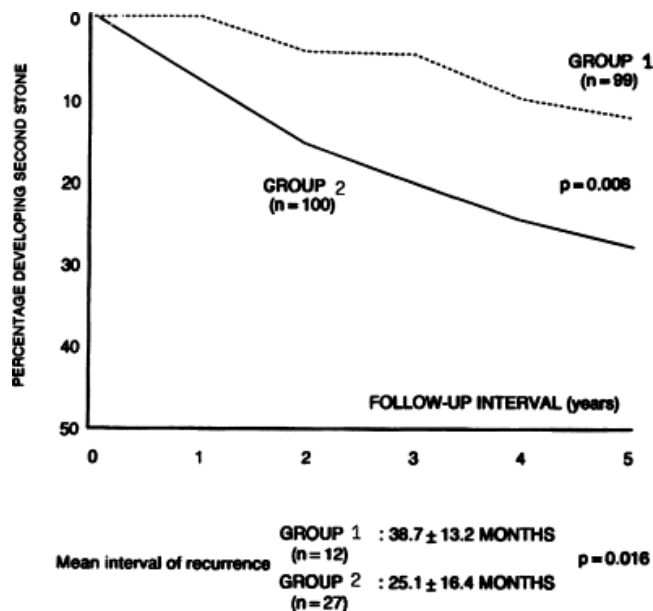
direction. For example the lowest range of urine volumes, 1 to 1.24 liters a day, raised risk by about 1.5, 3.2 and 1.7 fold in the 2 female (red) and one male (blue) cohort. The first bar lower part was below 1, so the increase in risk was not significant in a statistical manner. The other two bars did not go below 1 so the risk was significantly high (not likely a finding due to chance).

From there upward, more urine volume lowered risk with some spotty bars crossing the line at 1 until by 2.25 liters a day all bars were below 1. Even though as a group stone formers do not produce a lower urine volume than normal people, the first graph I showed, low urine volumes were more common among people who became stone formers during years of observation, which implies that low volumes cause stones.

More Water Prevents Stones

We have two facts. As a group stone formers both adults and children have about the same urine volume as those without stones. Yet, if you follow healthy people over time, those who become stone formers have particularly low urine volumes than those who do not. Does low volume cause stones?

A good way to tell is an experiment. Among people who have formed a stone, will a considerable increase of urine volume prevent more stones? That [trial has been done](#) and the answer is 'yes'. Here is the key picture from the article.



Both groups are people who had formed one calcium oxalate stone each. Group one, randomly selected, were coached by nurses to push their urine volumes over 2 liters a day while Group two people were left with just the advice to stay hydrated. By year five, urine volumes were 2.62 vs. 1.01 liters a day, respectively. So the Group 1 people had volumes that predicted stone risk in the three cohorts followed over time, and the Group two people had urine volumes predicted to reduce risk of stones.

By five years, 12 Group one and 27 Group two patients had formed at least one new stone, and the time it took to the recurrence was 38 and 25 months, respectively. So water can reduce new stones. It is interesting, is it not, that water in even large amounts did not stop stone formation altogether. After all, 12/100 people formed another stone over five years despite over 2.5 liters of urine flow a day.

Racial Differences in Stone Formation

Compared with white kidney stone formers, those of more recent African ancestry have markedly lower urine volumes. Apportioning total risk of crystal formation, [low urine volume](#) is the main apparent reason for their stones. This was not surprising because eating the same diets, black men and women have lower urine volume flow rates than comparable whites (referenced in the above article). As one would expect, serum vasopressin - the hormone that controls kidney water conservation - levels are higher in the black subjects.

As would be the case if vasopressin levels are high, drinking more water can raise urine flow only if more sodium is ingested, and this was found in black stone formers encouraged to drink more to prevent kidney stones. White men and women drinking more water readily excrete the water in their urine, but black people retain a higher fraction of what they drink which enlarges their systemic fluid volume. The higher volume of retained water triggers mechanisms that increase urine sodium loss. One presumes that water conservation was crucial during human evolution in Africa, although this is speculative.

Urine Volume and Stones

If we look at all four lines of evidence and ask what is the plausible underlying role of urine volume in stone disease, it would seem most significant but dependent on the excretions of the stone forming salts.

As a rule, stone former urine values overlap with normal people, and the relationship between urine volume and risk of becoming a stone former seems concentrated in the lowest urine volume groups 1-1.24 liters a day. In the water trial, Group 2 patients indeed had an average urine volume close to 1 liter a day and formed more stones. But even with a urine volume over 2.5 liters a day, Group 1 patients formed 12 new stones, so the higher volume cannot have countered all of the stone risks they had.

It is among black stone formers that low volume seems most prominent, for although I did not mention the fact their urine losses of stone forming materials like calcium are not increased. In some other cases, habitual or work related or other factors can lower urine volume so it becomes a main cause of crystal formation and stone disease.

The black stone formers, overall, seem most instructive concerning the situation over evolutionary time, when water could easily be scarce. It would have been most important then to minimize urine losses of calcium, for example, so as to reduce risk of stones.

URINE CALCIUM

The Overall System

In the boldest possible terms systemic calcium dynamics must maintain a critical blood concentration of calcium for cell function and bone and, at the same time, minimize urine calcium so as to reduce risk of crystallization that would damage kidneys. The system has the other requirement that, because calcium comes in with food, and rather irregularly, kidney removal of calcium must be regulated so as to match the net amount taken in from food to the bloodstream. These requirements are achieved by regulation of food calcium absorption, urinary calcium losses and movement of calcium in or out of bone.

A moment of thought will make clear to you that if the blood calcium must be very constant from minute to minute and food is eating irregularly then bone must provide minute-to-minute buffering. Between meals bone marrow must leave as calcium is lost in the urine and enter during the brief intervals where food calcium is entering the blood.

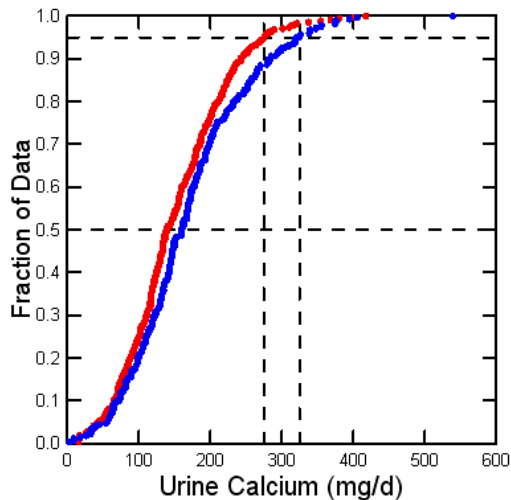
As a final complexity, human kidneys filter very large amounts of calcium into their tubules and reabsorb almost all along their length so the urine loss of calcium is primarily dependent on the fraction of the filtered calcium reabsorbed.

Full detailing of all the regulators controlling absorption of food calcium, reabsorption of filtered calcium and movement of calcium in and out of bone is not my intent here. Rather, I would like to focus on the settings they are brought to in order to satisfy the requirements I have already outlined, because it is those final settings that determine things evolution could work on such as crystallization in the urine or kidneys, or failure to regulate blood or bone calcium.

Kidney Tubule Calcium Reabsorption

Typical Normal Values for Adult People

Technically, we estimate reabsorption over short time periods with elaborate measurements. But an overall view needs a better perspective.



Let us say that over a few days, consider 4 as a reasonable number, we eat 20 millimoles (mg = 40 mg/millimole x 20 or 800 mg per day) or 80 millimoles of calcium (3200 mg) in 4 days. Urine losses must equal the amount absorbed daily.

The graph to the left shows urine calcium losses in large numbers of normal women (red) and men studied in metabolic balance units over the past century. The median is about 160 mg/day or 640 mg in 4 days, 20% or so of that eaten. The range, however, is very wide. For example 75% of normal appearing people have urine calcium excretions of 200 mg/d and 10% as high as 250 mg/d or more.

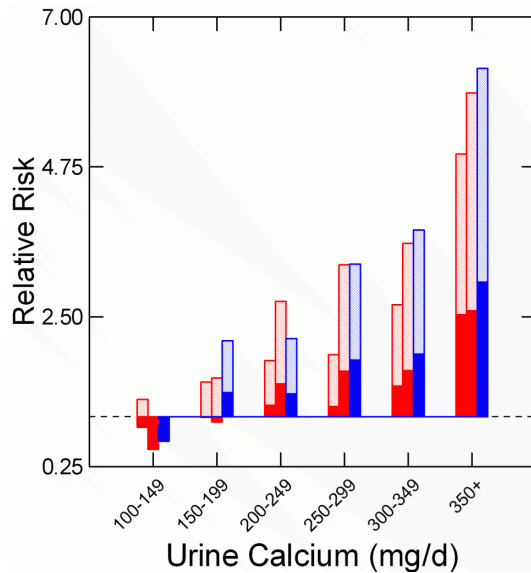
The kidneys filter a lot of fluid a day, let us say 125 liters/d is a reasonable mixed average for adult men and women combined, giving 500 liters over the 4 days. The fluid will contain the concentration of ionized calcium, which is about 1.2 mmol/liter, so we will filter into the tubules 600 millimoles of calcium.

If urine losses are to equal the amount absorbed (16 millimoles over 4 days) the absorption of the filtered calcium must be 97.3% leaving 2.66% of what is filtered in the urine. I showed you in my earlier graph that the median urine volume of patients and normal people is 1.5 liter/day, giving 6 liters over 4 days. The calcium concentration in the urine will average 16 millimoles/6 liters or 2.66 millimoles/liter about 2.6 times higher than in the blood.

These averages arise from continuous adjustments all geared to keep the serum calcium constant - that is what the body regulates from minute to minute. At any one time, calcium can be entering at higher rates, so bone mineral stores might rise, or at lower rates when bone acts like a storage battery and donates calcium to the blood. Overall, for the four days bone mineral is not changed.

Urine Calcium and Stone Formation

Just like the graph for urine volume, one can link increasing levels of urine calcium with risk for new onset of kidney stones in the two female and one male cohort followed over many decades.



Below 150 mg/d, close to the median for normal people, risk is at baseline. Thereafter risk rises continuously, reaching to an average of 6 fold at 350 mg/d of urine calcium. So stone formation is linked to urine calcium, and no doubt the urine calcium is causing the stones by increasing the urine load.

How does the urine calcium rise?