

THE PHYSIOLOGY OF KIDNEY STONE PREVENTION

A Narrative for Patients and Physicians

[A companion to kidneystones.uchicago.edu](http://kidneystones.uchicago.edu)

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PREFACE

*"This was a Poet - It is That
Distills amazing sense
From ordinary Meanings - " Emily Dickinson¹*

Our cells never left the sea. Sea salts temper the blood that bathes them². Because our bodies cannot make or destroy the salts or the water, kidneys must balance removal against intakes with a great exactness, even though intakes can be incredibly random³. While they balance removal against intakes, the kidneys must also control salt concentrations in the blood within the narrow limits required for life.

$$\text{RENAL REMOVAL} = \frac{[\text{INTAKE} + \text{PRODUCTION}]_{\text{days}} - [\text{GROWTH}]_{\text{years}}}{\left\{ \begin{array}{l} \text{WATER} \\ \text{SODIUM} \\ \text{POTASSIUM} \\ \text{CHLORIDE} \\ \text{CALCIUM} \\ \text{PHOSPHATE} \\ \text{MAGNESIUM} \\ \text{PROTONS}^* \end{array} \right\}} \text{MAINTAIN BLOOD VOLUME AND SALT CONCENTRATIONS}$$

^{*}, acid, from metabolism and diet.

At the same time, the calcium and phosphorus to make our bones must match our growth - over years, and from our middle years into old age must match our decline.

Then there is oxalic acid, an end product of metabolism whose calcium salt makes up the bulk of modern stones. Because it can be toxic, kidneys must

rapidly remove oxalate we produce and eat.

Given all this, can we be surprised that as they balance water, oxalate, and the salts, kidneys produce stones, perhaps incidently? Doubtless millenia of evolution weeded stone forming out as a great danger to survival. But incompletely, as some people are more prone than others to create stone forming urine⁴.

Because our kidneys must respond with exact precision to what we eat and drink⁵, it is our choices that control urine composition and therefore stone forming potential. My goal is to show how this control is exerted, because that knowledge can improve stone prevention.

Who will wish to read this? I hope patients and their families. Likewise physicians with an interest in the salts, in kidney stones, and the kidneys. What do I hope they will gain? A more subtle and nuanced view of how stones result from behavior and inheritance. Therefore a more thoughtful use of fluids and diet to prevent stones⁶.

Fred Coe, October 2022

¹ Footnotes are the 'other' text in this book - not poetry, perhaps, but my other self, as it were.

² I understand the list includes water and protons and the atoms that make salts. But 'salts' gets the idea across.

³ A balance less than perfect over many days, would create fatal accumulations or deficits.

⁴ I imply here a genetic component, well known to exist.

⁵ They must balance losses against intake and maintain steady blood concentrations at the same time!

⁶ This book complements the website. Neither is complete by itself

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SECTION ONE

Brief and unillustrated, this section introduces the systems that control urine kidney stone risk in response to diet and fluids. They regulate the composition and volume of the blood and modulate urine chemistry to fit the needs of what they aim to accomplish. In doing so they alter saturation with respect to the stone forming crystals, so stone risk can be visualized as a byproduct of systemic regulations that sustain life⁷ responding to what we eat and drink.

WHICH STONES CONCERN US HERE

My focus is on calcium oxalate, calcium phosphate, and uric acid kidney stones^{8,9}. Prime amidst peers as immediate stone risks¹⁰ are urine concentrations of calcium, oxalate, citrate and urine pH. In turn these reflect the balance between excretion of water, calcium, oxalate, citrate, and acid. Physiologies ancient and central to life vary these excretions so as to regulate concentrations and volume of blood¹¹. I imagine these urgent systems as indifferent to urine concentrations unless stones were a great enough disadvantage¹² during our evolution to force compromises.

My role here¹³ is to tell how the systems work and relate to one another, and how current treatments seek to alter their functioning so as to reduce urine concentrations and therefore new stone production¹⁴.

WHICH PHYSIOLOGIES CONCERN US HERE

Regulation of water balance, sodium balance, calcium balance, acid base balance, and oxalate balance¹⁵. Sodium matters here because it affects calcium excretion. Acid because it affects calcium and citrate excretions and urine pH. Calcium and oxalate balances have obvious roles. Phosphate balance is central to calcium balance and bone metabolism, and I plan to detail it in Section two, but urine pH controls calcium phosphate crystallization far more than phosphate

⁷ *In brief this is my main thesis.*

⁸ *Cystine stones are covered well on the site. Drug induced stones and rare genetic disorders causing stones are not part of this writing.*

⁹ *The links abound because this monograph complements the website, neither being sufficient unto itself.*

¹⁰ *Urine phosphate and urate excretions are relatively weak regulators of stone risk including risk for uric acid stones which depends mostly on urine pH.*

¹¹ *As they rule over blood these haughty princesses and princes disdain all that urine is, its complexity being mere and inconsequential as against their high calling.*

¹² *I mean the heartless culling of the vulnerable - stone formers dead or left by the way as tribes moved on.*

¹³ *Literally tell about, whereas in section two I illustrate them in detail and with references to the site and to outside science papers.*

¹⁴ *I consider this an exact summary of what I am after, and why.*

¹⁵ *That oxalate seems relatively minor among the great physiologies is to say it is a lesser system even if the molecule plays a great role in crystallization*

excretion so excretion is not one of the prime stone risks. The same for uric acid excretion - stone forming is overwhelmingly dependent on urine pH¹⁶.

SATURATION

Stone Prevention is To Lower Saturation

Like silt in a river, kidney stones form when urine flow is insufficient to carry away the calcium, oxalate, phosphate¹⁷ and uric acid¹⁸ kidneys must excrete. Hiding in that word 'insufficient' is all the rest - inhibitors like citrate, acidity or alkalinity that determine if calcium phosphates or uric acid will crystallize, and a myriad of ions that can compete with each other to reduce crystal formation. But ultimately, the big issues are volume flow, calcium, oxalate, citrate, and pH¹⁹.

These culminate in *saturation*, the true physical gauge of crystal forming propensity.²⁰ Unlike the uncertainties of physiology, saturation arises from thermodynamic principles that hold under all conditions we care about here. Saturation is our compass and map for stone prevention, a 'fixed point in the turning world'.

Saturation as an Image

Imagine saturation as a dance. Calcium is an atom with 2 positive charges. Oxalate, phosphate, and citrate are molecules each with two negative charges that can bind²¹ to calcium and make calcium oxalate, calcium phosphate²², or calcium citrate pairs in urine. Water is a molecule with both a negative and a positive charge so it can 'dissolve' these salts - keep them mixed in with itself - up to a point. Ultimately, a pair - like calcium oxalate - becomes so abundant that pairs are more likely to join with themselves than with water²³ whereupon they form solid crystals and leave the solution to become - perhaps - the core of a kidney stone²⁴. Saturation is that abundance of pairs - like calcium oxalate - in solution just sufficient to keep a mass of solid crystal bathed by that solution constant - not growing, not dissolving²⁵. Calcium citrate so binds

¹⁶ *I myself first proposed total urine urate excretion as a calcium oxalate risk factor, but time has eroded my enthusiasm for that thesis which is not considered in this monograph.*

¹⁷ *I mean the urine pH is too high (phosphate) or too low (urate) to tolerate what must be excreted to maintain balance.*

¹⁸ *Protonated, uric acid has low solubility; unprotonated urate salts are highly soluble. I use 'urate' to encompass 'total urate species' with fewer words.*

¹⁹ *pH gauges acidity (lower pH) or alkalinity; for now it saves words, later on I will define it properly.*

²⁰ *Charles Pak first used this felicitous phrase in his earlier writings, and I have never found better.*

²¹ *Bind because negative and positive attract one another*

²² *I realize phosphate can have 1 or 2 charges depending on pH; we need a picture here, not a blueprint.*

²³ *Most of the charge is between the pairs, so charge exposed to water diminishes vs. the mass of pairs until the pairs leave as a solid phase (this is a simplistic vision of a reality shown better on the site).*

²⁴ *Most crystals wash away in the urine, only some stay, grow, and become a stone*

²⁵ *So we speak of saturation with respect to a given pair - calcium oxalate, calcium phosphate, etc. Each pair behaves independently of the others - more or less (we are at the end of what this section can accomplish)*

to water it has a very great solubility compared to calcium oxalate or calcium phosphate²⁶. That is why one can have very high urine citrate concentrations without risk of calcium citrate crystals forming²⁷.

The Systems that Affect Kidney Stone Formation Have More Important Matters to Deal With

Urine flow reflects water balance which regulates blood²⁸ sodium concentration. Urine sodium reflects sodium balance that, in tandem with water balance, regulates the volume of blood and, almost incidentally²⁹, urine calcium. Urine calcium reflects regulation of blood calcium concentration against changes in diet calcium, sodium, protein and acid loads³⁰. Urine citrate and pH reflect the control of blood pH against diet acid and alkali loads, and acid balance also affects urine calcium. It would seem that incidentally and in passing, these vast systems control urine saturation with stone forming salts. I think they hardly notice³¹. Urine oxalate reflects maintenance of blood oxalate at very low concentrations over a wide range of oxalate production and absorption from food³². Urate behaves much like oxalate, kidneys aim to match excretion to production so as to keep blood levels from rising³³. Phosphate concentration must be kept within a reasonably narrow range³⁴.

The Peculiar Role of Refined Sugar in Stone Disease

Dextrose, table sugar, is a dimer of glucose and fructose refined from sugar cane and sugar beets. The glucose half raises urine calcium and lowers urine volume at the same time, so saturation and stone risk rise³⁵. The loss of calcium without food calcium means bone mineral loss. The fructose part raises liver production of fatty acids and creates insulin resistance, fostering obesity, diabetes, vascular disease³⁶, and uric acid stones from low urine pH. Use of refined sugar is regulated by ourselves. We like and eat it by choice though unnecessary and not healthy³⁷.

²⁶ *It takes calcium out of circulation, away from oxalate or phosphate. Think handsome dude at a party, calcium is the pretty girl.*

²⁷ *The abundance of calcium citrate pairs at solubility is vastly higher than for calcium oxalate or phosphate pairs.*

²⁸ *I will let 'blood' stand for the much larger volume of water outside our cells, and leave to purists and later chapters a more perfect naming.*

²⁹ *Sodium balance serves the circulation, urine calcium has no known relationship to that purpose*

³⁰ *Long ago the protein effect was ascribed to it being an acid load. We now know it is protein itself. Diet can impose an alkali load which decreases urine calcium, or net acid load which increases it.*

³¹ *An admittedly silly remark but on reflection not necessarily wrong.*

³² *Oxalate is secreted out of blood by GI and kidney cells through the same transporter with the seeming purpose of efficient removal. Oxalate appears to be a preferred substrate for SLC26A6 that transports chloride.*

³³ *This is silly as stated; evolution has sought to prevent gout from excessive blood urate which would reduce the fitness of the individual.*

³⁴ *The blood product of calcium x phosphate controls bone mineral stability.*

³⁵ *Later on I shall illustrate this effect and provide references.*

³⁶ *The site link is to a detailed article on fructose, lipids, insulin resistance and how my love for sugar cooled.*

³⁷ *One should be circumspect about nutrients, but refined sugars do seem utterly devoid of virtue.*

Fruits - the natural source of fructose - are healthy because of quantity. Eight oranges make up a 6 - 8 ounce glass of juice. Do any of us eat eight oranges at one sitting? The same for apples and pineapples, and all the rest. Juice extracts away the pulp and leaves the sugar.

Refining sugar from plants is just a more extreme example. We get the pure powder so we can bake with it, or stir it into chocolate. Refined sugar powerfully influences two of the systems - water regulation and calcium regulation, and is part of everyday life. Government recommendations now aim at much lower intakes than in the past. To me refined sugar is purely evil³⁸.

24 Hour Urines Show Us What Diet and Fluids Do to Average Saturation

Because urine chemistry varies remarkably with meals and sleep, stone prevention depends upon 24 hour urine collections to gauge daily *averages* of saturation with respect to the main stone crystals. The goal is to shift the balance between volume flow, calcium, oxalate, citrate, and pH to lower saturations, which means acting upon systems essential for life. It seems to me we will take more considered actions the better we understand those systems, and thus make treatments as efficient as possible³⁹. The problem of averages is hidden peaks we cannot know about⁴⁰.

WHAT THE FIVE⁴¹ SYSTEMS ACHIEVE

They evolved to maintain blood volume and composition as closely as possible to the needs of the body despite that we eat and drink only at intervals yet our kidneys lose water, sodium, calcium, and acid or alkali every one of the 1440 minutes in every day. They must balance losses against irregular intakes controlled not by them but by the caprice of chance and choice and still keep blood volume and composition stable. To achieve this, all five⁴² have sensors to gauge what they must regulate and powerful means to maintain internal conditions within a narrow range of variation despite a very wide range of diets and fluids⁴³.

³⁸ *One can sense that as I progressed the writing my passions rose up and prompted me to further extremes.*

³⁹ *This assumed link between understanding and treatment has guided my entire life as a physician and scientist, yet I know it is an untested assumption as likely wrong as right.*

⁴⁰ *Sleep is the most dangerous time as urine volume falls and urine calcium of stone formers does not fall as much as among normals.*

⁴¹ *Systems that balance urine removal against blood entry of water, sodium, oxalate, calcium, and acids.*

⁴² *Oxalate secretion is presumably regulated by its blood concentration, perhaps - we do not know this as yet - as sensed by the transporter that secretes it. Oxalate regulation is not so clear as for the other four.*

⁴³ *Phosphorus and magnesium come and go like ghosts in this book because not central to stone formation.*

Water Balance

Water balance is driven by brain sensors for blood sodium⁴⁴ concentration. Given a rise, the brain responds with thirst and the pituitary gland⁴⁵ with a hormone called arginine vasopressin (AVP) which controls how much water kidneys lose on a minute to minute basis. A sugar load can do the same - reduce urine volume flow. Since drinking follows thirst only irregularly, kidneys have been endowed with the power to inject relatively fresh water into the blood when water intake is insufficient^{46,47}. A fall in blood sodium suppresses AVP and kidneys rapidly excrete water in excess of sodium.⁴⁸ *Conscious high fluids can drive urine volume upward and reduce stone risk, but any lapse of extra fluid leaves the system free to its inherent regulation status which undoubtedly will be lower volume flow*⁴⁹.

Sodium Balance

Sensors throughout the vascular tree inform the brain about the stretch of large vessels⁵⁰. The brain responds through the autonomic nervous system and through an elaborate hormone system which includes renin, angiotensin 2 and aldosterone. The system links stretch to kidney sodium loss. Because water balance keeps blood sodium concentration constant, increased sodium intake increases blood volume and vessel stretch. As a result diet sodium controls urine sodium, the volume of blood, and therefore the state of the circulation. *Because kidneys link urine calcium loss to sodium loss, diet sodium controls urine calcium*⁵¹.

Calcium Balance

Calcium receptors on the surfaces of many cells, including those of the parathyroid glands and kidneys⁵², gauge blood calcium concentration and signal release of parathyroid hormone (PTH) and production of active vitamin D (1,25D), respectively. These in turn signal kidney, bone, and the GI tract to keep blood calcium constant. Depending on diet calcium and sodium, on refined sugar use, and perhaps on genetics, bone mineral may increase, decrease or remain stable and, of course, urine calcium may rise or not to promote kidney stones⁵³. *This system maintains*

⁴⁴ *I know that blood contains other osmotic solutes but sodium is so preeminent I omit the others here.*

⁴⁵ *The posterior lobe, essentially an extension of the brain cells.*

⁴⁶ *Concentration of urine sodium + potassium exceeds blood; sodium concentration of systemic blood exceeds renal vein blood.*

⁴⁷ *The main electrolyte in blood is sodium (140 mEq/l, vs. 4 mEq/l for potassium). In urine potassium and sodium may be equal in concentration so we need to consider both*

⁴⁸ *The sodium concentration of blood exceeds urine sodium + potassium. cursory but sufficient here.*

⁴⁹ *Italics make the main point. Conscious effort is pitted against a computer like water regulation, and will in all likelihood lose more often than not.*

⁵⁰ *Including the atria of the heart. Forgive simplifications here, we are at an early stage.*

⁵¹ *The link between urine and diet sodium depends on the water balance system, so one might refer to the sodium / water system as one in normal circumstances. This unity is not always appreciated.*

⁵² *Kidney calcium sensors increase urine calcium as blood calcium rises*

⁵³ *For the moment I omit FGF23 and phosphate balance, for clarity*

*stable blood calcium concentration and perhaps bone mineral stores; urine calcium loss is balanced to diet intakes so as to achieve these ends.*⁵⁴

Acid Balance

Certain kidney cells sense blood pH (acidity or alkalinity) which signals them to excrete acid or alkali into the urine. The system aims to maintain a constant blood pH by balancing urine acid or alkali losses to match diet intakes and metabolic production of acids. Kidneys treat citrate as alkali, perhaps because when metabolized citrate takes up a proton - the acid radical⁵⁵. Our interest here is when diet or disease make urine overly acidic or alkaline, and whether citrate is retained in the body or lost into the urine where it can defend against stones. Acid loads raise urine calcium and alkali the converse⁵⁶. *The systems seeks interior pH regulation, and urine pH and citrate and changes in urine calcium appear as an incidental byproduct*⁵⁷.

Oxalate Balance

Oxalate⁵⁸ is made by liver cells, and absorbed from food both through intestinal cells and between them. GI cells can secrete it from blood back into the gut lumen. The net of food absorption - GI secretion + liver production are the oxalate load kidneys must remove.

Kidneys readily filter oxalate and can secrete or reabsorb it in balancing urine excretion to net blood uptake. As the urine excretion increases, secretion plays an increasing role. Stone patients seem to excrete a higher fraction of the oxalate they filter out of blood, either because their cells secrete it more or reabsorb it less⁵⁹.

Spinach, rhubarb, rice bran, buckwheat groats, and almonds are the highest oxalate foods. Wheat berries, corn grits, baked potatoes, soy flour, and navy beans rank just below them. But foods with lesser oxalate contents but higher intakes can matter, so the article lists over 170 candidate food types of concern.

High diet calcium reduces oxalate absorption⁶⁰, enough so that one can focus on eliminating the foods with most oxalate in them such as the ones I just highlighted⁶¹. Unlike for water, sodium, calcium, and acid base balance, kidneys need not conserve oxalate in order to maintain blood levels, but merely remove it in response to load⁶². *High calcium diet is important to reduce*

⁵⁴ *For kidney stone patients this could seem heartless, but the body interior has precedence over urine. One suspects evolution disfavored stone formation thus minimized urine calcium for prevalent diets*

⁵⁵ *I am aware there are more exacting ways to state this and also aware that most readers will content themselves with this colorful if inexact naming*

⁵⁶ *Acid loads cause bone mineral loss and reduce renal calcium retention so urine calcium rises; alkali do the opposite. I do not know if this was ever of evolutionary significance.*

⁵⁷ *Citrate is just one of many food anions whose metabolism produces alkali, but it has special transporters perhaps because of its remarkable position in the citric acid cycle.*

⁵⁸ *Oxalic acid is so strong that both protons dissociate in blood and urine, thence always called oxalate.*

⁵⁹ *The site article references these points made here in brief.*

⁶⁰ *This requires calcium to be present in the meals that contain most of the day's oxalate.*

⁶¹ *Frankly, if diet calcium is 1000 to 1200 mg from foods eaten in main meals, one need not be driven into a frenzy over each mouthful for fear of oxalate.*

⁶² *I have seen no evidence to the contrary and know of no systemic need to maintain blood oxalate above a specific level, only to keep it below levels that might lead to tissue crystallization*

oxalate absorption so diet oxalate restrictions can be less stringent. Highest oxalate foods need to be avoided. So do substrate molecules like Vitamin C which the liver can convert into oxalate.

THE 24 HOUR URINE AVERAGES PEAKS AND VALLEYS

All the systems are open and dynamic⁶³. They must cope with meals and fluids taken consciously and at unpredictable times yet maintain blood volume, concentrations of sodium and calcium, and pH within very tight boundaries despite the fact that water, sodium, calcium, oxalate, and acid or alkali are constantly lost in urine, water and sodium and alkali through GI secretion, water and sodium in sweat, and water through respiration⁶⁴. *The 24 hour urine stone risk results therefore hide peaks and valleys but disclose the mean or average pressure toward crystal formation.*

Water

When we drink, kidneys can rapidly dispose of water to keep blood sodium constant. Between drinks, kidneys can inject relatively sodium free water into our veins⁶⁵ so blood sodium need not rise. When doing the latter, kidneys raise concentrations of sodium, calcium, and many other materials above blood levels and stone risk is easily elevated. Since water is lost in urine every minute, and we drink as we choose, the system is not ideally suited to prevent stones. *Between drinks, urine volume may fall rapidly and stone risk increase without conscious notice; 24 hour urines conceal this. Fluids are therefore important but not ideal in isolation as a stone prevention because the system is alert and ready to lower urine volume with sugar loads and whenever surplus water ceases.*

Sodium

Because kidneys track blood volume to control urine sodium losses, urine sodium tracks diet sodium sluggishly - averaging over about 3 - 4 days. A high sodium meal does nothing to urine sodium until enough water is conserved to dissolve that sodium and blood volume increases. The same going downward - constant low diet sodium gradually shrinks blood volume. Kidneys can conserve sodium so well we need only a little to survive, yet usually eat 5 to 10 times more than that. Since urine calcium follows urine sodium, consistent high sodium diets increase stone risk and consistent low sodium diets decrease it⁶⁶. *One good or bad day means nothing, but*

⁶³ *Open because water, sodium, calcium, acids/alkali and oxalate pass through the blood from food and metabolism to urine, dynamic because blood levels must stay stable against fluctuating flowthrough rates.*

⁶⁴ *This sentence was deliberately made too long as an emphasis on the equality of the components*

⁶⁵ *The system balances the sum of urine sodium and potassium concentrations against blood sodium concentration for reasons I define in Section Two.*

⁶⁶ *Because we must fill the tank with sodium - so to speak - in order to raise urine sodium loss, one high sodium meal can be atoned for by several more disciplined ones - a crucial nuance for stone prevention.*

constant high sodium will raise urine calcium and stone risk because urine calcium must accompany sodium⁶⁷.

Calcium

Between meals kidneys continuously lose a trickle of calcium in the urine and there is no way to keep blood calcium concentration constant except bone donate calcium by dissolving some mineral⁶⁸. With meals, the opposite applies. Food calcium cannot safely be allowed to enter blood and increase calcium concentration appreciably. Of course diet calcium can enter bone. But kidneys must efficiently remove diet calcium as it comes into the blood if blood calcium rises. Therefore one must expect a surge of urine calcium with every meal that has calcium in it⁶⁹. Refined sugar is like a meal in that urine calcium rises, but odd in that urine volume falls. Bone loses calcium as urine stone risk increases.

Between the trickle and the surge, and given no connection whatsoever between the calcium and water systems, urine calcium concentration is free to promote stones without any obvious biological regulators intervening. Because we drink with meals, the surge is somewhat protected against, but the trickle, perpetual and silent, always poses risk for stones and bone mineral loss⁷⁰. *Low diet sodium and thiazide can reduce urine calcium and stone risk⁷¹. Low refined sugar obviates surges from sugar.*

Diet Calcium and Urine Oxalate

Urine oxalate strongly affects CaOx saturation and depends in part on GI oxalate absorption which is itself controlled by the balance between diet oxalate and calcium. High calcium diet can reduce oxalate absorption presumably by combining with food oxalate in the GI tract⁷². *Diet calcium must be eaten with meals that contain most of the day's oxalate so as to reduce oxalate absorption⁷³. Low calcium diet can increase stone risk from high urine oxalate.*

Acid Balance

Each meal imposes a load of acid or alkali which kidneys must remove. Because living cells tolerate changes in blood pH poorly, the blood pH is 'buffered' against these incursions so acids

⁶⁷ *Some may accuse me of a plodding style in this phrasing but it is so basic and essential for stone prevention I want it emphasized.*

⁶⁸ *Some have spoken of 'labile bone calcium' but I cannot imagine calcium in bone not coordinated with phosphate into some crystal like octocalcium phosphate, or brushite. Others assume residual calcium in the GI tract spans periods of low calcium intake - to me an unproved and unlikely idea.*

⁶⁹ *With apologies I am explaining the reason for what I know happens. Perhaps Nature has a different reason.*

⁷⁰ *Experts will realize I am propounding some unproved ideas which are obvious enough to take seriously while awaiting experimental tests*

⁷¹ *There is nothing we can do to reduce risk from the trickle or the surge except reduce calcium loss via low diet sodium or drugs.*

⁷² *My explanation for why calcium lowers urine oxalate is often used but not rigorously proven. But well proven is the observation that giving calcium with oxalate greatly reduces oxalate appearance in the urine.*

⁷³ *Whether this reasonable advice affects stone recurrence awaits its trial, or may live on as too reasonable to reject.*

or alkali can pass through with minimal change in blood pH itself⁷⁴. Kidneys can rapidly filter and excrete excess food alkali as bicarbonate. Less rapidly, kidneys remove protons by producing and excreting ammonium ion, and by titrating urine buffers such as phosphate with protons their cells can secrete out of blood⁷⁵.

Two food amino acids - cystine and methionine - contain sulfur our cells oxidize to sulfuric acid⁷⁶. The main food alkali are molecules - like citrate - metabolized by taking up a proton. We can estimate acid /alkali load from urine measurements. Because alkali is removed more rapidly than acid, urine pH tends to rise with meals, and fall between⁷⁷. If you look closely, blood itself shows a slight parallel change. Alkali loads lower urine calcium, acid loads raise it. *In otherwise normal people high potassium alkali from foods will raise citrate and pH, and also lower urine calcium, so it protects against stones.*

Citrate

This molecule is at the center of the main pathway for producing energy from metabolism of food - the Krebs, or citric acid cycle. Present in mitochondria of nucleated cells like ours and immensely ancient, this cycle oxidizes fats, sugars and protein to create ATP that powers cells like electricity powers our modern lives.

Kidneys make provisions for citrate befitting its ancientness and grandeur. Filtered out of blood like most small molecules and ions, kidneys reabsorb it back into blood by a special transporter - NaDC1 - that is itself regulated by blood pH: low pH, citrate reabsorbed, high pH citrate is lost in urine. When reabsorbed citrate is metabolized by kidney cells as citric acid, taking up a proton to make bicarbonate alkali for the body. When we give citrate, the same⁷⁸.

Though merely one of a myriad of metabolites in food and urine, citrate concerns us for its powerful ability to bind calcium and to slow formation and growth of calcium stone crystals. *Although one can give potassium citrate as a supplement, food can provide all we need from fruits and veggies which have additional health benefits*⁷⁹.

EVOLUTION

All of these systems evolved in humans over hundreds of thousands of years⁸⁰ so as to optimize fitness as measured by successful reproduction. Of course they were shaped by the foods available, the energy requirements for successful reproduction, and the availability of water.

⁷⁴ *It contains considerable bicarbonate that can take up or release protons so pH remains nearly constant as kidneys remove the surplus alkali or acid*

⁷⁵ *Acid load from a 30 minute meal may require hours for kidney removal, hence the crucial importance of blood buffers.*

⁷⁶ *Most agree this is the main origin of acid from food*

⁷⁷ *Some will be aghast at this statement which is certainly true and not well studied.*

⁷⁸ *Citrate as the potassium salt is used to increase urine pH and citrate excretion. In principle diet should suffice but it does not, usually.*

⁷⁹ *This applies to calcium stone formers but not to uric acid stones created by a low urine pH against which diet may often not prevail.*

⁸⁰ *Primates evolved with mostly the same systems over millions of years. These are ancient physiologies.*

Because stones can form in adolescence and early adult life and would greatly reduce fitness, urine chemistries must have evolved against crystallization.

But we migrated out of Africa only 30,000 to 50,000 years ago, and within the past two centuries experienced industrialization and modernity. Fluids, diet, activity, everything evolution shaped us around have changed remarkably in a tiny needle point of time, and everything is out of tune. The great systems still maintain blood volume and blood sodium, calcium and oxalate concentrations and pH as they always have. But whatever provisions evolution mustered to regulate urine chemistries in defense against stones clearly no longer hold as stones are very common⁸¹.

THE END OF SECTION ONE

We have the main points

The systems that regulate blood volume and composition create saturation as an incidental byproduct. Refined sugar does the same - raises stone risk as an incidental byproduct of our pleasure in eating it⁸².

On the surface, evolution did not seem to prepare against stones. But since stones would be very dangerous without modern treatments, one imagines that the systems evolved around the common diet and fluid rhythms prevailing over vast swathes of time in such a way that stones did not destroy our species. Of course refined sugar did not exist then. My view is that high diet sodium and sugar, and low food potassium and calcium distort everything, and ideal prevention is to redress those distortions.

The message is clear enough - diet change can reduce urine stone risk in significant numbers of routine calcium stone formers⁸³. It may also improve general health with regard to bone and cardiovascular disease, and diabetes. The approach accords with informed opinion as reflected in the US diet guidelines.

Some Reflections on Stone Prevention

I have found that patients (and not a few physicians) perfectly well understand the main points in stone production and prevention but have not convinced themselves that the benefits outweigh the effort and expense of diet change.

⁸¹ *All of my inferences about evolution and stones are just that. I hope genetic studies will ultimately test these kinds of inferences.*

⁸² *It is the indifference of the life sustaining systems that most interests me. They vary urine composition to control blood levels cells must have. When we seek to change their behavior we can only deflect them toward one or another extreme.*

⁸³ *Uric acid, cystine, struvite stones are special and reflect diseases more than the imperfect fit between our physiology and our diets.*

Personally, I did not give up my habitual candy and cookie love affair until I had studied rather deeply into what sugar can do. It was as the enormity of the potential damage became clear that what I had always loved became anathema.

In the same way, high fluid intake for stone prevention can seem more fragile when one encounters the power of systemic water balance. How well can conscious will stand up to a system refined over hundreds of millenia to conserve water and to crystals that never sleep but like computers respond to any burst of saturation with growth or new formation? Will anyone who encounters this reality really want prevention to depend only on fluids when so much more can be accomplished?

The mind does not automatically link urine calcium to sodium, however much science says they link. But a look at the reality of the two may change how one feels about reducing diet sodium. It was that way for me with sugar and fat production, how easily my cookie turns into blood fatty acids.

The truly strange regulation of calcium balance between and with meals must surely move one to provide calcium with a majority of meals and shun sugars that act like meals but are only fragments.

That diet calcium reduces urine oxalate is the same: how more useful diet calcium than the obsessive and unnecessary distraction of measuring out every particle of diet oxalate until one hardly knows what to eat.

As for citrate as a treatment to move acid base balance in an alkaline direction, it may appear comical to squeeze lemons into water and drink so miserable a beverage when the richness of fruits and veggies around us can provide all the potassium and citrate we could ever need⁸⁴.

Why Do We Need Section Two?

Section Two presents the evidence for Section One⁸⁵. You can take my word for it, or inspect what data we have to date. One might want Section Two because Nature is beautiful, a wonderment, its details increasingly delightful as we approach them more and more closely. Perhaps beauty itself arose there as an ideal we can represent but never match.

I begin with inheritance but move swiftly to saturation as the center of crystallization. I then turn to the sodium /water system in detail, as two main clinical treatments involve changes in fluids and diet sodium. Then the calcium system, with all of its remarkable complexity comes in layers: How it looks in general, how it runs as a system, and finally into the thicket of the signallers and receptors. Sugar comes in here, as an undesirable regulator of kidney calcium handling, and then oxalate balance because so affected by diet calcium. Oxalate has its brief role in the play. At the last, acid base and citrate, and effects of acid base balance on urine calcium and bone.

⁸⁴ *Once again, I omit uric acid stones whose low pH underpinnings arise from disease that will not reliably yield to diet and must be treated with considerable supplemental alkali*

⁸⁵ *Presented below the demands of a scientific review but not so far below as to lose value. The site articles are referenced and used in the section, and some references are to the original reports on PubMed.*

SECTION TWO

STONES ARE FAMILIAL AND PRESUMABLY INHERITED

Familial Risk of Kidney Stones

Kidney stones are remarkably familial. This recent Swedish study of 8.09 million parents and 8.85 million offspring is countrywide with spousal data to control for diet, habits and the like. Kidney stones occurred in 90.5 per 100,000 patient years among the parents and 94.2 for their offspring. The standardized incidence ratio (rate in offspring of stone formers vs. non stone formers) was 1.94 (1.62 to 1.96 95% CI). Spousal incidence ratios were insignificant. Other family studies referenced in the article all make the same point⁸⁶.

Monogenic Traits

Cystinuria and primary hyperoxaluria are relatively common examples. A wide range of other 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, all of these highly instructive natural experiments comprise a tiny minority of stone patients. One presumes they have arisen throughout human evolution, those with disease died, but carrier heterozygotes did not thus preserving the disorders⁸⁷.

Multigenic Factors

This massive meta analysis culled out genetic variants of the vitamin D receptor (VDR) and urokinase genes as having strong effects on risk of kidney stones in general populations. Whether or not they will be of use in predicting new stone onset remains an open issue, and their significance likewise⁸⁸.

Some Stones Arise from Systemic Diseases or Infection

Struvite stones arise from infection in the urinary tract, wherein bacteria produce crystals through their metabolism of urea. Primary hyperparathyroidism is a systemic disease arising

⁸⁶ *Multiple factors that raise saturation are obviously familial, such as hypercalciuria - that can be bred for in rats.*

⁸⁷ *Of course I have elided mountains of monogenic traits as this book cannot hold them all except it become a tome. The reference gives on to longer lists, which themselves add more unto near infinity.*

⁸⁸ *I believe heterogeneity of 'stone formers' blurs population based genetic studies so much that progress will be slow and that family studies are more promising. But I am not a geneticist.*

from abnormalities of parathyroid glands. It can be familial or sporadic but produces stones directly from an excess of parathyroid hormone. Sarcoidosis and some malignancies lead to overproduction of 1,25 dihydroxyvitamin D, which raises urine calcium and causes stones⁸⁹. Bowel diseases produce stones via water loss and high oxalate absorption⁹⁰.

It is not that these diseases do not help us understand how stones form. They do. But they do not help us understand how common stones reflect normal physiological systems driven outside their evolutionary limits by diet or the demands of life in general, which is our concern here.

STONES ARE AN 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. Even 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 although their average age of onset, around 35 or so, is well past the middle of reproductive years, stones often begin during adolescence. Even so, they would tip the balance against those who form them⁹¹.

They Occured in Antiquity

Despite all this, stone passage has been described into antiquity. Rhazes wrote of them in the 900s, Hippocrates in the 400s BC, and a kidney stone has been reported in a mummy. They have accompanied humans, apparently, despite all their disadvantages. This review nicely positions available evidence in historical time. But human evolutionary time is of a different magnitude, spanning 100 millenia or more, and evidence for stones during that vast interval is not available so far as I know⁹².

⁸⁹ *Once again, I leave lists to one side. This site article expands on the point and links to another article that tabulates specific causes and their manifestations in blood and urine.*

⁹⁰ *The site has articles about bariatric surgery and ileostomy, and references papers on small bowel disease.*

⁹¹ *I have argued an obvious point excessively I fear. Imagine stone passage sans surgery, antisepsis, anesthetics - you have the horrors of medieval stone cutters with 90% death rates. Of course stones in hunter gatherers would be tragic and unsupportable.*

⁹² *I have not been a proper scholar here. But the few reviews I cited say nothing of the matter and surely their authors would have been more ambitious than I.*

SUPERSATURATION IS THE EFFICIENT CAUSE OF STONE CRYSTALS

Without crystals stones are mere protein aggregates, 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. Those laws culminate, for us, in gauging urine saturation and therefore stone forming propensity.

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 *equals* the number flying away⁹³. That point of stable crystal mass we call solubility. Like the hive to the bee, crystals are attractive to their constituents that 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 arrive⁹⁴.

The gorgeous painting is by Pieter II Brueghel (1564-1638)- La Danse de noces, 1600, Musée des beaux-arts de Quimper. It introduces the next idea, that crystals are patterned like dancers in a dance.

⁹³ *Perhaps the image of drowning bees will make me seem a ridiculous author, but maybe not.*

⁹⁴ *Forgive me my search for suitably colorful images about colorless ions unimaginably tiny and numerous. I am after some sense of crystal formation. The articles on the site are more rigorous and link to authentic references.*

The Constituents of Crystals Attract Each Other - Like Dancers

When there is as yet no crystal, stone crystal constituents are not exactly like bees. They are binary, charged negative or 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, 2 negative sites at higher urine pH⁹⁵. 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, as in the preceding picture, 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, 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. The link is to a video I made.



I need not be totally binary. Sometimes molecules form crystals with themselves - uric acid for example. They are like the beautiful 'Women's Dances' I saw once at an orthodox Jewish wedding. Notice the patterning - as in a crystal.

Men, too. My grandfather's generation danced the Kazatsky, wherein men display their balance, and athleticism. 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 uric acid molecules

together.

The dancer to the left is not my grandfather, but he looked that way, at least as I remember him⁹⁶.

⁹⁵ *At pH 6.8 one half of phosphate ions will have 2 negative charges.*

⁹⁶ *My Pilates instructor believes that with practice I may achieve the so-called 'Pistol Jump' which resembles what I saw so long ago. As of today I feel as far from such an achievement as from unassisted flight over the rooftops of Chicago.*

SATURATION QUANTIFIES CRYSTAL FORMING PROPENSITY

Arises from Physical Chemistry of Solutions

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 degree of saturation, a single expression that sums up the tendency for crystals, and therefore stones, to form, or dissolve, or grow.

Crystallization Risk Pivots Around Solubility

There is a level of saturation at which the constituents of a crystal enter and leave the crystal at the same rates, so the crystal neither grows nor shrinks. Called the '**solubility**', it is the axis around which all crystallizations pivot. At a saturation above solubility, 'supersaturation (SS)', crystals must grow, and if not present will tend to form. Below solubility, 'underaturation', crystals cannot form and can shrink if present⁹⁷.

Supersaturation (SS) is Necessary for Stone Formation

Let me be perfectly clear. Degree of saturation governs crystallization everywhere in the universe. In water as much as in molten steel. 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. It is for that reason that supersaturation is **necessary** to produce stone crystals but not **sufficient**.

Concentration Product Activity Product and SS

A urine at solubility with calcium oxalate crystals - the crystals neither grow nor dissolve - will have a particular calcium times oxalate concentration product⁹⁸ - the solubility product. A product above that means SS, below undersaturation⁹⁹.

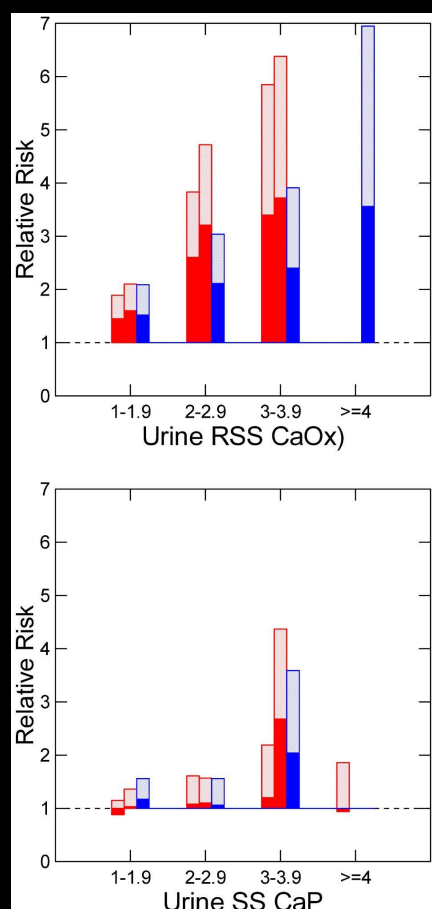
⁹⁷ *You may have noted, with annoyance, I have yet to say what 'saturation' is made up of. I tell it just below because right here would make matters too dense. The bees and dancers were to create a receptive state of mind, to dilute the numbing forthcoming complexity.*

⁹⁸ *The product of the crystal constituents reflects that calcium and oxalate enter the crystal structure together.*

⁹⁹ *One can measure SS accurately by adding crystals and determining change in the concentration product, but such an assay is not economical for patient care.*

The free ion activity product¹⁰⁰, more refined and reliable, is usually calculated from a number of individual complexes - eg. oxalate with calcium, with magnesium, with potassium etc, calcium with citrate, a crucial binding material. A computer program that mathematically considers all the possible combinations for calcium and oxalate together can calculate the free ion activity product¹⁰¹. The ratio of the free ion activity product in the urine to that at solubility gives an excellent measure of SS.

For calcium phosphate crystals, the same, except urine pH matters because it determines whether urine phosphate will have its needed 2 charged sites¹⁰². Depending on the foods eaten, urine may be acid - lower calcium phosphate saturation, or rise, the opposite. Oxalate always has 2 charged sites in human urine so pH plays a minor role.



SUPERSATURATION PREDICTS NEW STONE ONSET¹⁰³

The graph plots three cohorts, of normal women (red) and men (blue). Calcium oxalate supersaturation is in the upper panel calcium phosphate the lower. Over the years, some became kidney stone formers. The vertical axis plots the relative risk of having become a stone former against increasing ranges of SS.

The tops of the bars are the mean (average) risk of becoming a stone former, the bottom of the lighter less densely filled bar - where it joins its more solid looking red or blue - is at the lower 95th percentile. So if that bottom is not below 1, risk is elevated¹⁰⁴. For example, all CaOx bottoms lie above 1.

Calcium Oxalate SS vs. RSS

Through an unfortunate choice, the real SS values were divided by the mean SS value from a group of about 50 normal people to make an index (RSS, or relative SS) in which that normal mean was set to 1. To get the real value you have to mentally multiply these

¹⁰⁰ **The free ion activity product.** A charged atom (calcium) or molecule (oxalate) in water is called an ion. 'Free ion' means calcium and oxalate ions not bound except to each other. 'Activity' means (crudely speaking) the ability of the ion to combine with other ions.

¹⁰¹ This is the usual method vendors provide for patient care

¹⁰² At pH 6.8 about 1/2 of phosphate has 2 charges

¹⁰³ I mean by 'predicts' 'associates with new onset of'. Because "The future never spoke...", 'predict' is not as correct here as in: 'if you fire steering rocket 3 for 0.04123 seconds we predict the space capsule will rotate by 0.0026594 degrees'.

¹⁰⁴ In other words the likelihood that the mean is not above 1 (no increase in risk) is 5%

values by about 3.3. So SS above 3.3 fold raises risk by about 2 fold, and thereafter risk rises steadily up to 7 fold, in men.

Not shown, the reference is a RSS below 1 - or a true SS of below 3.3. This is instructive in that such a degree of SS, over 3 fold above the solubility, does not measurably raise risk of becoming a stone former.

Calcium Phosphate (CaP) SS

Calcium phosphate SS values, shown in the lower panel of the graph, are not altered by a correction factor, so a SS of 1-1.9 means from solubility (SS=1) upward. The graph makes clear that risk begins above 1. Thereafter, risk does not rise smoothly, but rather peaks in one sector, 3 - 3.9. SS values were ≤ 4 except in one female cohort.

Interactions Between Calcium Phosphate and Calcium Oxalate Crystals

The differences between CaOx SS and CaP SS vs stone risk are remarkable but not inconsistent with what we know about these two crystal species and how they interact.

The first crystals that form in urine are brushite, a rather soluble and unstable crystal¹⁰⁵. Oxalate molecules can pull the calcium out of brushite to make calcium oxalate, and brushite can convert into much more insoluble hydroxyapatite (HA) - which is the main crystal of bone and most CaP kidney stones. As a result, brushite is to calcium oxalate and HA crystals like tinder to oak.

Without brushite as tinder, CaOx crystals require a higher SS to form. Urine is usually supersaturated with respect to HA. But given brushite as an organizing template, HA forms more rapidly.

All of this means that CaP SS is behaving as one would expect. Any CaP SS can create brushite, and brushite essentially catalyzes formation of the sturdier CaOx and HA crystals¹⁰⁶.

URINE OXALATE¹⁰⁷

Like urine volume, calcium, citrate, and pH, urine oxalate arises from a homeostatic system involving multiple organs. The kidneys filter oxalate out of plasma and also secrete it from plasma into tubule fluid. As our cells cannot metabolize oxalate, its urine loss must match the sum of what is absorbed from food and produced by the liver. Present data indicate that about half of urine oxalate is absorbed from food and the other half from production from metabolic

¹⁰⁵ *I know that octocalcium phosphate may form as well or in place of brushite. That is detailed on the site.*

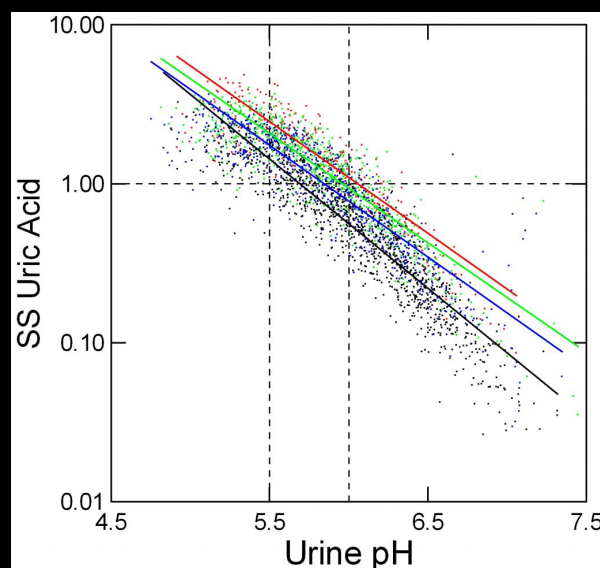
¹⁰⁶ *The truth about SS and these crystallization reactions lies deeper than I can tell about here. The linked site articles have references that will satisfy almost all curious bystanders to material science.*

¹⁰⁷ *The three links do tell a large fraction of the oxalate story in relation to stones.*

precursors of which ascorbic acid seems the main component. Management of urine oxalate by selective diet change and proper balance of diet calcium and sodium¹⁰⁸ are detailed on the site.

URIC ACID SS¹⁰⁹

Unlike the calcium crystals, uric acid SS (vertical axis) depends so strongly on urine pH (horizontal axis) and urine volume (line colors) the amount lost in urine plays only a minor role in stone production¹¹⁰.



Urine volumes of 0.5 to 1 (red), 1 to 1.5 (green) 1.5 to 2 (blue) and above 2 liters /day (black) progressively lower SS, but below pH 5.5 (left hand dashed vertical line) almost all of the 24 hour urine collections (each one a microdot) stand above a SS of 1 (dashed horizontal line). Above pH 6 (right hand dashed vertical line arising between 5.5 and 6.5), virtually all points stand below 1. So urine volume swings SS from above to below 1 only in the narrow range of pH 5.5 to 6.

Put more bluntly, unlike the complexity of the calcium oxalate and calcium phosphate salts, uric acid stones are due mainly to low urine pH,

and prevented by whatever means can raise pH above 6. I consider the causes of the low urine pH later in this book¹¹¹.

CYSTINE SS

Cystinuria arises from genetic defects in the renal transporters that reabsorb filtered cystine. Merely the surplus of cystine is enough to cause cystine stones. SS is not calculated but directly measured by consumption of urine cystine into preformed cystine crystals added to an aliquot from a 24 hour urine collection. Essentially one brings the urine to solubility and divides the original cystine concentration by the solubility to get an exact saturation estimate¹¹².

¹⁰⁸ *The site details a high calcium reduced sodium diet. The latter minimizes urine calcium, the former reduces oxalate absorption and benefits bone.*

¹⁰⁹ *Because uric acid and cystine molecules crystallize reliably supersaturation links closely to stones and one does not need epidemiological evidence to prove linkage as for SS CaOx and SS CaP.*

¹¹⁰ *This is the reason that total urine urate excretion is itself a most minor stone risk*

¹¹¹ *They are not comprehensible until we have discussed acid base balance*

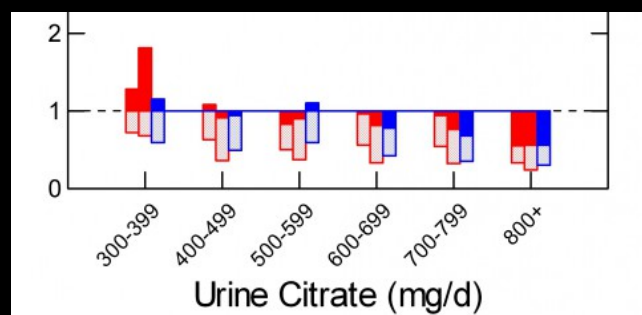
¹¹² *Most vendors cannot produce cystine supersaturations. The company (LithoLink) I founded and sold to LabCorp does this using a method I invented. The test was not profitable when I owned the company.*

How one uses fluids and cysteine binding agents to prevent stones is well described on the site. One should mention that cystine SS is not as generally available from commercial vendors as, for example, CaOx and CaP SS¹¹³.

URINE INHIBITS CALCIUM CRYSTALLIZATION

Citrate Inhibits Stone Crystal Formation

At its usual urine concentrations, citrate is a grand inhibitor of stone formation. It binds calcium in a soluble form, so it is not free to create crystals with oxalate or phosphate. It bonds to the surfaces of crystals and interferes with their growth. It can snatch calcium atoms off crystal surfaces so they shrink. As tiny groups of atoms and molecules come together to form the initial nuclei of crystals (nucleation) citrate interferes in both of the above ways so nucleation cannot



proceed. We can accurately calculate the effects of citrate on supersaturation, and can measure its ability to halt nucleation, though the latter is a research procedure, too complex for medical practice.

Citrate Excretion Predicts Stones

In the three same cohorts as in prior figures, risk of becoming a stone former fell as the amount of citrate lost in the urine rose. You can see this because the upper end of the solid colored bars, the upper 95% confidence limit for risk, was always below 1 for urine citrate values above 600 (bars 3 in from the left). As urine citrate fell to its lowest level, 300-399 mg/d, the risk bars cross 1 meaning risk is neither reduced nor increased. In between, from 400 to 600 mg/d, bars 2 and 3 in from the left, the risk bars crossed 1 in at least one cohort.

This implies that when citrate excretion goes below 600 mg risk is not reliably reduced by citrate¹¹⁴. But the data are not vigorous until citrate falls below 400 mg/d, so whereas below that point one wishes to act it is harder to persuade one to treat from 400 mg/d on up.

Inorganic Pyrophosphate Inhibits Stone Crystals

This small molecule is a powerful inhibitor of calcium phosphate crystallization, and plays a crucial role in regulation of bone mineral. Kidneys produce inorganic pyrophosphate and there is

¹¹³ *might seem overly casual about an important and complex disease here, but that is not my intent. The site does offer a fine review, and the links are to detailed articles. The main physiologies are so complex I dare not add more beyond them.*

¹¹⁴ *This should surprise no one. Citrate cannot drive stone formation, merely reduce it. Inadequate citrate leaves a person more prey to accident and chance - like an unbuckled seat belt, disdain for vaccines, or age itself.*

enough of it in urine to inhibit calcium phosphate formation. Since calcium phosphate crystallization seems catalytic for calcium oxalate and calcium phosphate stones, one would think this molecule would have many scientific publications. But the PubMed search “inorganic pyrophosphate AND kidney stones” yielded 10 papers, only 2 of them after 1992. I have referenced (above) the better of these two. The one other paper since 1992 documents lower amounts of inorganic pyrophosphate in urine of stone formers vs. normal people, but numbers are small.

We scientists seem shy about this molecule. It must be important. I predict that whoever mounts an enthusiastic and well organized effort aimed at the role this molecule plays in clinical stone disease will surely win renown among scientists and physicians, and the admiration of grateful patients everywhere in the world¹¹⁵.

Myriads of Urine Proteins Inhibit Stone Crystals

These have baffled and eluded us mainly because so numerous. Almost everyone who has worked on causes of kidney stones has at one time or another tried to find **the** most important of the protein crystal inhibitors, and there are still no candidates that one can measure with hope of predicting stones.

It may be that the question is wrong. Because numerous, the proteins may be a general background that is not a ‘cause’ of stones because not variable enough among people to create deficiencies sufficient to cause stones. After all, many of the proteins may be in urine not as part of a controlled process aimed at urine chemistry but as an unregulated means of disposal.

An exception may be urine uromodulin, produced in the thick ascending limbs of the kidney, highly regulated, and related to kidney diseases. This molecule prevents the aggregation of crystals, reducing their potential to achieve clinically important sized stones. Uromodulin is almost always present in stones, but that could be non specific adsorption. Mutant mice lacking uromodulin form multiple renal crystals and develop kidney disease, as do humans with this mutation, but the relevance of this mutation to the mass of common human stones is moot at the present time¹¹⁶.

PLAQUE AND PLUGGING FOSTER STONES

Calcium stones grow in at least three different ways. Some grow over deposits of HA embedded in the renal papillary tissue (plaque) exposed to urine by loss of the protective papillary membranes (urothelium)¹¹⁷. Others grow over HA crystals that plug the terminal ends of kidney

¹¹⁵ *Science has remarkable gaps like this one, utterly incomprehensible. I never studied inorganic pyrophosphate, and do not know why.*

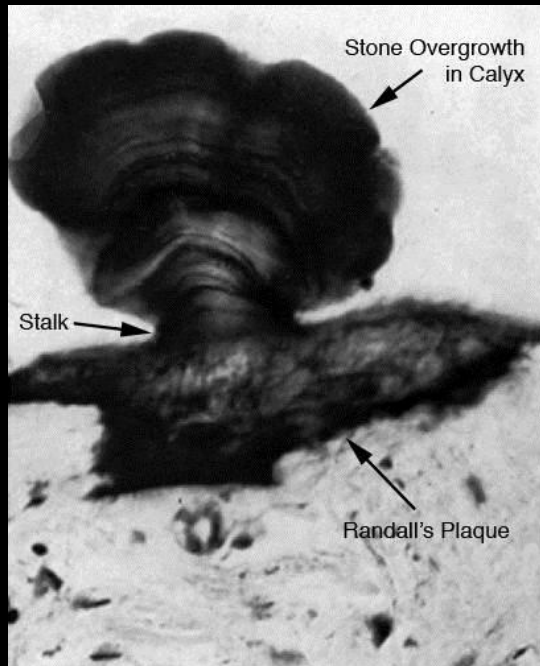
¹¹⁶ *I think it is time to study UMOD as a stone cause because we now have more refined tools and better understand its many forms in urine.*

¹¹⁷ *We do not know how physiology results in plaque nor why the urothelium gives way so urine ions can grow over it.*

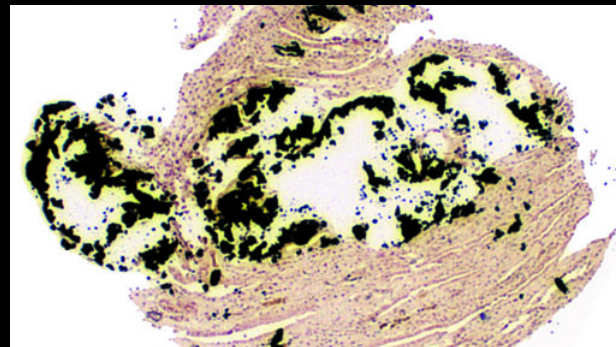
collecting ducts from which the final urine emerges¹¹⁸. Some seem to form on neither substrate and presumably form in urine within the renal collecting system¹¹⁹.

Why the variety? - unknown.

Plaque



This wonderful picture taken in 1940 by W.A.D Anderson shows a stone growing out of a base of Plaque embedded in human kidney papillary tissue. Plaque forms inside the kidney papillae along the ascending limb of the loops of Henle - the region in which kidneys concentrate urine¹²⁰. This locale and certain other aspects of kidney anatomy and calcium physiology have given rise to a working theory that needs further testing¹²¹. If true the theory implies that high fluid intake may reduce plaque by reducing kidney functions that concentrate urine¹²². Likewise for other measures that might accomplish the same¹²³.



Plugs

This biopsy from a patient who formed calcium oxalate stones¹²⁴ shows the end of a collecting duct filled with crystals. Around it is kidney tissue¹²⁵. The crystals inside the duct are calcium phosphate. Extruding out into the urinary space (to the left) is an overgrowth of calcium oxalate.

¹¹⁸ *We view this as a random expression in tubules of the stone forming propensity of the urine.*

¹¹⁹ *In free solution as opposed to on a preformed crystal surface.*

¹²⁰ *If you do not know the thin limbs, pass by as you do not need to know right now and they will be back*

¹²¹ *Called the 'vas washdown' hypothesis it proposes that people with high urine calcium concentrate calcium in the papillum thus raising local SS for CaP near the ascending limbs.*

¹²² *The countercurrent multipliers and exchangers require a buildup of sodium chloride and urea in the papillum which constant high water intake dissipates*

¹²³ *For example inhibitors of vasopressin.*

¹²⁴ *One can isolate such a plug and determine the kind of crystal structure within the plug and the overgrowth*

¹²⁵ *On inspection, the tissue will be disturbed by inflammation and fibrosis. Experts will note that the lining cells have been destroyed.*

How They Form and What They Mean¹²⁶

Like stones themselves, plaque and plugs form from crystallizations, and howsoever elaborate the biological niches in which they form crystals are forever in thrall to the laws of atomic combination. Plugs form in the final urine¹²⁷.

Plaque and plug abundance are easily estimated during stone surgery and digital imaging can make permanent records. We believe more plaque means more stones will form, and that plugs injure kidneys raising the importance of vigorous stone prevention. But we lack trials and large scale prospective studies here, which makes me unwilling to say more.¹²⁸

24 HOUR URINE STONE PANELS ARE REMARKABLY INFORMATIVE

Urine volume and excretions of calcium, oxalate, citrate (because it binds calcium), and urine pH along with phosphate comprise the main factors in saturation. Urine sodium, potassium, magnesium, ammonium, and sulfate form complexes with calcium and oxalate, and affect saturation because they enter into calculation of free ion activity products¹²⁹. Urine citrate is our one proven inhibitor of new stone onset. Urine creatinine estimates consistency of 24 hour urine samples¹³⁰. Urea nitrogen estimated protein intake from the protein catabolic rate equation¹³¹.

If coupled with a fasting serum to measure calcium, phosphate, uric acid, magnesium, sodium, potassium, chloride, and total CO₂, this same panel permits estimates of the functions of the five main physiologies as well¹³². The kidney stone 24 hour urine is a powerful clinical instrument that gives profound insight into critical systemic regulations if one learns how to use it - and uses it¹³³.

¹²⁶ *The site articles are very detailed unburdening this text which has other primary purposes*

¹²⁷ *Presumably crystals form in the final urine as it exits the ends of the nephron, and plug the duct. This is free solution crystallization that forms a surface for other stones to grow on.*

¹²⁸ *I am surprised by the indolence of my surgical colleagues who have not mounted prospective multicenter observational studies to test if plaque abundance predicts more stones, and if plugs correlate with progressive papillary deformation or increasing kidney tissue inflammation.*

¹²⁹ *All of these are charged and 'distract' calcium, oxalate, phosphate from binding to each other to make stone crystals.*

¹³⁰ *Produced by muscles, it is constant from day to day*

¹³¹ *Protein intake affects urine calcium excretion - more protein more calcium*

¹³² *One has excretion rates and estimates for fractional reabsorptions of calcium, phosphate, uric acid and sodium; food alkali intake using urine potassium excretion and GI anion calculation (explained later on); acid excretion (ammonia and titratable acidity from pH and phosphate); kidney function (creatinine clearance).*

¹³³ *Remarkable to me as a clinical instrument ignored by almost all nephrologists seemingly bewildered by or dismissive of such richness of information to guide diet management of kidney disease*

FIVE PHYSIOLOGIES CONTROL URINE SATURATION

All of the urine loss rates that control saturation are themselves controlled by the five great physiological systems this book concerns itself with. Each system aims toward the needs of the body in response to diet, water intake, ambient temperature, rate of exercise, pregnancy, lactation, and growth. Of these, diet, water intake, and exercise are most under conscious control, and therefore most accessible to change.

As I have already said, I work under the presumption that throughout our evolution the systems that set urine levels of each of the individual contributors to urine saturation aimed toward the general fitness of the individual which included the propensity to form stones¹³⁴. Put another way, what we have resulted from numerous compromises suitable over evolutionary time but not always suitable to the conditions imposed by high civilization.

All five are open systems - urine losses from blood must equal net inputs from diet, fluids, and metabolism. Urine losses are continuous, meals and fluids are intermittent and random. Furthermore, urine losses must be regulated to as to maintain constant blood levels of sodium, calcium, pH and total blood volume¹³⁵. In some cases, like blood volume, stability is reasonable as a 3 or 4 day average. In others, serum calcium, stability must be minute to minute. This offers massive opportunities for evolution to center on combinations of regulation that optimize fitness¹³⁶.

In Section one, I introduced these systems each with a brief precis. Now I offer them back in much more detail¹³⁷. My purpose is to create a shared vocabulary and sensibility concerning what they do and how, so at the end of it all we can turn to the treatments we use for stone prevention and understand them in relation to the systems they disturb in the service of clinical care¹³⁸.

THE SODIUM / WATER SYSTEM

We care about the sodium system because urine calcium is linked to urine sodium, so much so that low sodium intake is a mainstay of stone prevention. We care about the water system because fluid increase is also key for stone prevention. I believe that understanding how these

¹³⁴ *How bold - to place stone forming so high that evolution would concern itself with it. But if you consider their deadliness in life primitive, I may not seem wrong.*

¹³⁵ *I focus here on only the most primitive facts - eg. phosphate is omitted but will return for its moment on the stage.*

¹³⁶ *Oxalate differs as no data support a need to control blood oxalate within upper and lower limits. The system seems mainly to concern brisk removal.*

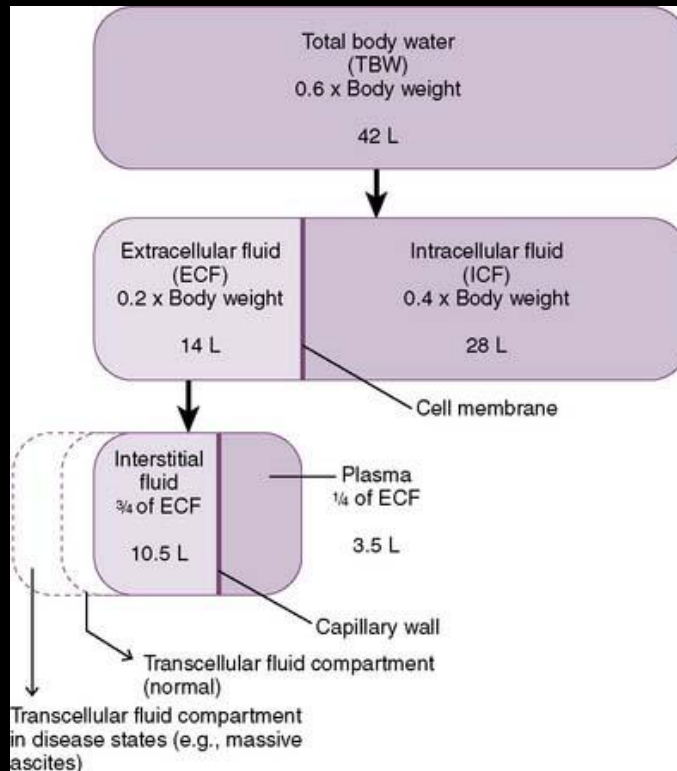
¹³⁷ *Far less, though, than in a scientific review or textbook chapter that would be inaccessible to the more general audience I aim for here.*

¹³⁸ *This is a high ambition, a thing difficult but not impossible. To understand treatments in terms of how they work is to embrace them with a confidence otherwise unattainable.*

two systems interlock and function makes for more intelligent and sustained sodium and water management in stone prevention, by patients and their physicians¹³⁹.

Where Water and Sodium Are

I borrowed this nifty picture that derives from a respected textbook. It saves me the task of



saying in text how much water is in our cells, outside cells, and how the latter is divided into water in the plasma and in the space between the capillary walls and cells.

Because sodium is 140 mEq/l in the ECF (defined in the picture) and about 10 mEq/l inside our cells, the sodium pool in the ECF is $140 \text{ mEq/l} \times 14 \text{ L} = 1960 \text{ mEq}$ and inside the cells about $28 \text{ L} \times 10 \text{ mEq/l} = 280 \text{ mEq}$. I should pause and say these are illustrative estimates which vary a lot with age, sex, obesity, illness and the like¹⁴⁰.

How Sodium and Water Balance Interact

Because water balance acts to maintain a constant concentration of sodium¹⁴¹ in the ECF, sodium balance regulates ECF

volume which powerfully controls urine calcium excretion. This loopy overlap of two huge biological systems makes salt and water balance hard to understand yet such an understanding lets us see into stone disease - or its absence - in contemporary patients and during an evolutionary history that took place for a long while in Africa, where temperatures were often high, and water and sodium limited in supply. I have a weedier version on my site¹⁴².

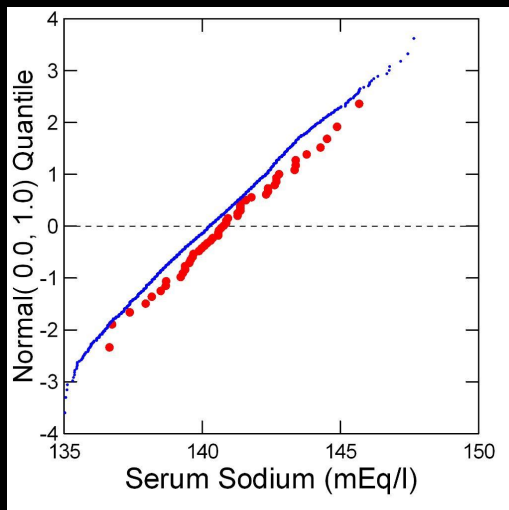
¹³⁹ *I cannot help but marvel that understanding can imaginably be less than essential for the conduct of medical care. Yet I know a quiet skepticism impugns its claim on necessity. In matters of love, one senses less doubt.*

¹⁴⁰ *Even so, most of our sodium is outside our cells.*

¹⁴¹ *The sensing cells sense cell volume changes and so can respond to glucose, urea and other solutes, but sodium is preeminent being so high in concentration and efficiently extruded from cells by active transport. Higher sodium will draw water from cells and the obverse.*

¹⁴² *Though more detailed it is still readable by a general audience. I recommend it as entertaining, and in honor of Professor Arthur Guyton whose work it celebrates.*

SODIUM

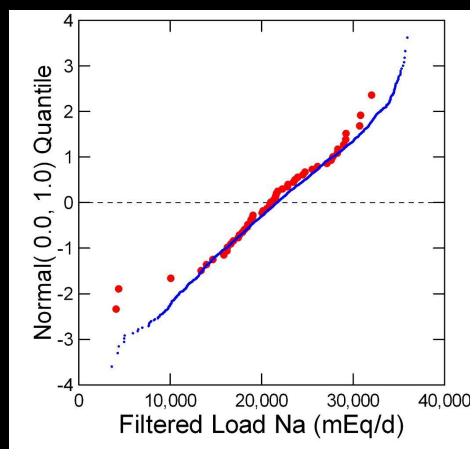


Serum Sodium¹⁴³

Plotted against the normal distribution on the vertical axis, where 0 is the mean and numbers show standard deviations¹⁴⁴ above and below it, the serum sodium concentration makes a straight line - so it is normally distributed as we would expect¹⁴⁵.

The mean is 140 mEq/l, which is listed in all routine lab reports. The blue line is thousands of measurements we have made from kidney stone patients¹⁴⁶. The red dots are from people without known disease, so called normals. Their mean is a bit higher than the stone formers.

The range from 135 to 145 is 3 standard deviations (SD) which includes 99.7% of the data. Two SD, 95% of the data, are about 137 to 143 mEq/l. The normals cover about the same range, though being fewer one finds and expects less extreme values will show up by chance.



If we take 140 as the center point and 3 mEq/l as the top and bottom 95% values, serum sodium is rather stable - $3/140 = 2.1\%$ 95% of the time.

Renal Filtration of Sodium

Our kidneys begin their work by filtering a very large amount of water and small molecules out of the blood. They do this, perhaps, because our genetic forebears were fresh water fish whose gills absorbed plentiful water that needed removing. There may be a deeper reason. High filtration reduces the time required to clear

¹⁴³ I have used 'blood' sodium because graphic, but here I show values from the blood serum. Since the rest of blood is mainly red blood cells this is the blood water concentration cells 'see'.

¹⁴⁴ 1 SD above and below the mean includes about 68% of the data, 2 SD about 95%, 3 SD about 99.7%.

¹⁴⁵ The 'normal' function really does model inherited traits and many systemic functions. The underlying mathematics are not complex but do not say why it is so versatile. This entertaining article proposes to explain why things in general follow the normal function.

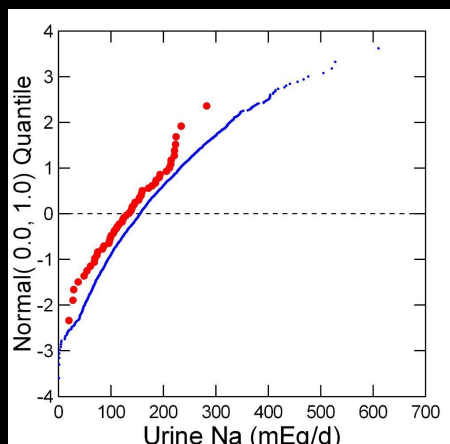
¹⁴⁶ I opened the kidney stone laboratory in 1969 and have collected 24 hour urine and fasting serum data ever since in machine readable form. In about 2012 Joan Parks, my long term collaborator, tabulated pretreatment data from which I have made this and related figures. Since she retired the data have less metadata, and less purity of subject definitions.

metabolites and toxins out of the extracellular fluid, a fact not usually noted in textbooks¹⁴⁷.

Because sodium atoms are freely filtered, and filtration rates average around 140 l/d in adults¹⁴⁸, the amount of sodium filtered is astounding - between 5,000 and 35,000 mEq/day with an average of about 21,000¹⁴⁹.

If 21,000 is taken as the mean, 95% is between about 12,000 and 35,000, about 50% on either side. So filtration is vastly more variable than the serum, which makes some sense if changes in filtration are part of the way in which the serum is kept constant despite variation of sodium intake.

At 21,000 mEq of sodium filtered per day, the 1960 mEq of ECF sodium would be filtered out 21,000 mEq/d / 1,960 mEq or 10.7 times/day. Since this would be lethal in less than an hour, the kidney must reabsorb almost all of that sodium to make the amount lost approximate the amount taken in, which is the case.



Urine Sodium Loss

More or less, the urine sodium matches sodium intake if averaged over about 4 days. Sweat losses in a sedentary average person are about 15 - 30 mEq/d and rise a lot with exercise¹⁵⁰. The intestines absorb about 95% of the sodium we eat (data in the above link). So the net sodium kidneys contend with is $(0.95 \times \text{diet sodium}) - 22$ (22 being the rough average of 15 and 30).

Given this, the amount of urine sodium a day, shown here, more or less reflects climate and human choice of what to eat and how much to exercise. Unlike serum sodium and filtered sodium this is a function of society, choice, taste and habit. In our sample of mostly urban middle aged people, the mean of 160 mEq/d spreads up to 300 at the 95th percentile, or about 50%, and downward to about 30%. Some values are very low, perhaps deliberate low sodium diets or considerable exercise - we eliminated incomplete urine collections¹⁵¹.

Fraction of Filtered Sodium Excreted (FENa)

If you divide the amount in the urine by the amount filtered you get an average of about 0.7% (the x axis is in fractions so 0.01 is 1%). The range is from about 0.3% to 1.3%, a very large

¹⁴⁷ *The linked article is my exposition of this otherwise seemingly unrecognized property of filtration. I have disdained publishing in a traditional journal so obvious a mathematical point.*

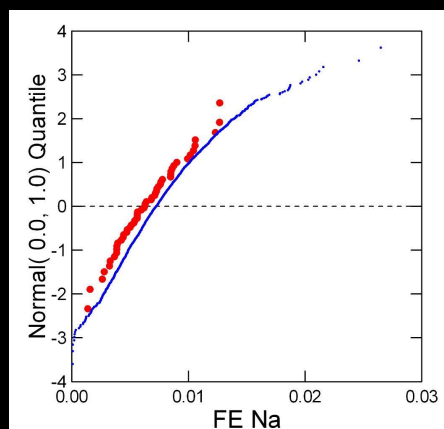
¹⁴⁸ *I realize I have not as yet presented filtration rates, but the mean value shown is correct and usable for the main point at issue here.*

¹⁴⁹ *I am aware that one gets 19,000 from my example.*

¹⁵⁰ *Evidence for these useful numbers are in the preceding linked article*

¹⁵¹ *During her 30 years in the program, ending in 2012, Joan Parks scrupulously edited all data allowing me to say so overweening a thing.*

variation around 0.7%, about 40 - 80% of the mean. This is what you expect for a function that controls serum sodium and is not itself controlled around a biologically important set point.

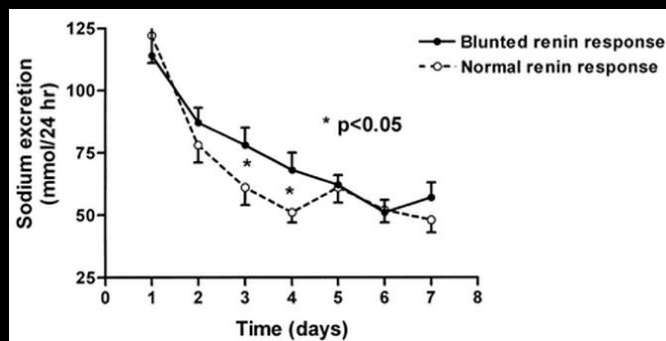


Did you notice that the normals have a lower FENa, a lower urine sodium, and a higher serum sodium than the stone formers? Perhaps, you might say, form a stone and drink a lot more water, so your serum will dilute a bit. Not a bad thought, remember it for a while.

Response of Urine Sodium to Diet is Sluggish

The fundamental purpose of the sodium /water system is to maintain blood sodium concentration and blood volume within proper ranges¹⁵². Since the blood concentration of sodium is fixed, more sodium means more ECF volume, and the reverse¹⁵³.

Here is one of a number of similar experiments I could use for illustration¹⁵⁴. Sodium intake was lowered from about 125 to about 50 mEq/d in humans and urine sodium measured. It took about 4 days for equilibrium. Some subjects who took longer had an abnormal response of



renin, a factor involved in sodium control. But the main message is 3 - 4 days overall for equilibration.

If you draw a mental line at 125 mEq, where they started from, it is apparent that sodium was lost from the body during the adjustment amounting to about 50 mEq between days 1 - 2, 20 mEq between days 2 - 3 (for the open dots, as a convenience), and perhaps 12 mEq between days 3 - 4,

or a total of about 80 mEq (80/1960 or 4% of the total extracellular sodium pool.

If the sodium concentration in the extracellular fluid is kept constant, this would require 0.57 liters of water be lost, 0.57/14 or 4% of the extracellular water, about 1.2 pounds of body weight. Done the other way, adding diet sodium, gives about the same time kinetics.

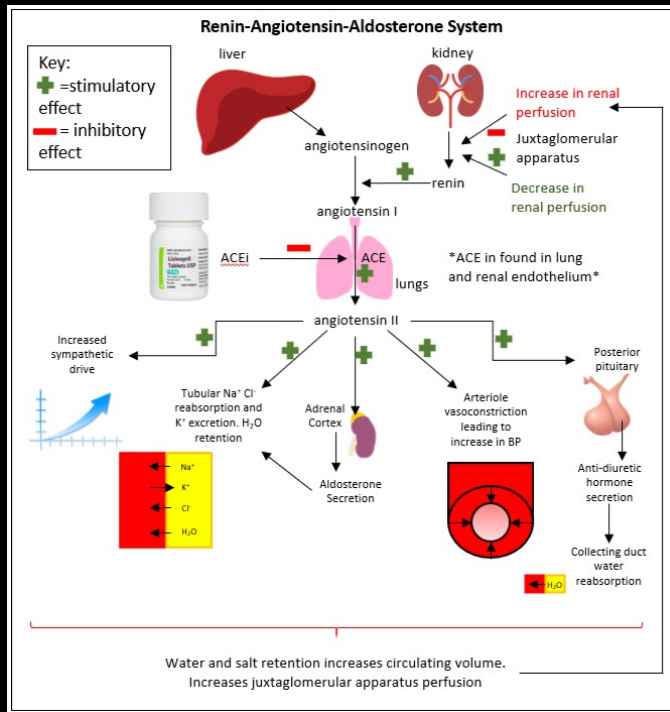
So the system is sluggish yet the sluggishness is not intrinsic. I mean by this that sodium filtration is so vast in comparison to diet intake that urine sodium losses could in principle respond to match intake in minutes if reabsorption of filtered sodium had evolved, for example,

¹⁵² *We know sodium concentration centers on 140 mEq/l give or take 3 mEq/l, so assume it is 'proper'. We do not measure blood volume routinely but assume the brain knows what is proper. I recognize the sophistry in this last remark and prefer to leave 'things' that way.*

¹⁵³ *By 'blood' I mean ECF volume in reality but prefer a more simple expression.*

¹⁵⁴ *The site article lists the original publication of these data*

to alter immediately upon a lowering of diet sodium¹⁵⁵. Evolutionary choices over vast periods of time were otherwise, so adjustment takes days¹⁵⁶.



How Do Kidneys Know How Much Sodium You Absorbed?

From the Brain

The brain receives information constantly about the arterial blood pressure and about the stretch of the large blood vessels and the atria of the heart. If blood pressure falls, the autonomic nervous system raises pressure back toward baseline by signaling the tiny and myriad resistance vessels (arterioles) throughout the body to constrict, and by signaling the heart to beat more forcefully¹⁵⁷. This system is very rapid. It is shown in the little blue graph on the left of the illustration.

The same for a reduction in stretch of the vessel walls, but the response is most dramatically enacted by the kidneys - see below¹⁵⁸. A fall in stretch entrains a sequence of responses that increase sodium retention¹⁵⁹.

From Itself

Let's now go back to the graph of urine sodium over time after an abrupt change, on the prior page, showing what happens when diet sodium goes down. At first the kidneys do not know - how could they? So they maintain urine sodium loss as it was, and as a result the ECF sodium pool falls and water leaves to keep sodium concentration constant. We did that arithmetic just above.

¹⁵⁵ *I do not mean this lightly. The massive sodium filtration could have made sodium regulation work on a minute to minute basis, like water. The high filtration is opposed by 1) remarkably high reabsorption that is 2) linked to the volume of the ECF, producing sluggish regulation as a 'choice' that required two separate major offsets against the high filtration.*

¹⁵⁶ *Unconfused because indifferent to absolute. Selection for fitness creates a terrible beauty born out of heartless culling. Does this not teach us something?*

¹⁵⁷ *For familiarity, this is why you can stand up yet have adequate blood pressure to your brain.*

¹⁵⁸ *This is misleading in a way. The brain senses the fullness of the circulation, pressures in the large arteries, stretch of the great veins, perhaps more all at the same time.*

¹⁵⁹ *Because we cannot routinely measure it, 'fullness of the circulation' has an undeserved metaphysical appearance. In healthy people, call it urine sodium excretion, for that is the integrated response over days.*

Because stretch in the great vessels falls, the autonomic nervous system signals as already noted. Likewise, the volume pumped out of the heart with each contraction will be lower because the blood volume will be lower. The illustration (above) helps with naming and where things are.

The arterioles¹⁶⁰ that feed the million or so filters of each kidney, the glomeruli, sense a loss of stretch from each heartbeat. They also sense increased autonomic nervous system signaling. In response they release renin, an enzyme that cleaves angiotensinogen (made by the liver) to angiotensin 1 which is itself processed to its active form, angiotensin 2 (A2) in the lungs and kidney¹⁶¹ by angiotensin converting enzyme (ACE) in lung and kidney vessels.

A2 maintains blood pressure as blood volume falls by directly signaling the resistance vessels of the body to constrict, and by increasing sympathetic nerve signaling. A2 increases sodium reabsorption by a direct hormone action on kidney cells. A2 stimulates the adrenal gland to produce aldosterone, which additionally raises reabsorption of filtered sodium.

With less blood flow from the heart, filtration itself can fall, but A2 constricts the outflow arteriole so pressure in the glomerular capillaries, and therefore filtration, tends to stay constant¹⁶². Finally A2 signals the brain to release vasopressin, the main regulator of water balance, and also create a sense of thirst (section just below on water).

The result is the graph I showed you. Urine sodium falls gradually as ECF volume falls, and the kidneys perpetually lag volume because ***it is the fall in volume that tells them to retain more sodium.***

You might imagine, and you would be correct, that reduced diet sodium would, so long as it applied, reduce the volume of blood, the output of the heart, and the blood pressure, and you would be right. It is a prime treatment to lower blood pressure. Blood pressure and blood volume would be permanently dependent on a higher level of A2 and aldosterone¹⁶³. This presumably would be closer to how we evolved, for during our millenia in Africa sodium was not abundant (salt mining began only about 6,000 years ago) and sweat losses from heat presumably higher than now¹⁶⁴.

¹⁶⁰ *Called the afferent arterioles they are for kidneys both mind - sentient and articulate (release renin, the controlling hormone), and pilot - physically control the inflow of blood to the organ.*

¹⁶¹ *Do not yield to fear, these so many names culminate in A2 - focus there and 'things' will be clear.*

¹⁶² *A garden hose multiply perforated attached to the faucet (afferent arteriole) and clamped at the other end (efferent arteriole). As ECF volume and the output of the heart (city water pressure) fall, the afferent arteriole (Faucet) opens to keep filtration (spray from the perforations) running and A2 constricts the outflow clamp to the same end - good spray, green grass.*

¹⁶³ *This is why one cannot say if aldosterone or renin or A2 is 'normal' except in relation to urine sodium excretion.*

¹⁶⁴ *Our powerful hormone systems, I am saying, run differently, perhaps, from their design optima. Because of salt mining, I presume, and lower sweat losses after our migration from Africa into Eurasia.*

Summary of The Important Message

Directed by the fullness of the circulation, sensed as blood pressure and stretch of the large vessels and atria of the heart, kidney sodium reabsorption maintains a reasonable balance between diet sodium intake and urine sodium loss. It can do this because the brain maintains water balance so as to keep serum sodium concentration constant as the amount of sodium in the ECF goes up or down. In other words, retention or loss of an amount of sodium results in retention or loss of a closely matched amount of water. The gain or loss of water raises or lowers the volume of the ECF, including blood, and therefore the blood pressure and vessel wall stretch information kidneys use to regulate urine sodium loss.

This is why sodium balance is sluggish and exact. Renal reabsorption, and even filtration of sodium respond to increases or decreases of ECF volume, so they are lagging indicators, always playing catchup in either direction. It is also why water balance, which is so important for stone disease, is at the heart of sodium balance. For ultimately it is the retention or loss of water¹⁶⁵ that kidneys sense in order to regulate sodium excretion¹⁶⁶.

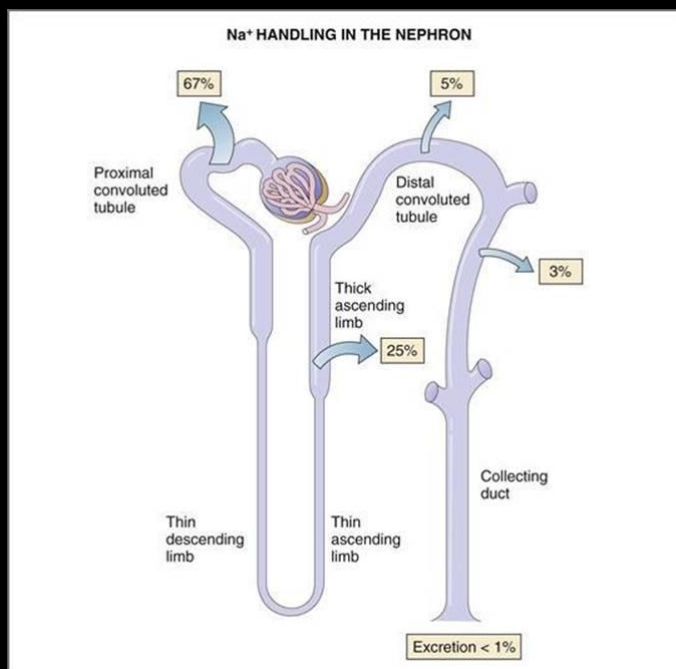
Where Sodium is Reabsorbed

Proximal Convolted Tubule

The garden hose filter, the glomerulus, drains into the proximal convoluted tubule (PCT) where a majority of sodium and water is reabsorbed. A2 and the sympathetic nervous system are preeminent among many powerful hormones that increase reabsorption by the cells of that segment¹⁶⁷.

Thick Ascending Limb

The thin loops (on diagram) do not reabsorb appreciable amounts of sodium chloride¹⁶⁸. The thick ascending limb (TAL) reabsorbs far more sodium chloride



¹⁶⁵ *Just to head off mistakes, water intake cannot importantly influence sodium balance because as plain water dilutes blood sodium (slightly) AVP falls promptly and renal water losses rise (promptly).*

¹⁶⁶ *Experts will have noticed my deliberate vagueness about where in the kidney sodium is reabsorbed, and where A2 and aldosterone act. Those who know do not need, and those who do not know have not needed such complexity right now. It follows just below.*

¹⁶⁷ *There are many others, but that is for a different kind of book.*

¹⁶⁸ *We speak about sodium, but chloride (or another charged ion) must accompany it - chloride as a comparatively passive partner. 'Appreciable' means small by comparison to other tubule segments.*

but no water, thus diluting the fluids within it¹⁶⁹.

In general the TAL reabsorbs sodium chloride delivered to it at a fixed rate so the concentration reaching the macula densa (where the two glomerular vessels meet the tubule) depends on filtration and PCT function¹⁷⁰. Higher sodium signals back to the glomerulus to reduce filtration - negative feedback loop¹⁷¹.

Distal Convuluted Tubule

Sodium is reabsorbed with chloride through a special transporter regulated mainly by aldosterone. This segment is strongly regulated and along with the collecting ducts regulates sodium balance¹⁷².

Collecting Ducts

Sodium is reabsorbed here apart from chloride creating a charge difference between the tubule fluid and blood. Aldosterone powerfully controls this transport. Potassium can be moved from blood into tubule fluid because of the charge difference¹⁷³.

SODIUM WITH AND BETWEEN MEALS

By design, urine sodium is indifferent to the immediate effect of a given meal. A high or low intake is integrated by volume sensing. Between meals, sodium reabsorption has such a range it can adapt to any imaginable circumstance. Tubules can reabsorb over 99.99% of filtered sodium and lower urine sodium close to 0¹⁷⁴. The crucial blood sodium concentration is controlled by water regulation, freeing the sodium system from that restraint. Under the excesses of modernity, normal kidneys can easily remove 250 mEq of sodium daily, albeit with risk of rising blood pressure and cardiovascular disease¹⁷⁵. To put things differently, the sodium system is so resilient that one can tolerate near absence or great excesses of diet sodium for long periods¹⁷⁶.

¹⁶⁹ *Hundreds of nephron diagrams haunt the web, I like this one for its utter simplicity.*

¹⁷⁰ *This is partially true. Reabsorption can be regulated by blood calcium concentration and vasopressin.*

¹⁷¹ *Called tubulo-glomerular feedback this is a crucial regulator of renal function. It does not per se regulate sodium loss to balance intake but balances filtration to tubule reabsorption. As a gauge to our focus, consider that this massive topic can have only a bit part in the play!*

¹⁷² *We will return to this segment in detail concerning calcium handling*

¹⁷³ *My colleagues will leave this section fuming with discontent and regard me as insufferably vague and lazy about details I know very well. But what I put down is enough for our purposes here, as they may come to see.*

¹⁷⁴ *So long as kidneys are healthy. With disease sodium losses may rise - this would be fatal if diet sodium were very low in relation to sweat losses.*

¹⁷⁵ *After great pain a formal feeling of consensus has come upon all responsible scientists that excessive sodium intake raises cardiovascular disease risk, industry sponsored disputations notwithstanding.*

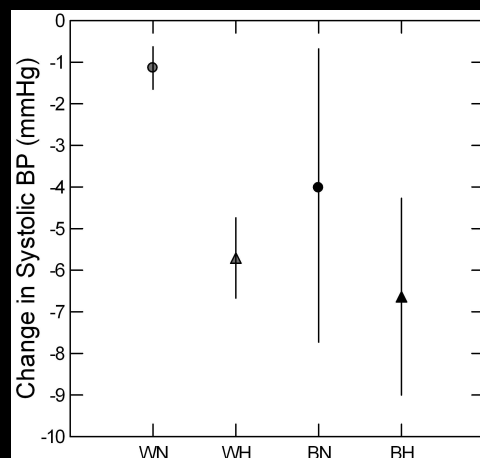
¹⁷⁶ *One must comment that extreme sodium restriction causes serious disease within populations. See the article by Roy Moxham in the linked journal. During famine, absence of adequate sodium is especially pernicious.*

EFFECTS OF REDUCED DIET SODIUM

It is time to illustrate that reducing diet sodium lowers blood pressure and raises key hormones related to the pressure and volume of the blood. I have chosen the 2020 Cochrane¹⁷⁷ analysis of the effects of changing diet sodium on blood pressure, renin, aldosterone, and the sympathetic nervous system hormones epinephrine and norepinephrine. Likewise, effects on blood lipids.

The information all arises from *experiments* done on people. Diet sodium was deliberately altered and responses of blood pressure, hormones, and lipids measured. So the change in sodium intake *caused* the changes measured¹⁷⁸.

Blood Pressure



In this and subsequent plots, the symbol is the mean change, the top and bottom lines are the 95% confidence interval. In white people with normal blood pressures, a change in sodium intake from 203 to 65 mEq/d lowered systolic BP by about 1 mmHg - a tiny change. Among white hypertensives (174 studies, about 6,000 people¹⁷⁹) the change was about 6 mmHg, clinically significant. Changes in black people (8 studies, 350 people) were not remarkably different between hypertensives and normotensives, or white hypertensives as 95% CI overlap¹⁸⁰.

The authors point out that mean BP, which is calculated from systolic and diastolic pressure changes less, because the diastolic BP is not as responsive to reduced sodium. However, present guidelines for BP control emphasize systolic BP, and trials have focused on it in middle age and older people - who have the majority of strokes and other cardiovascular disease.

Hormones

Renin

From what I have already written you would expect reduced diet sodium to raise renin levels, and that is true (upper left panel). The change is less among people with high blood pressure

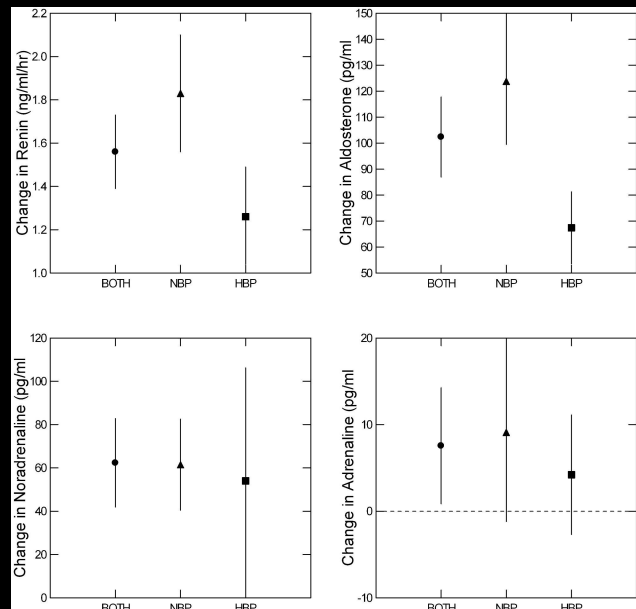
¹⁷⁷ *These investigators are a 'gold standard' in selection of sound trial publications and the pooling of data to draw from their ranks reasonably sound summary data.*

¹⁷⁸ *Infected as by some cultish tic, meta-analysts call all human experiments 'trials', a word properly used when a drug is 'tried' as suitable or not. The finer word 'experiment' that means an artificial or contrived reality, somehow fails to engage their odd sensibilities.*

¹⁷⁹ *These numbers are approximate. For the details one needs to review the linked article.*

¹⁸⁰ *I show systolic BP because many trials have identified it as a better predictor of stroke and other disease in general populations.*

(HBP). More renin means in general a higher production of $A2^{181}$, which would support blood pressure when the ECF volume is reduced. It would also increase PCT sodium reabsorption¹⁸².



Aldosterone

Aldosterone (upper right panel) rises just like renin. This is the expected response as $A2$ stimulates aldosterone production by the adrenal gland. Aldosterone stimulates sodium reabsorption in the DCT and in the collecting ducts, and is crucial for sodium conservation¹⁸³.

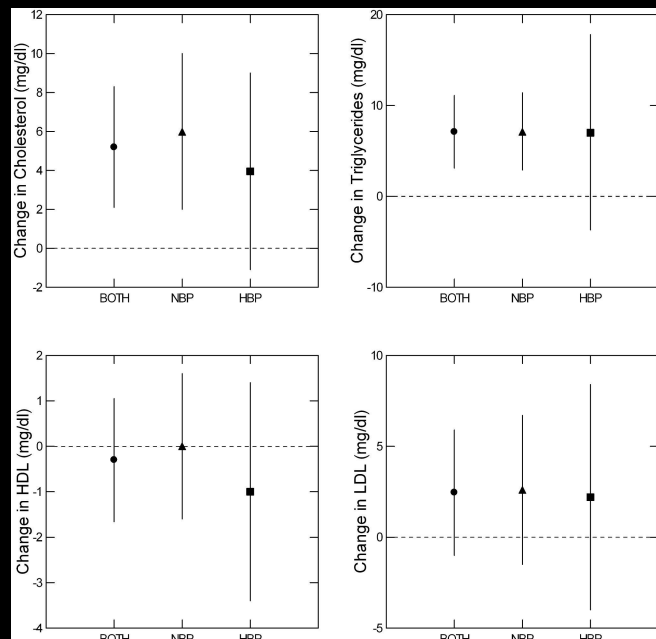
Catecholamines.

Noradrenaline and adrenaline are two adrenal gland hormones that control the

resistance vessels of the body and therefore blood pressure. The former (lower left panel) rises with reduced diet sodium, the latter only rises when you combine normotensive and hypertensive people to get narrower 95% CI (BOTH; the lower 95% CI does not cross 0). These hormones help maintain blood pressure as ECF volume falls, and signal the kidney to produce renin.

Blood Lipids

In normotensive people, reduced diet sodium increases blood cholesterol by about 5 mg/dl and triglycerides by about 7 mg/dl. Changes in HDL and LDL cholesterol are not significantly different from 0 as the 95% CI crosses the line at 0. Among those with high blood pressures none of the changes are significant, perhaps because the numbers of subjects is smaller.



¹⁸¹ More $A2$ will constrict the efferent arteriole (think clamp at the end of the garden hose we described earlier) so filtration can remain steady as the output from the heart falls with less ECF volume.

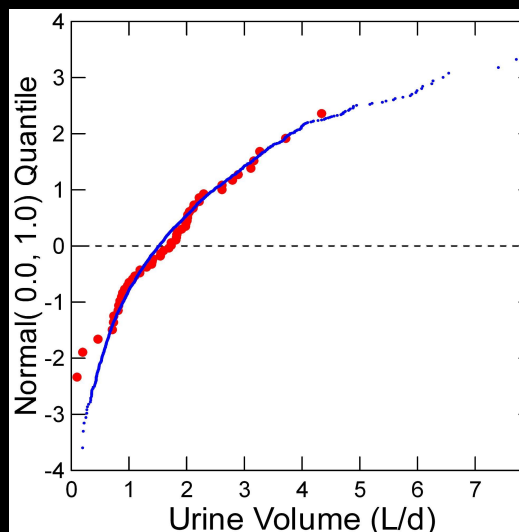
¹⁸² It is the kidney that produces renin, from specialized cells in the afferent arterioles of the glomeruli. They sense reduced stretch and produce more renin. $A2$ directly stimulates PCT sodium reabsorption.

¹⁸³ You will have noticed that changes in renin and aldo are muted for high blood pressure people (HBP). I shan't say more.

These changes are real, if small. It is as though the fall in BP, which has significant benefits, is to some extent tempered by slight rise in lipids¹⁸⁴. Physicians should measure lipids in people who actually achieve reduced diet sodium, and perhaps make adjustments in diet or use of statins for the cholesterol. As triglycerides are strongly increased by refined sugar, these results increase the need to and benefits from reducing sugar intake.

HOW WE MAY HAVE BEEN BEFORE MODERNITY¹⁸⁵

We would have had lower blood pressures, certainly, and lower ECF volumes. Therefore the output of the heart would have been lower in general than now. Key hormones, renin, A2, aldosterone, and catecholamines all would have been higher. Renal sodium reabsorption would



have been higher as a fraction of filtered load, because of higher A2 and aldosterone. Filtration would not necessarily be lower even if the output of the heart was lower because higher A2 would tend to keep pressures in the glomerular capillaries from falling¹⁸⁶.

Lipids are difficult to interpret as our diets were certainly very low in refined sugar, meaning that triglycerides would be much lower in general. As for cholesterol, we were so radically different one can say little.

WATER BALANCE

Urine Volume

You would think that stone formers had lower urine volume than non stone forming people, but that is not true in general. 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.

¹⁸⁴ *Possibly you can sense my indifference to these changes. I have a lifelong skepticism about the vigor of the lipid CV disease linkage, and these are very small changes. Even so, that is mere opinion.*

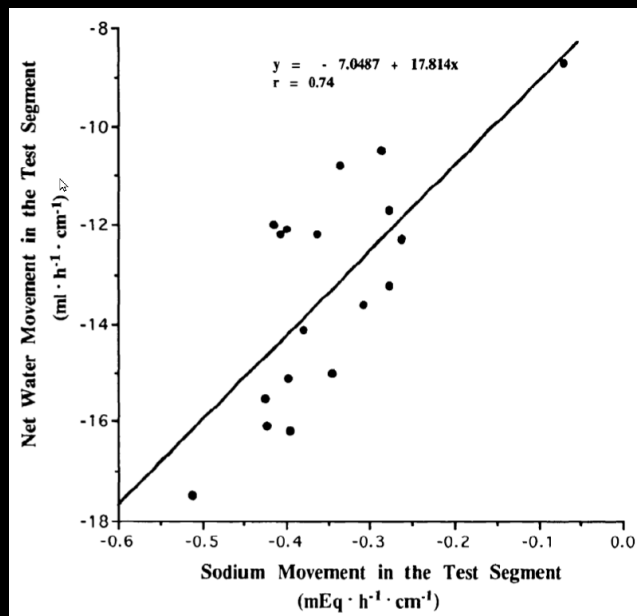
¹⁸⁵ *I indulge myself here. Of course we cannot test anything I say about the remote past. But one can infer a bit from these remarkable collections of data.*

¹⁸⁶ *I mean by this that with chronic low sodium intake (low by current standards) our cells would have experienced higher levels of these key hormones throughout life. All are powerful regulators, meaning our cells were influenced importantly in a different way during much of our evolution. If evolution selected for fitness, then one proposes we are best served by these higher hormone levels and low diet sodium. This is my challenge to scientists: Can a proposition like this be tested by experiment?*

Points for the two groups overlap. Some who do and some who do not form stones have very low 24 hour urine volumes, but there is no bias to lower volumes in stone formers¹⁸⁷. 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.

Water Intake

We all know water intake is controlled by thirst, as well as habit, culture, and even amusement - flavored waters, alcoholic beverages. Water enters the ECF upon absorption and, if the ECF volume is 14 liters, every liter retained dilutes the fluid sodium by 1/14 or about 7%. That is far greater than the variability of ECF¹⁸⁸ sodium concentration (that tracks with ECF osmolality). Unlike sodium balance, which varies the size of the ECF sodium pool, water balance varies the concentration of sodium¹⁸⁹ in that pool, and whereas cells cannot generally sense amounts of ECF fluid they certainly can sense blood sodium concentration.



So you might imagine that urine flow rate rather closely matches water uptake, not over days but over hours or even minutes, and that would be true and we all know it. Drink a lot extra and your bladder will tend to fill over an hour or so. But what does extra mean? If you drink after a day playing beach ball, fluids may be low so extra water is simply retained. If after a lot of fluids you add in more, urine flow will probably rise right away.

Water Absorption

As a rule, cells do not move water itself but move small molecules like sodium or glucose creating osmotic differences - differing concentrations of the small molecules across

membranes - along which water will move passively. The figure shows how movement of water into blood from human intestines follows movement of sodium. Glucose or amino acids from meals will facilitate water absorption (From J. Appl. Physiol. 77(3): 1178-1184, 1994.) But this does not

¹⁸⁷ *This does not mean that if one follows people over time those who become stone formers may not display lower 24 hour urine volumes from those who do not. My graph compares people who have had stones to those who have not, and knowledge may alter behavior.*

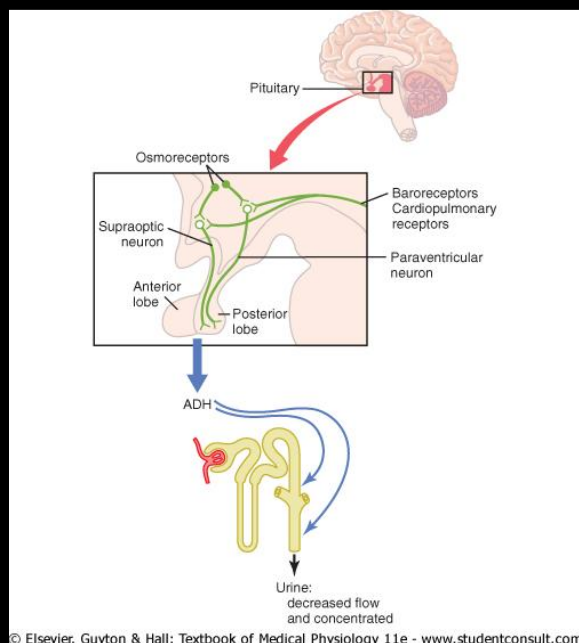
¹⁸⁸ *Blood water (not red blood cells) has the sodium concentration of the ECF. The body cell mass contacts water filtered out of blood as it traverses the capillaries which surround all cells, called the interstitial fluid shown a few pages back on the water compartment diagram. The fluid returns at capillary end because it was filtered without its proteins which osmotically draw it back in.*

¹⁸⁹ *I will repeat this - sodium is so predominant among the 'osmotically active' materials in blood I name it alone, for simplicity.*

mean that one needs to eat in order to absorb the water we drink. There is sodium available from secretions in the duodenum to allow water absorption.

Given high exertion and a need for abnormally brisk hydration, as in runners, football players, and the like, sports drinks, which generally contain sodium and sugars, can improve athletic performance¹⁹⁰. These drinks are not intended for sedentary life as the extra calories and sodium are unhealthy unless high athleticism depletes sodium and water, and makes great demands on sugars to power peak muscle performance¹⁹¹.

A major pathway for water absorption is through water channels (Aquaporins) and the whole intestine, from stomach through to colon is rich in these molecules. No surprise there. In addition to the 2 liters or so of water absorbed from diet, the intestines secrete and reabsorb about 7 liters more. Nowhere near the 150 liters of fluid filtered and reabsorbed by kidneys, but substantial. The aquaporins in the kidney are regulated by a crucial hormone (see below) but no such regulation has been proven for the intestine¹⁹².



Urine Volume Flow Mainly Reflects Blood Sodium Concentration

The Brain and Vasopressin

Certain brain cells have a dull life. They sense blood sodium concentration¹⁹³. If it goes up they signal release of AVP, made in the hypothalamus and stored in and released from the posterior pituitary gland. This hormone, AVP, signals certain kidney cells to make their membranes

permeable to water by inserting aquaporins into those membranes¹⁹⁴.

If serum sodium rises, think beachball in August, or a sausage and cheese pizza (or both), AVP levels rise, and kidney cells insert more aquaporins into their membranes to reabsorb filtered water so it is not lost in the urine. If serum sodium falls, think lots of water, AVP levels fall,

¹⁹⁰ *The sodium and potassium replace sweat losses that can be tremendous, and the sugar does indeed give muscles an 'energy burst'.*

¹⁹¹ *I followed this side path having long battled against 'sports drinks'. They sound healthy and are - if you are an athlete.*

¹⁹² *A priori I would have guessed that regulation was not favored by evolution. Absorbing all the water and sodium seems best for survival - the kidneys can remove excess.*

¹⁹³ *A fall in ECF osmolality allows water into the cells causing stretch and the converse. Glucose and urea comprise significant ECF osmolality but because they can move in and out of cells they do not force water to do so as effectively as sodium whose cell concentration is tightly regulated.*

¹⁹⁴ *Cells of the collecting ducts, the termini of nephrons wherein fluid is adjusted toward the final urine.*

kidney tubules become more like glass tubes and a higher fraction of filtered water leaves in the urine.

So when we talk about drinking water to prevent kidney stones, we are talking about deliberate suppression of AVP release by a slight downward push on serum sodium concentration.

The Brain and Thirst

If serum sodium rises the brain registers thirst so we drink more water. We all know this. But if you step back, the brain is signaling our kidneys and our behavior in the same direction, as if our whole self were like an organ. A2 also regulates thirst as noted in the sodium section¹⁹⁵.

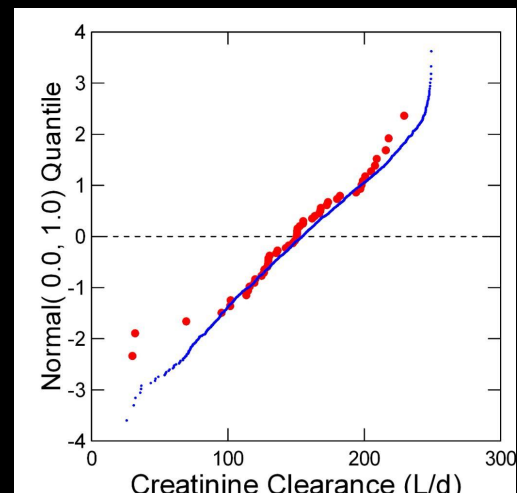
Fluid Volume and AVP and Thirst

The brain knows the volume of the blood by sensing stretch in the walls of the large vessels and the atria of the heart. So a day of beachball is not the same as a large sausage and cheese pizza.

The former stimulates AVP and thirst both because ECF volume is down and ECF sodium concentration is up. So on the beach AVP will rise to correct serum sodium and help maintain blood pressure. The name, vasopressin arose because it can do this latter.

In a less charming example, thirst may be the sole symptom of hemorrhage, as blood volume falls even though serum sodium remains constant. But that is taking us off our path and we must not loiter.

The picture above cartoons the brain and pituitary. The inset shows baroreceptors (pressure, stretch) and osmoreceptors (sodium concentration, mainly) interacting to control release of AVP into the circulation where it influences aquaporin insertion into the collecting ducts (last part of the nephron where fluid is most concentrated/diluted). The figure omits A2 as a mediator of thirst, for simplicity and clarity, but we know about it.



KIDNEY WATER HANDLING

Kidneys Filter and Reabsorb a Lot of Water

I mentioned before that glomerular filtration rate (GFR) - 99% water - averages about 140 l/d in adults. Filtration is estimated using urine and serum creatinine concentrations, a common

¹⁹⁵ *Remember, A2 rises when the fullness of the circulation falls.*

method¹⁹⁶. The mean is about 140 l/d for both sexes combined - where the curving line of data points crosses the dashed line at 0. Values vary from as low as 40 to as high as 250 l/d. Part of it is size; small women will filter less than very large men. Filtration varies with sodium intake - more sodium, more filtration. Also with protein intake - more protein, more filtration.

I already showed that the mean urine volume from these same people was under 2 l/d (about 1.8l/d or so). This means that on average urine volume is 1.8/140 or around 1.2% of filtered water - call it 1% for simplicity. So kidneys must reabsorb about 99% of all the water they filter.

We have already considered how they do that. When AVP signals insertion of aquaporins into kidney tubule cells, they permit water to move from tubule fluid back into blood¹⁹⁷.

Reabsorption of Filtered Sodium and Water Are Independent

But that last footnote cannot be perfectly true, can it? What we know will let us remove extra water without sodium, but will it let us conserve water while eliminating extra sodium? Will it let us eliminate a **lot** of water without losing extra sodium? Maybe so, but is there no provision thus far to separate water from sodium reabsorption¹⁹⁸?

There is such a provision. Let me now re-introduce the biological design element¹⁹⁹ that separates reabsorptions of sodium and water.

The Thick Ascending Limb of Henle's Loop

The lovely drawing below shows one of the million nephrons in a single human kidney. Fluid filtered out at the glomerulus (labeled 1) flows down a hairpin tube of which we center attention on the thick ascending limbs (labeled 6). Nephrons most inward have very long thin limbs (labeled 4, 5) those least inward have abbreviated thin limbs (labeled 4) but all have the thick limbs. Collecting ducts gather nephrons as a river its feeder channels²⁰⁰.

Without details, the cells of the thick ascending limb reabsorb sodium and chloride in abundance but are impermeable to water - they separate salt from water. In doing this, they permit independent regulation of sodium and water excretion by the kidney.

¹⁹⁶ *If urine creatinine comes only from filtration out of blood plasma (not entirely true but reasonable for practical purposes) then urine excretion must equal plasma creatinine concentration, P_{cr} , times the filtration rate (GFR): $P_{cr} * GFR = U_{cr} * V$, where U_{cr} is urine creatinine concentration and V is urine flow rate: $GFR = V * (U/P)_{cr}$. GFR thus measured is called 'creatinine clearance'.*

¹⁹⁷ *I know you had a momentary pause there - remember sodium is being reabsorbed, and so is glucose, and amino acids, so water can move back into blood as these osmotically active molecules move. No aquaporins, the water is stuck inside the tubules and leaves in the urine.*

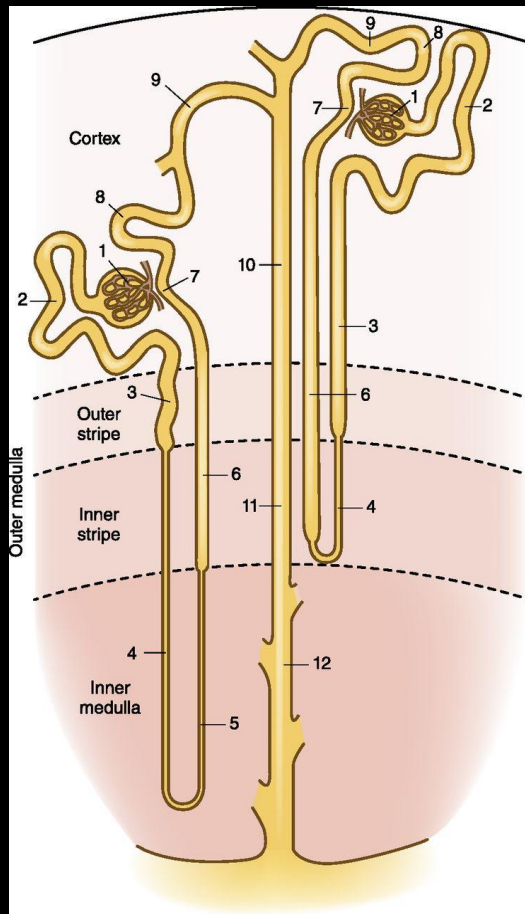
¹⁹⁸ *The answers to all three are, in fact, 'yes'. In principle. But at the extremes, perhaps not. Think about how dilute tubule fluid can become sans aquaporins and a demand to reabsorb sodium - can the cells reabsorb when the fluid is very dilute? Are there more reliable ways to engineer a kidney?*

¹⁹⁹ *We are at a crucial point in the water / sodium story - their independence from one another. If you are tired come back later as this material is of the highest import and complicated.*

²⁰⁰ *I am aware that we walked this path before, but now we pause to inspect one portion of it with a greater love and attention.*

When Water is Abundant

Imagine what kidneys can do with this separation and you will be correct. The filtrate



concentrations of the main salt, sodium chloride, is that of blood which is that of the entire ECF volume. The fluid leaving the top of the thick limb (at 7 on the picture) is dilute - sodium chloride has been removed without water.

If AVP is low, because plasma sodium is low (remember, low means a tiny deviation below the usual), the rest of the downstream nephron cannot reabsorb water efficiently. But that rest of the tubule can reabsorb sodium chloride as efficiently as is required by the needs for sodium balance. This means that the urine is dilute with respect to the all important sodium. Water is leaving without sodium, so serum sodium will rise until AVP comes back up and water can be reabsorbed along with sodium. At the same time, sodium excretion sluggishly follows the dictates of ECF volume.

I cannot but mention a refinement here. Some sodium is reabsorbed not with chloride but *as if* in exchange for potassium in the collecting ducts²⁰¹. Though not a true pawn takes pawn exchange, along the latter parts of the nephron, especially the collecting duct, potassium is pumped out of plasma into the tubule fluid and that movement is partly balanced by

reabsorption of sodium. **So it is the sum of sodium + potassium that makes up the majority of salt solutes in the urine**²⁰².

When Water is Not Abundant

If AVP is high, because serum sodium is high - even a tiny bit high! - or ECF volume is quite low, the rest of the nephron, as I have shown thus far, can reabsorb water so efficiently that water and sodium will be reabsorbed together - the urine concentration of sodium + potassium will be that of the filtrate²⁰³.

²⁰¹ **As sodium reabsorption without chloride makes tubule fluid negative in charge vs. blood sodium can move from blood into tubule fluid. Potassium 'secretion' broadly links to sodium reabsorption. The reality of this is more complex but we have enough for now.**

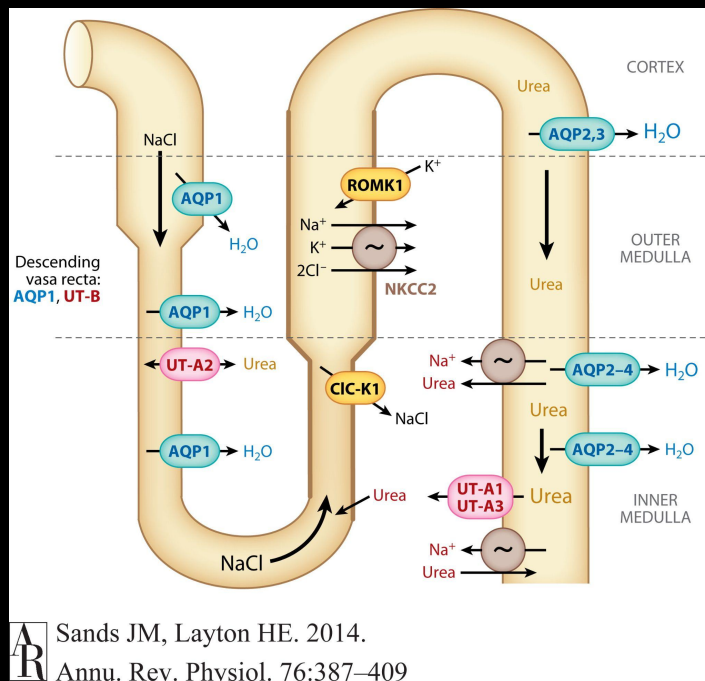
²⁰² **It is probably in poor taste to bold this mundane assertion. Being the two main 'electrolytes' in urine, free water clearance calculated from then is often named 'Electrolyte free water clearance'**

²⁰³ **Because of the sodium potassium 'exchange' in the collecting duct this is not a remarkably bad statement.**

But this would not do, it could not correct the serum sodium back down. That would require that sodium (sodium + potassium as noted before) be lost in excess of water²⁰⁴ - that salt concentration in the urine be higher than in the filtrate. The thick limb and tubules cannot accomplish this given what I have said. More has to be added.

KIDNEYS AS DESALINATION PLANTS

My Disclaimer in Advance



Sands JM, Layton HE. 2014.
Annu. Rev. Physiol. 76:387–409

The kidney, not just the thick limb, can go further, squeeze water out of the tubule fluid and concentrate the sodium + potassium chloride above that of serum. That extra water goes back in the blood in the renal veins and dilutes the serum sodium back to its normal value²⁰⁵. The kidney is a biological desalination plant that can make relatively fresh (less salty) water out of a more salty filtrate and return it to the body. [Here is a fine review about what we know.](#)

A Reasonable Sense of How Urine is Concentrated²⁰⁶

This lovely drawing is from the linked article by professors Sands and Layton. For those with enough background the original article is rigorous far beyond what I would place here, and possessed of a wry charm.

Use Sodium Chloride

The thick ascending limb reabsorbs filtered sodium (and potassium) with chloride which is pumped out into the space around blood vessels and tubules, the 'interstitium' of the outer medulla. Water is trapped inside the tubule²⁰⁷. The incoming blood to this interstitium flows close

²⁰⁴ In other words the concentration of the two exceeds that of the filtrate, which is to say of the blood

²⁰⁵ In blood, potassium is only 4 mEq/l vs. sodium at 140 mEq/l, but because potassium comes to make up a significant portion of urine electrolyte concentrating the sodium + potassium above blood sodium is enough.

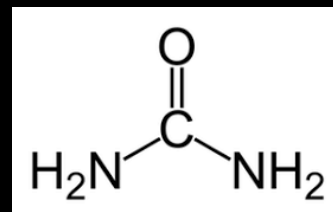
²⁰⁶ Experts will recognize I am narrating the passive counterflow model which is plausible but incomplete.

²⁰⁷ We already discussed this point as the way we create free water excretion.

by the exiting blood, so some destined to leave leaks sideways into the inflow²⁰⁸. This traps the sodium.

Use Urea

When AVP is not suppressed, the dilute fluid loses water into the blood through the cortical collecting duct AQP2,3 (upper right corner). The blood and tubule fluid have the same concentration of molecules that affect water movement (osmosis) but differ in composition. The tubule fluid has a higher concentration of urea - an end product of protein metabolism, and lower concentration of sodium chloride. In the outer medulla, the same: urea concentrates, far above blood levels, because of all the sodium chloride in the interstitium.



At the end of the collecting ducts, urea can move out into the interstitium through the UT-A1,3 channels that AVP signals cells to insert into the membranes. The urea raises the osmotic pressure in the interstitium - it billows upward.

Add More NaCl

Filtrate in the proximal tubule (upper left of the picture) loses some water because of the high outer medulla NaCl loading. Then, even more is lost in the descending thin limb so the fluid is concentrated. Most of the concentrated material is, of course, NaCl²⁰⁹. The Ascending thin limb is not permeable to water but to NaCl, which increases the inner medulla with NaCl. This adds to the urea, so the collecting duct water extraction is even higher, and the urea entering from the UT-A1,3 transporters more concentrated. Of course this increases water extraction in the descending thin limb.

A Cycle Leading Higher and Higher²¹⁰

You get the idea. The urea ramps up descending limb water extraction, the ascending limb NaCl ramps up interstitial osmolality by adding to urea, the two ramp up collecting duct water extraction which increases urea concentration, and so forth. What limits all this is the blood. Even though vessels counterflow, trapping urea and NaCl, eventually the concentrations are so high above blood we reach a threshold. Urine can be concentrated to an osmolality of 1,200 mOsm/kg, vs blood of 280 mOsm/kg²¹¹.

²⁰⁸ *This kind of countercurrent trapping was used in Rome. Incoming hot water to the baths flowed next to the exiting warm water.*

²⁰⁹ *Because the TAL has not selectively depleted the fluid of NaCl so urea is relatively minor.*

²¹⁰ *I understand that my narrative gives only a vague impression of how kidneys can squeeze water out of filtrate to donate fresh water back into the blood. But do we need more here? Is that not enough? If not, there is the article - lucid as diamond.*

²¹¹ *The seductive charm of the passive counterflow model should not mislead us. When represented in computer programs the model does not properly predict urine concentration.*

MEASUREMENT OF RENAL WATER HANDLING

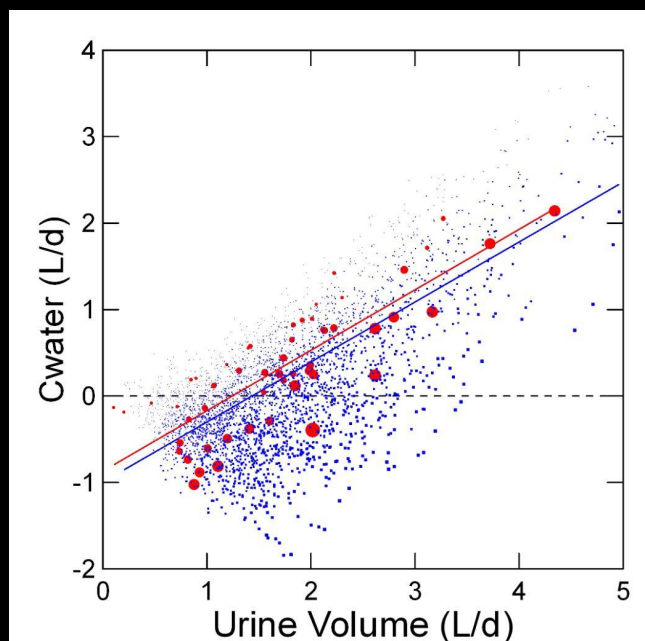
Physicians and scientists can gauge the function of the kidney with respect to urine concentration and dilution. Since stone disease arises from renal concentration of key solutes, such a gauge is worth knowing about²¹².

The Idea of Solute Free Water Clearance

Call urine concentration of urine $\text{Na} + \text{K} = S$ (S stands for solute, things dissolved in urine that affect water movement across cells). Measure S in a sample of urine. Call this U_s . In the blood²¹³ call blood plasma $\text{Na} + \text{K}$ concentrations P_s . Now, calculate the fraction of water you have to add or remove to make $U_s = P_s$. Clearly, that fraction is U_s/P_s . Above 1 means too little water (add more in), and the converse²¹⁴.

But the kidneys made this urine, so <1 means extra water in the urine, and the converse. Since $U_s/P_s = 1$ means no extra water either way, $(1 - U_s/P_s)$ gives us the fraction of urine water the kidneys reabsorbed (minus) or the fraction 'extra' they eliminated. So, if V is the urine flow rate

$C_{\text{water}} = V \times (1 - U_s/P_s)$, gives the rate free water is delivered into the urine (C_{water} positive, the ratio is below 1) or reabsorbed back into the blood (C_{water} negative).



Cwater in Patients and Normals

As urine volume goes up, C_{water} generally rises, but individuals (each point in the graph below) may be above or below the 0 because excreting or conserving water (Symbol size is set by U_s/P_s , for interest).

Does this really mean the kidney is returning relatively fresh water into the circulation when C_{water} is negative? Yes. If you were paddling a tiny canoe in the renal veins, you

would find the blood sodium concentration below that of the general circulation when C_{water} is negative.

²¹² *Curiously, the stone community, perhaps most involved with renal water handling, has in general no interest in nor knowledge of how to calculate what the kidney is doing with it.*

²¹³ *Once again, I mean ECF but 'blood' will do here as that is where we filter out of, and plasma specifically, thus the use of P_s .*

²¹⁴ *This should seem common sense. If not, think about two boxes of socks. Box 1 has 96 red and 4 blue, box 2 has 45 red and 45 blue (90 socks). Call the total number of socks in each box S_b . How many socks must be added or removed from box 2 (the urine) to make $S_{b2} = S_{b1}$? It is $100/90$ (the replacement fraction) \times what is there - $1.111 \times 90 = 100$, so the number to add is $100 - 90$ or 10 socks. I made red sodium blue potassium.*

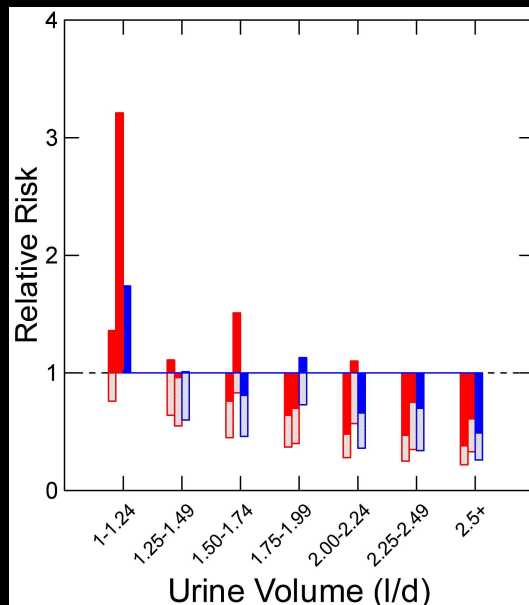
A Urinary View of Free Water Clearance

Of course evolution aimed at both constant and biologically ideal blood sodium concentration under wide ranging conditions of sodium and water availability and losses. Urine conditions would have been secondary to that requirement. But the kind of urine produced matters to us, who study kidney stone disease.

Positive C_{Water} means that for the most part filtered materials will range nearer to or perhaps below their serum concentrations, meaning supersaturation is less likely²¹⁵. When C_{Water} is below 1, as is very common in the graph, filtered materials may be higher in concentration and supersaturation more common, depending on the other factors that control it.

This means that urine volume is not as good a clue to saturation as is C_{Water} . For example, at 2 l/d, C_{Water} varies from -1 to +0.5 (Take a look back at the graph). In the latter situation urine solutes are below those in the filtrate, and the converse. Saturations will also depend on the fraction of filtered calcium reabsorbed, is that not true?

Although our data are slight, is it not interesting how more negative than in normals is C_{Water} in the stone formers²¹⁶?



URINE VOLUME AND KIDNEY STONES

Low Urine Volume Raises Risk of Stones

Although our own data do not show lower urine volumes in stone formers vs. normal people, long term observations of large normal populations have demonstrated that those people who become stone formers during years of observation have lower urine volumes than those who do not become stone formers²¹⁷.

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.

²¹⁵ *This is approximate and not always true. For example, oxalate is secreted into tubule fluid. Even when C_{Water} is high, the free ion product for CaOx or CaP can be above solubility.*

²¹⁶ *When we estimate supersaturations we essentially take up C_{Water} into the concentrations of the urine molecules and ions used, so C_{Water} itself is not needed to estimate stone risk.*

²¹⁷ *Once again I wish to remind everyone this is my regraphing of the remarkably important work of Gary Curhan and his group at Harvard. He presently is Chief Medical Officer of a data analysis company.*

As in all the prior graphs, mean risk of stones is at the end of the bar, and the 95% limit at the end of the filled colored portion. For the highest three septiles, risk is solidly below 1. For the next three moving downward in volume some spotty bars crossed the line at 1 meaning risk. The lowest volume conferred considerable risk (far left threesome).

The meaning is clear and yet not entirely so. Certainly volumes below 1.25 l/d are high risk and below 1.75 l/d risky in the sense that some bars reach above 1. Surely, volumes above 2.25 l/d associate with low risk. So what is the best compromise between risk and nuisance? That requires a trial, and we have one²¹⁸.

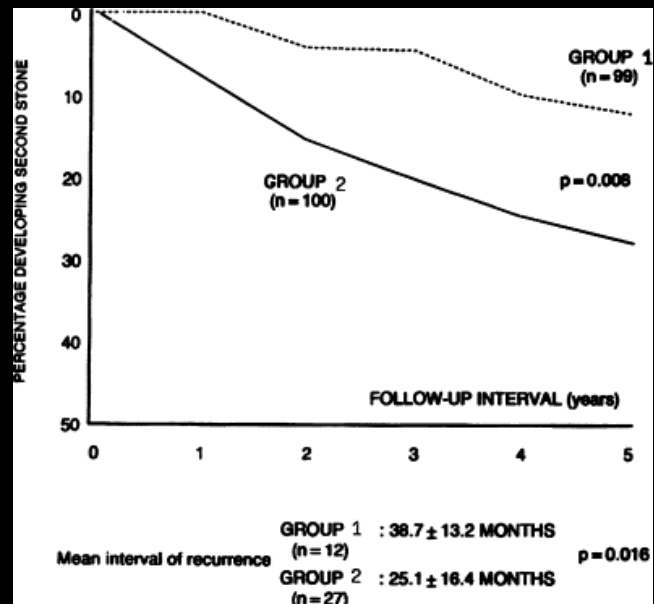
More Water Prevents Stones

Both groups on the graph (page below) are people who had formed one calcium oxalate stone each. Group 1, randomly selected, was coached by nurses to push urine volumes over 2 liters a day while Group 2 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 2 people had urine volumes predicted to reduce stone risk.

By five years, 12 Group 1 and 27 Group 2 patients had formed at least one new stone, and the time it took to the recurrence was 38 vs 25 months, respectively. So more water can reduce new stones and delay the formation of those new stones that do form compared to the very low urine volume of 1.01 l/d on average.

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 day²¹⁹. Likewise, there were single stone formers - only one prior stone each. Why was water not a more exacting prevention?

My suspicion rests on variability of human nature vs. computer like exactness of crystals²²⁰.



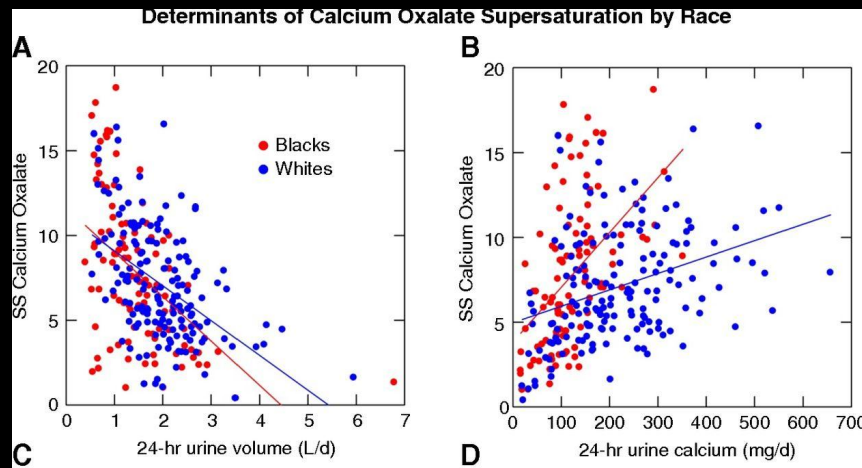
²¹⁸ ***Trials are very important. The original reference and details about this trial are in the link. The word trial is proper here as one is 'trying' a means to an end.***

²¹⁹ ***By this remark I wish to question those who insist on water alone as a reliable stone prevention. If the pattern of this trial held, 24% of people producing over 2 liters/d of urine would form more stones over 10 years!***

²²⁰ ***Crystals never sleep, never lose interest. Over the many days and years, did patients collect 24 hour urines of 2.5 liters made of floods and droughts by day and trickles by moonlight?***

The high flow average of 2.6 l/d certainly must burden people. Would stone rates really be significantly different if one compared the 2.6 l/d to some more reasonable average - perhaps our mean value of 1.8 liters/d? Is it really smart to rely only on water?²²¹

Racial Differences in Stone Formation



Compared with white kidney stone formers, those of more recent African ancestry have markedly lower urine volumes and low urine volume appears to be the main reason for their stones. In the left panel from that publication, supersaturation for calcium oxalate varied with 24 hour urine volume, as expected, but points for blacks (red)

clustered at the left (low) end of the range.

Urine calcium had a much greater effect on supersaturation (right panel) because of the lower volume, but blacks had lower urine calcium than whites²²².

This was not surprising because eating the same diets, black men and women have lower urine flow rates than comparable whites (references in the above article). As one would expect, serum AVP levels are higher in black subjects²²³. Although this is speculative, one presumes that water conservation was crucial during human evolution in Africa.

Moreover, when challenged to drink more, black stone formers raised urine volume but also urine solute excretions, so C_{water} did not rise as it does in white patients.

Despite this demonstration that low volume arises from biology, it is not reasonable to assume that low volume caused kidney stones to any appreciable extent during our long evolution in Africa, for the reasons I have already presented. So the low volume, if indeed present during that time, may have been offset by their lower urine calcium excretion, itself not prejudicial, hopefully even beneficial to successful reproduction²²⁴.

²²¹ *I find water alone burdensome, inefficient - as noted, and disrespectful in that multiple urine abnormalities may be left untreated - and diet infelicities as well. Why would anyone choose such a mediocre approach to patient care when a better diet is so generally valuable?*

²²² *This is shown by their crowding into the left hand portion of the graph.*

²²³ *I left it to those interested to look up the references from the linked article so as to avoid overloading this rather slim document.*

²²⁴ *The racial difference is surely genetic, and deserves considerable research.*

URINE VOLUME AND KIDNEY STONES REDUX

Risk from Urine Volume Depends on Stone Forming Salts

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 significant but dependent on the excretions of the stone forming salts. Although in general stone formers do not have lower average urine volumes than normal controls, at equivalent urine volumes stone formers seem to have more negative C_{water} , meaning higher concentrations of salts. This has not been explored in detail.

On the other hand, risk of **becoming** a stone former seems concentrated in the lowest urine volume group, 1-1.24 liters a day. In the water trial, Group 2 patients, who formed more stones, had an average urine volume close to 1 liter a day. But even with a urine volume over 2.5 liters a day, Group 1 patients formed 12 new stones in 5 years, so the higher volume cannot have countered all of the stone risks they had. In fact, the authors noted that urine calcium was higher in those who formed stones (not shown here).

Black People Have Low Urine Volume Calcium Loss

Black stone formers seem most instructive concerning the situation over evolutionary time, when water could easily be scarce. Highly efficient renal water conservation would seem a powerful adaptive response during our long sojourn in Africa. It would seem important then to minimize urine losses of calcium, as they seem to do. Of course, we cannot say what was the situation then as we all eat diets massively different from those during the majority of evolution.

The black stone formers also raise the question of whether some white stone formers still tend to higher renal water conservation than others, and therefore become stone formers. Is it true that challenged by a water load some white stone formers, perhaps those presenting with low urine volumes²²⁵, would behave as do black stone formers and fail to produce positive free water clearance?

WATER WITH AND BETWEEN FLUIDS

Unlike sodium balance, water balance must be rapid as people are free to drink large volumes of water in short periods of time. Because aquaporins can leave cell membranes in minutes as AVP falls, and because kidneys filter massive amounts of water and the thick ascending limb dilutes filtrate efficiently, C_{water} can exceed 2 liters/d (1.4 ml/min), as on my graph, and in brief bursts even higher (10 ml/min or more). This does leave room for excess water to lower serum

²²⁵ *The 'low flow' patients always intrigued Joan Parks and I. Despite much encouragement, few raised their urine volumes even though low volume was a prominent factor in their stone disease. We never considered the link to evolution because the black stone former work by Anna Zisman came so late in our careers.*

sodium as can occur in psychiatric diseases. Likewise for any drugs that interfere with renal sodium handling (diuretics) or AVP regulation (eg. antidepressant drugs).

Of equal interest, renal water conservation (negative C_{water}) can provide up to about 3.5 l/d of fresh water. On my graph you can see several people at 2 l/d, and these were not at the extremes one may find in desert conditions. Far from losing water between drinks, kidneys can provide water back to the circulation, but always at the expense of stone risk unless other systems compensate²²⁶.

ADAPTATION TO HIGH WATER INTAKE

Against my skepticism that high fluids alone efficiently prevent stones is a subtlety about water regulation I rarely hear about from my colleagues.

Lessons from Primary Polydipsia

When extreme and constant as in primary polydipsia²²⁷, suppression of AVP leads to washout of renal medullary urea so that osmotic concentrating power is reduced. If you deprive people with this behavior of water overnight they cannot concentrate the urine normally. After a few days, they can as they rebuild the medullary NaCl and urea concentrations²²⁸.

Why does constant very high water intake do this??

Because without AVP fluid cannot leave the collecting duct in the cortex, or the medulla. This prevents concentration of urea. Likewise the urea transporters are removed from the membranes. Gradually, the circulation will remove the excess urea, and we have lost a major force for urine concentration²²⁹. Stop the excess water, AVP will rise, and the system rebuilds the medullary hypertonicity.

What About Stone Formers?

This clinical experiment and what we know raises a question of clinical importance not well studied. Given the AVP suppression we attempt in stone formers, using 2 to 4 liters of water a day, do they exhibit a fall in maximal urine osmolality after an overnight fast?? After all, urine volumes in primary polydipsia often exceed this.

In a wonderful antique study, patient numbers 15 through 24 (below) all were diagnosed as having 'primary polydipsia'. Numbers 25 through 29 were normal people. The others nearby had diseases affecting AVP and can be ignored here.

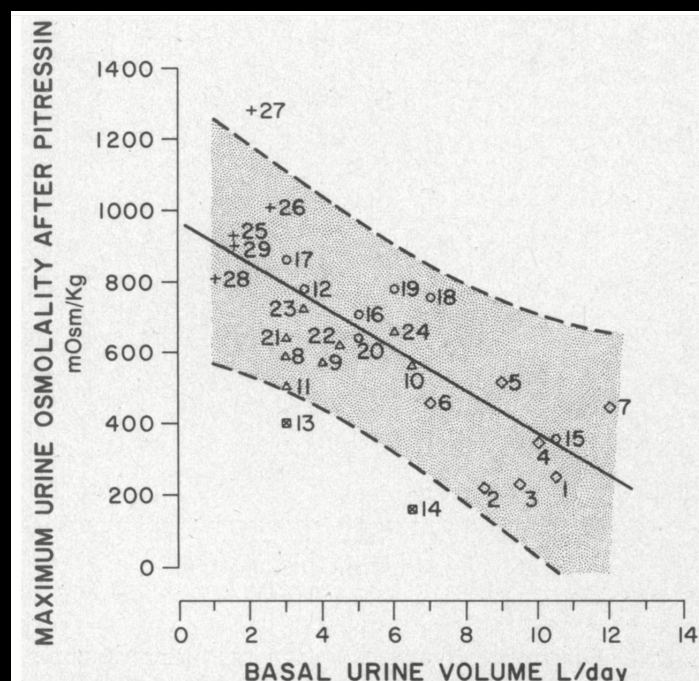
²²⁶ *You will find that urine calcium is so influenced by urine sodium that under real conditions of low fluids such as hot climates low urine volume will be offset by low urine calcium losses from sodium depletion. I do not think this is mere coincidence, but cannot prove the point.*

²²⁷ *For psychiatric reasons some people drink huge excesses of water, enough to lower serum sodium concentration.*

²²⁸ *The washout has been well demonstrated in animals, in humans it is inferred.*

²²⁹ *All we have left is the outer medulla which raises osmolality to 400 mOsm/kg.*

The vertical axis shows the highest urine osmolality after being given vasopressin - the best the kidney could do. The x axis shows the urine daily volume before this treatment. If we focus on 2



- 4 liters/d of urine volume, cases 17, 21, 22, 23 illustrate lesser concentration vs. the normals. At a bit higher volume, 4 to 6 liters/d, we have the same for cases 16, 18, 19, 24, 24. Stone prevention rarely demands above 4 liters of urine daily so the higher values are mainly in support of the idea.

Sustained very high water intake can reduce maximal urine concentration, as washout predicts. Our usual 2.25 - 3.5 l/d prescriptions seem to cause some washout that might help prevent stones. If water concentration is indeed less efficient, temporary lulls in fluids by day, and after nightfall will be, perhaps, less dangerous²³⁰.

HYPONATREMIA

Towards the end of this book I detail this problem further, but pause here to acknowledge its importance. Well enough to raise fluids, reduce diet sodium, and - as below - use thiazide diuretics for stone prevention. But in some patients we may lower blood sodium, and that is a hazard I want to afford a proper prominence. Chronic hyponatremia, even modest (serum sodium 135 or thereabouts) may impair brain function. Below that things worsen.

Hyponatremia and stones are epidemiologically linked²³¹. A well done meta-analysis showed benefits of high fluid intake for stone prevention and low risk for hyponatremia. Even so, physicians need to check serum sodium when low sodium diet and high fluids are combined, especially with thiazide. I have no rules to offer here, merely that physicians have their irreplaceable role in patient care, and understand to fulfill it.

CALCIUM

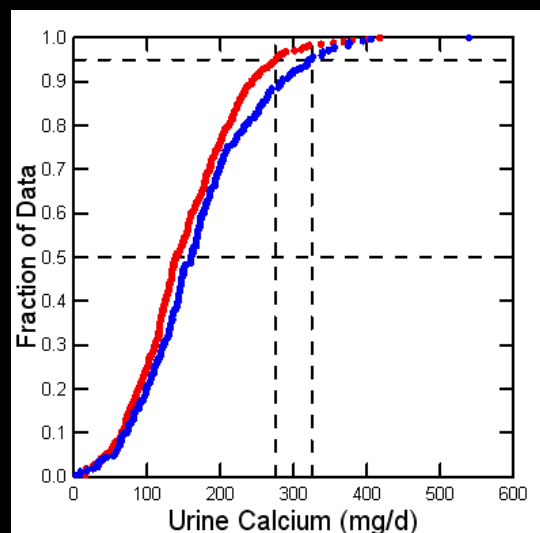
Just like the sodium and water biologies, calcium biology seeks a constant interior environment, in this case blood calcium concentration and - possibly - bone mineral stores as well²³². These requirements are achieved by regulation of food calcium absorption, urinary calcium losses and

²³⁰ *One might profitably reproduce this kind of work in stone formers, as a gauge as to washout and the creation of a safety margin.*

²³¹ *A recent study purports persistent hyponatremia preceded stones as if causal. I doubt the timing was accurate, but everything is possible.*

²³² *I have no evidence that bone mineral stores control systemic calcium balance, only the opposite.*

movement of calcium in or out of bone. If lower urine calcium and consequent risk of crystallization increased fitness during evolutionary time, calcium biology may also seek some compromise between internal regulation and calcium absorption to control urine calcium losses²³³.



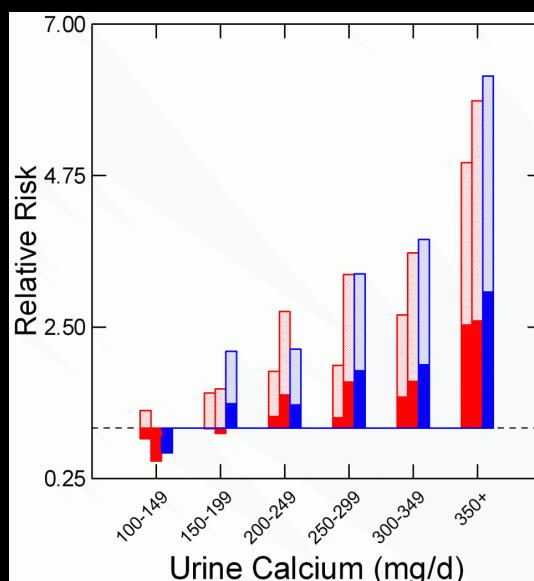
Since blood calcium must be constant from minute to minute and food is eaten irregularly, bone must provide minute-to-minute buffering. Between meals bone mineral must enter blood as calcium is lost in the urine, and calcium enter bone when food calcium is entering the blood²³⁴. If so, then bone mineral is prey to urine calcium loss and diet calcium sufficiency.

URINE CALCIUM

Urine Calcium Among Normal

Adult People

The graph below shows urine calcium losses in large numbers of normal women (red) and men studied in metabolic balance units over the past century²³⁵. The median is about 160 mg/day, women excrete slightly less calcium than men, and the range is wide. For example 75% of normal people have urine calcium excretions of 200 mg/d (20% above the mean) and 10% as high as 250 mg/d or more. The horizontal dashed lines mark the 95% percentiles for both sexes, once a common dividing line for calling an individual 'hypercalciuric'²³⁶.



Urine Calcium and Stone Risk

Just like the graph for urine volume, epidemiologists have linked levels of urine calcium with risk for new onset of kidney stones in two female (red) and one male cohort followed over many decades. Below 150 mg/d, close to the median for normal

²³³ *I mention this pure conjecture without information to support it - mere imagining.*

²³⁴ *Unless absorption of food calcium remaining in the bowel between meals can match urine losses. This would depend on diet intake, would it not? And on some regularity of intake, too. Speculation.*

²³⁵ *I collected these data from papers published between 1900 and 2015. Using calipers I got the approximate numbers from points on their graphs. The compilation is published only here and on my site.*

²³⁶ *For isolating subjects in a research about extreme calcium excretion, it is still a fine criterion, but clinically valueless and to be shunned.*

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, no doubt by increasing saturation.

This figure illustrates the fallacy of naming in medicine. For decades, 'hypercalciuria' was diagnosed when urine calcium exceeded the upper 95% percentile among non stone forming people. We now understand that urine calcium loss is a graded stone risk, beginning near the median urine calcium excretion rate, so 'hypercalciuria', if used to signify disease risk, should apply to values above 150 mg/d²³⁷.

'Hypertension' now names a systolic blood pressure above 130 mmHg - the minimum at which increased risk of stroke can be detected. Ideally trials for stone prevention should seek prospective relationships between urine calcium during treatment and new stones despite treatment so as to provide treatment goals for the future²³⁸.

Latent Stone Risk in Normal People

That stone risk begins at just above the median urine calcium of normal men and women seems odd when viewed from an evolutionary standpoint in that crystal formation in kidneys would have reduced the fitness of a human population. So we must presume that values we have over the past century or so, obtained mainly in the US and Europe, are higher than those during our long past, and as we consider the control of urine calcium look for possible mechanisms that might cause such elevation²³⁹.

CONTROL OF URINE CALCIUM - Overview

For calcium, as for the size and concentration of the ECF sodium and water pools, kidneys are servants of higher order regulators that manage the internal environment of the body. So first we need to know *how* kidneys vary urine calcium when signaled, then who gives them their orders.

Serum Calcium and Calcium Filtration

The serum calcium not bound to blood proteins but free for filtration, the so called ultrafilterable (UF) calcium (upper left panel of figure), has a mean around 1.18 mmol/l, lower 95th percentile of 1.12 and corresponding upper value of 1.26, about 5% on either side. This is larger than sodium, but still reasonably well regulated²⁴⁰. Because stone formers and normals have

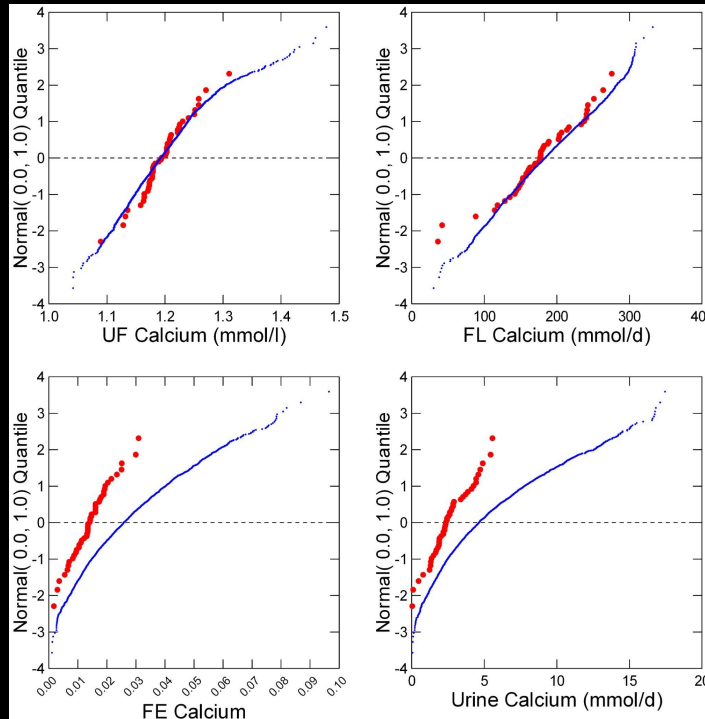
²³⁷ *This may shock some physicians and patients but is not untrue. A urine calcium value of 200 mg/d is sufficient to confer measurable risk.*

²³⁸ *I mean to emphasize that observational data such as on this figure are not a substitute for controlled trials in which urine calcium is brought to specific ranges and new stones counted. For blood pressure this was done and stroke rate counted.*

²³⁹ *We are now in a realm near philosophy, which borders on science as poetry on prose.*

²⁴⁰ *For purists, these UF calcium values were calculated. Blood calcium ion, the actual cell signalling, is lower than UCa and measured by electrode systems.*

overlapping filtration rates (shown earlier) and UF calcium, their filtered calcium (upper right panel) overlap with a mean of about 180 mmol/d (7200 mg). The remarkably straight line on this probability plot indicates it is normally distributed, like height.



Fraction of Filtered Calcium Excreted (FE_{Ca})

Normal people have about the same FE (lower left panel) for calcium as for water, about 1%, stone formers double that for calcium, not water or sodium (as we have already seen). Urine calcium (lower right panel) is equivalently higher in stone formers vs. normals as is their FE_{Ca}, for the latter is simply urine calcium divided by filtered calcium which is the same for them both.

The 24 hour urines and single fasting morning blood samples are excellent for illustrating the higher urine calcium of stone formers, and that higher urine calcium of stone formers reflects

reduced kidney cell reabsorption of filtered calcium. But this latter point, crucial to understanding variation of urine calcium, is best explored using shorter urine collection periods with closely timed blood samples²⁴¹.

CONTROL OF URINE CALCIUM - Detailed View

Fraction of Filtered Calcium Excreted

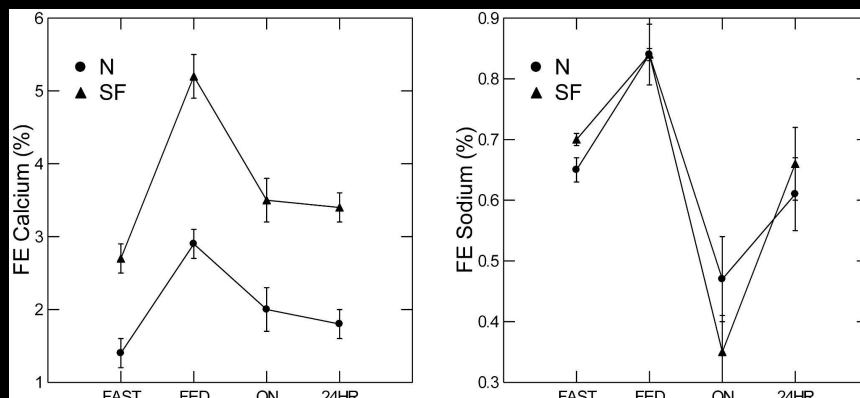
In men and women normals and calcium stone formers, we have measured filtered load and the details of calcium reabsorption fasting and after eating prescribed meals in a clinical research center.

The fraction of filtered calcium in the urine (left panel of the figure below) among the stone formers (SF) exceeded that among normal controls, fasting, fed, overnight, and in the entire 24 hour period properly averaged. Points are means and bars are standard errors. All of the apparent differences are highly significant statistically²⁴².

²⁴¹ **A single morning blood is an indirect gauge of filtered calcium over the 24 hours of these urine collections. We need shorter urine samples with bloods drawn at their mid-periods for finer work.**

²⁴² **The statistical testing is in the original publication**

Fraction of Filtered Sodium Excreted

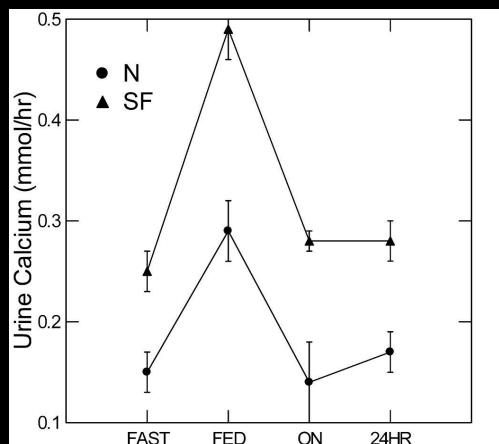


By contrast to calcium, fractional excretion of sodium (right panel) was the same for stone formers and normal people in all four phases. So the differences between these two groups somehow involve calcium but not sodium handling by the kidneys²⁴³.

Total Calcium Excretion

Here, instead of a fraction of filtered calcium, are the actual amounts of urine calcium (left panel) in units of mmol/hr (1 mmol = 40 mg). Fasting, fed, overnight, and over the whole 24 hours the stone formers are higher than the normals.

If you multiply the small looking value for patients in the 24 hour urine average, of about 0.28 mmol/hr, x 24 hours x 40 mg/mmol you get 268 mg/d, which is in the higher stone risk category, whereas the lower value for normals of about 0.14 mmol/hr gives 134 mg/d, a value at baseline stone risk.



Where is Calcium Reabsorbed?

As already mentioned in prior sections, kidneys are made of a million or so individual nephrons, and filtered fluid is processed along their length as along the assembly line for making cars, or chips²⁴⁴.

Filtered calcium first goes through the proximal tubule where 65% of filtered calcium is Reabsorbed. The TAL reabsorbs another 25%. Both PCT and TAL mainly

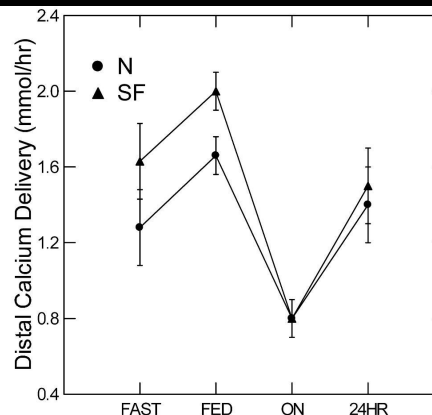
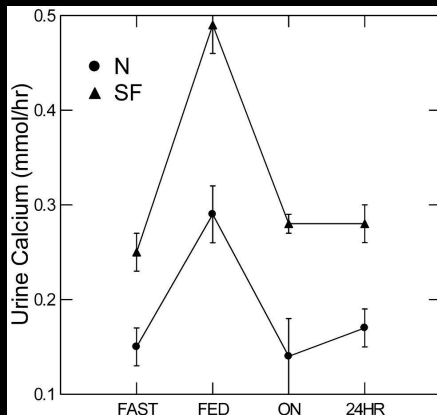
reabsorb calcium between the cells that line the tubule, using forces generated by reabsorption mainly of sodium. The DCT and a segment directly after it called the connecting tubule (CNT) reabsorb a critical 8% or so of filtered calcium, and this is through the cells, and tightly regulated²⁴⁵.

²⁴³ *Although I have referenced the source, I feel compelled to emphasize that these figures are drawn using data (Table 2) from our original publication.*

²⁴⁴ *Where calcium is reabsorbed matters because patients reabsorb it less well than normal and the locale(s) of abnormality may lead to better ways to lower urine calcium loss*

²⁴⁵ *Most believe final regulation of calcium balance occurs in this distal segment, though proof is lacking.*

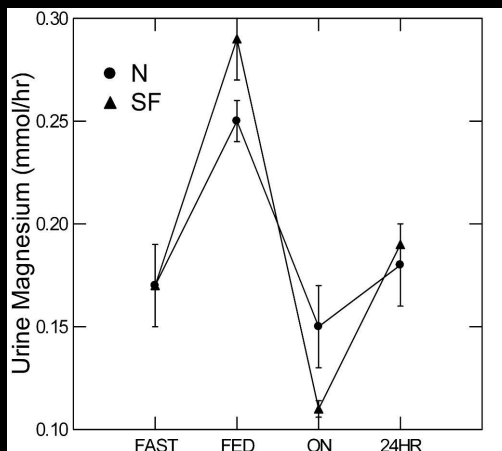
Where Along the Nephron Are Stone Formers Abnormal?



We can estimate calcium delivery out of the proximal tubule, which we call distal calcium delivery. It is far higher than urine calcium²⁴⁶. For example, the 24 hour values for normals and stone formers is 1.3 and 1.6 mmol/hr or 1,248 and 1,536 mg/d.

Overnight and over 24 hours the two groups have the same delivery out of the proximal tubule, yet urine calcium is much higher in patients²⁴⁷, so the difference in urine calcium between them must²⁴⁸ arise beyond filtration and the proximal tubule. This could be the TAL or DCT+CNT

Fasting and fed, patient values for distal delivery are higher in patients. Though not statistically significant, part of the 24 hour calcium difference might arise from PCT²⁴⁹.



Urine Magnesium Excretion

The other major divalent cation in blood and urine, magnesium is absorbed less completely in PCT than calcium, both are reabsorbed in TAL through similar pathways²⁵⁰, and in the DCT through entirely different channels (TRPV5 and TRPV6, respectively). Lack of abnormality in SF is evidence for a DCT origin of the patient difference in calcium from normal²⁵¹.

With meals, magnesium loss increases just like calcium. Compare 'FED' AND 'FAST' on this graph to those for calcium just above. So the food effect is

²⁴⁶ We measure clearance of lithium that is reabsorbed in PCT like sodium but very little thereafter. We take the fraction of filtered calcium leaving the PCT as that of lithium as an approximate estimate.

²⁴⁷ Compare 'ON' and '24 hour' for urine calcium on the left to distal delivery on the right.

²⁴⁸ Our estimate of calcium fractional delivery from that of lithium assumes they closely covary but that assumption is not proven.

²⁴⁹ This is an active research area, important because the responsible segment(s) indicate likely transporters and signalling causing hypercalciuria and therefore possible drug targets to prevent stones.

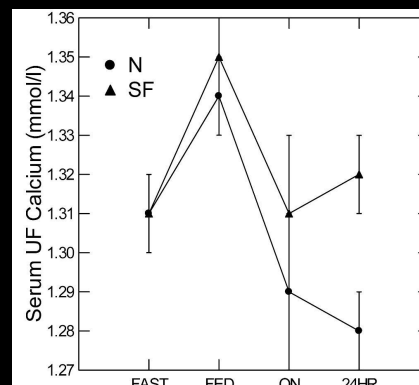
²⁵⁰ Both are reabsorbed mainly between cells driven by a strong voltage difference between tubule fluid and blood - tubule fluid relatively positive.

²⁵¹ The original publication proposed the same. SF do not excrete more Mg than normals, fasting or fed, only more calcium. The DCT is a place where Mg and Ca are handled through different pathways.

common to patients and normals, whereas the patient offset, higher losses fasting and fed in patients than normals, is limited to calcium.

Blood Filterable Calcium

Blood ultrafilterable calcium (UFCa) rises with meals in normals and SF alike. The increase is about 0.04/1.31 or around 3% and was statistically significant. So during meals that were, in this case, quite rich in calcium (about 1,200 mg/d), food calcium entry or perhaps bone mineral loss (very unlikely) was enough to raise blood calcium. It was not a rise in renal calcium reabsorption because FE calcium rose considerably with meals meaning that calcium reabsorption fell.



The 'overnight' UFCa values were in fact those just before leaving the CRC at 8 PM. The 24 hour urine serum samples were taken when the urine was brought in at 6 am before the study protocol and had a separate blood drawn at that time. Although the SF value appears higher than that for N, it was not significant on statistical testing²⁵².

TWO PHASES OF URINE CALCIUM CONTROL

Fasting and overnight, stone formers lose a higher fraction of filtered calcium (but not Mg) in the urine than normal people and therefore lose more calcium in the urine. By contrast, food makes urine calcium (and magnesium) rise in both to the same extent²⁵³.

The Food Effect

We have just noted in the above figures that urine calcium and magnesium excretions go up by about the same increment in normals and stone formers, the latter from a higher fasting position. Likewise, regulation of serum calcium during meals was not exact as serum values rose despite a fall in calcium reabsorption. The 'food effect' seems common to everyone, and being common to magnesium and calcium alike, probably arises from the TAL²⁵⁴.

Likewise, being the same for patients and controls alike, the food effect does *not* contribute to the higher 24 hour urine calcium of stone formers. Instead that higher 24 hour urine excretion arises from the fasting and overnight periods²⁵⁵.

²⁵² Because the error bars are wide. If you double the upward bar for normals (95% upper limit of the mean) and of the downward bar for SF, they will touch.

²⁵³ By about the same increment, or fractional increment. Stone former increments always seem a bit larger.

²⁵⁴ Because both Ca and Mg are reabsorbed between cells driven by a voltage potential difference

²⁵⁵ This may be one of the most interesting points I make in the entire book. However eye catching the food effect may be, it is the general behavior of all people whereas 'hypercalciuria' as we measure it arises from the modest but prolonged patient effect, mainly overnight - that being about 1/3 of the human daily cycle.

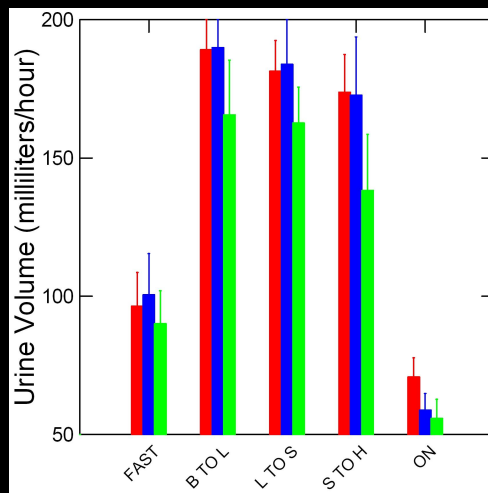
The Patient Effect

The fasting and overnight difference in calcium but not magnesium or sodium seems a trait of stone formers and not normals, what I might choose to name the 'patient effect'. What causes the patient effect remains, like the cause of the food effect, an open research topic at this time. But because the patient effect involves calcium but not magnesium or sodium, the DCT seems a most likely locale²⁵⁶.

For bone, the patient effect is an exaggeration of the leaking faucet, the steady excess of calcium loss, that must be made up for by bone. The food effect is some composite. If diet calcium is ample, bone may recharge from it. If not, bone mineral is in peril²⁵⁷.

CIRCADIAN INTEGRATION OF WATER, CALCIUM, OXALATE AND pH

During our research we have collected and published data on urine chemistries over the 24 hour day. This permits us to show how critical determinants of stone forming behave at various moments in life²⁵⁸.



Water

We drink as we eat, so fasting and overnight urine volumes are low. B, L and S abbreviate the three meals, and H is when people went home. The usual 24 hour urine collection cannot show you this remarkable variability, and therefore they blur the reality for any one person. Multiple samples like these are impractical for clinical care.

Normal people are in red, calcium phosphate stone formers in blue, and calcium oxalate stone formers in green. There are no significant differences between them, meaning regulation of fluid balance is not

abnormal. The lagging volumes in calcium oxalate stone formers are not statistically significant.

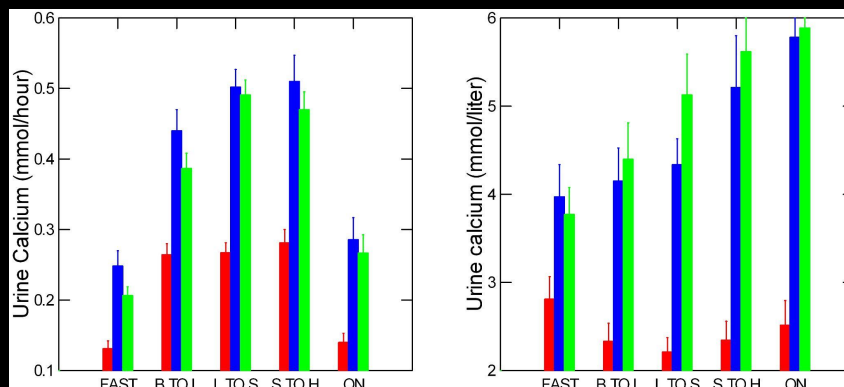
²⁵⁶ *This is the state of affairs as I write this. Clearly our next experiments should aim at testing the two ideas.*

²⁵⁷ *I hardly need to emphasize that the food effect is by far the more important of the two, being common to everyone and a potential cause of bone mineral loss after growth has ceased. Imagine how bone responds to afternoon snacks of a chocolate bar, or sugared beverage.*

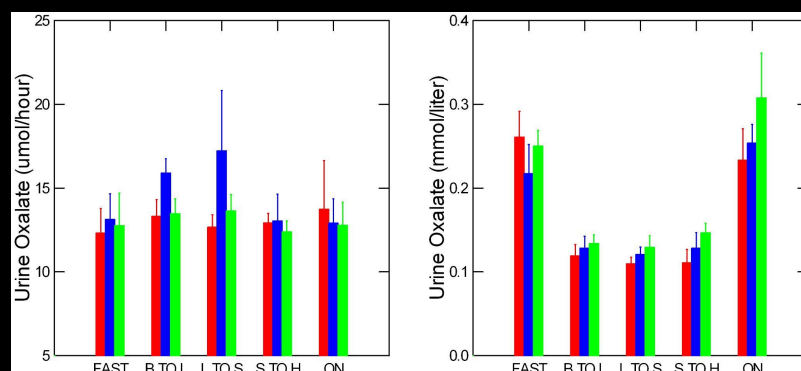
²⁵⁸ *The research was a disproof of the idea that calcium sensing in the collecting duct reduced water reabsorption so as to protect against stones. For this we needed the circadian data shown here.*

Calcium

I already showed the patient effect and food effect, and here they are in the left hand panel showing calcium excretions. The patient effect is present fasting and overnight (Blue and green bars so much above the normal red bars). The food effect increments are similar for SF and N²⁵⁹. So one might say the patient effect appears additive to the food effect.



The right panel shows the calcium concentrations which decline in normals and rise in SF. ON is remarkable for sustained high calcium losses in SF and - given low urine volumes - extremely high calcium concentrations²⁶⁰.



Oxalate

Although urine oxalate is not controlled with urine calcium, I need it here to complete the story about saturation and stone risk. Excretion rates are nearly flat (Left panel) and concentrations all go down with

meals because urine volume goes up. Mostly, normals and patients align. There is no food effect²⁶¹ when, as in these studies, diet oxalate is modest - 90 mg/d - and diet calcium adequate - 1200 mg/d. But when diet oxalate is high, or calcium low, this may not be the case²⁶².

Urine pH

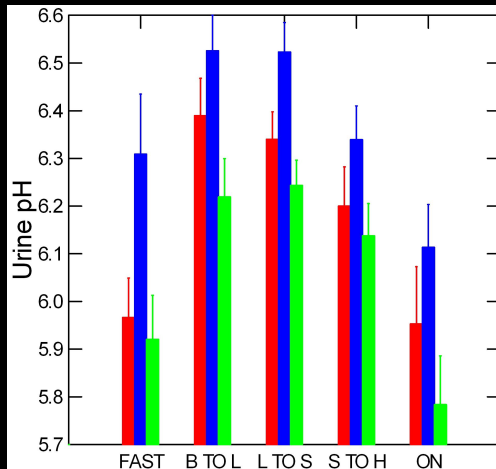
In the final section of this work I detail the systems regulating systemic acid balance, and show this same graph for other reasons. I put it here for your convenience as it powerfully affects calcium phosphate saturation.

²⁵⁹ The increments for SF are higher if one uses a caliper or has the original data available.

²⁶⁰ Overnight seems one of many points but it is 8 hours long. From awakening to first meal is generally shorter.

²⁶¹ The CaP SF (blue) do seem to have some food effect but it was not significant in our sample. It might be with more subjects.

²⁶² A spinach meal with no diet calcium causes a spike in urine oxalate, for example.



Urine pH rises with meals, in everybody, but is higher in calcium phosphate stone formers than in the normals (blue bars). By contrast, calcium oxalate stone formers have lower urine pH than normal, especially overnight²⁶³.

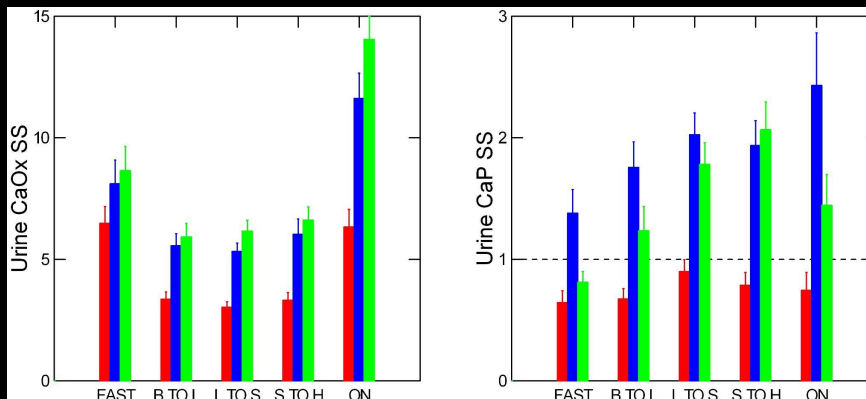
SATURATION AS A RESULT OF LOWER CALCIUM REABSORPTION CONDITIONED BY URINE

VOLUME, OXALATE AND pH.

After all my prior talk about the primacy of saturation, I would be remiss indeed if I did not present values throughout the day for the two main calcium salts, calcium oxalate and calcium phosphate.

Calcium Oxalate Saturation

The two are not identical. That for calcium oxalate (left hand panel) is highest fasting and overnight. Remember the risk threshold for stones begins about 3 fold. Normal people will be at or below that because of



or below that because of their low daytime values, whereas the stone formers are above 5 fold virtually at all times.

I already showed you that urine oxalate does not vary much throughout the day and its concentration falls during meals as a consequence of higher

urine volumes. So the main driver of the supersaturations is the interplay between water and calcium regulation in the normals and stone formers²⁶⁴.

²⁶³ One might say this is a necessary difference given the geological proof of higher urine pH in calcium phosphate stones.

²⁶⁴ Essentially this is a way of saying it is the calcium excretion difference that most affects supersaturation and risk of CaOx crystal formation.

Calcium Phosphate Saturation

I showed you earlier that calcium phosphate supersaturation begins to confer risk of stones when above 1, and find it notable that the normal means never exceed this value whereas mean values for both kinds of stone formers always do. Overnight²⁶⁵ is clearly the worst in terms of risk. This rise in CaP SS is driven by high urine calcium and pH and low urine volume²⁶⁶. It rises with meals because both urine calcium and urine pH rise.

AN INTEGRATED VIEW OF URINE CALCIUM AND STONE FORMATION²⁶⁷

Hypotheses

We have strong reasons to *presume* that the range of urine calcium excretions found among people in general reflects an underlying range of renal tubule calcium reabsorptions, highest in those with the lowest urine calcium and the reverse. We must *presume* these reabsorption rates are genetically determined and are part of the mechanisms that link calcium absorption to calcium excretion in the service of constant blood calcium levels and stable bone mineral stores.

Clearly, people with lower levels of calcium reabsorption lose more urine calcium, resulting in higher urine calcium concentrations, higher calcium salt supersaturations, and formation of calcium stones. If we then collect people with and without stones, we must find, as we did, that the former have 'abnormal' tubule reabsorption, or a reabsorption 'defect'. Both words are incorrect. Stone formation identifies people with lower than average renal calcium reabsorption²⁶⁸.

So, understanding calcium stone formation is really to understand what brings about the wide distribution of tubule calcium reabsorption in humans.

But that wide distribution appears limited to what I have called the patient effect - the higher fasting calcium losses among stone formers. The food effect appears more or less the same for patients and normals alike and is of universal importance.

²⁶⁵ *Lightly said but so crucial. How can one intervene with fluids by moonlight? Diet is long passed and the patient effect reigns sovereign. This may be a central issue in stone prevention.*

²⁶⁶ *The higher urine pH of CaP stone formers appears slight (0.2-0.4 units) but pH is a logarithm so the difference in acidity (proton concentration) across that range is large.*

²⁶⁷ *Though wearying, I have tried to say 'calcium stones' in place of 'stones' in these sections, assuming not all will understand that uric acid, cystine, and struvite stones cannot possibly arise from calcium disorders. Here and there I have missed a 'calcium' and no doubt some will triumph in finding an 'error'.*

²⁶⁸ *Thus we search for the mechanisms giving a wide range, not for a specific disease or abnormality.*

Black Stone Formers Support the Hypotheses

Black stone formers have remarkably low urine calcium excretion rates. This must be hereditary and quite possibly beneficial during evolution in Africa²⁶⁹. Their more recent temporal association with the African climate may have preserved a genetic structure more ideally suited to that environment. To date, we have not critically compared food effects between black and white normals or patients²⁷⁰.

Stone Former Hypercalciuria is Familial and Genetic

Since stone forming is strongly familial, one expects the same for hypercalciuria - fasting urine calcium losses at the upper end of the normal range. That is true. Relatives of calcium stone formers with relatively high urine calcium excretion exhibit the same trait even without stones. Animals can be bred for higher urine calcium (evidence for both in this article).

Children with calcium stones, the most common type, were generally hypercalciuric in a large cohort study we performed in multiple urology practices in the US. Their urine calcium exceeded that of their non stone forming siblings and of matched children from the same neighborhoods. But many of their relatives had abnormally high urine calcium levels compared to the matched controls, even if they did not form stones. No other risk factor, urine volume, oxalate, citrate or pH differed between the stone forming and the control children²⁷¹.

WHERE DOES THE 'EXTRA' URINE CALCIUM COME FROM?²⁷²

How Balance Experiments Work

How can you determine the balance of calcium - the net of that absorbed and that lost from bone stores? You do it the hard way. People eat a fixed diet for many days (6, usually) and you collect all the urine and stool during those days. The difference between what was swallowed and what is in the stool is the net absorption. The net absorption divided by the amount swallowed is the fractional calcium absorption²⁷³.

²⁶⁹ *Their data support the hypothesis by providing an example of a population with distinctly high calcium reabsorptions, low urine calcium loss, and stones from what appears to be genetically conditioned low urine volume.*

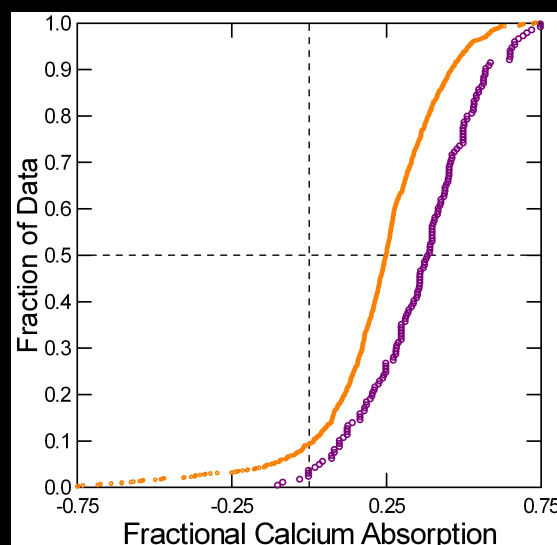
²⁷⁰ *I have already shown that it is low urine volume that causes stones in black patients.*

²⁷¹ *The Chicago stone group has long been accused of an excessive focus on calcium as opposed to oxalate as crucial in stone formation. It is not the one or the other, but that urine calcium seems more variable among the common run of patients.*

²⁷² *I mean the patient effect, the trickle of extra calcium loss fasting and overnight.*

²⁷³ *It is precisely from papers reporting balance experiments that I derived the data on urine calcium distributions in men and women. This is more from the same collection.*

Balance is net absorption minus the amount lost in the urine during those same 6 days. If this sounds like a lot of work, you are right, and each tiny or large point on the graphs I will show you is from one of those 6 day periods.



Fraction of Food Calcium Absorbed

Given the wide range of renal calcium reabsorption and corresponding urine calcium losses, we must presume a similarly wide range of intestinal calcium absorption rates. That is a true presumption. The negative points on the graph below (points to the left of the vertical dotted line at 0) mean that losses in the stool exceeded calcium swallowed - this is almost always during very low calcium diets when calcium is secreted into the intestine from saliva, pancreas, bile, and duodenum in excess of diet intake.

The orange dots show the fraction of diet calcium absorbed for the same large group of unselected people whose urine calcium values I showed earlier. The purple points are from people with kidney stones and high urine calcium losses.

Both vary over a wide range, but the average (median, at the horizontal dotted line of 0.5) is much higher for the stone formers, who have higher urine calcium losses. This graph is from [my main article on stone former urine calcium elevation](#).

It appears that the intestines 'know' to absorb an increased fraction of calcium in the diet when urine calcium is high - as in the stone formers. One can balance the other. Surely we are observing a regulated system of considerable subtlety, presumably evolved to maintain the skeleton and also keep blood calcium concentration constant despite variations in diet calcium.

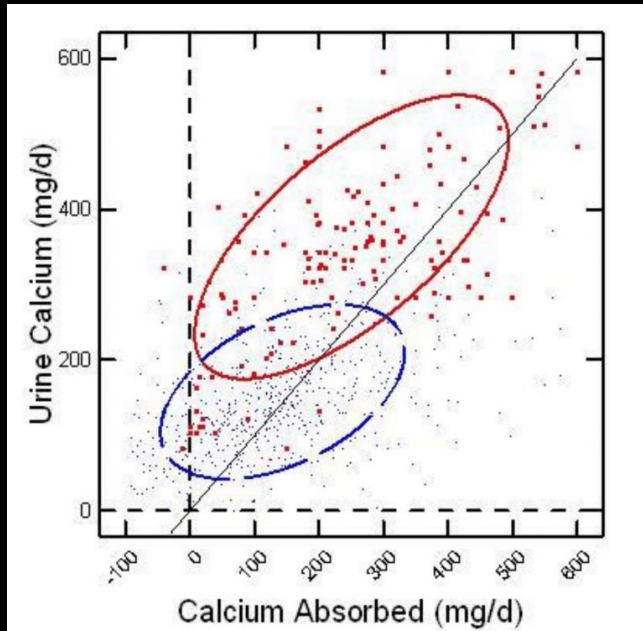
Calcium Absorption and Urine Calcium are Closely Linked

Urine Calcium Tracks Calcium Absorbed

Below, I have plotted urine calcium losses against the amounts of calcium absorbed from their food during the 6 day urine collections. [Blue is all of the adult men and women whose urine calciums I showed before.](#) Red is from stone forming patients who had higher urine calcium losses. Each point is a 6 day balance study. The ellipses help visualize the two populations²⁷⁴.

²⁷⁴ They are 68% confidence ellipses. Their slope reflects correlation between the y and x axes. Normal points are so numerous I plotted them in microdots to reduce clutter.

Urine calcium loss (vertical axis) tracks with calcium absorbed (horizontal axis), over a wide



range for both. Being selected as stone formers, the red points have higher urine calcium and higher absorptions, but within both groups urine excretion and intestinal absorption are obviously correlated.

The Slopes Differ

The stone formers increase urine calcium more per unit of calcium absorbed than do the normals. For every mg/d increase of calcium absorbed the normals lose about 0.28 mg/d of calcium in the urine (28%) whereas for the patients the loss is 0.53 mg/d per increase in mg/d calcium absorbed (53%). This difference in slopes is highly significant statistically²⁷⁵. The whole set of urine values is set higher (by 180 mg/d) for the stone formers (intercept of the

regression) as they are selected by their stone forming for higher urine calcium losses.

One would not have expected the difference in slopes²⁷⁶. The simplest guess as to how urine calcium links to calcium absorbed is that a fixed proportion of the absorbed calcium be lost in the urine. This would more or less allow for stable bone mineral. That the higher urine calcium people, the patients, lose so much higher a fraction of their absorbed calcium in the urine increases their risk of losing bone mineral.

The Fasting (Patient) Effect Causes the Slopes to Differ

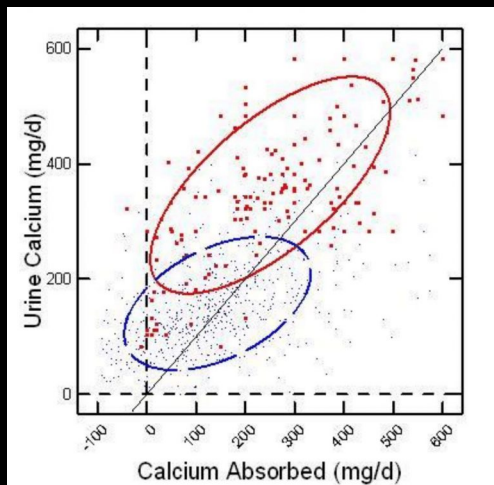
Given that the food effect is the same for stone formers and normals, the fixed proportion I alluded to would be from the patient effect, the constant offset of reabsorption fasting and fed. As in a house with leaky windows, to keep room temperature (serum calcium) steady the furnace (GI calcium absorption) has to increase as we see in stone formers. And yet, a higher fraction of the heat coming from the furnace is lost through the windows (higher slope of urine calcium on GI calcium absorption).

So the whole system is inefficient with heat (calcium). Even so, the furnace and window losses track as closely as the thermostat (sensing of serum calcium and transduction to GI absorption) allows.

²⁷⁵ Of course I have the data set and used a general linear model for urine calcium including normals and stone formers and estimated the significance of the cross product of subject type x calcium absorbed.

²⁷⁶ The mismatch between absorption and urine loss in SF seems unlikely as an evolutionarily sound direction. I have to presume something in modern diets - perhaps sodium - causes it, which leads to possible experiments.

Calcium Balance is Imperfect



The diagonal line of identity on the graph we just saw divides points into two groups. Left of the line, urine calcium exceeds calcium absorbed - bone mineral is being lost. To the right of the line, the opposite. I put a copy of that same graph here for your convenience.

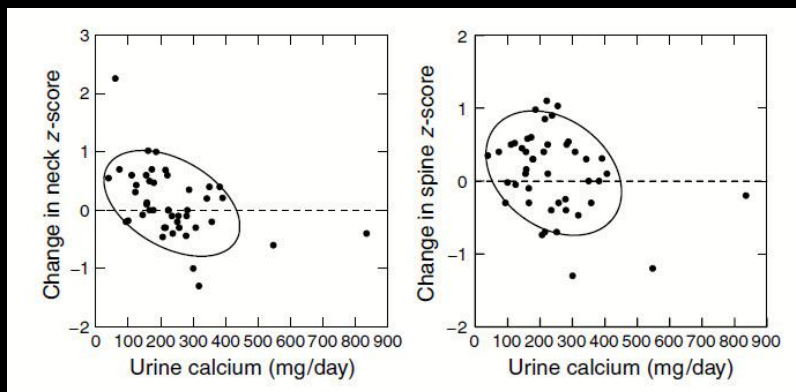
Normals

On average, the normal adults excrete about the same amount of urine calcium (on the vertical axis) as they absorb from their food (on the bottom axis) because their points are roughly bisected by the slanted line of identity. This means that about half are losing and half gaining bone mineral at the time of their balance study.

This is not a surprise, as diet will strongly influence balance. There is an obvious weighting of more points to the left of the line, and that is compatible with the fact that adults lose bone over time, especially women.

Stone Patients

As my little vignette suggests, almost all of their points are left of the line - their bone calcium balance is mostly negative. This predicts that the higher urine calcium of stone formers associates with bone mineral loss, and that is true. Fractures, likewise. Positive balance in the stone formers requires a very high net calcium absorption. Given the average fraction of diet absorbed of about 30% in stone formers, this would be about 1000 mg/d of diet calcium.



units) of bone mineral density from normal is more negative in patients with progressively higher urine calcium. Both negative slopes, for hip (left panel) and spine (right panel) are highly significant.

Calcium Loss Predicts Bone Mineral Loss

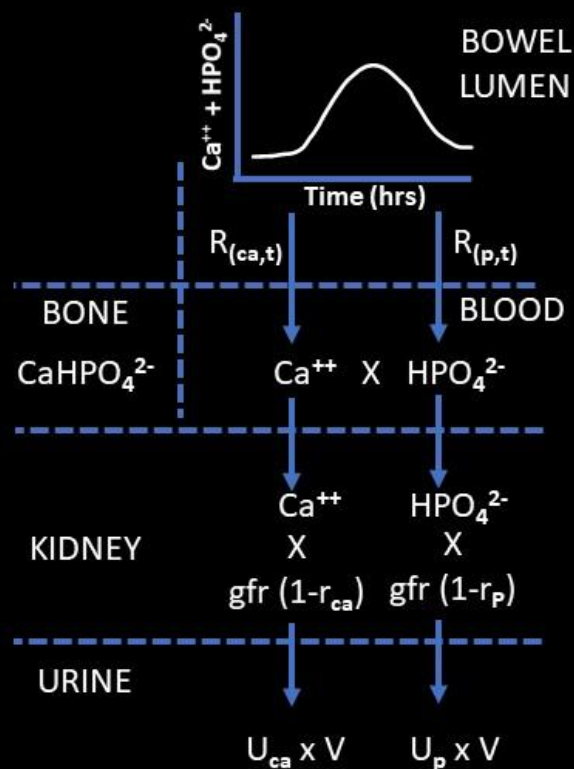
It should also be true that the higher the urine calcium loss (window leak) the higher the loss in bone mineral (heat stored in the walls) and that is also true. This figure, which also is on [the site article on genetic hypercalciuria](#), shows that over three years the deviation (SD

Things Are More Complex Than They Seem

The balance calculation is simple: How much calcium swallowed, how much in the stool - all averaged over 6 days: 1000 mg/d eaten, 800 mg/d in the stool, 200 mg/d absorbed, 150 mg/d in the urine, 50 mg/d into bone. But such balances are relatively small differences between large numbers each with its own uncertainty. Whereas mass plots of data collected over a century give a sense of how things go, usual studies of a dozen or more people use calcium isotopes and complex kinetic models to track absorption and bone uptake and release of calcium²⁷⁷.

WHY SHOULD BONE BALANCE BE REDUCED IN STONE FORMERS?

Our house with leaky windows will not be enough of a model for bone, so let's make a more expansive - if less picturesque - image.



Fasting and Overnight

We begin with the belief that the whole system aims at constant serum calcium, shown in the figure below as a divalent ion in blood. It is true that calcium is always being lost in the urine and that loss is the product of the filterable calcium (UFca), filtration rate (gfr) and the fraction of what is filtered not reabsorbed ($1-r_{\text{ca}}$) where r_{ca} is the fraction reabsorbed. All this must be true, this tiny equation reflects conservation of matter (calcium in this case).

We know r_{ca} is lower than normal in stone formers and is the proximate cause of their hypercalciuria (patient effect).

Bone Mineral Dissolves

Fasting, we must presume there is no reasonable source of calcium to match urine losses except bone and residual food calcium left between meals. That latter is plausibly

²⁷⁷ One might question my taste as an author to bring into this modest book such arcana, but otherwise one loses a sense of reality. Bone sips up and loses tiny fractions of diet calcium - 50 /1000 mg in my not unreasonable example - 5%. How uncertain that result given 5% errors in diet and stool calcium!

significant only when we regularly eat reasonably calcium rich foods²⁷⁸. This point has not been resolved experimentally that I know of.

Bone mineral as brushite - like crystals (CaHPO_4) is in physical equilibrium with the blood product of calcium and phosphate ions, shown in the figure with their charges. Being an equilibrium, fall of calcium or phosphate in blood is to say bone mineral donates more to keep the product at solubility.

Fed

The sketch at the top of the figure is calcium and phosphate in food absorbed over hours²⁷⁹.

When we eat, whatever calcium is in the meal will contribute to blood calcium. R stands for the rate of calcium or phosphate entry in mmol/hr - that is why 't' is part of the subscript. In theory, this calcium will be both lost in the urine and enter bone mineral.

But our system is set, we have assumed, to keep blood calcium as steady as possible.

The food effect is a lowering of fractional reabsorptions of calcium and magnesium (not shown). That lowering makes urine calcium more dependent on filtered load, so that any increase of blood calcium will raise urine calcium more efficiently (larger slope of calcium loss on blood calcium). As well, calcium can control r_{Ca} , something for later on.

Of course when food has calcium in it, bone can recharge its mineral, and presumably does. But glucose alone²⁸⁰ produces the same changes in urine calcium and magnesium as a complete meal containing calcium, so the food effect is a response to nutrients in general, and may not be so much aimed at only blood calcium but also as a way to remove other material in food. Of course, the sugar effect means that meals without calcium must deplete bone mineral²⁸¹.

The Link Between Calcium Absorption and Urine Loss

The simple model offers multiple possibilities. When meals do not have sufficient calcium, blood calcium must signal low, even if by the tiniest margin, and increase R for GI absorption, and perhaps reduce tubule calcium reabsorption fasting and fed. Bone may signal. Later on I will tell about the signallers such as we know them. But the model gives us a skeletal structure that surely will permit everything we presently know about calcium regulation.

Stone Formers Have Excess Bone Disease

About 30% to 65% of stone formers have reduced bone mineral density (BMD). The table (below) from the linked article documents fractures. I presume both reduced BMD and increased fractures reflect the negative calcium balance I just showed you, but that has not been proven.

²⁷⁸ *If calcium intake is quite low for 4 days, what do we imagine is left in the intestines to balance steady urine calcium loss?*

²⁷⁹ *The little curve is just a hand drawing. The time course for Ca and P absorption after a meal will be a complex function of meal composition and vary widely among people as well.*

²⁸⁰ *It is detailed in the following section*

²⁸¹ *One cannot be bold enough. Sugar snacks must be bad for bone.*

So we have an oddity. Urine calcium appears genetically controlled. Urine calcium seems linked to calcium absorption and that means elaborate systems exist to make that linkage. Why, then, have we maintained throughout evolution a risk for bone disease in those who dwell in the higher ranges of urine calcium loss^{282?}

Skeletal sites	Prevalence		Percentage (%)
	Total number of patients	Number of patients with low BMD	
Vertebral spine	975	388	40
Hip	450	141	31
Radius	627	410	65

Abbreviation: BMD, bone mineral density.

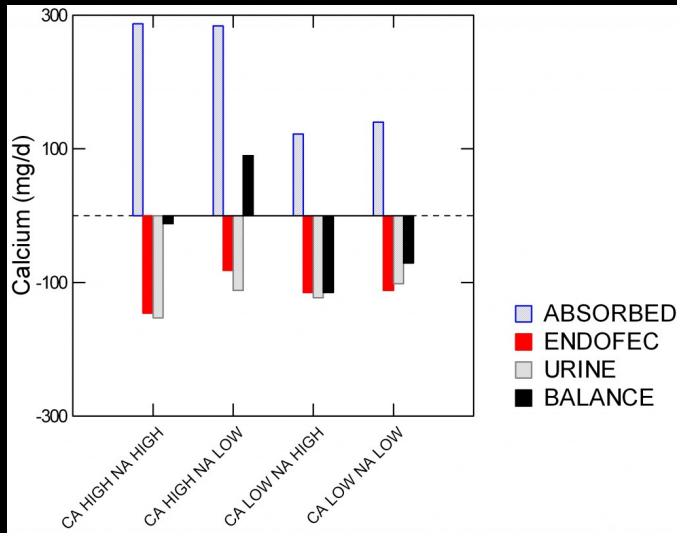
How Calcium Leaves

and Enters Bone

As already mentioned, the outer shell of bone mineral is brushite²⁸³, the very same crystal that forms readily in urine and initiates calcium stone disease. The inner layers are hydroxyapatite, which is the main constituent of calcium phosphate stones. The one converts to the other in urine and in bone.

Bone has a considerable circulation, and the saturation of blood with respect to brushite is almost exactly at brushite solubility. So even a slight fall in serum calcium or phosphate can mobilize bone from the outer layers, and the opposite. This has been proven in cultured bones. Osteoclast bone cells can actively dissolve bone mineral, osteoblasts can produce bone, but

these cellular processes control bone architecture and long term remodeling, not minute to minute mineral balance. So outer layers of bone can serve as storage batteries on a power grid, ironing out transient imbalances between calcium uptake from food and kidney calcium losses²⁸⁴.



Sodium and Calcium Absorption

I mentioned just above that calcium absorption is not so easy to measure. Intakes can be over 1000 mg/d, fecal

losses perhaps 800 mg, leaving 200 mg of absorbed calcium. Since each of these large numbers has perhaps a 10% error, we cannot know the difference between them with

²⁸² *Is evolution indifferent to bone because for millennia we bred and died young?*

²⁸³ *I have said before, brushite/ octocalcium phosphate, meaning early CaP crystal forms*

²⁸⁴ *In cultured bone this is demonstrable fact, as one would imagine. Using stable isotopes one could in theory measure on and off rates from bone as the blood Ca x P product was deliberately varied.*

exactitude. When I presented hundreds of balance studies, we could get a clear picture, but in any one person variability would limit conclusions.

For this reason, modern balance work uses isotopes to get a more precise picture, and in doing so offers a novel perspective. The above graph portrays results from a group of perimenopausal women who each ate the same diet but using additives made high or low in calcium or sodium in all four combinations. As is obvious, net bone mineral calcium balance was positive (black bar above the 0 baseline) only with a high calcium low sodium diet²⁸⁵.

But the orange bar (second from the left) is my focus here. It measures calcium secretion from blood into the gut lumen by pancreas, duodenum, and saliva. This 'endo fecal' secretion offsets calcium absorption through the intestinal epithelium. Notice how the high sodium high calcium bar is longer than the low sodium high calcium bar. This means high sodium increases calcium secretion reducing net calcium absorption.

The three organs all use sodium in their transport process, just like the kidney and GI tract, so it is not a surprise that high sodium might increase organ calcium secretion into the gut lumen²⁸⁶. But here are data showing the effect.

High diet sodium can cause bone mineral loss (negative balance) not only by raising urine calcium, but by raising losses from organ secretion in the GI tract lumen.

BLOOD CALCIUM REDUX²⁸⁷

Size of the ECF Calcium Pool

We are now ready to look more closely at the calcium that must be regulated for the health of the cells, and that is the ECF calcium ion concentration. Blood calcium is between 90 and 100 mg/l, or 2.25 to 2.5 mmol/l. Given the 3.5 l of blood plasma, that is a pool of 7.8 to 8.7 mmol - call it 8.25 mmol average. Of this about 1.2 mmol/l is filterable²⁸⁸ by kidneys and through capillaries to interact with cells, the rest is bound to albumin. In blood, 1.2 mmol/l x 3.5 l = 4.2 mmol. The ECF unbound calcium pool will be 14 l x 1.2 mmol/l or 16.8 mmol, call it 17 mmol.

Turnover of the ECF Calcium Pool

We filter 200 mmol/d and excrete on average 4 mmol/d, meaning urine loss is 25% of the whole ECF pool and the pool is filtered and reabsorbed 200 mmol/d/17mmol or 11.7 times/24 hr, meaning 48.7%/hour! The cells use calcium for signaling and movement in and out of cells is tightly regulated so cell water calcium is not an extension of the ECF calcium pool.

²⁸⁵ *This study is among the best evidence for benefit of low sodium to maintain bone balance*

²⁸⁶ *Surely effects of diet sodium on organ secretion abound, but I am tiring at this point and deign to open up yet another possibly massive topic for inquiry.*

²⁸⁷ *I find as irresistible as it is exhausting some numerical estimates of things, as here. Do they not reassure one about the logic, and confer some feeling of a greater understanding - if illusory?*

²⁸⁸ *This is the ultrafilterable calcium we studied way back at the beginning of the calcium story.*

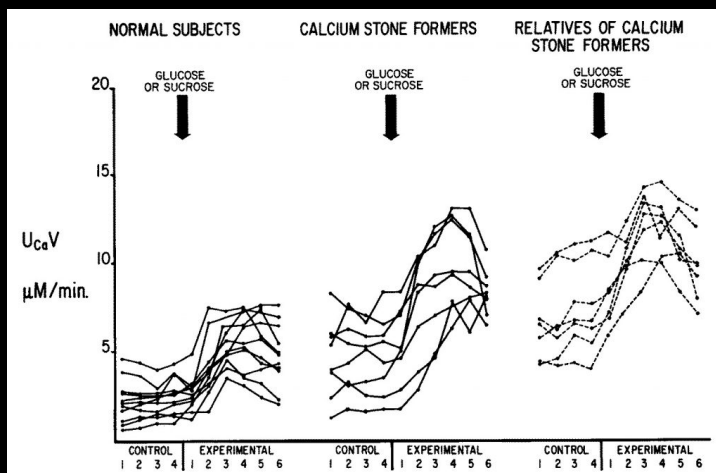
The Food Effect

Consider a meal with 330 mg of calcium and 20% absorption, or 66 mg calcium absorbed.²⁸⁹ Say it is absorbed over 4 hours or 16.5 mg/hr (0.41 mmol/hr). Urine calcium in normal people fed such a diet in fact approximated about 0.3 mmol/hr, a value more or less suggesting a decent balance of loss to intake (0.1 mmol/hr). If there were no food effect, urine loss would remain at the average of 4 mmol/24 hr or 0.166 mmol/hr, substantially below estimated entry.

Regulation of ECF Calcium Concentration

These purely speculative but not unreasonable figures suggest what must be happening with meals. With ample diet calcium and normal kidney function, bone must be taking up an order of magnitude of about 0.1 mmol/hr of calcium as a result of absorption rate and the food effect. Without the food effect the uptake into bone must be about double to keep ECF calcium constant.

Why offer these figures?? Because they suggest direct experiments on blood UF calcium during meals, incorporating isotopes to measure influx might be very instructive as to bone biology or at least the disposition of absorbed calcium²⁹⁰.



EFFECT OF SUGAR ON URINE CALCIUM²⁹¹

Calcium Loss with No Diet Calcium

In this ancient and lovely study, normal people, stone formers, and their relatives were given a simple sugar drink. The stone formers and especially their relatives started at a higher baseline (the patient effect), and all three rose about the same amount (food effect).

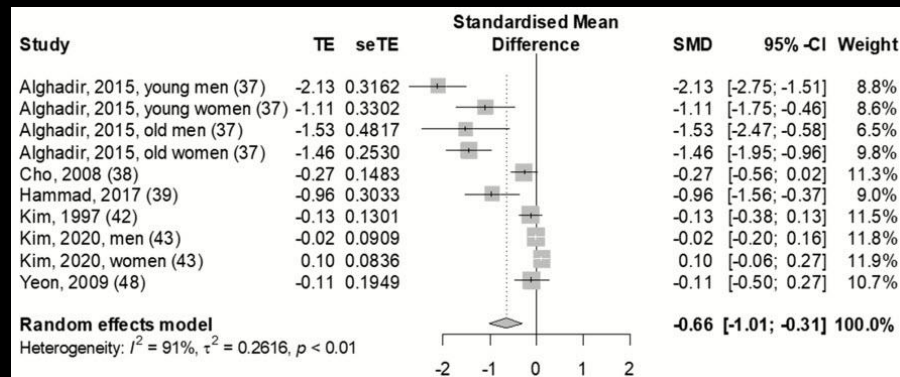
But, there was no calcium in the drink. This was calcium from bone. So we have in this an example of at least one nutrient that can raise urine calcium losses without supplying any

²⁸⁹ *I have chosen ideal diet calcium and normal fractional absorption as already presented.*

²⁹⁰ *How provocative, and how likely my betters will tell me it is a silly notion. I am not so sure.*

²⁹¹ *Sugar is one of the major issues for this book but the systems that use sugars are so vast I cannot include them. So I have limited things to the calcium and urine flow rate effects*

calcium intake²⁹². Sugar intake appears correlated with kidney stone onset. In three cohorts observed over decades, Curhan et al found about 4% of the risk for new stone onset arose from sweetened beverages.



Sugar Can Promote Bone Mineral Loss

More to the point, does sugar lead to bone disease? Indeed a recent meta analysis of available studies

disclosed a reliable association. Bone mineral density was significantly related in a negative way to intake of sugared beverages in 5 of the available studies, and overall for the set of studies.

This result is of especial importance because the sugar nutrient effect I just showed you is

general to everyone. I imagine

stone formers would fare worse than average, beginning as they do from a higher fasting urine calcium loss and strong tendency toward reduced bone mineral balance²⁹³.

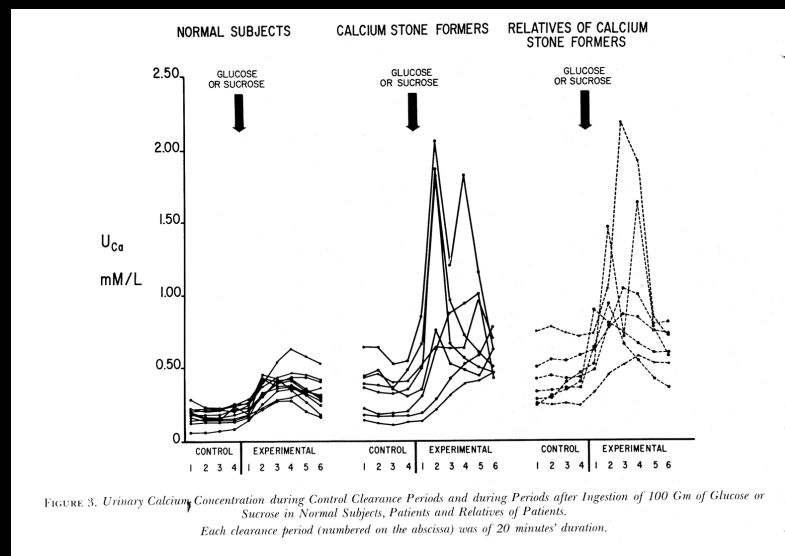


FIGURE 3. Urinary Calcium Concentration during Control Clearance Periods and during Periods after Ingestion of 100 Gm of Glucose or Sucrose in Normal Subjects, Patients and Relatives of Patients. Each clearance period (numbered on the abscissa) was of 20 minutes' duration.

Urine Volume Falls with Glucose

From the same wonderful study, urine calcium concentration rises dramatically in stone formers and their relatives because not only does urine calcium loss increase

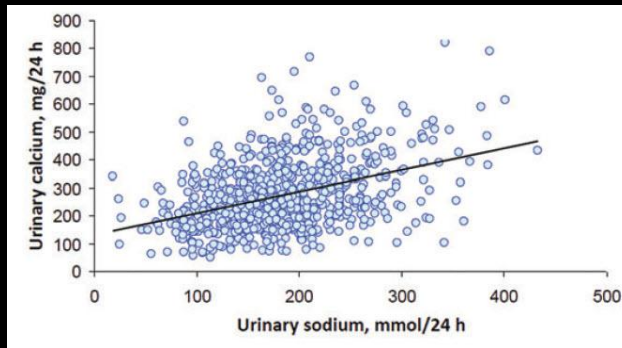
(food effect) but glucose reduces urine flow rate.

In more detailed studies, this same investigator (Dr Jacob Lemann) showed that the fall in urine volume flow was associated with a fall in urine sodium loss, suggesting increase of sodium and water reabsorption by the tubules. Proximal tubule would be a reasonable site as it is where glucose is absorbed, and glucose reabsorption is part of the mechanism for sodium and water

²⁹² Essentially this exhibits the food effect with no input of calcium, and one can calculate approximate bone mineral losses. Certainly blood UF calcium will remain stable, and therefore bone is giving up calcium at a rate to sustain higher losses. Bone mineral / blood equilibrium is a good mechanism for this.

²⁹³ This completes my vision.

reabsorption²⁹⁴. This sharp rise in urine calcium concentration must promote an increase in saturation with respect to calcium stone forming salts and therefore increase risk of stone crystal formation²⁹⁵. Thus, sugars provoke stones and threaten bone. To me, no amount of refined sugar is too low²⁹⁶.

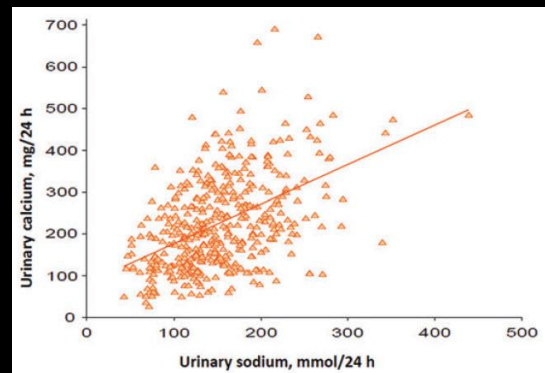


DIET SODIUM ALTERS URINE CALCIUM²⁹⁷

Dependence of Urine Calcium on Urine Sodium in Stone Formers

No doubt exists that urine calcium rises with urine sodium, in other words with sodium intake. The point is so important, I am copying here two wonderful figures, from Parma and Dallas.

In 1192 male kidney stone patients (left) a rise of one mEq (23 mg) a day in sodium is associated with a rise in 0.77 mg of calcium; this means 77 mg/day of calcium for every 100 mEq of diet sodium. Among 760 women (right) the increase was 0.95 mg/d of calcium per mEq of sodium, or 95 mg of calcium for every 100 mEq of sodium - a greater dependency. Of course, these are regressions so the sodium effect is added to the baselines (intercepts) of 132 mg/d in men and 81 in women. Women have a generally lower average calcium but a higher sodium dependence than men.



Greater Dependence of Urine Calcium on Urine Sodium in Stone Formers

I presented in my site article a figure compiling all available primary individual measurements of calcium and sodium for stone formers and normals, and put it here as well. The primary data for this are available as a link on my site article.

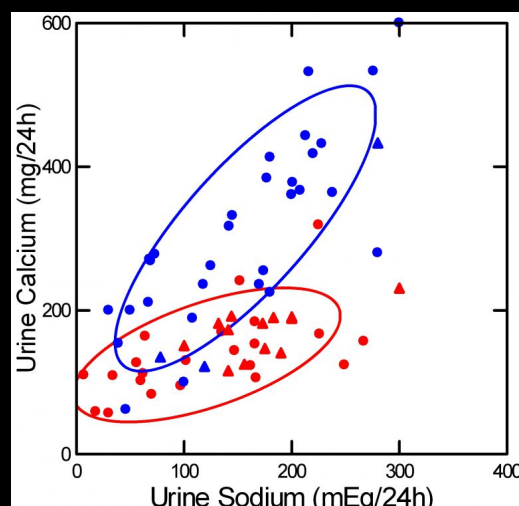
²⁹⁴ *Tempted as I was to include the sodium data, this text simply cannot become a medical review and remain generally useful - if it is indeed such even at this point.*

²⁹⁵ *I have already noted Curhan's data showing increased stone risk with increasing sugared beverages.*

²⁹⁶ *Are converts not most devout - to absolute? Sugar was my long ago love.*

²⁹⁷ *I have repeatedly implied that modern high sodium diets may be a major factor causing stones and bone disease by raising urine calcium. This section offers some evidence.*

On this figure, stone formers are in blue, round symbols are actual experiments in which diet



sodium was deliberately varied and triangles are simple observations. The much higher slope dependency of urine calcium on urine sodium is obvious. [I have detailed the sodium calcium link in the article on hypercalciuria.](#)

Of note, a 100 mEq increase of sodium associates with about 65 mg/d increase of urine calcium in normals and nearly 200 mg/d in stone formers. This latter is a higher dependency than in the prior figures from Dallas and Parma and the balance studies, but these are mostly results from deliberate changes in diet sodium, not population associations²⁹⁸.

[In a multi-ethnic population](#) of non stone forming people not included in this figure, a 100 mEq/d increase in diet sodium (2300 mg) produced 1 mmol (40 mg) increase in urine calcium, and this slope dependence was the same for white, black, and South Asian people. The average urine calcium values were 4.6 (184 mg), 3.33 (133 mg), and 3.16 (126 mg) mmol (mg)/d respectively. These dependencies in non stone formers, of 40 mg/d calcium for every 100 mEq of sodium are far lower than those in the stone formers of 77 mg/d for men and 95 mg/d for women²⁹⁹.

HOW DIET SODIUM MIGHT CONTROL URINE CALCIUM

Diet sodium will control the fullness of the circulation and therefore the functioning of the vast autonomic and renin/angiotensin/aldosterone systems. In a general sense, higher fullness results in higher glomerular filtration, reduced proximal tubule sodium and water (and calcium) reabsorption, reduced distal nephron sodium reabsorption and all taken together raise urine sodium and calcium.

Filtration

I have already shown you that filtered loads of calcium are the same in normal people as stone forming people, even though the latter have much higher urine calcium losses. So effects on calcium filtration are not a good explanation for how diet sodium affects urine calcium³⁰⁰.

²⁹⁸ *At some later date I intend to explore these slopes more completely in my site article and will amend this section.*

²⁹⁹ *I think available evidence is sufficient to say sodium effects on urine calcium are higher in stone formers than normals and go on to experiments to find out how that happens.*

³⁰⁰ *Filtration must have a tremendous effect on urine calcium but I mean by this that we can detect changes in urine calcium with sodium without detecting changes in filtration. Ideally this needs to be studied experimentally.*

Proximal Tubule

In the proximal tubule, calcium reabsorption is linked to sodium and water reabsorption. When diet sodium falls, proximal tubule sodium reabsorption is increased by A2, as I told you, and also by the autonomic nervous system and other factors. So reduction in diet sodium will reduce distal calcium delivery as it increases sodium reabsorption and the converse. This makes proximal tubule an attractive possibility for the diet sodium effect.

Thick Ascending Limb

Here, calcium is reabsorbed via an electrical potential generated by sodium reabsorption linking the two. AVP may increase TAL reabsorption, linking it to reduced vascular filling or even to reduced water intake³⁰¹. This could help link urine calcium to urine sodium³⁰².

Distal Convoluted Tubule

Calcium reabsorption is controlled by TRPV5, a channel that permits calcium entry into cells through which it passes back into blood. This channel is regulated by hormones but not remarkably by sodium³⁰³.

Why the Higher Slope of Urine Calcium on Urine Sodium in Stone Formers?

We do not know³⁰⁴. There could be a greater sensitivity of the proximal tubule to diet sodium in the stone formers, but the graphs I showed earlier did not show a significant difference in distal delivery between SF and controls.

A more attractive idea is that delivery of calcium out of proximal tubule is the same for normals and stone formers but because more distal site reabsorption is lower a given delivery leads to a greater change in urine calcium³⁰⁵. This requires more research.

³⁰¹ *No one has tested if water intake alters calcium excretion, so far as I know.*

³⁰² *The distal convolution and collecting ducts are unlikely sites linking urine sodium and calcium. I say nothing about them in the text.*

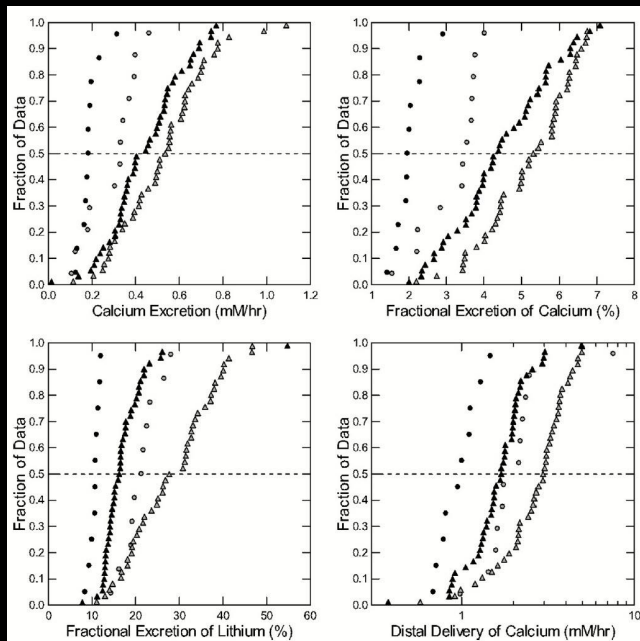
³⁰³ *I detail this in a later section. Here I mean only to establish the calcium /sodium relationships along the kidney tubule*

³⁰⁴ *There comes to all of us at some point or other when a particular topic has created what one might call a psychic exhaustion, and that has happened here. The problem is outstanding, my insights valueless for the moment.*

³⁰⁵ *Urine calcium = distal delivery x % delivery excreted. If the % rises, urine calcium rises more for a given delivery.*

THIAZIDE DIURETICS LOWER URINE CALCIUM

I wrote a [very good article on this for the site](#) and do not need to repeat the material here. Most importantly, these drugs lower urine calcium and prevent kidney stones. But a close look at our one study of how thiazide works³⁰⁶ gives some insight into tubule sites for the food and patient effects³⁰⁷.



Thiazide Reduces ECF Volume by Causing Sodium Loss

Being diuretics, they reduce renal sodium reabsorption in the later parts of the nephron³⁰⁸. This reduces the sodium pool and therefore the water volume of the ECF and as a result increases proximal tubule reabsorption of sodium - and calcium, which is linked to that of sodium³⁰⁹. Saying things differently, for any given diet sodium intake thiazide will cause a lower ECF volume and therefore a higher proximal tubule reabsorption than in the absence of the drug. The drug used here, chlorthalidone,

has a 23 hour half life, so is more or less acting similarly throughout the day and night.

Thiazide Lowers Urine Calcium

On the graph, fed periods are triangles, fasting are circles, thiazide points are dark, control non thiazide points are gray. The drug lowered calcium excretion in the fed and fast states (Left upper panel). The fraction of filtered calcium excreted also fell (upper right panel).

Thiazide Lowers Delivery out of Proximal Tubule

We use lithium clearance to estimate delivery of sodium out of proximal tubule, and the fraction of filtered lithium in the urine fell fasting and fed (lower left panel). Because calcium and sodium

³⁰⁶ We studied 4 men, before and after 6 months of chlorthalidone, 25 mg daily for stone prevention.

³⁰⁷ When writing the original paper we did not think about the two effects as separate.

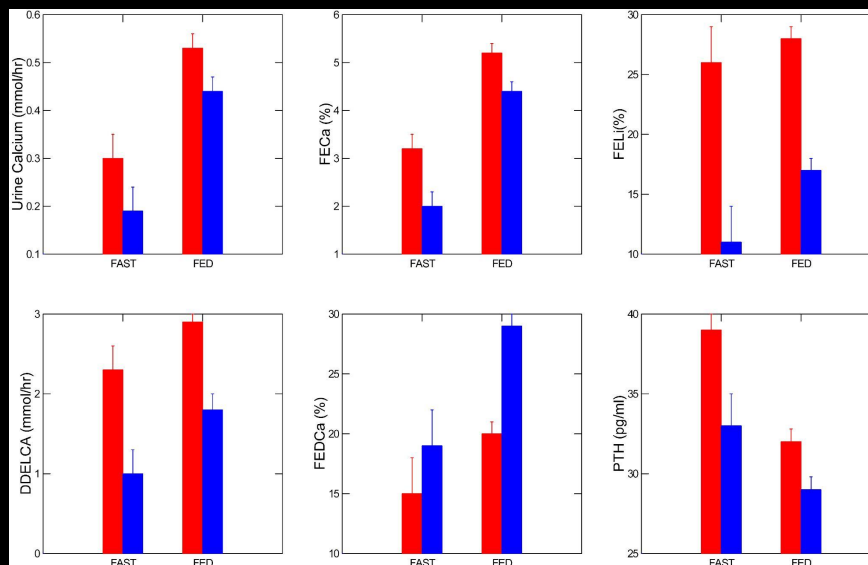
³⁰⁸ They block sodium reabsorption via the sodium chloride cotransporter in the first part of the distal convoluted tubule.

³⁰⁹ Volume depletion raises A2 and aldosterone, the latter stimulates potassium loss in the collecting ducts.

reabsorption are linked in the proximal tubule, the delivery of calcium downstream (lower right) fell³¹⁰.

DETAILS OF THIAZIDE EFFECTS

Here, I have graphed averages of the many dots on the prior figure to better present thiazide effects on urine calcium and its regulators fasting and with food. From the original paper, I indicate which changes from the drug are statistically significant. Blue bars are with, red bars without thiazide.



Urine Calcium

Thiazide lowered urine calcium (upper left panel, blue bar is below red, control bar) fed, but not fasting (the fasting fall was not significant). It lowered FECa fasting and fed³¹¹ (upper middle panel).

It did not alter the response to food (compare red and blue bars fed vs fast for food effect³¹²).

Proximal Tubule

Thiazide lowered FELi, the fractional excretion of lithium, fasting and fed, which means it increased proximal tubule sodium reabsorption. Possibly, by stimulating proximal reabsorption, it enhanced food response as the food increase of FELi is significant only with thiazide.³¹³

Distal Calcium Delivery

DDELCA, the product of UF calcium, glomerular filtration and FELi (lower left panel) rose with food only with thiazide and was lower with thiazide fasting and fed. This is expected since

³¹⁰ We presented data on proximal delivery before based on lithium. Lithium is reabsorbed like sodium in the proximal tubule but not thereafter (apart from variable and modest reabsorption in the thick ascending limb). Water, calcium, magnesium are reabsorbed with sodium though not in a 1:1 manner.

³¹¹ Visual impressions are misleading; the significances come from the publication. Error bars are larger fasting (fewer observations), so differences are not significant for calcium fasting.

³¹² Once again, I refer to statistical analysis in the paper - visual impressions are often misleading.

³¹³ The thick ascending limb and collecting duct (via ENaC) can reabsorb lithium. Possibly volume depletion increased the fraction reabsorbed there, bringing out a food effect arising from those tubule segments. Alternatively, PCT may indeed respond to food by reducing reabsorption.

filtration rate and serum calcium did not vary significantly with thiazide and DDELCa mirrors FELi.

FE of Distally Delivered Calcium

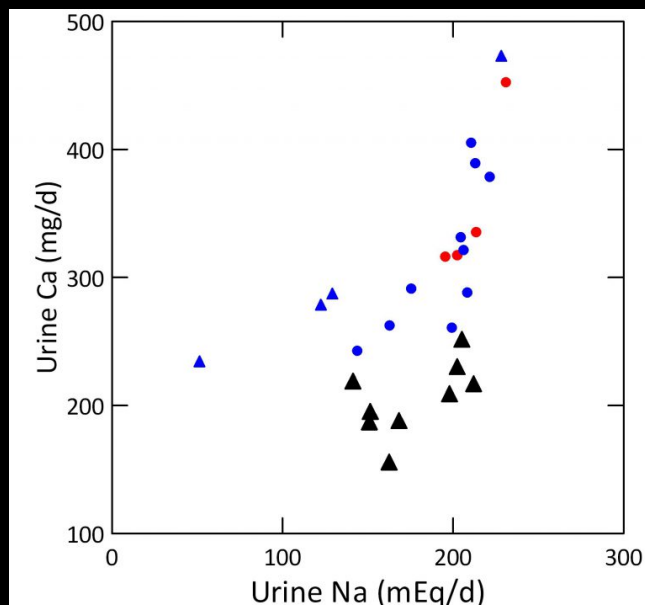
The ratio of urine calcium / DDELCa, FEDCa (lower middle panel) rose with thiazide in the fed but not fasting period. Furthermore, unlike anything else we have observed, thiazide increased it from 20% to 29% ($p < 0.05$)³¹⁴.

Serum PTH

This hormone stimulates calcium reabsorption in the distal convoluted tubule. Food reduced PTH, and thiazide further reduced PTH fasting and fed³¹⁵. The reduced PTH could increase FE of distally delivered calcium as in the lower middle panel³¹⁶.

SODIUM LOADING WILL OFFSET THE EFFECTS OF THIAZIDE

Because the ECF fluid volume will rise with sodium intake, the more sodium we eat the higher



the volume thiazide must act to reduce. Moreover, as high sodium continues, the final ECF fluid volume the drug can achieve will be higher and therefore the less the drug can lower delivery of calcium downstream³¹⁷.

Low Sodium Diet and Thiazide have Additive Effects on Urine Calcium

In this figure from [another article on the site that details use of thiazide for stone prevention](#), the circles relate urine calcium to urine sodium in urine samples taken during a prospective randomized trial of

³¹⁴ *Being a ratio this means urine calcium did not fall as much as DDELCa, as if proximal tubule reabsorption was upregulated by the drug and later nephron segments down regulated in relation to calcium handling.*

³¹⁵ *The reductions shown on the graph were statistically significant.*

³¹⁶ *The reduced PTH would do exactly this: DCT reabsorption would fall as DDELCa fell so FEDCa would rise.*

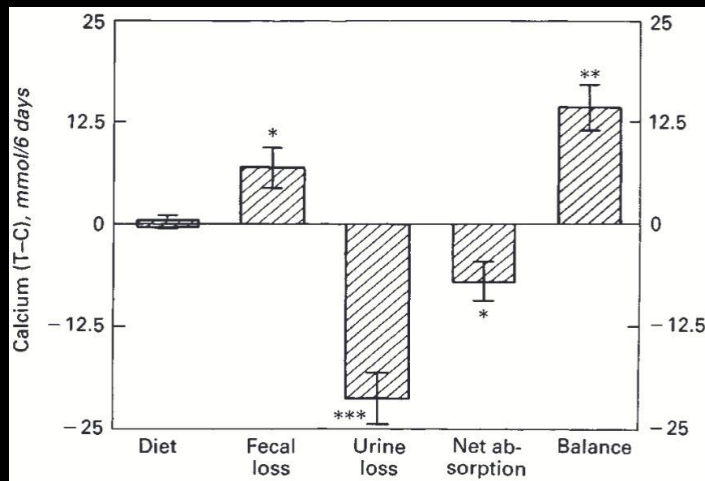
³¹⁷ *Higher sodium intake will also increase delivery of sodium to the distal tubule where sodium cannot be normally reabsorbed via the blocked Na/Cl cotransporter. The sodium will be reabsorbed in the collecting duct which increases potassium loss in the urine.*

thiazide for stone prevention. The black triangles show the further reduction of urine calcium by thiazide at a given level of urine sodium³¹⁸.

In effect, reduced diet sodium and thiazide are synergistic. Each *independently* lowers urine calcium, so a low sodium diet can often substitute for thiazide to permit the use of a lower dose than that required at high sodium intakes.

Thiazide Drugs Do Not Raise Urine Volume

Some people think a diuretic increases urine volume, but we who have read this far know that is impossible. Urine water loss must compensate for water intake, and sodium loss for sodium intake. But reduced ECF volume from the drug can trigger thirst and release of AVP so people drink more. That would increase urine volume. I have no proof, but suspect people may crave and eat more sodium.



THIAZIDE INCREASES BONE CALCIUM BALANCE

Thiazide can reduce urine calcium more than it reduces GI calcium absorption leading to retention of calcium presumably in bone.

In this study done in 1988 we found as others had found that thiazide like drugs (chlorthalidone 25 mg in this study) promote bone mineral retention. The balance measurements are as those I reviewed much earlier in this section. The diet was fixed so there were no differences between treatment (T) and control (C) periods. Stool loss of calcium rose, urine loss fell, net absorption fell, but the difference between them, which is bone balance, rose unambiguously³¹⁹.

This was not foregone. The drug clearly affects GI calcium absorption³²⁰ as well as renal tubule reabsorption, and the balance between them could not have been predicted without this kind of experiment.

³¹⁸ The paper detailed urine calcium response in the control (blue dot) and thiazide arms so I could plot actual values of urine calcium vs sodium in the randomly selected treated vs. control patients.

³¹⁹ One would expect secretion of calcium from blood into the GI tract lumen to fall with thiazide because of reduced ECF volume which would act like a low sodium diet. The fall in calcium absorption, though found by others, is therefore a surprise.

³²⁰ Once again, I suspect thiazide effects on GI epithelial transport and organ secretion are well studied but lack the energy (or desire?) to pursue them in this first edition of the book.

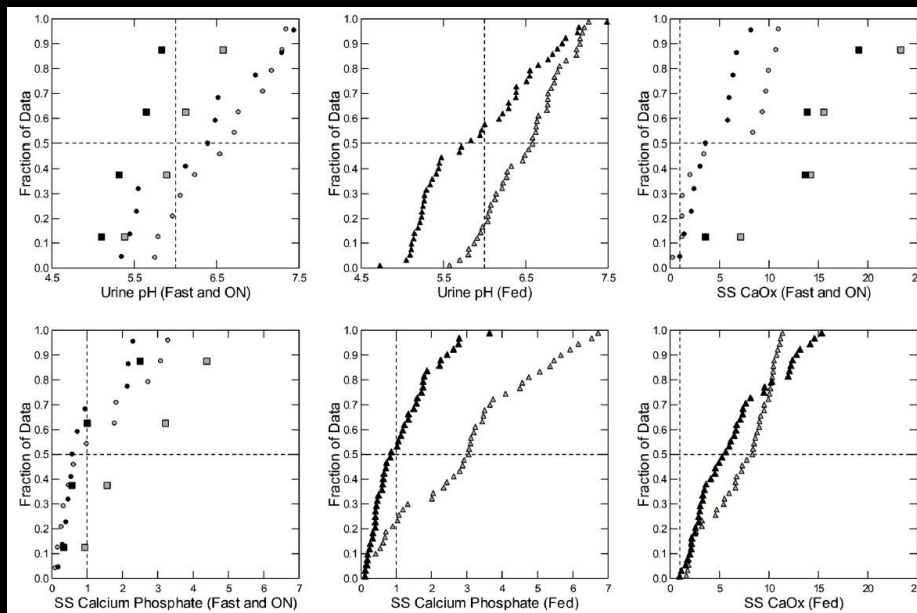
THIAZIDE LOWERS URINE pH AND SS CAP AND CAOx

Presumably because it acts on the GI tract, thiazide reduces GI anion, absorption from the diet of anions that are metabolized as acids and therefore generate bicarbonate.

Fed, thiazide reduced GI anion by 1.91 mEq/hr; changes during fasting (-1.73) and overnight periods (-1.1) were not statistically different from 0.

Thiazide reduced fed urine pH (upper middle panel of the figure just below) significantly (5.9 vs. 6.4) and overnight (upper left panel, black boxes³²¹ more acid than gray boxes) but the effect was not statistically significant (5.47 vs. 6). Fasting (upper left panels), urine pH was not impressively reduced.

Fasting and overnight, thiazide had modest effects on SS CaOx (Upper right panels) and only



modest effects fed (Lower left panel). But perhaps because urine calcium and pH both fell, thiazide reduced SS CaP overnight (lower left panel, black vs gray boxes) and fed (lower middle panel, black vs gray triangles) markedly.

Given our earlier consideration of the nucleating role brushite and octocalcium phosphate crystals play in

fostering CaOx crystals, it is not at all unlikely that this powerful effect on CaP SS is crucial for the effect of thiazide on CaOx stones³²². Surely the meager effects on CaOx SS of an effective stone prevention for CaOx stones calls for this kind of thinking.

FINAL WORDS ABOUT THIAZIDE

At heart, thiazide is a diuretic that causes sodium and therefore ECF volume depletion with the expected fall in blood pressure and increase in proximal tubule reabsorption. Clinically, trial data show that low sodium diet and thiazide are synergistic. It does not seem to alter the food effect

³²¹ *Each box is one overnight for each of the 4 men, before and during thiazide. We made many more measurements fasting and fed, thence having more symbols to show.*

³²² *This is a bold and unconventional statement many will resent but should be tested. I think I am right.*

for calcium, but simply lowers urine calcium both fasting and fed. Perhaps because it lowers PTH, it lowers total calcium excretion less than it lowers calcium delivery as measured from lithium clearances. Thiazide lowers urine pH and GI anion absorption, the latter presumed to cause the former³²³. Presumably because it lowers urine calcium and urine pH, the drug reduces new calcium stone formation³²⁴. Fortunately, the drug appears safe for bones, and therefore one can use it long term as is done for stone prevention and for treatment of high blood pressure.

Thiazide can raise risk for hyponatremia especially when diet sodium is low and urine volume high. Physicians need to be vigilant³²⁵.

THE HORMONES THAT REGULATE CALCIUM AND PHOSPHATE³²⁶

If you wish to skip this very detailed section, [this link will take you to acid base balance](#). If not, prepare yourself for a lot of details. I cannot apologize for the plentitude but comment that they reflect how important it must be to control calcium handling.

The mineral system aims to maintain a constant and particular blood calcium concentration despite irregular inflows from meals and constant urine losses. At the very center is the cell surface calcium receptor (CaSR) that lets cells³²⁷ know the blood calcium concentration from minute to minute, or even by the second.

When blood calcium falls, parathyroid gland cells respond by secreting parathyroid hormone (PTH), and the opposite. Kidney proximal tubule cells respond to falling blood calcium by producing more 1,25 vitamin D (the active form of the vitamin), and the opposite³²⁸. Kidney cortex TAL cells respond by reducing calcium reabsorption when blood calcium rises, and the opposite. The CaSR also plays a role in the distal convoluted tubule and collecting ducts³²⁹. Because PTH up-regulates kidney calcium reabsorption, falling blood calcium increases renal calcium reabsorption via the rise in blood PTH.

³²³ *GI anion absorption is a measure of food alkali detailed in the acid balance section. A fall is like an acid load so urine pH would fall.*

³²⁴ *This site article details the trial data which are very convincing for thiazide and worth a look. Because detailed on the site I omitted the trials here.*

³²⁵ *I tire of documenting that routine clinical practice matters. Most people do just fine, but here and there serum sodium can fall and the only reasonable protection comes from physicians.*

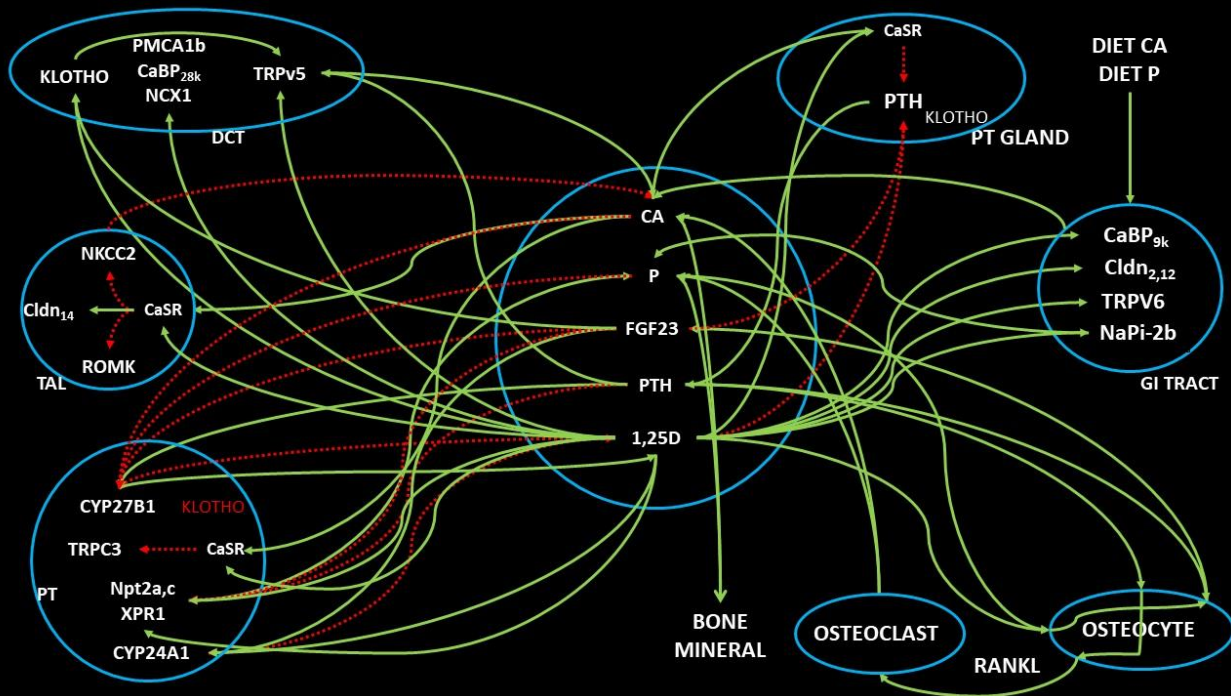
³²⁶ *This whole section came late in my writing as I hoped to avoid too much detail. But as I read through the book it appeared a leafless tree so I wrote the least detailed version I could write while remaining a true reporter of what science has offered here.*

³²⁷ *Parathyroid cells and renal and thick ascending limb cells seem predominant among peers*

³²⁸ *This does not seem regulated by the CaSR.*

³²⁹ *I have to moderate my impulses toward increasing detail or this text will fail a general audience*

The General Layout³³⁰



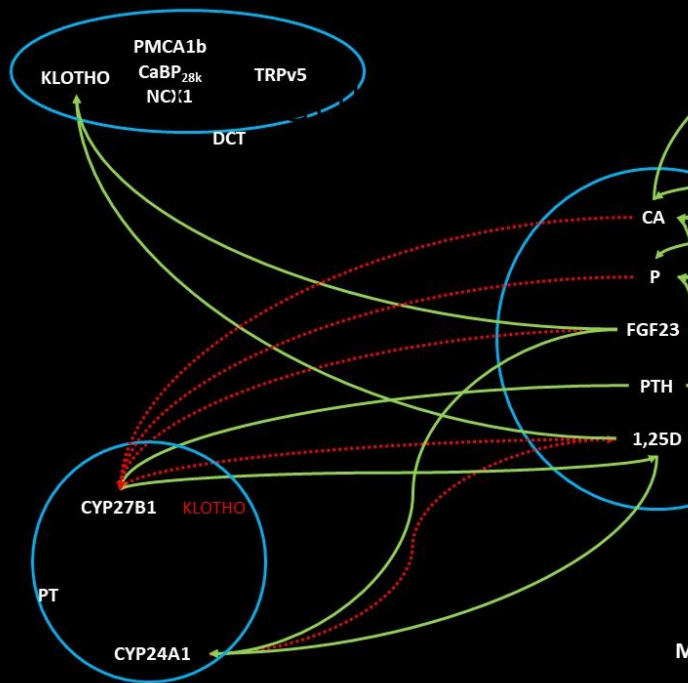
The blue ellipse at the center is blood³³¹ with concentrations of calcium, phosphate, PTH, 1,25D and FGF23. Green lines mean blood levels increase what the arrowhead points to, and the reverse. Red lines the opposite. At the left, kidney proximal tubule (PT), thick ascending limb (TAL) and distal convoluted tubule (DCT). Upper right is the parathyroid glands (PT glands), and right below them the GI tract, with bone at bottom right.

The Vitamin D Family

Vitamin D made by the skin with energy from sunshine is converted to 25 hydroxy vitamin D₃ in the liver (25D). This is the form we buy OTC and the form physicians measure as serum vitamin D. It binds to the vitamin D receptor (VDR) 1000 times less avidity than its next of kin (below) but is present at about 1000 times higher concentration. Kidneys and other cells convert 25D to 1,25 dihydroxy vitamin D₃ (1,25D, calcitriol, CT). Production is tightly regulated and seems a main regulator of intestinal and renal calcium handling as well as myriads of other systemic functions. 1,25D bound to its receptor (VDR) enters cell nuclei and regulates production of particular genes - like that for PTH, as an example. As such it is relatively slow in action, over hours or even days.

³³⁰ The mess of overlying red and green lines is useful for an impression of how things are. As I go over the various regulations I will remove unnecessary lines so you can see what does what.

³³¹ Blood plasma or serum, actually, wherein we measure things



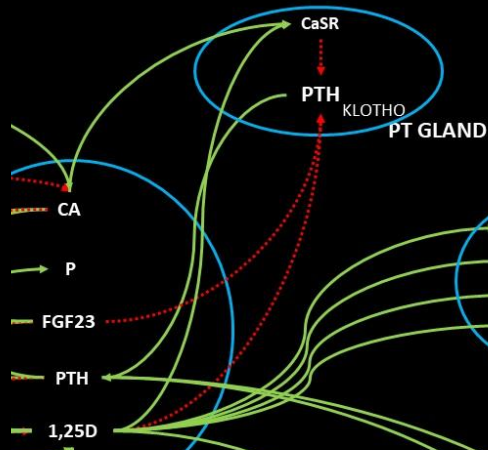
Regulation Of 1,25D Production

In the renal proximal tubule (PT at lower left) 1,25D is made from 25D by an enzyme CYP27B1 which is stimulated by PTH and inhibited by blood calcium, phosphate, 1,25D, and FGF23, a hormone from bone osteocytes. Klotho (red) is a hormone from DCT without which FGF23 cannot inhibit CYP27B1. Klotho is stimulated by FGF23 and 1,25D.

1,25D is metabolized by CYP24A1 which is itself increased by 1,25D and by FGF23. The dashed red arrow pointing to 1,25D simply means this enzyme reduces its serum level.

Regulation of PTH Secretion

Increase of serum calcium stimulates the PT gland CaSR which in turn suppresses release of preformed PTH from storage granules. This lowers serum PTH. The process is very fast, so tiny changes of serum calcium can be regulated back to normal by increase or decrease of PTH.



1,25D downregulates the genes responsible for PTH production, a relatively slow and adaptive process. It also increases abundance of PT gland CaSR amplifying the signal from calcium. FGF23 down regulates PTH. Klotho is necessary for this action. In all three cases the result is a lower serum PTH for a given serum calcium level.

Summary of 1,25D, PTH, FGF23 Calcium Regulation

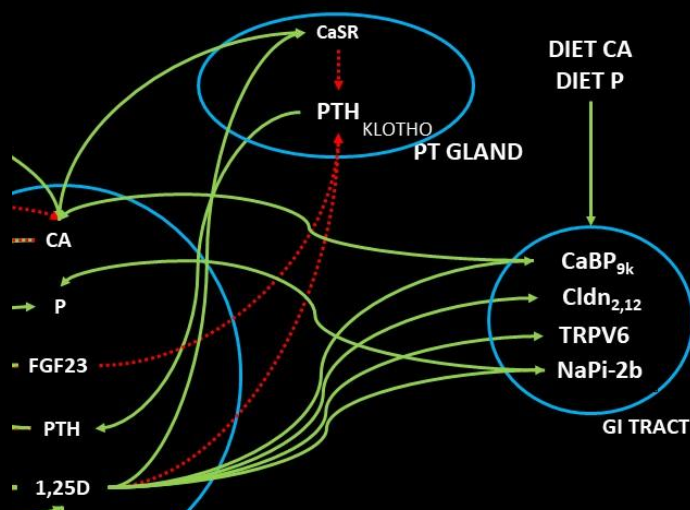
Let's stop here and reflect on this system. Any fall in serum calcium will increase PTH release and 1,25D production. PTH will increase 1,25D production further. But 1,25D suppresses its own production and that of PTH. The latter is by increasing PT gland CaSR abundance, which amplifies the calcium signal, and by reducing synthesis of PT hormone by the gland. A fall in

serum phosphate³³² will also stimulate 1,25D production. Being independent of PTH and calcium, the increase can lead to high urine and serum calcium. This occurs with inherited disorders of tubule phosphate transport, and is a rare cause of kidney stones <https://pubmed.ncbi.nlm.nih.gov/30109410/>. There are other examples beyond this monograph.

In real life, the 1,25D effect will be muted as serum calcium will mainly fluctuate around a stable mean controlled by the calcium - PTH interaction. But consider a chronic reduction of serum calcium, which mainly will occur from a low calcium diet, or excess kidney loss of calcium. We presume that 1,25D and PTH will conspire, then, to raise serum calcium by acting on the GI tract, kidneys and bone, and that presumption is absolutely true³³³. FGF23 is most important when phosphate balance is altered as in chronic kidney disease, but the hormone has effects in normal people.

Diet Calcium and Phosphate Absorption

Intestinal absorption of diet calcium occurs through the intestinal cells and between them. TRPV6 allows calcium to enter the cells of the duodenum, small intestine, and colon. Because its abundance is increased by 1,25D, more can traffic into the blood from food.



The claudins (Cldn) regulate what can pass *between* the cells, and both claudins, 2 and 12, are increased by 1,25D.

Calcium binding protein (CaBP_{9k}) in intestinal cells carries calcium from TRPV6 to where it leaves the cells to enter the blood. Increased absorption raises the serum calcium, thence the long green arrow from the GI tract back to the serum calcium. Food phosphate is reabsorbed by sodium phosphate cotransporter 2b (NaPi-2b) stimulated by 1,25D.

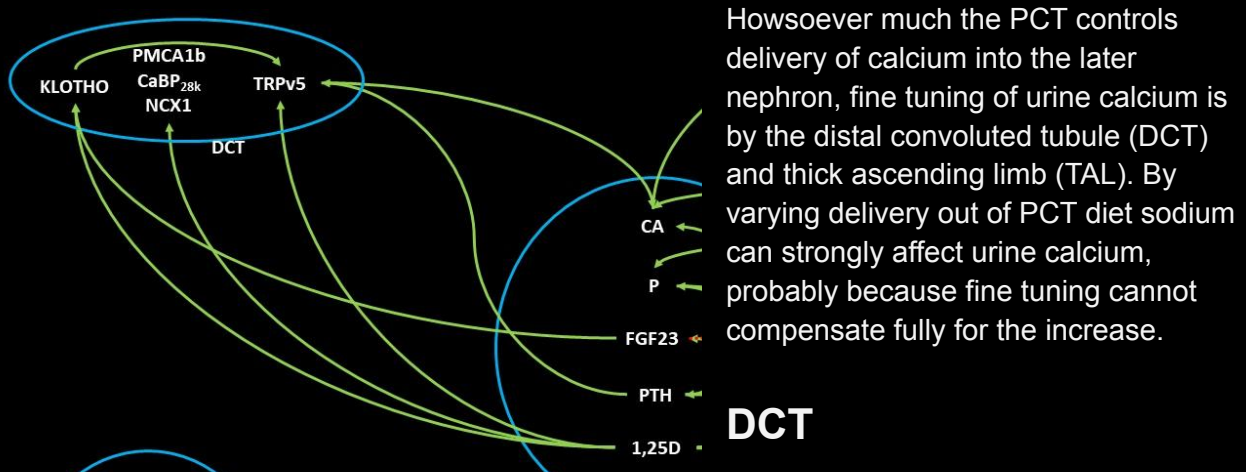
³³² Serum phosphate regulation is far less intense than calcium, so in general this occurs with phosphate depletion or chronically reduced tubule phosphate reabsorption.

³³³ It is impossible to present this topic without reference to the conditions in which the systems are fully activated. But without such conditions one needs to consider all of the regulators shifting up and down in concert smoothing blood calcium swings in service of cell function.

Summary of 1,25D, PTH, FGF23, and GI Tract Calcium Regulation³³⁴

One can say the bundles of green lines from 1,25D to the GI tract dramatize that this one hormone more or less controls absorption of calcium and phosphate, modified by diet availability. Because PTH and low blood calcium stimulate 1,25D, low calcium diet or excessive kidney calcium loss must increase GI calcium absorption. Here is part of the system that links GI absorption to renal calcium loss and diet calcium content. Of course, increased GI calcium absorption will act to raise blood calcium back to normal.

RENAL CALCIUM REABSORPTION



Howsoever much the PCT controls delivery of calcium into the later nephron, fine tuning of urine calcium is by the distal convoluted tubule (DCT) and thick ascending limb (TAL). By varying delivery out of PCT diet sodium can strongly affect urine calcium, probably because fine tuning cannot compensate fully for the increase.

TRPV5 is the main entry port for calcium into DCT cells. Once inside, calcium is ferried to the blood side of the cells by the calcium binding protein CaBP and exits through two channels, named PMCA1b and NCX1. Klotho is a necessary anchoring molecule to secure TRPV5 into the cell membrane. 1,25D increases the abundance of klotho, CaBP, the exit channels, and TRPV5 - thus fosters calcium retention.

1,25D regulates as a slow and adaptive process of the time scale of intestinal absorption changes - hours to days. As always, higher calcium reabsorption from a greater abundance of channels and transporters will raise serum calcium all other things being equal.

By contrast, PTH is a minute to minute regulator via TRPV5 (the long green arrow from PTH to TRPV5). Increased calcium reabsorption will raise serum calcium, thence the long green arrow from TRPV5 pointing to serum calcium.

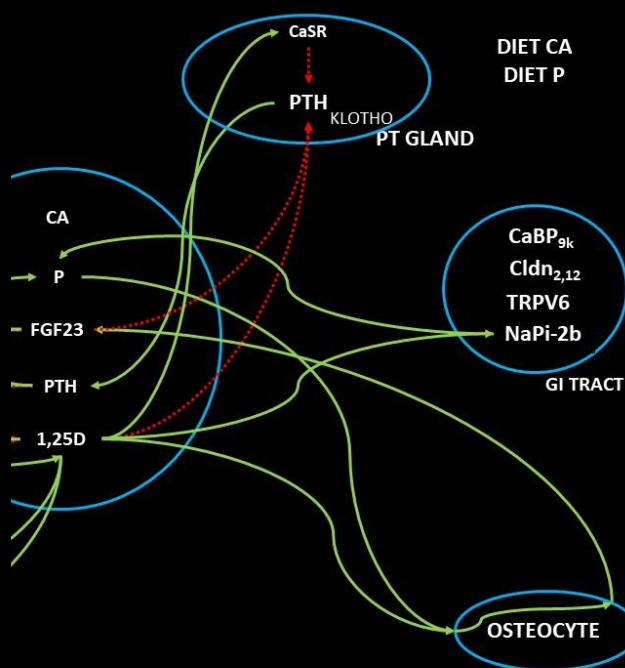
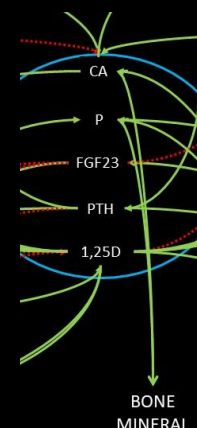
³³⁴ *It must be evident that the GI tract, howsoever powerful, will be slow in restoring serum calcium from low to high and powerless against high serum calcium. That is for bone and kidney to deal with.*

disproportionate given the Cldn_{14} selectivity. But the apical DCT CaSR I mentioned previously can reduce the disproportion by the DCT reabsorbing some of the sodium chloride³³⁹.

The CaSR is not responsive only to calcium. Amino acids and other nutrients can stimulate it and mimic the effects of calcium. For this reason, TAL is an ideal candidate to produce the food effect. This proposition has never been tested.

Bone Mineral is In Equilibrium with the Blood Ca x P Product

Just as in urine, bone surface crystals³⁴⁰ can form and dissolve in response to saturation of the fluid that bathes them, the ECF; and bone has an ample circulation. This means that small variations of saturation can mobilize calcium and phosphate from bone mineral, or drive both into bone mineral. We have already noted this, but up till now have not considered calcium's counter ion, phosphate, and how it is controlled³⁴¹.



SERUM PHOSPHATE, PTH AND FGF23

If you go back to the full drawing you will see FGF23, phosphate, 1,25D and PTH are wrapped up together, so much so that explaining it has called for two separate portions of the original figure.

FGF23 Production: Relationship with PTH

Osteocytes produce FGF23 under control of blood phosphate concentration and 1,25D. That is reasonably simple. FGF23 then feeds back to suppress PTH, as does 1,25D. Klotho

is required for PT suppression. So, via FGF23, blood phosphate can control PTH.

³³⁹ This is part of the DCT CaSR story I should not elaborate here

³⁴⁰ These are brushite - like, and far more soluble than the apatite crystals that make up the bulk of bone

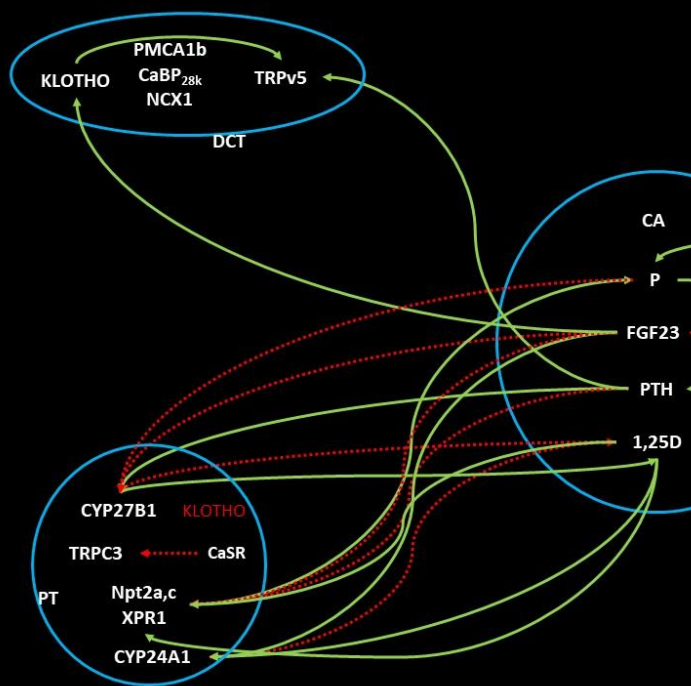
³⁴¹ By nature, a bone crystal equilibrium with blood Ca x P product will be time limited only by lags caused by blood circulation through bone. But the effect is to maintain the product, so a fall of serum calcium or phosphate should trigger bone mineral release of calcium and phosphate. This has not been studied in humans to my knowledge.

1,25D Stimulates GI Phosphate Absorption

Because it raises phosphate absorption, 1,25D can indirectly stimulate FGF23.

Diet phosphate is absorbed to a large extent between intestinal cells, driven by the high lumen concentration compared to blood. The H_2PO_4^- form is preferentially absorbed which is favored by a more acid interior in the proximal (closer to the stomach) parts of the small intestine. This seems independent of 1,25D.

It is also reabsorbed actively through the cells. Entry from the lumen into intestinal cells is coupled to sodium via the NaPi-2b transporter whose abundance is increased by 1,25D. How phosphate gets out of the cell into the blood is not as yet known. At least in animals whose VDR has been abolished genetically, a low phosphate diet can up regulate the transporter, but the human relevance of this is unknown.



FGF23 Reduces Phosphate Reabsorption

FGF23 inhibits the Npt2a,c phosphate reabsorption channels in PCT (lower left), and PTH does the same. 1,25D increases the abundance of both Npt2a,c and the basolateral XPR1 channel through which phosphate exits into blood. But these regulators have different timings. PTH effects on phosphate reabsorption are very rapid, within minutes, whereas FGF23 release from osteocytes in response to serum phosphate or 1,25D is relatively sluggish - over many hours to days. As already noted, FGF23 inhibits CYP27B1 and therefore production of 1,25D, the kind of negative feedback

seemingly everywhere in the calcium/phosphate system.

FGF23 Regulates DCT Production of Klotho

Klotho has been mentioned as critical for TRPV5 and also for PT gland. FGF23 increases its production. Although I erased the lines for clarity, 1,25D increases abundance of TRPV5 and the calcium binding protein and exit channels, so it enhances DCT calcium reabsorption.

Many Other Factors Affect Renal Phosphate Reabsorption

Apart from 1,25D, PTH and FGF23, phosphate reabsorption has other regulators. Reabsorption is increased by low diet phosphate (in part less FGF23, but perhaps other mechanisms), alkali loads, growth hormone, insulin, insulin-like growth factor 1, epidermal growth factor, and thyroid hormone. Reabsorption is reduced by high diet phosphate, acid loads, klotho - not as part of FGF23 action but independent, low serum potassium, estrogen, calcitonin, dopamine, and glucocorticoids ('steroids' in the vernacular).

THE MULTIPLE NEGATIVE FEEDBACK LOOPS

Dizzying at first, but like the steps of a dance reasonable if taken one at a time and if one considers that a main purpose is regulation of blood calcium and leave for a moment regulation of bone cells - which comes next.

Blood Calcium

Blood calcium, 1,25D, and FGF23 all down regulate PTH; PTH acts to raise blood calcium via TRPV5, 1,25D, and bone, and to lower blood phosphate via kidneys. Blood calcium down regulates kidney calcium and magnesium reabsorption via TAL CaSR.

Blood Calcium and Phosphate

Blood calcium, phosphate, FGF23 and 1,25D all down regulate 1,25D; 1,25D raises blood calcium and phosphate via TRPV5, Klotho, and GI calcium and phosphate absorption, but raises FGF23 which lowers serum phosphate via kidneys. Blood phosphate and 1,25D stimulate FGF23; FGF23 lowers 1,25D, PTH, and blood phosphate.

Kinetics of Regulation

If you look at the overall pattern, blood calcium is regulated rapidly: PTH and CaSR on kidney and bone mineral equilibrium. Phosphate is regulated rapidly by PTH and bone mineral equilibrium. The general poise of the system is regulated more slowly by the 1,25D / FGF23 system.

Models

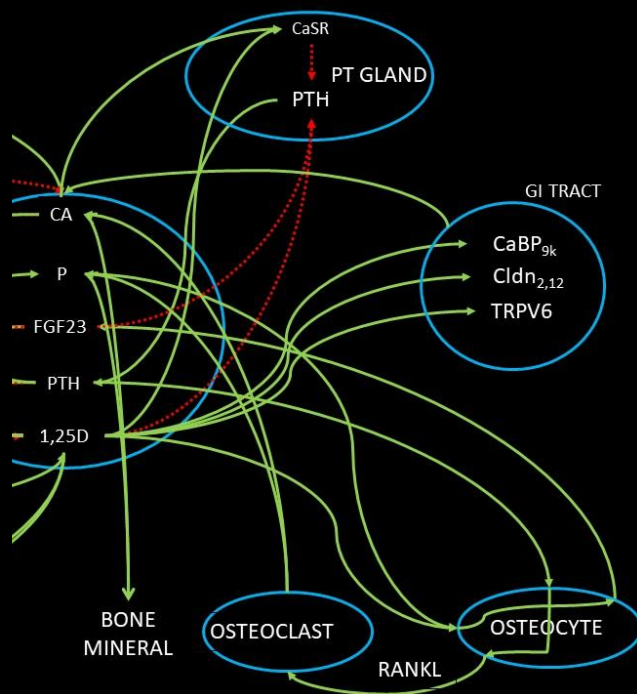
To fully appreciate how changing one thing affects the system of linked negative feedback loops one needs to write a computer program. Advanced modeling attempts have focused on genes and metabolism. This recent paper on bone remodeling after injury illustrates the extreme difficulty of model making. So while a trivial - if enjoyable - model could be made of the serial negative feedback in this brief section, it would be a toy, or amusement, rather than a real contribution. A useful model would require massive consideration of cell behaviors and tables of

coefficients many of which do not presently exist for humans. This excellent paper makes the latter point³⁴².

CELL REGULATION OF BONE MINERAL

This is an oceanic science but our interests here need not venture much beyond the shore. We know blood Ca x P product is near the solubility product of surface bone so bone mineral will stabilize the blood product. But what do we know about the cellular contribution to bone mineral loss?

Constant High PTH Stimulates Osteoclastic Bone Mineral Loss



A steady increase in PTH, medicinal or from low calcium diet, will increase osteocyte production of RANKL which signals increase in osteoclast bone mineral breakdown. This will deliver more calcium and phosphate into the blood restoring both levels at the expense of bone mineral stores.

By contrast, intermittent PTH elevations, such as from medicinal use of PTH for treatment of bone disease, stimulates osteoblast production and new bone formation. Under this circumstance, osteoclast stimulation is coordinated with bone formation and net mineralized bone can increase. This is the basis for using PTH as a bone anabolic agent to reverse mineral deficits. PTH cannot be used beyond several years, and thereafter one must stabilize bone

mineral with a bisphosphonate agent or risk losing what has been gained³⁴³.

1,25D Can Simulate Osteoclastic Bone Mineral Loss

Acting through its receptor (VDR) this hormone exerts about 8 actions on bone. Perhaps the most familiar because already mentioned in this book, 1,25D stimulates RANKL which directly stimulates osteoclasts to dissolve bone mineral. This action is the same as PTH, which also

³⁴² *Linked negative feedback loop models depend on the interaction constants - by how much will y alter if x alters. Without that programs are trivial, and these constants are very hard to isolate in humans.*

³⁴³ *Patients often wonder why PTH can increase bone mineral yet hyperparathyroidism causes bone mineral loss - here is the reason. High PTH from low calcium diet - the same, bone mineral loss*

stimulates RANKL when given continuously. If we reflect on 1,25D and PTH they are in an antagonistic relationship in that PTH stimulates 1,25D production but 1,25D down regulates PTH. If both are somehow stimulated, bone is in jeopardy³⁴⁴.

1,25D also stimulates two genes (ANK1 and ENPP1) that increase bone cell production of inorganic pyrophosphate. We met this molecule as a urine inhibitor of crystallization, and it has that same role in bone. So this action of 1,25D reduces bone mineral formation.

In normal life, 1,25D, FGF23, PTH and other hormones act to regulate bone mineral and maintain normal bones. This is beyond what I can include here³⁴⁵.

RESPONSES TO COMMON DIET CHANGES

Low Calcium Diet

One means about 400 - 500 mg/d of calcium in an adult though even 600 or 700 mg/d may be insufficient for bone health.

Secondary Increase of PTH, 1,25D, and FGF23.

One must presume that slight reduction of serum calcium is the key signaller, although this has never been proven. The slight reduction will signal an increase of both serum PTH and of 1,25D, the latter mediated by higher PTH and reduced serum calcium. Increase in 1,25D will increase the efficiency of GI calcium absorption, which tends to offset the lower diet calcium. But it cannot fully compensate because the lower serum calcium and higher PTH are the *cause* of the higher 1,25D, and therefore of the increased calcium absorption.

The diet obligates a chronic increase of PTH *and* 1,25D. The slight reduction of serum calcium will reduce CaSR signaling to the TAL, and increased PTH and CT signaling to DCT TRPV5 will both increase kidney calcium reabsorption and tend to raise serum calcium back to normal. Finally, tonic increased PTH and CT signaling will increase osteoclast activity via RANKL leading to calcium and phosphate entry into blood from bone, with bone mineral loss.

Of special note to us, the final effect in long term balance studies will be that urine calcium excretion will track net calcium absorption. Though more efficient, absorption from food will be limited by diet availability. Urine calcium will fall because of higher PTH and 1,25D. If renal calcium reabsorption is reduced, as in hypercalciuric people, bone mineral balance will tend to fall more because PTH and 1,25D cannot lower urine calcium with their normal efficiency³⁴⁶.

³⁴⁴ *Both are stimulated by chronic low calcium diet, a most unideal situation an otherwise normal person can create.*

³⁴⁵ *We gaze upon a forest of cedars. I must stop my tour for I do not know the way further.*

³⁴⁶ *This homespun explanation for increased bone disease in stone formers is my humble offering and by no means properly proven. That is the plague of mineral metabolism - likely theory is often very hard to test in humans. Rodents, howsoever convenient for study, grow throughout life whereas we do not.*

PTH and FGF23 Can Affect the Plasma Ca x P Product

Increase of both PTH and FGF23 (from 1,25D increase) cannot but reduce renal phosphate reabsorption via signaling of Npt, though 1,25D increase in PCT phosphate reabsorption may blunt their effects. PTH and FGF23 will offset increased diet phosphate absorption via 1,25D signaling of GI NaPi-2b,c and increased serum phosphate delivery from bone mineral dissolution. A lot will depend on diet phosphate, it would seem. If rather high, serum phosphate and the Ca X P product will tend to be normal - unchanged from a higher calcium diet, but if also restricted the product could fall, increasing bone mineral loss.

A Well Known Clinical Paradigm - Secondary Hyperparathyroidism

We have derived from our knowledge of regulation pathways a condition clinicians have long recognized - secondary hyperparathyroidism: Increased PTH and 1,25D, normal serum calcium and phosphate, low or normal urine calcium excretion³⁴⁷, and bone mineral loss. Low calcium diet is never a good situation. For stone formers, it will increase urine oxalate - a matter not covered here, and promote stone formation. The high PTH can mislead into unneeded parathyroid surgery³⁴⁸.

High Calcium Diet

Bone Benefits

One usually means 800 to 1200 mg/d of calcium.

This is the inverse of a low calcium diet and overwhelmingly preferred for everyone, including stone formers. PTH and 1,25D will be relatively suppressed (vs lower diet calcium) as will be FGF23. Urine calcium will be higher as TAL and DCT reabsorption will be relatively lower. Bone mineral is protected by reduced PTH and well maintained Ca x P product. In stone formers the higher urine calcium can be controlled by lowering diet sodium³⁴⁹. This is the scientific basis of the kidney stone diet - a high calcium, low sodium diet (with low oxalate added).

In long term balance studies, calcium absorption will be high (absorption between cells will be high) and tubule calcium reabsorption reduced (lower PTH and CT) so urine calcium will tend to track with calcium absorbed into the blood³⁵⁰.

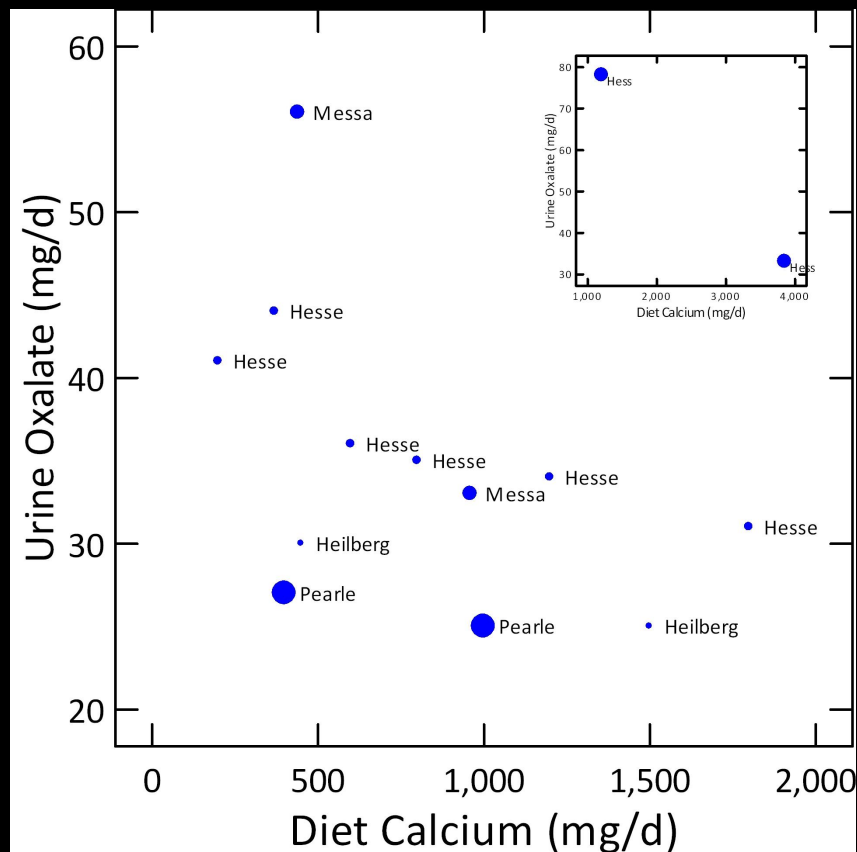
³⁴⁷ *In people with a genetic form of hypercalciuria, a low calcium diet may coexist with high urine calcium, a combination apt to mislead physicians into unneeded parathyroid surgery.*

³⁴⁸ *A rude clinical fact - high PTH with normal serum calcium enlarges PT glands so surgeons may be misled into surgery neither required nor advisable.*

³⁴⁹ *The effects of sodium on urine calcium have been so detailed that no further mention is required - except for this reminder.*

³⁵⁰ *Earlier, I reviewed the study of a high calcium low sodium diet to increase bone mineral balance. Urine calcium and endo fecal calcium secretion are both reduced by the low diet sodium so high calcium intake can increase bone mineral. High diet sodium raises both urine and endo fecal calcium loss, so bone balance becomes negative.*

Lowers Urine Oxalate³⁵¹



In multiple studies detailed on the site increasing diet calcium intake reduces urine oxalate excretion. The names refer to the main authors of the original articles. Size of symbols gauges diet oxalate intake (specified on the site).

In the insert is an experiment in which massive diet oxalate raised urine oxalate to nearly 80 mg/d and very high diet calcium lowered it to the normal range³⁵².

High Calcium Low Phosphorus Diet

It is not that one sets out to eat such a diet, but when

general nutrition is less than ideal one may use calcium supplements that contain no phosphate - calcium citrate or carbonate for example and not eat sufficient diet phosphate. Calcium supplements with meals can reduce phosphate absorption.

Serum phosphate and cell phosphate will fall, lowering FGF23. Serum calcium ion will rise as less will be bound in soluble calcium phosphate salts, so PTH will fall below that from a high calcium normal phosphate diet. 1,25D will be under opposing forces, less drive from PTH, down regulation from serum calcium, less down regulation from FGF23 and phosphate, and an increase is the usual result which further raises calcium absorption and serum and urine calcium.

If diet phosphate is too low phosphate depletion may adversely affect muscle, including the heart. Generally one recognizes that serum phosphate has fallen below normal and attempts to restore general nutrition to a more normal state.

³⁵¹ *This remarkably important work has been difficult to place in this monograph. I could have placed it with oxalate regulation, but that would be clinically obscure. I have instead made links to this location so it will be found from wherever oxalate is discussed*

³⁵² *The reasons for high calcium diet therefore include both bone mineral sparing and reduced stone risk from lower urine oxalate. It can seem very surprising to patients who form calcium stones when physicians endorse high diet calcium intakes. Of course low diet sodium is a necessity.*

SEVERAL SELECTED DISEASES

Primary Hyperparathyroidism

Imagine the sheer chaos if PT cells themselves begin to produce excess PTH. [I have detailed this on the site](#) but pause here to look back from our present heights. Constant high PTH will raise 1,25D and calcium absorption, and also cause bone mineral loss via RANKL. PTH increases kidney calcium reabsorption via its effects on TRPV5 but higher serum calcium reduces TAL calcium reabsorption via the TAL CaSr. So both blood and urine calcium are almost always high. Serum PTH may be normal because high blood calcium suppresses PTH release, giving a PTH that is too high for the prevailing calcium level. Just as high PTH with normal blood calcium is almost always secondary, normal PTH with high blood calcium is almost always primary hyperparathyroidism³⁵³.

Mild Chronic Kidney Disease (CKD)

Glomerular filtration and 1,25D production both fall. The former reduces phosphate filtration, and the latter unleashes PT cell PTH release so serum PTH rises. A slight fall in serum phosphate is not rare in the earliest stages. Sustained high PTH will evoke bone cell mediated bone mineral release and help normalize 1,25D. The picture is so much like secondary hyperparathyroidism that one cannot really differentiate them, especially as people with early and mild CKD may have low calcium intake as well.

As filtration falls more, phosphate retention will increase FGF23, high PTH will progress, bone will suffer. Release of bone mineral into blood with falling filtration can raise the blood Ca x P product with consequent mineral deposition in soft tissues. This is not the forum to continue the conversation³⁵⁴.

Genetic Defect of Phosphate Reabsorption

Imagine [genetic defects of the proximal tubule phosphate transporter NaPi2c](#), so that phosphate reabsorption is reduced. Called hereditary hypophosphatemic rickets with hypercalciuria, you would imagine from what we have already discussed that blood phosphate and the calcium x phosphate product would be low, 1,25D would increase - released from the down regulation by phosphate, and this last would raise GI calcium absorption, suppress PTH and therefore DCT calcium reabsorption, and lead to hypercalciuria and kidney stones. Bone mineral formation would be reduced by the low Ca x P product - osteomalacia³⁵⁵. This [fine review of HHRH genes and physiology](#) is an excellent overview.

³⁵³ *Another rude clinical fact. If serum calcium is high and PTH normal, PHPT is the likely diagnosis, often left untreated for excessive periods because unrecognized.*

³⁵⁴ *While I am not abashed by the topic and could continue, it is not of primary interest here.*

³⁵⁵ *We must be selective here about range. A long term low product allows normal formation of the proteins that mineralize in bone, but crystals will not form so the bone in children can bend (rickets) or fracture along stress lines in adults (osteomalacia).*

In a series of 13 cases studied as adults that I have chosen as illustrative, 3 had renal crystallizations, high urine calcium and 1,25D, 2 of the 3 had low PTH. A low blood Ca x P product would be expected to reduce mineral formation in bone and some (not the 3 with renal crystals) had osteomalacia (bone formed the protein in which mineral would form, but mineral deposition was below normal). Some patients had this bone disease. Not all patients, including one of the ones with renal crystals, had low blood phosphate.

In other words, just having gene defects for a transporter does not reliably predict a specific 'phenotype' or disease pattern. Other studies report generally the same. Unexpectedly, cysts may be a not uncommon associate in patients with abnormal phosphate transport genes, as an example of how surprising gene/phenotype studies may be³⁵⁶.

Withal, given a documented gene defect and hypercalciuria and high serum 1,25D and reduced PTH, and stones, along with reduced serum phosphate and increased FE phosphate one can use oral phosphate replacement in hopes of reversing the underlying problem. I have one such case I am treating along with his referring physician and we have documented a fall in 1,25D, increase of PTH, and fall in urine calcium.

Genetic Defect of 1,25 D Production

Imagine that CYP24A1 is defective. The breakdown of 1,25D to its inactive metabolite 24,25(OH)₂D is deficient. Therefore serum 1,25D will be high. This will suppress PTH production, raise GI calcium absorption, and promote bone calcium loss. Serum calcium may be elevated or normal, because PTH and serum calcium itself are major regulators of renal calcium reabsorption. Urine calcium will be high, promoting stones.

How will one suspect such a problem? To me the best clue is that PTH will be low normal or even low, 1,25D high, and urine calcium rather high and unresponsive to diet sodium or even thiazide because a primary regulator is abnormal.

In real life, cases vary a lot in their expression, and even gene mutations are not sure proof that the mutation is causing disease. One reasonable approach is to measure - in a patient with mutation of the gene - the metabolite of the enzyme (24,25(OH)D in relation to the stable storage form of vitamin D (25D): the 25(OH)D/(24,25(OH)D ratio. A high ratio supports the idea that the enzyme activity is not normal. Ketoconazole can compensate for the defect by reducing 1,25D production³⁵⁷. Rifampin, a drug used for tuberculosis is also effective and perhaps easier to tolerate. I mention these treatments to prompt physicians and patients in a relatively obscure area of practice³⁵⁸.

³⁵⁶ *The links between gene defects known to be significant and the actual findings in patients are at best elastic so details of a given case vs. gene defects require a lot of thought before deciding on treatment.*

³⁵⁷ *For enthusiasts, this is an excellent review of the entire topic.*

³⁵⁸ *By this vague and clumsy wording I mean rare disease treatments are often hard to find, so I have left clues.*

Genetics and Me

Up to recently I have viewed genetic studies for stone disease as more interesting than useful. My first gene abnormality, in a patient I thought had renal tubular acidosis, turned out positive and did influence treatment - but the experience (massive forms, delays) was awful. Recent experiences have been better as genetic testing matures into routine clinical orders and physicians become familiar with the results. Right now is in between. But when I encounter low serum phosphate or low PTH in hypercalciuria, I am primed to order gene tests. Likewise in the phosphate stone formers whose urine pH is so very high for no good reason³⁵⁹.

AN ATTEMPT AT SYNTHESIS FOR CALCIUM

Fasting

The bedrock seems to be an integrative system that maintains a constant serum calcium level under changing conditions of diet calcium. It does so by a fast system of bone mineral in physical equilibrium with the blood brushite³⁶⁰ supersaturation, and PTH and blood calcium modulation of kidney calcium reabsorption, and also by a slower adaptive system of 1,25D and FGF23 that regulates intestinal calcium uptake and renal calcium and phosphate reabsorption according to longer term (days) averages of diet calcium intake³⁶¹.

It would seem that the general setting of the system is genetically variable, some people having a lower and some a higher fasting urine calcium for a given stable calcium diet. These latter appear prone to calcium stone formation. One presumes this variability has had adaptive value over evolutionary time, but also poses risk of a disease to those at the upper end of the urine calcium range, a disease that would reduce reproductive potential.

Food

In addition, the system seems to have a general response to food in which calcium and magnesium reabsorptions both fall, more or less the same in stone formers and people in general (food effect). This must lead to bone mineral and cell magnesium loss over time in all people if nutrients are commonly presented without sufficient calcium and magnesium³⁶².

³⁵⁹ *Indeed I now have three clinical instances for gene ordering. How spare!*

³⁶⁰ *Although I have said this before, 'brushite' stands for early calcium phosphate crystallizations including brushite, octocalcium phosphate, etc.*

³⁶¹ *The awful and long sentence is deliberate so as to bring to mind the winding path between blood calcium and its regulation.*

³⁶² *I am of two minds. Shall I say it is the thick ascending limb that mediates this, or shall I say nothing?*

Stones Over Evolutionary Time

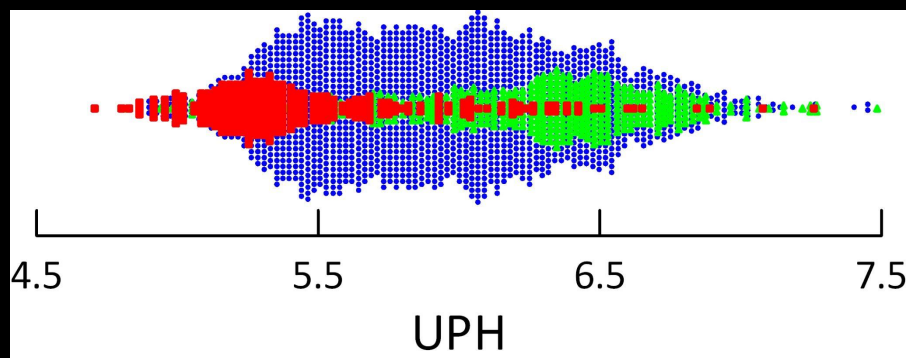
This leaves us wondering at Nature and her secret powerful behaviors³⁶³. What might have protected against stones during evolution, and what might be the value, if any, conferred by the higher end of the range for urine calcium? What value does the food effect confer, and is it actually aimed biologically at mineral metabolism or at other features of renal response to nutrient intake?

You might expect that I will now unroll the great scrolls of knowledge hidden to this point and present to you 'the truth's superb surprise'³⁶⁴. But no. We are at the end (or at least my end) of the road. Beyond is all desert and mountain, a wasteland scattered with the bones of those who tried and failed in the unmapped wilderness of an alluring, treacherous terrain.

THE ACID BASE BALANCE SYSTEM - Overview

Major Systemic Regulation

As for water, sodium, calcium, magnesium, phosphate and oxalate, diet and metabolism present the body with daily loads of acid or alkali which the kidneys must remove so as to keep the acidity³⁶⁵ of the blood constant. And just as bone serves as a storage battery for serum calcium, offering calcium or taking it up, the ECF has a powerful bicarbonate buffering system³⁶⁶ that can take up or give back acid or alkali to blood so as to keep its acidity constant.



Controls Kidney Stone Type

The mode of renal acid excretion affects the kind of kidney stone crystals. Higher urine pH values lead to phosphate

stones (green), low pH to uric acid stones (red)³⁶⁷. Because oxalic acid has a very low pKa it has two charges at all urine pH values and calcium oxalate stones can form at any urine pH

³⁶³ *'This is my letter to the world/that never wrote to me/the simple news that Nature told/with tender majesty' (Emily Dickenson).*

³⁶⁴ *Emily Dickenson's superb phrase: 'Tell all the truth but tell it slant'.*

³⁶⁵ *I mean pH but because bicarbonate level seems regulated as well, I use the broader term.*

³⁶⁶ *I know red blood cell hemoglobin is part of the buffering system but choose an easy beginning*

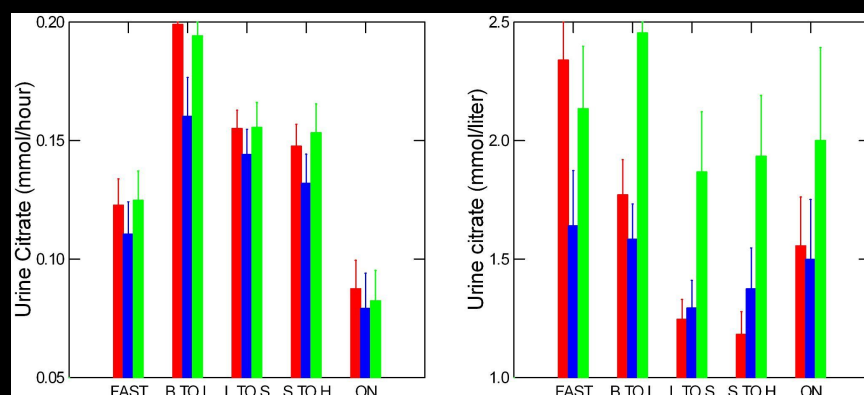
³⁶⁷ *The red and blue connote any uric acid or CaP in stones, and urine pH probably varies over years, so stones are geological relics with traces from many periods of a person's life.*

(blue)³⁶⁸. We have already noted that urine pH is higher in CaP stone formers as compared to CaOx stone formers, and will discuss the low urine pH of uric acid stone formers later in this book.

Controls Urine Citrate

Our only established urine crystal inhibitor and our main urine calcium binding molecule is controlled by systemic acid base balance. When balance is alkaline³⁶⁹, citrate is high, and low when we face an acid load. That is why potassium citrate is a useful drug - it provides alkali so urine citrate rises. But patients can have disorders that misregulate citrate in relation to urine pH so potassium citrate will not work right or even might worsen things.

Curiously, urine citrate hardly differs between stone formers and normals (red), either in excretion rate (left panel) or concentration (right panel). The CaOx stone formers (green) who have lower urine volumes actually have the highest citrate concentrations. CaP stone formers (blue) do have the lowest citrate excretions, but differences are not significant.



In normal people urine citrate and pH tend to rise together, which is the case for CaOx stone formers. But in CaP stone formers urine pH is higher than normal and urine citrate is not higher, so the two do not track quite right.

To understand urine pH and citrate we have to

understand the system that controls acid base balance, of which citrate and pH are simply components.

I have already written a nifty introduction to acid base balance, food acids and alkali, and kidney acid excretion, and strongly suggest you glance at it as we go along if you need to refresh your knowledge. I write it again here in brevia. The article focuses on a main sex difference in acid base balance, incidently, that I cannot cover here in as much detail³⁷⁰.

³⁶⁸ *I have detailed how an initial nucleation of calcium phosphate as brushite can initiate calcium oxalate crystallization. This is more amply detailed on the site.*

³⁶⁹ *When alkali predominates in diet so alkali or little acid needs be removed*

³⁷⁰ *Women extract more alkali than men eating exactly the same diet. How they do so - unknown. That they do so is certain, and the extra alkali raises urine pH. We believe Nature so contrived to spare bone mineral, but have no evidence to support the claim.*

THE ACID BASE BALANCE SYSTEM - Detailed View

Protons and pH

The gauge of acid - base is the concentration of hydrogen ions (H^+) in water. Pure water contains 10^{-7} mol/l of hydrogen ion and is referred to as 'neutral'. pH, the logarithm of $1/H^+$ concentration, is convenient given the huge range encountered. Pure water is pH 7, neutral, acid solutions are those with pH below 7 and alkaline have pH above 7³⁷¹.

The Bicarbonate Buffer System

Let's Make Carbonated Water

Suppose we have a jar of water with a stopper through which runs a glass tube. We attach the tube to a tank of carbon dioxide (CO_2) gas and begin raising the pressure of CO_2 in the water. The CO_2 will form carbonic acid (H_2CO_3) in the water:



This acid will give off its hydrogen into the water and drop the pH to the equilibrium for the H_2CO_3 molecule - pH = 3.6, making a small amount of HCO_3^- , bicarbonate. The negative sign shows where the H^+ was attached on the bicarbonate (HCO_3^-).

You have made carbonated water. Go ahead, mix drinks with it. It will have an acid taste. It can dissolve your countertop marble and your tooth enamel. You notice the double arrows (\rightleftharpoons) meaning this can go either way, so if you reverse things and let CO_2 out the reactions run backward (the carbonated water loses its bubbles and its acidity)³⁷².

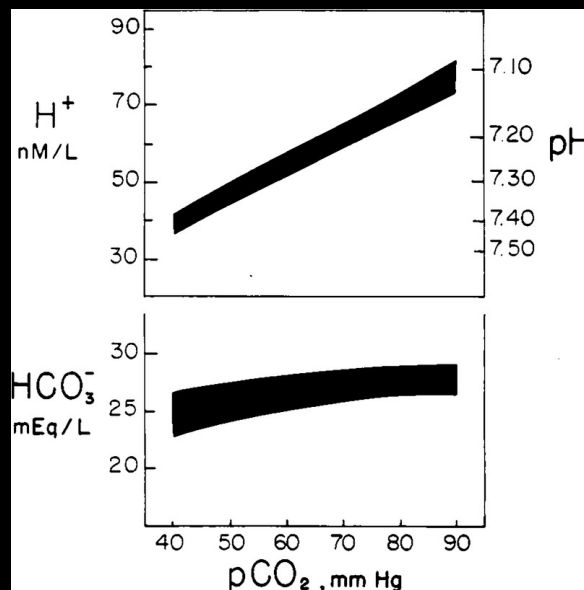
Let's Gas Blood or Even People With CO_2

When we do the same for a sample of blood, the protons (another name for hydrogen ions in water) will be taken up on the hemoglobin in red blood cells, making more and more bicarbonate. As you reach about 40 mm Hg of partial pressure for CO_2 (pCO_2), bicarbonate concentration will be about 24 mmol/l, pH about 7.4, whereas in the water you would have about 2 mmol/l and pH about 3.6.

³⁷¹ The range for pH is from 0 to 14 in water solutions, meaning proton concentration varies over a range that would require 14 '0's to write out. Blood is normally 7.4 and in normal life hardly varies more than 0.1 pH unit during the day.

³⁷² The enzyme carbonic anhydrase speeds up the reaction of $H_2O + CO_2$ to make H_2CO_3 . It is present in kidney and red blood cells.

The figure shows humans in whom $p\text{CO}_2$ was experimentally varied up and down in the operating room before a scheduled surgery, over 50 years ago. As $p\text{CO}_2$ was increased, blood bicarbonate rose because red cell hemoglobin³⁷³ took up protons from the carbonic acid making more bicarbonate. The bicarbonate leaves the red cell in exchange for chloride³⁷⁴.



This is how CO_2 from cell metabolism leaves tissues and gets to the lungs, incidentally³⁷⁵.

Let's Add Food With More Acid than Alkali Acid

We eat a steak and skip the veggies. The acid from food is discussed in the section below, for now just allow that food can be an acid load.

Bicarbonate Falls below the thick line on the graph³⁷⁶

It falls because the protons make blood bicarbonate into carbonic acid that rapidly becomes CO_2 gas. This is not a problem because the lungs can remove CO_2 as rapidly as they need to³⁷⁷.

The Lungs Cannot Compensate Properly

The brain senses the pH of blood, and as it falls even a tiny bit signals a deeper respiration so the $p\text{CO}_2$ goes down and pH comes up.

Sounds good?

It is not. You have lost bicarbonate. What will you do with the next meal if it also has acid in it? You have not made back the bicarbonate decomposed by the acid³⁷⁸.

³⁷³ I already told you - in a footnote - that red cell hemoglobin is a crucial buffer. It is how we get the huge concentration of blood bicarbonate at the $p\text{CO}_2$ of 40 mmHg.

³⁷⁴ The loss of bicarbonate (negative charge) is balanced by ingress of chloride to maintain charge balance

³⁷⁵ We have not room nor need to explore this beautiful, cultivated, garden of knowledge.

³⁷⁶ Because the thick line is the confidence limit band, values below it mean bicarbonate has been used up in buffering protons added to the solution, by metabolism of protein in this illustration.

³⁷⁷ By releasing the carbon dioxide the lungs keep the pH of the blood constant but the blood buffer is lower and cannot be replaced except if the lungs retain carbon dioxide. That will make bicarbonate out of carbonic acid so blood pH will fall (more acid).

³⁷⁸ The blood buffers must be regenerated or they will deplete and blood pH eventually fall.

The Bone Cannot Compensate Properly

Bone mineral is in equilibrium with the blood. We said that many times already. As pH falls a tiny amount dissolves giving up phosphate that can take up the protons from the steak³⁷⁹. More bicarbonate is made and all is well. The extra calcium goes into the urine.

Sounds good?

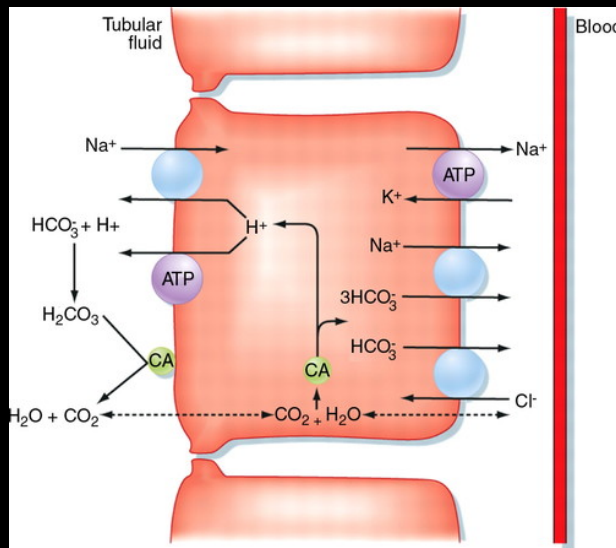
It is not. You have made back the lost blood bicarbonate but you have sacrificed bone mineral. What will you do with all the meals to come if your diet remains more acidic than alkaline? The US diet is more or less that way for most of us³⁸⁰.

The Kidneys Can Compensate Perfectly and For a Lifetime

The kidneys can excrete acid into the urine thus making new bicarbonate. They literally transport acid out of the blood into the tubule fluid and send it on its way. Respiration is a minute to minute fine tuning. Bone mineral, the same. The kidneys are slower (many minutes, hours) but powerful and exact. They can do this meal after meal for a lifetime, and that is how things happen.

HOW KIDNEYS REMOVE ACID

Proximal Tubule



Here is a proximal tubule cell - we have discussed these cells earlier. The link is to the source, a nice review.

Pumps Protons Out of Blood

On the blood side, a pump uses energy from ATP to remove sodium from the cell and add potassium in exchange. On the tubule fluid side, an exchanger lets sodium in - there is much less sodium inside the cell than in the tubule fluid - but only in exchange for protons.

A second transporter on the tubule fluid side uses energy from ATP to just pump protons.

³⁷⁹ Bone phosphate combines with calcium to make crystals because it has negative charges where protons once bound. Dissolve the crystals and protons will be buffered on the phosphate.

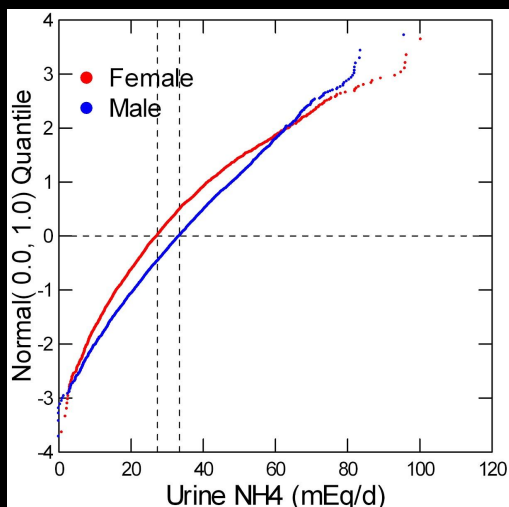
³⁸⁰ I have in passing articulated the case that acid loads from diet can reduce bone mineral. This is debated and unsure according to experts in that rarified domain who have disagreed with one another.

Does Not Make New Bicarbonate

The $p\text{CO}_2$ inside the cell is like that in blood so removing protons makes more bicarbonate as CO_2 becomes carbonic acid and gives up its proton, like we saw a few minutes ago. The bicarbonate goes into the blood through channels along with sodium.

In the tubule fluid, the protons make filtered bicarbonate into carbonic acid that breaks down to CO_2 and water, the CO_2 helps keep up $p\text{CO}_2$ in the cell. CA is an enzyme, carbonic anhydrase I mentioned before in a footnote. It speeds up the formation of carbonic acid from CO_2 and water, and also its breakdown back to CO_2 and water.

But with all this, there is no new bicarbonate. Filtered Bicarbonate is reabsorbed, a zero sum game³⁸¹. Sodium reabsorption is the main benefit³⁸².



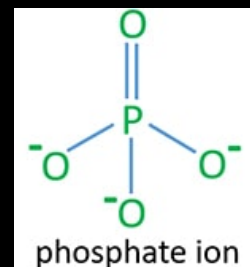
Makes Ammonia

The same cells can produce ammonia by metabolizing an amino acid called glutamine. Protons can add to the ammonia and be lost in the urine as ammonium ions: $\text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+$. This makes new bicarbonate at the expense of degrading an amino acid, but we can afford this.

Ammonia has so strong an avidity for protons³⁸³ that it competes against bicarbonate for them. It has a complex fate as it goes downstream along the nephron that I will leave out here but is in the linked reference.

Adult men and women stone formers make similar amounts of

ammonia, men a bit higher. It is essential that the ammonia leave in the urine. If it returned to the blood the liver would metabolize it to urea liberating the protons that the kidney added³⁸⁴.



The Late Parts of the Nephron Titrate Phosphate

We have already reviewed how phosphate combines to make CaP kidney stones and bone mineral. Here we view it as an acceptor and donor of protons.

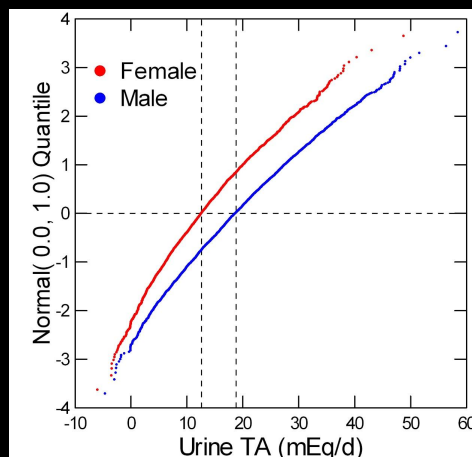
³⁸¹ A consequence of high GFR is relentless filtration of bicarbonate: $140 \text{ l/d} \times 24 \text{ mmol/l} = 3360 \text{ mmol}$ bicarbonate filtered. Total ECF bicarbonate is $24 \text{ mmol/l} \times 14 \text{ l} = 336 \text{ mmol}$ so ECF bicarbonate is filtered and reabsorbed 10 times /day.

³⁸² As bicarbonate is removed from tubule fluid water moves back into blood because the concentration of solute in tubule fluid is below that of blood - water moves because of 'osmotic' forces.

³⁸³ The pH at which it is 1/2 protonated is nearly 11, far above blood pH of 7.4

³⁸⁴ These graphs, like those earlier, are from normals and stone formers we have studied over the years. All points are 24 hour urines.

You can see phosphate has three negatively charged oxygens (O^-) each of which can bind a proton. One is so strong an acid that it never has a proton in it in any living system. Another is so attractive to protons it will not give it up until pH 11, meaning a very alkaline environment not present in living tissues. The middle one is the swing proton, about 1/2 protonated at pH 6.8: $HPO_4^{2-} + H^+ \rightleftharpoons H_2PO_4^-$. In HPO_4^{2-} the strong site is one negative charge, the swing site is 1/2 occupied.



At blood pH and in the filtrate from blood, of 7.4, 75% of phosphate is HPO_4^{2-} so the average charge is about 1.8. Kidneys can titrate this to as high as 90% or more of $H_2PO_4^-$.

This so-called titratable acidity (TA) only begins to form in the later nephron when all of the bicarbonate has been reabsorbed because bicarbonate will take up almost all protons leaving little or none for titrating phosphate³⁸⁵. This is because as soon as it forms carbonic acid the acid decomposes to CO_2 .

Among the same stone formers for which I showed urine ammonia, TA is clearly much smaller in amount averaging about 15 mEq vs 30 or so mEq/d for ammonia. Men produce more TA than women.

Kidney Acid Excretion

Given all this, kidney acid excretion is the sum of $NH_4^+ + TA - HCO_3^-$, this last means bicarbonate that was filtered and escaped full reabsorption. Kidney stone 24 hour urine measurements include the first two measurements. The last measurement is not practical because urine will lose CO_2 over time and thus lose bicarbonate³⁸⁶.

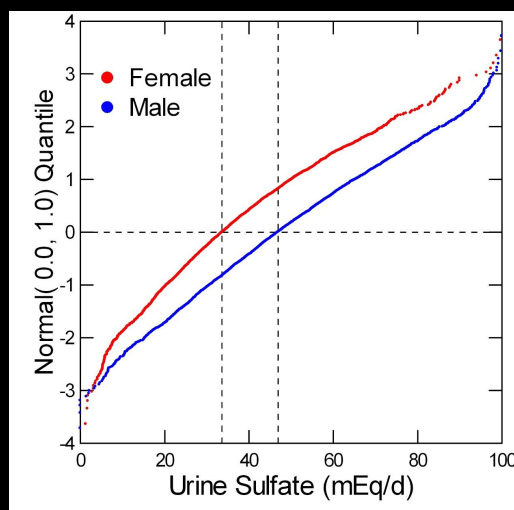
Almost no other branch of medicine, including general nephrology that cares for people with kidney disease, make use of these measurements, a fact I find astounding as all routine hospital and commercial labs can measure ammonia, and TA is easily calculated³⁸⁷. Readily available, yet invisible to physicians, acid excretion is a crucial kidney function that deteriorates with kidney disease.

³⁸⁵ *Kidneys titrate not only phosphate but also creatinine, urate, and citrate. I have estimated that 80% or more of TA is phosphate being so plentiful as it is.*

³⁸⁶ *I do not present kidney acid excretion at this point as I want first to show diet acid and alkali loads. So please wait a bit until the grand finale.*

³⁸⁷ *From urine pH, and the pKa of 6.8 for phosphate assuming a blood pH of 7.4. Most labs do not even calculate it! One cannot titrate urine back to blood pH because CaP crystals will form removing buffers as you measure.*

DIET ACID AND ALKALI



Diet Acid Load

Diet acid is mainly from cystine and methionine, two amino acids in the protein we eat. Both contain sulfur that is oxidized to sulfuric acid whose residue, sulfate, is excreted in the urine. Its protons are buffered by ECF bicarbonate which decomposes to CO_2 .

Therefore, diet acid load can be expressed as simply urine sulfate³⁸⁸.

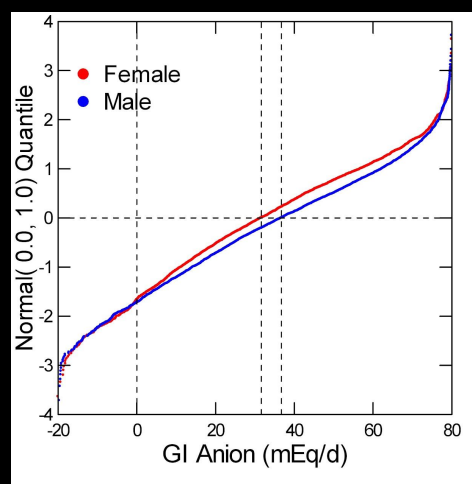
Female stone formers produce less sulfate a day than men. About 35 - 45 mEq/d are reasonable average values for each sex (vertical dotted lines are at the means).

As the footnote comments, sulfate has the potential artifact that food additives include sulfate anion, not acid, thereby inflating urine sulfate and estimates of acid production. The liver incorporates nitrogen from amino acids into urea, a harmless product kidneys readily remove. Urine urea is a proxy for amino acid nitrogen not scavenged into new protein production or into other nitrogen containing materials like purines. Therefore one might use it as a gauge of protein intake and consequent acid load³⁸⁹.

Diet Alkali Load

Diet alkali is mainly nutrients that can be metabolized by the body cells only in their acid form, meaning they have to take up a hydrogen ion from blood bicarbonate buffers. As this happens, more **bicarbonate is produced** from CO_2 . Molecules missing their proton are negatively charged and must be associated with their positive counter ion, which in food is almost always sodium, potassium, calcium, or magnesium³⁹⁰.

Other nutrients may have to donate a proton in order to be metabolized. They will be positively charged and



³⁸⁸ *I am aware that sulfate as the sole diet acid is controversial, that some schools favor PRAL (potential renal acid load) estimated from food diaries. Likewise, food additives may include sulfate anion which inflates acid production.*

³⁸⁹ *My informal regression analyses show that urine urea nitrogen indeed correlates better with acid excretion than does sulfate. But of course only that fraction of protein composed of cystine and methionine can produce acid via oxidation of sulfate so units are very odd. So odd I cannot imagine using urea nitrogen as a proxy for acid load, and do not so do.*

³⁹⁰ *Food alkali is called GI anion because it arrives with food from the GI tract.*

require a negatively charged counter ion of which chloride and phosphate are the main examples.

Urine GI Anion Measures Net Diet Acid /alkali Load

On an overall basis, urine excretion balances absorbed diet sodium, potassium, calcium, and magnesium, four elements whose systemic stores cannot be permitted to dwindle or accumulate. We have already discussed how balance is achieved for sodium, potassium, calcium, magnesium, and phosphate. Chloride balance parallels that of sodium and potassium³⁹¹.

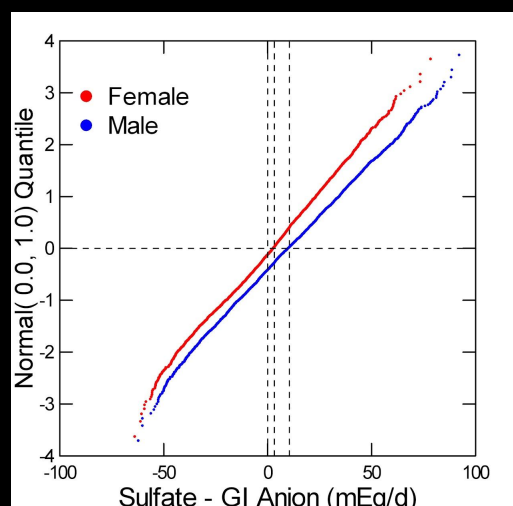
To some extent positively charged atoms (cations) and negatively charged atoms or molecules (anions) accompany each other, as NaCl, for example, or potassium phosphate. But if you take the difference between the positive and negative charges in urine, there will invariably be a gap which is filled by charged nutrients - amino acids, fatty acids, complex carbohydrates for example.

This gap is called the urine GI Anion:

$$\text{GI Anion} = [\text{Na}^+ + \text{K}^+ + 2 \times \text{Mg}^{++} + 2 \times \text{Ca}^{++}] - [\text{Cl}^- + 1.8 \times \text{Phos}]$$

Each must be expressed in mEq - its atomic or molecular weight multiplied by the number of charges. The 1.8 for phosphate is because that is its net charge at the pH of blood (the mean of single + double charged forms).

GI anion (shown in the graph on the preceding page) is about the same for men and women stone formers, and approximates the amount of ammonia excreted - about 30 - 35 mEq/d.



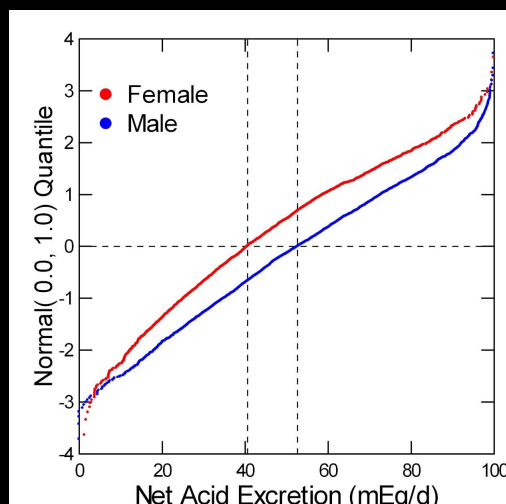
Net Diet Acid Load

If we take the difference between sulfate, from methionine and cystine, and GI anion, we get an approximation of the net acid load imposed on the blood bicarbonate buffers, which the kidneys must remove.

This net is small, 3.1 and 10.4 mEq/d for women and men, respectively (dashed vertical lines just above 0 on the graph). Both distributions of points are, incidentally, straight lines on this normal function graph meaning they follow the normal distribution function - usually this is a natural process like the distribution of

³⁹¹ In this section we will be showing average 24 hour excretions for people not eating specified diets. Whereas urine pH and therefore TA can vary rapidly - hours - with food acid or alkali, ammonia production rises more slowly in response to acid - days. So renal acid excretion can lag diet acid loads - think big steak. Therefore acid base 'balance' is at best approximate for the data we have available.

heights - and suggests that GI anion might be regulated by the intestines. The same for sulfate production³⁹².



Net Acid Excretion

By contrast, net renal acid excretion, the sum of ammonia + TA minus urine bicarbonate is far higher, about 40 mEq/d in women and over 50 mEq/d in men. The huge gap between sulfate - GI anion (the net systemic acid load) and renal acid excretion cannot reflect real physiology because in short order the kidneys would make bicarbonate in great excess of loss from diet acid, and acid base balance could only be achieved by constant urine bicarbonate losses. This latter is not the case, urine bicarbonate losses are

generally not above 10 mEq/d³⁹³.

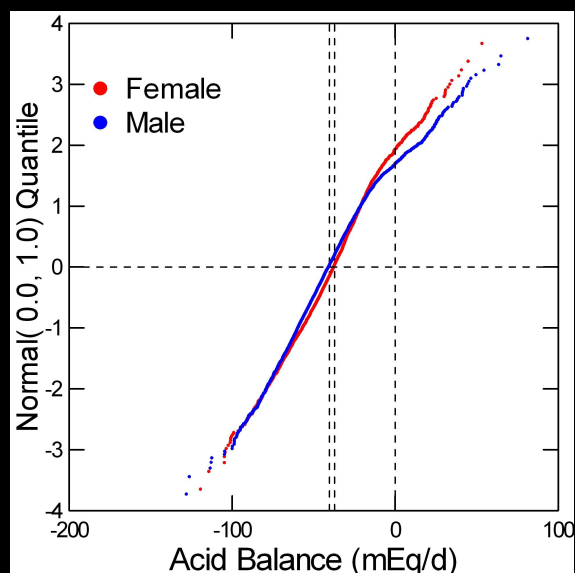
Net Acid Base Balance

To make this point clearer, here is the net acid balance:

Urine $[\text{SO}_4 + \text{HCO}_3] - [\text{GI Anion} + \text{NH}_4 + \text{TA}]$

Sulfate represents acid load from cystine + methionine, urine bicarbonate represents urine alkali loss, which is the same as acid gain into the bicarbonate buffers of the blood. GI anion represents alkali from food, and ammonia and TA production of new bicarbonate from proton buffering on those two substrates.

Just as is obvious from comparing the prior two graphs, that for sulfate - GI Anion and renal acid excretion - acid balance is way below 0, on the order of 40 mEq new base added/day in both sexes³⁹⁴.



³⁹² You might wonder if this complex set of inferences is too rickety to house such an important personage as diet acid load. The GI anion from charge difference, inspected closely is sturdier than one might expect, and sulfate is directly measured though contaminated by sporadic food additives.

³⁹³ Net acid excretion is faultless, as measured directly and related to renal function through sturdy linkages.

³⁹⁴ Once again I am startled as I write this that almost no kidney disease physicians nor bone physicians use these measurements despite that any routine 24 hour kidney stone urine has all of them in clinical form from national vendors. Accordingly they do not use the measurements in guiding their practices.

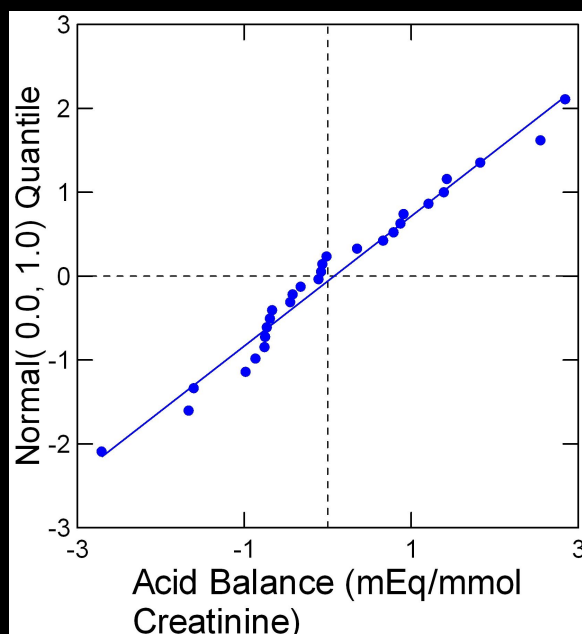
This is not 'balance', so we have left something out³⁹⁵.

That something is that cells produce acid that contemporary clinical measurements, even those as sophisticated as the 24 hour urine stone panel, do not measure.

CELL METABOLIC ACID LOAD

Urine Negatively Charged Molecules Not from Diet

Animal metabolism produces an acid load of metabolites formed and released from cells with a proton that ECF bicarbonate must buffer. Unlike GI Anion, and urine ammonia, TA, and bicarbonate, metabolic acid is not measured except in research laboratories.



These acids are in general too strong for the kidneys to titrate - the urine pH cannot go much below 4.5 and most of these molecules require a lower pH to take up protons. So they are in the urine, possess a negative charge and are part of the GI anion calculation although they do not represent food anion³⁹⁶.

Urine Titratable Anions Account for the Missing Acid

This graph comes from [a paper we published in the past few years](#) that presents all of acid base balance including urine metabolic anions. The mean is very close to 0 (0.078 mEq/d/gm urine creatinine). It is net acid balance as just presented but titrated urine anions (OA_u) are

added to the left side of the equation³⁹⁷:

$$\text{Urine } [SO_4 + HCO_3 + OA_u] - [GI \text{ Anion} + NH_4 + TA]^{398}$$

³⁹⁵ I find this remarkable gap arising as it does from rather well established measurements, astounding. Not so much for its size as for a near absence of comment in routine teachings for physicians.

³⁹⁶ The quick witted among you have already recognized the problem: an anion is an anion, how do we know if it came in as a nutrient (takes up proton) or from cells as acid (donates a proton). We cannot know except through regression analysis - see below.

³⁹⁷ Multivariate analysis of acid excretion vs. titrated anion vs. sulfate can estimate the 'acid' portion of the titrated anions.

³⁹⁸ Urine titrated anions are a mix - some food anions that escaped metabolism, some came into blood from cells as acid. Both are part of the GI anion calculation, being anions. That things sum to 0 is predictable, as all the measurements are in one aliquot of urine and charge balance is required by conservation.

We Are Very Far From Our Goal

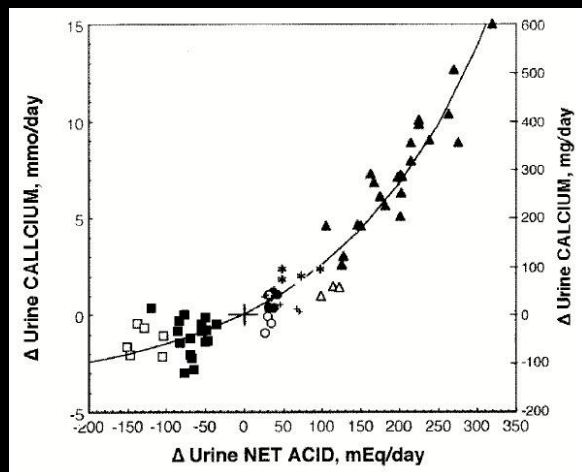
All this is nice, and about the best we have, but not at all finished. Titration of urine organic anions is presently a research endeavor, not clinically applicable. GI Anion is a powerful tool but substantiated only decades ago in a few studies. Overall acid balance has not been studied using titration of urine organic anions with a constant and controlled diet³⁹⁹.

But at least we have a workable framework, and for kidney stone disease this is crucial as stone disease is very sensitive to acid base physiology. But even here we have no published systematic study of organic acid production⁴⁰⁰.

DIET PROTEIN, ACID LOAD, AND KIDNEY STONES

Diet Protein is an Acid Load

There can be no doubt that increasing diet protein raises urine acid and calcium excretion, but how it does the latter is controversial.



As I already noted, on the one hand, proteins are made of amino acids, and two such, cystine and methionine, produce an acid load. They contain sulfur that the cells oxidize to sulfuric acid, leaving sulfate in the urine as a residue. Protein acid load therefore depends on the amount of these two amino acids in the total protein mix, and urine sulfate gauges acid load.

This seemingly arcane matter is important because acid loads from any cause reduce renal calcium reabsorption. Unless balanced by

increased diet calcium, the increased urine calcium can reduce bone mineral stores. Since protein imposes an acid load, many have believed that diet protein causes bone mineral loss.

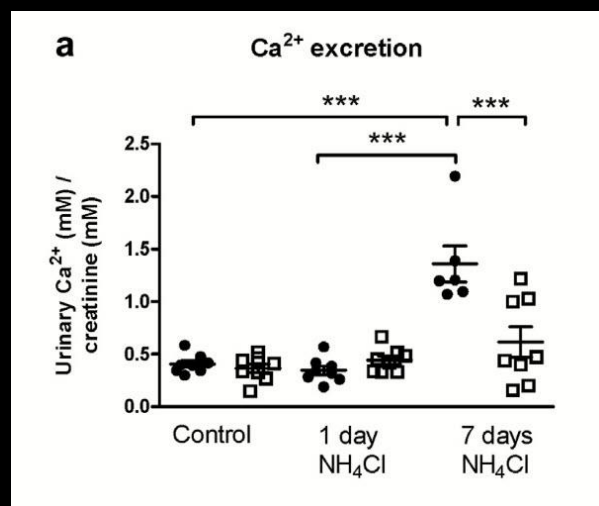
Acid Loads Raise Urine Calcium

Under a wide range of acid base balance induced by diet and loading with either acid or alkali, urine calcium varies directly with renal acid excretion. The changes in calcium excretion arise

³⁹⁹ A long ago study using a diet free of organic anion proved that titratable anion was acting as an acid.

⁴⁰⁰ You can infer from the writing that untracked wilderness borders our patio on three sides, so while we chat amiably about what is there, we are seated in safety, not making new trails.

from changes in tubule calcium reabsorption - reduced reabsorption increases calcium loss. This is a reason why potassium citrate can lower urine calcium - by imposing an alkali load.



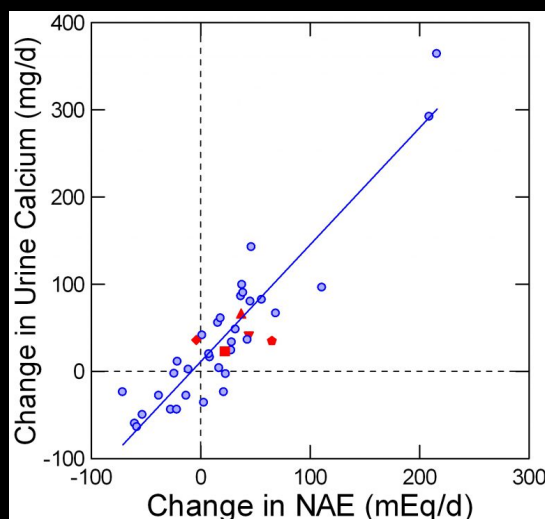
How Acid Loads May Raise Urine Calcium

Linkages between acid base balance and renal calcium reabsorption have been difficult to determine. A recent paper suggests that OGR1, a proton sensing G coupled protein, may be a crucial signaller. When challenged with an acid load, the KO mice (open squares) did not increase urine calcium, whereas control animals (Closed circles) did. The site along the nephron where signaling links to transporters is unclear but the authors favor TRPV5 in the DCT.

In the KO animals, bone osteoclast signaling also failed to rise normally with acid load, and acid load is said to increase bone mineral loss via increased osteoclast function⁴⁰¹.

Protein Acid Load Correlates with Urine Calcium

In meticulous balance studies (each dot is a balance study), this correlation is blatant and obvious - pale blue dots on the figure. As NAE, net acid excretion, rises, so does urine calcium. The graph is from the linked article⁴⁰².



Protein not Acid Raises Urine Calcium

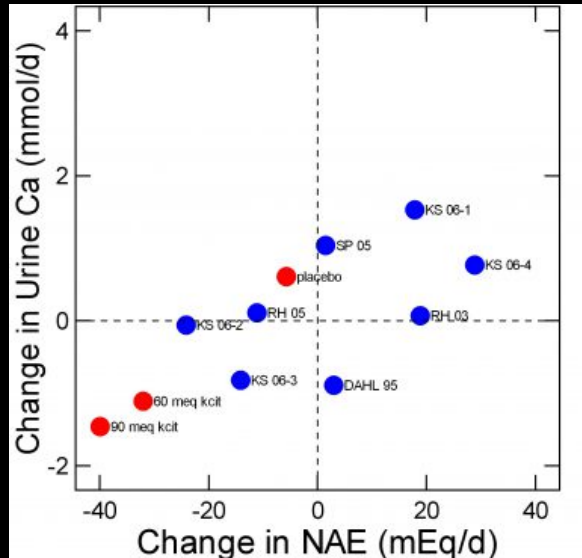
But, in an ingenious experiment, alkali was given in an amount that neutralized the acid (red diamond and square on the graph) and urine calcium remained about the same. This suggests

⁴⁰¹ *This is a very recent paper, and the role of OGR1 is a new addition. I put it here because I like the work and believe it.*

⁴⁰² *As protein intake varies, urine acid excretion varies directly, this during balance studies with fixed diets*

that protein itself, not its acid component, raises urine calcium. Put another way, it is something about protein but not its obvious ability to create an acid load^{403,404}.

Role of Protein in Bone Loss is Controversial



The Urine Calcium Part of Balance

If one plots individual balance studies - each with many subjects - change in renal acid excretion, a reflection of acid load, correlates with increasing urine calcium. The blue dots are the acid load from protein. If one fixes the diet and progressively lowers acid load using potassium citrate (red dots) urine calcium falls. The blue dot labels identify specific studies detailed in the original site article.

Of importance, the 60 mEq/d potassium citrate load (the highest dose common in stone prevention) clearly lowered urine calcium below the placebo. The 90 mEq/d was even more dramatic but is higher than we generally use in

stone prevention.

Of course, this graph is apples and oranges, protein providing acid vs. alkali neutralizing acid loads from a fixed diet. It makes the point that both affect urine calcium. But the prior graph showing the red diamond - protein load with alkali to neutralize the acid - is best: protein can raise urine calcium sans acid. On the other hand, the red dots on this graph make the point that a lot of alkali can lower urine calcium⁴⁰⁵.

Balance Itself

The blue dots on the next figure - below - show bone mineral balance for a range of diet protein loads expressed in terms of their acid load to the body. There is no obvious regression of blue dots such that more or less protein loading alters bone mineral balance.

On the other hand, at a fixed diet protein intake, progressive potassium citrate loading increased bone mineral balance. A lot of the power in the red dot regression is from the highest point, at

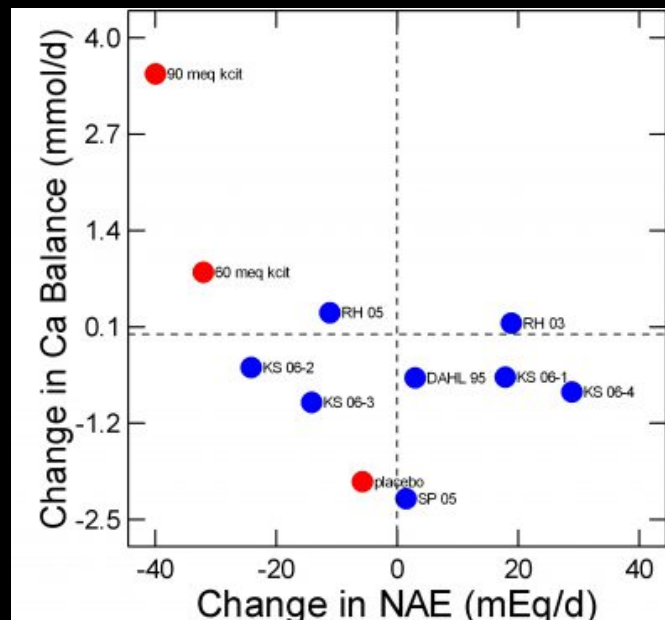
⁴⁰³ *This can be confusing. Renal acid excretion reports acid balance signaling to that organ, and we have no reason to doubt that in healthy people acid excretion more or less balances acid load. In these balance experiments with fixed diets, acid excretion is - more or less - acid load.*

⁴⁰⁴ *Some amino acids signal through the CaSR and could therefore reduce TAL calcium reabsorption and cause the protein effect on urine calcium (the food effect). Urine Mg measurements could clarify that point.*

⁴⁰⁵ *Obviously, I view the protein + alkali as showing the food effect is independent of acid. I have to assume alkali increase calcium reabsorption thereby lowering urine calcium. In other words they act at different sites in the kidney.*

90 mEq/d of potassium citrate. At the point at 60 mEq/d, the top of what we use in stone

prevention, the change in bone balance would not have differed remarkably from the mass of blue points.



Why Protein Does Not Reduce Bone Balance

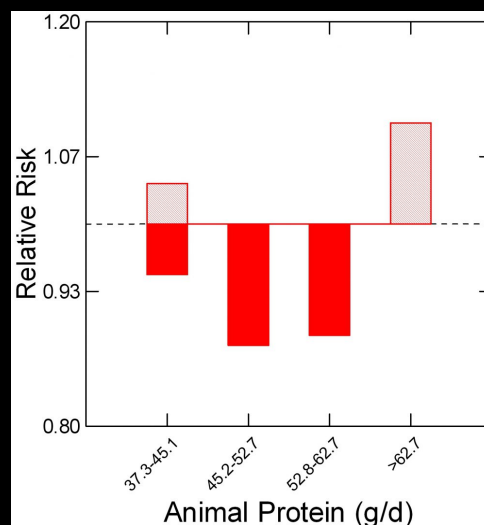
Since protein clearly raises urine calcium by reducing renal calcium reabsorption, how can it not reduce bone mineral balance? The only feasible way is if protein increases calcium absorption and that is the case. Sage bone physicians tell me protein is good for bones, up to a point. We leave this here, as it is no longer relevant to my main purposes⁴⁰⁶.

What Have I Been Saying?

Acid loads raise urine calcium loss and can deplete bone mineral. Acid loads from protein do not appear to deplete bone mineral in so obvious a way as acid loads not from protein but from methionine, or ammonium chloride. Protein itself can increase urine calcium excretion even if its acid load is neutralized - food effect. Alkali loads, from potassium citrate as an example, lower urine calcium and increase bone mineral balance (raise calcium reabsorption). So, one might say, lots of fruits and veggies will be good for bones, and plenty of protein will not uniquely imperil bone mineral⁴⁰⁷.

DIET PROTEIN DOES NOT RAISE STONE RISK

Urine calcium powerfully predicts stone risk, and protein or other acid load raises urine calcium, ergo protein load should predict stone risk. But using the same three cohorts that established the risk relationship between stone onset and urine



⁴⁰⁶ *Kidney stone prevention via diet is my main purpose. Surely 90 mEq/d of medicinal potassium citrate improves bone balance but I want to emphasize that a diet rich in fruits and veggies can give that much or more potassium alkali - and considerable pleasure, too.*

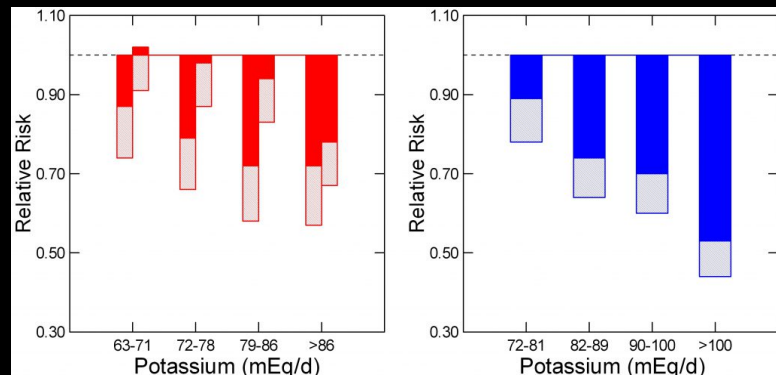
⁴⁰⁷ *All this complexity to conclude that whole foods in a relatively well balanced array seem good for us.*

calcium, the Curhan group found risk of stone does not vary with animal protein intake. That's that. Unlike prior studies, there was no need to separate the sexes which are combined here.

At the upper extreme, above 62.7 g, protein/d, around 0.9 - 1.1 gm/kg/d, there is a hint of increased risk (the bar does not cross 0) but we find no dose response as was obvious for calcium, urine volume, urine citrate, and supersaturations⁴⁰⁸.

DIET POTASSIUM

Potassium from plant or animal tissue that was once alive (food) will always be accompanied by a negatively charged partner, usually a metabolizable anion, or phosphate⁴⁰⁹. So urine potassium strongly correlates with GI anion - and gauges alkali in our diet. Diet potassium absorbed into the blood by the GI tract must all be excreted in the urine to maintain balance⁴¹⁰.



Correlates with Reduced Stone Risk

Urine potassium correlated strongly with protection against new stones in the two female (red) and male (blue) cohorts. The tops of the light portions of the bars do not - except in one instance - cross 0. And, there is a strong dose response curve. Potassium in food arises most from fruits and veggies, although present in meat and even dairy products.

Mechanisms of Stone Protection by Diet Potassium

Citrate

Urine citrate (upper right panel on the graph below) rose with urine potassium (upper left hand panel). This is because potassium in fruits and veggies comes as a salt with citrate and with similar food nutrients that are metabolized to alkali by the body cells as they use them to

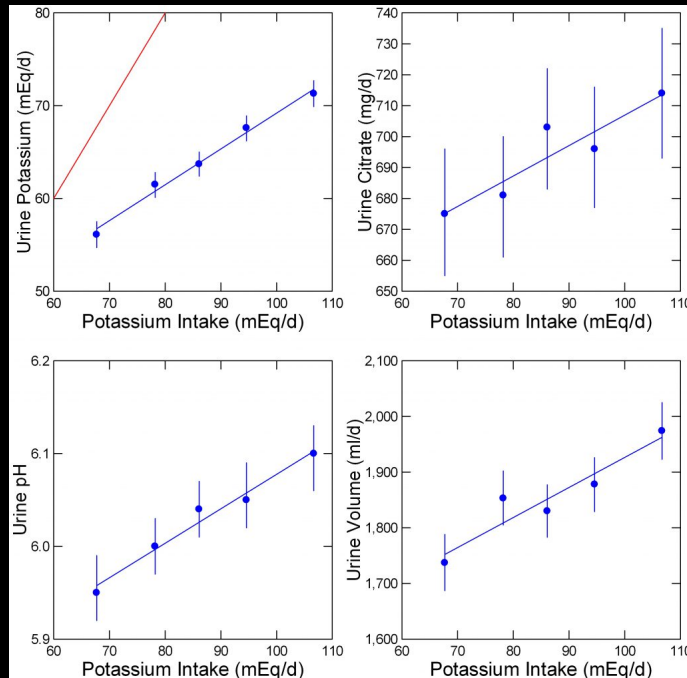
⁴⁰⁸ *I certainly inveigh against excessive protein intake above 1.1 gm/kg in patients with increased urine calcium. It is unnecessary, and perhaps does increase stone risk not detectable in these cohorts.*

⁴⁰⁹ *This is because most potassium is in cells and not accompanied by chloride - as in blood - but by metabolic anions or phosphate.*

⁴¹⁰ *This monograph does not explore potassium or magnesium balance. Unlike sodium and calcium, both are mainly within cells, and I suspect that transient positive and negative balances are tolerated so long as cell stores remain adequate. But over a day or two potassium balance must be maintained or blood potassium can rise and become a lethal problem.*

produce energy⁴¹¹. Citrate lowers stone risk by binding urine calcium, and inhibiting crystal growth.

Proof of the alkali potassium link is in the lower left panel. As urine potassium rises, urine pH rises in parallel.



Citrate and Potassium Redux

Clinicians all have observed that potassium depletion from thiazide or GI losses lowers urine citrate⁴¹². The mechanism seems related to depletion of renal cell potassium which may reduce pH inside the cell and lead to increased citrate reabsorption⁴¹³.

Volume

Urine volume rises with urine citrate because fruits and veggies have a high water content. So as their intake rises, urine volume will rise to remove the surplus water. That is an obvious

protection against stones⁴¹⁴.

Diet vs. Urine Potassium

The upper left panel is a useful note about diet questionnaires. Estimated diet potassium citrate from the patient reporting is very strongly correlated with urine potassium as directly measured, making one believe that patient reporting can be very reliable. The downward offset from the line of identity sloping (red line at top of panel) and reduced slope may reflect less than complete absorption of diet potassium.

⁴¹¹ *I said this already and repeat it because I want to repeat it to make sure everyone understands this point.*

⁴¹² *Of course these are not the same, GI losses usually include loss of alkali imposing an acid load on blood buffers.*

⁴¹³ *This is to say that potassium itself may increase urine citrate in people whose diets have led to - minor - potassium deficits. This is an unproven idea worth testing. Potassium loads did not increase urine citrate in healthy young men, but that may not be an ideal experiment.*

⁴¹⁴ *Whereas one doubts high fluids will prevail against the inherent water conserving mechanisms for water balance, diet habits towards high water content foods may help because more reliable. This is mere conjecture.*

WHAT IS IT I HAVE SAID?

High diet potassium from fruits and veggies raises protection against calcium stones. Urine citrate will rise, and urine volume as well. Urine calcium will fall. If combined with low diet sodium to lower urine calcium further, and with deliberate care to maintain a urine volume around 2 liters/d we have a rational basis for diet stone prevention. High diet calcium lowers oxalate absorption and protects bone, completing what we have called the kidney stone diet.

One might say I have more or less accomplished my main objective, and need only consider the other major consequence of abnormal acid base metabolism, which is uric acid stones.

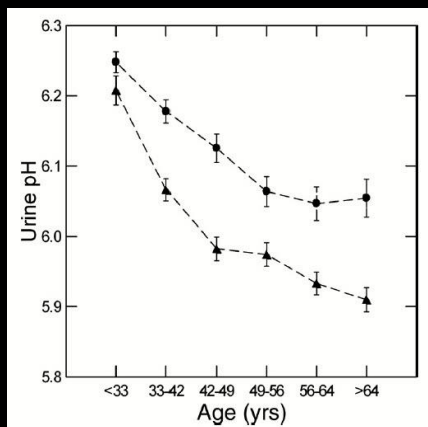
URIC ACID STONES⁴¹⁵

As I showed earlier, uric acid stones form when urine pH is below the normal average of 6. What exactly makes urine pH so low constitutes the sole mystery of such stones⁴¹⁶.

Age

Uric acid stones occur in later life. Women, lower panel of the graph just above, form more CaP stones than men (upper panel, open squares), but with age both sexes begin to increase uric acid stones (open diamonds).

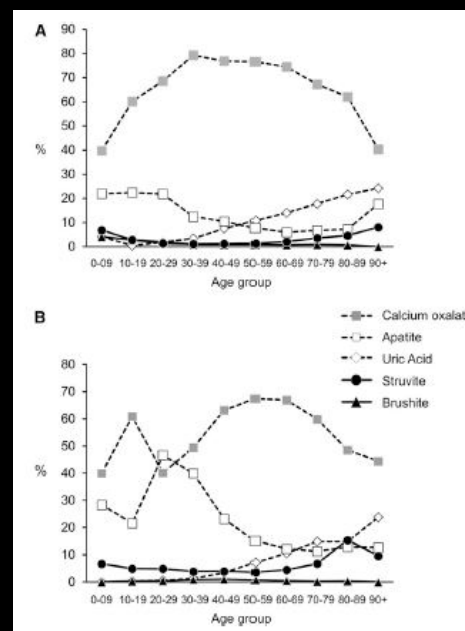
Urine pH falls with age, especially in men (triangles, right hand graph), and men form more uric acid stones than do women. Although the average pH in men over age 64 is only 5.9, whereas uric acid crystallization



occurs at pH below 5.5, within that mean of 5.9 the downward spread is more likely to reach 5.5 than at the higher means in younger men, and in women.

Overweight and Obesity

Using data from our own records and those from the stone center at UTSW Medical School, Dallas, we found that urine pH falls with increasing body weight adjusted for urine



⁴¹⁵ *This is an abrupt transition from calcium stones with all their complexity to stones dominated by urine pH. I do not apologize for the abruptness, as it corresponds to the truly different nature of uric acid stones and their ease of prevention.*

⁴¹⁶ *This is a very bold statement and I take pride in its simplicity.*

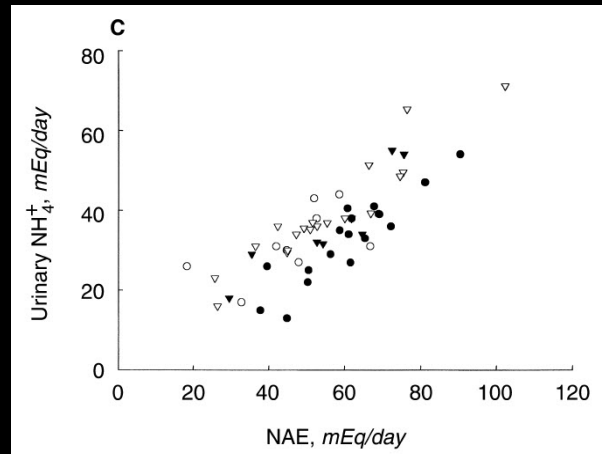
creatinine, in other words body weight /muscle mass ratio - a kind of BMI.

Once again, the mean lowest urine pH is 5.85, far above pH 5.5, and the same argument holds as for age. In our age study, we adjusted for BMI, so the fall in pH we found was in addition to that from BMI.

Low Urine Ammonia

Why kidneys lower urine pH down so low as 5.5 is partly **low urine ammonia production**. We can understand that reduced ammonia production will force the kidneys to lower urine pH and increase titratable acid excretion, the signal presumably being a slight reduction in blood pH or bicarbonate levels⁴¹⁷.

In this figure from work by the Dallas group ([also in the main article](#)), urine ammonia is plotted vs. total renal acid excretion: ammonia + TA - bicarbonate. It is the graphical representation of what I just wrote - ammonia is a smaller fraction of acid excretion in the uric acid stone formers (filled black symbols) than normals and calcium stone formers.

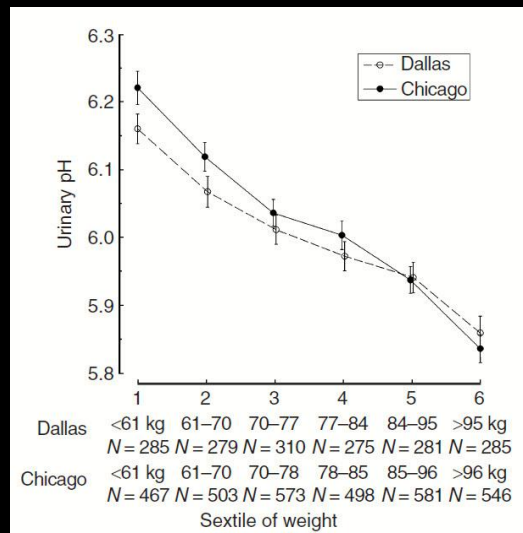


In the main article I show their data that acid loading could not raise urine ammonia as it did in normal people - further evidence for something wrong⁴¹⁸.

Insulin Resistance and Diabetes

Uric acid stones are associated with the so-called 'metabolic syndrome' of high blood pressure, abnormal lipid metabolism, and insulin resistance. What better than to ask if uric acid stone formers were indeed insulin

resistant. Compared to lean young normal people, uric acid stone formers were indeed less responsive to insulin infusion, but not compared to comparably obese and older people who, while not slim and athletic, did not form uric acid stones nor produce an abnormally acid urine⁴¹⁹.



⁴¹⁷ If we stop and contemplate this, it is a natural proof that kidneys seek a specific blood pH - too little ammonia, they lower pH in order to raise TA and maintain acid excretion

⁴¹⁸ From my multiple referencing of it I want people to look at the main article which is more detailed

⁴¹⁹ In other words, uric acid stone formers and ordinary overweight middle aged people have similar insulin sensitivity but the uric acid stone formers produce a much more acid urine.

Finally, diabetic people with low urine pH around 5.5 but no uric acid stones raised their urine ammonia normally when given an acid load. This means that perhaps urine pH is lower in diabetes because of insulin resistance but it is not from abnormally low ammonia production⁴²⁰.

Clinical Uric Acid Stones

I wrote a separate clinical article because the reality of uric acid stones for patients and physicians is a lot messier and varied than what I have written thus far. Many forms of bowel disease lower urine pH because of GI alkali loss. Gout somehow associates with low urine pH and uric acid stones.

And people may form both uric acid and calcium stones. For those, clinically, one always wants to assure that urine pH will not fall below 5.5 in the future.

The clinical article on the site is so similar to what I would write here, instead of repeating myself I suggest you follow the link and read there. It is excellent⁴²¹.

RENAL TUBULAR ACIDOSIS

As if a bookend to uric acid stones, this disease causes an irreparably high urine pH and consequent calcium phosphate stones. RTA arises from a mixture of gene defects involving the cells that acidify urine and create titratable acidity - the intercalated cells of the collecting ducts. It can also occur when diseases damage those same cells. Finally, it can occur if proximal tubule bicarbonate reabsorption is reduced by drugs or disease.

Like uric acid stones, I have written a long article about RTA on my site and could not do better here because the levels of detail on the site and in this book are similar⁴²².

PHYSIOLOGY OF THE MAIN TREATMENTS FOR CALCIUM STONES

We now have a shared vocabulary to discuss kidney stone treatments in physiological terms, and explore the potential for problems and successes depending on how we use them. I will assume a common knowledge at this stage and simply draw upon that shared knowledge minimizing explanations. Nothing here goes beyond what we have already explored.

⁴²⁰ *Diabetes somehow lowers urine pH despite a normal renal ability to produce ammonia*

⁴²¹ *Yet it, like this account, leads to one big thing: Potassium citrate prevents uric acid stones if you raise urine pH above 6. "That is all you know on Earth and all you need to know".*

⁴²² *In fact, this book could well use a review of the physiology that regulates urine pH and is disrupted in dRTA, but as in other vital yet peripheral instances I prefer to add in a subsequent edition. This first version is a 'try out'.*

What comes concerns calcium stone formers. Uric acid and cystine stones have their own special needs and have been well covered as separate issues on the site. Likewise for bowel diseases, primary hyperparathyroidism and any other systemic diseases⁴²³.

FLUIDS

To say 'raise urine volume' means to suppress AVP by drinking water in the absence of thirst. It is the wilful disruption of a system that normally guides itself. With every lapse of conscious effort the system will revert to its own guidance. Kidneys will remove excess water, whereupon AVP will rise to its normal ambient level and urine volume flow rate as well. The result will be peaks and valleys of urine flow⁴²⁴.

Among the worst is food without enough fluids, as urine calcium and pH both will rise without increase in urine volume. The higher the salt content of a meal, the higher the risk from a lapse of conscious drinking. It is not that sodium will increase urine calcium. That is a sluggish process over days. It is, rather, that salt will stimulate AVP. Of course it will also stimulate thirst, but people can decide how much to drink.

Overnight is even worse because we are asleep. If we drink at bedtime, we will be awakened. Those with high fasting urine calcium will have high overnight urine calcium and the highest recorded CaP SS. No trials guide us here. I have nothing but a maxim: If all we can do has not stopped stones, consider how beautiful is moonlight⁴²⁵.

A theoretical offset is that high fluids may reduce renal medullary concentrations of NaCl and urea that are essential for achieving highest urine concentration. This would reduce the risks from intermittent lapses of fluid intake⁴²⁶.

These are reasons why I disdain high fluids as a *sole* defense against stones. However perfect in theory, it pits mere will against the might of AVP regulation, fluids beyond desire against an indifferent, ancient, powerful life sustaining biology⁴²⁷.

REDUCED DIET SODIUM

Because urine sodium is a sluggish function of circulatory fullness, one bad day of meals is easily made up for. Contrast that with the constant threat posed by even a few hours when fluids

⁴²³ *All systemic diseases that cause stones require their own treatments, and uric acid stones stand out as having the one treatment. It is the 'idiopathic' calcium stones that numerically predominate and require multiple considerations.*

⁴²⁴ *The will is no match for the brain which does not distract itself from its programmed tasks - like blood sodium regulation.*

⁴²⁵ *I mean all we can do in addition to asking for higher fluid intake has failed, then one drinks by the light of the moon.*

⁴²⁶ *Proof of this idea in human stone formers is wanting. Someone should do the obvious experiment.*

⁴²⁷ *I will not be misquoted - "Fred snubs fluids for stone prevention" and the like. It is that I disdain it as a sole means for many reasons. Not the least is that other diet changes foster stone prevention and better general health and reduce dependence on voluntary high fluids.*

are the main treatment. The problem is that stone formers cannot know their urine sodium, nor their circulatory fullness.

What do we have from all our knowledge of physiology to help us here?

Simple.

Get diet sodium under seeming control, and prove it by 24 hour urine testing. Thereafter, make daily weight measurements with a decent bathroom scale, and pay attention. If diet sodium has risen and is enlarging the circulation, weight will follow - 1 kg/liter, or 2.2 pounds. Of course people add fat and lose it, but we all know that and can tell the one from the other. Lots of people weigh themselves every morning, and fine scales are now of modest cost⁴²⁸. If stone disease is enough to warrant it, one can recalibrate every 3 months, or 4, or 6, or 12, depending - a matter of choice, prudence, and convenience.

Unlike urine volume where epidemiology links specific volume levels to stone risk, nothing links diet (urine) sodium to stones. However we have US guidelines recommending below 100 mEq/d as an optimal diet intake and I have no compunction about recommending patients use it⁴²⁹. If you read the primary analyses of the subject by the National Academies, 'ideal' intake is 1500 mg or 65 mEq/d⁴³⁰. This is not a 'low sodium diet'. It is an ideal diet, simply 'low' compared to our present massive sodium excesses.

Perhaps more practically stated, the goal is to lower urine calcium, which we measure along with sodium. At 100, or the more ideal 65 mEq/d of urine sodium, urine calcium is what it will be given acid base balance, and diet calcium. At that point clinicians can make reasonable decisions about the next step.

HIGH CALCIUM DIET

With a foundation of high fluids and low sodium intake one can safely use 1,000 to 1,200 mg diet calcium in a calcium stone former. The purposes are to protect bone⁴³¹ and to lower urine oxalate⁴³². In the one trial (referenced in the footnote) high diet calcium lowered urine oxalate and low diet sodium prevented the high calcium intake from raising urine calcium. As a result, urine oxalate fell, urine calcium was steady, and SS CaOx fell as did new stone onset.

REDUCED DIET OXALATE

How can I but recommend this for all CaOx stone formers? It is not featured in this physiology narrative⁴³³ but is on the site. Not all patients need make much effort. High calcium diet often is

⁴²⁸ *This is a cheap and clever idea I find useful in practice.*

⁴²⁹ *This is a political compromise as 'less' or 'below' fails to tell the whole story.*

⁴³⁰ *The academies are not subject to compromise imposed by such political realities as food producers*

⁴³¹ *The best evidence is in this site article, the physiology has been discussed in this book.*

⁴³² *This overview article and this book shows that diet calcium lowers urine oxalate and how the low sodium high calcium diet can prevent stones.*

⁴³³ *I have given it its due respect. The site details oxalate management in multiple articles, and this is part of the site, not free standing.*

sufficient to lower urine oxalate. But no one treats CaOx stone formers without attention to diet oxalate and I do not want the massive emphasis here on physiology to somehow overshadow that clinical truth⁴³⁴.

Yet, I aver that high diet calcium is the first rational step as it lowers oxalate absorption and is a value unto itself. It is from there that I favor further efforts are diet oxalate reduction.

THIAZIDE

From all we have learned together, this drug should be added to low diet sodium⁴³⁵. It lowers urine calcium below what reduced sodium can accomplish and is most efficient when diet sodium is low. Not rarely, diet will have lowered urine calcium enough that thiazide is not needed.⁴³⁶ Low sodium diet also reduces potassium losses from thiazide⁴³⁷. Treatment of high blood pressure is best done with diet change and then drugs like thiazide, for analogous reasons. Quite often, the dose of thiazide needed to lower urine calcium will be lower when diet sodium is reduced⁴³⁸.

HYPONATREMIA - Low Serum Sodium

Powerful systems regulate serum sodium, and healthy people should tolerate high water intake to levels of even 3 liters/d and reduced diet sodium to levels of 65 mEq/d without difficulty. This recent review analyses available studies and points out that seriously low blood sodium concentration is not common. Even so, occasional people misunderstand the volumes of water needed and rarely this can be serious especially if anything interferes with AVP lowering. For example, many drugs interfere with AVP regulation⁴³⁹.

The message is simple. Patients have physicians, and physicians who prescribe high fluids and low diet sodium know how to instruct their patients and know which drugs their patients take. They know that exercise can deplete sodium stores, and that thiazide is designed to do this. There is no substitute for vigilant and informed physicians. As an extra precaution any patient should present all their drugs to their physicians and use the fluid intakes and sodium intakes their physicians recommend. One might add that measurement of serum sodium after some weeks of treatment cannot be a bad idea⁴⁴⁰.

⁴³⁴ *If I sound defensive, albeit. Oxalate arises from a complex biochemistry and arrives in urine via complex transporters but because they are a bit to one side of the main issues in this screed I have perhaps seemed to slight it - a misconception of seeming.*

⁴³⁵ *This is a very bold statement, and I stand by it unflinchingly*

⁴³⁶ *By this I mean the 24 hour urine chemistries display low stone risk. The only good diet trial had multiple components of which reduced diet sodium was but one.*

⁴³⁷ *By itself potentially dangerous, and a cause of low urine citrate.*

⁴³⁸ *I offer no proof of this but know from experience it is true. Lacking proof, I can still recommend beginning with the lowest possible dose when urine sodium has been brought down.*

⁴³⁹ *I will not clutter my pages here with material one can find easily on the web*

⁴⁴⁰ *I have encountered hyponatremia and fear it.*

POTASSIUM CITRATE

Being simply a specialized form of alkali, K citrate needs to be looked at not in relation to acid base physiology but in comparison to other forms of alkali. As for alkali themselves, their only purpose in stone prevention is increase of urine citrate and pH. For calcium stones, the topic here, it is simply to increase urine citrate.

What It Does

Because metabolized as an acid 10 mEq (the common size pill) can take up 10 mEq of acid from blood buffers producing 10 mEq of bicarbonate. Kidney PCT cells sense the alkali and reduce the activity of the citrate transporter so less filtered citrate is reabsorbed and can appear in the urine⁴⁴¹. Higher blood bicarbonate concentration from metabolism of citrate will increase filtered load of bicarbonate, and some may appear in the urine raising pH⁴⁴². Higher blood pH reduces kidney acid excretion, also raising urine pH. So the treatment increases urine pH and citrate together, the ratio of pH to citrate being variable among people⁴⁴³.

If citrate rises more than pH then SS CaP will be reduced because citrate binds urine calcium. If the opposite happens, SS CaP will rise. Given the interactions between CaP and CaOx crystals, one might expect this drug to be effective in stone prevention trials but variable depending on the pH / citrate response⁴⁴⁴. Physicians can decide about this for every patient.

Effects on pH and Citrate

Variables	Baseline	NaBic	KCit	P Value
Citrate (mg/24h)	287 (178-410)	495* (356-583)	491* (340-577)	<.001
pH	6.1 (5.7-6.6)	7.4* (7.0-7.7)	7.3* (7.2-7.5)	<.001
Sodium (mEq/24h)	159 (93-214)	215* (172-266)	178 (120-258)	.034
Calcium (mg/24h)	185 (132-246)	188 (129-252)	125* [†] (80-234)	.011

This table is from the site. Here is the original article These 16 calcium stone formers all had low urine citrate. Their average was 287 mg/d (1.49 mmol of citric acid). At the urine pH of 6.1, and given the third dissociation constant is 6.4, it has about 2.3 proton acceptor sites, so it amounts to 3.5 mEq of citrate/d. Each received 60 mEq/day of sodium bicarbonate or K citrate for 3 days in an alternating pattern 'crossover' model, so all 16 contributed to both treatments. The 60 mEq of NaHCO₃ raised urine sodium by 56 mEq/d, as expected.

At pH 7.4 and 7.3, citrate will have a valence of 3, so the mEq of urine citrate were 7.7 for both treatments, an increase of 4.2 or so mEq/d⁴⁴⁵. All received 60 mEq of base so about 56 mEq did

⁴⁴¹ ***This is a description. It is not true that 10 mEq of K citrate will result in 10 mEq of urine citrate. Some citrate may not be metabolized, for example.***

⁴⁴² ***Collecting duct protons used to reclaim bicarbonate reduce titratable acidity sans rise in urine HCO₃***

⁴⁴³ ***I have detailed citrate effects on the site and recommend a look there.***

⁴⁴⁴ ***One would wish to look into the two main citrate trials: Did those with more stones raise pH more than citrate?***

⁴⁴⁵ ***I say 'or so' because I have only the means, and differences between means are rarely equal to means of differences.***

not show up as increased urine citrate. Instead it presumably appeared as urine bicarbonate loss and suppression of renal ammonia and TA production⁴⁴⁶. That urine pH rose to that of blood is consistent with that idea.

So in these patients, exactly those for whom we would use it, citrate and bicarbonate gave identical responses, about 4 mEq of citrate/60 mEq of alkali⁴⁴⁷. This suggests that all of the citrate was metabolized as citric acid, because all of the bicarbonate was active as alkali. It also shows how little we understand control of urine citrate in those with low urine excretion rates.⁴⁴⁸

Practical Meaning

When, then, would one want to give potassium citrate? I say to those calcium stone formers with low urine citrate, below 400 mg/d⁴⁴⁹.

If pH rises and citrate does not, is the agent futile? In the same way that sodium bicarbonate was futile in the article tabulated just above - urine citrate rose far less than pH - CaP SS rises with pH. But urine calcium fell with potassium citrate, as it is known to, and that would reduce the rise in CaP SS. So it all depends on the response in a given patient. We know why sodium bicarbonate did not lower urine calcium, do we not⁴⁵⁰?

Must the Alkali be Potassium Citrate Pills??

Because it is only a form of alkali, alternative sources abound. I recently reviewed multiple OTC alkali remedies that might have advantages of price or taste. Diet alone will do if one eats enough fruits and veggies as I just showed in the work from Curhan's group. But remember that the 'citrate' content of a beverage or food is not a guide to its alkali function. Consider an unripe lemon, pH=3; the juice may be rich in citric acid but little of it is citrate (missing its proton). It already has its protons and is metabolized as is, giving no new bicarbonate to the body⁴⁵¹. Numerous commercial beverages and OTC alkali substitutes can substitute for the pills. Enterprising patients have purchased food grade potassium citrate and with a proper food scale measured out 1 gm (10 mEq) doses, saving the extremely inflated price for the pill form.

Often, one wants to replace potassium losses from thiazide, and for this one can use potassium chloride as a first choice. Because reduced cell potassium can lower urine citrate, just the chloride salt may avail. If with time that is not the case, potassium citrate is reasonable.

⁴⁴⁶ **Acid base balance requires this. The oral citrate must be metabolized or excreted in urine.**

⁴⁴⁷ **Urine levels of other anions may well have risen and these might combine with calcium and help prevent stones. Urine anion response to alkali has not been well studied. A PubMed search 'urine anions AND alkali intake' yielded no useful articles.**

⁴⁴⁸ **I mean by this, kidneys were removing a flood of alkali and citrate reabsorption remained higher than normal.**

⁴⁴⁹ **It is the threshold of increasing risk for new stone onset detailed earlier.**

⁴⁵⁰ **The sodium load would increase urine calcium as the alkali would reduce urine calcium - opposing forces**

⁴⁵¹ **This is why lemon juice, as an example, may not raise urine citrate.**

Potassium Citrate for Uric Acid and Cystine Stones, and Bowel Disease

I must emphasize once again these are special cases already referred to or covered on the site. All of the aforesaid concerned routine calcium stone formers⁴⁵².

THE MAIN DIET POINTS

As for the treatments, we are now in a position to summarize what is and what is not most important, sharing as we do a rich context to support our discussion. I have added site references here for convenience but if you have read this brief volume they would be familiar anyway.

Eat Well to Prevent Stones

With all we have considered together, it must be obvious that everything points to the benefits of a diet different from that in common use. We have called this diet the Kidney Stone Diet, but in fact it is the ideal diet as fashioned by US health authorities.

Certainly, much lower in sodium than usual, about 1500 - 2,000 mg/d. High enough in fruits and veggies to provide over 100 mEq/d of potassium, compared to the present US value around 60 mEq/d. The high potassium / reduced sodium diet is also considered ideal for blood pressure control.

Fruits and veggies will increase fluids reliably. I mean by this they provide fluids as we eat - important because the water balance mechanisms we have tend to conserve water unless presented with an habitual excess.

Extra water is valuable up to a point. In the one trial, 2.5l/d of urine lowered stone rate as a sole treatment. If all other matters are attended to, I have no reason to believe we need even that volume which does, after all, require at least 3 liters of fluids a day. This has never been tried explicitly.

Refined sugar should be as low as one can tolerate as it raises urine calcium and depletes bone of its mineral. It is useless altogether apart from boosting elite athletes to top performance⁴⁵³.

Protein from food seems of modest consequence. If it does indeed generally foster stones, the Curhan group could find little solid evidence of that fact, and I doubt it does. But extremes may matter. Total intakes above 1.2 gm/kg/d may best be modified downward. Protein supplements can raise urine calcium considerably and are best done away with.

⁴⁵² *I mean here that alkali use is mandatory to dissolve the organic acid stones, and dosing is gauged by their saturations.*

⁴⁵³ *Refined sugar is pure evil and better avoided altogether. There is no need for it in human nutrition. For stone formers urgency is perhaps higher as it raises urine calcium and reduces urine volume and mobilizes bone mineral in people already often prone to hypercalciuria.*

Diet calcium needs to be about where US recommendations lie, near 1000 mg/d from food. This will not raise urine calcium if sodium is controlled and ample alkali are present from fruits and veggies. It will reduce urine oxalate from food but for that to happen the calcium must be eaten when oxalate is eaten - with the main meals of the day⁴⁵⁴.

Of course, the highest oxalate foods can be shunned by any stone former, but given all the rest of the above I see no basis for obsession over every mg of diet oxalate. In fact, I am passionately opposed to an undue emphasis on diet oxalate because it leads to unhealthy food habits and distracts from all of the other equally important issues in stone prevention⁴⁵⁵.

Eat Well for Better Health

The coincidence between the kidney stone diet and US diet recommendations shows us that everyone should eat that way. There is no reason not to. One predicts blood pressure will rise less with age, and heart disease incidence will fall. Some evidence supports this notion, but is outside our present discourse.

THE PATIENT AND FOOD EFFECTS

Some people whose urine calcium values are at the higher end of the distribution (above 200 mg/d) form stones. This seems genetically determined. Called hypercalciuric people, they are above well matched normals fasting and overnight (The patient effect). Much of our diet changes aim to lower their urine calcium, which we measure over 24 hours.

But this 24 hour urine combines fasting and overnight excretions (patient effect) with the rise in urine calcium from meals (the food effect). Clinically we cannot measure fasting or overnight and 24 hour urine calcium - cumbersome and costly. So we do not know which part of their increased calcium loss our treatments correct.

The Patient Effect

Because fasting and overnight, this is of highest concern as a stone risk. People mainly drink with meals. Possibly low diet sodium will lessen this effect. Thiazide lowers fasting calcium. Likewise higher diet potassium alkali, or the two will synergize. Either way, some people are predisposed and always were throughout evolution, but how they ate and perhaps how they lived did not lead to stone forming.

⁴⁵⁴ *I say this because the main studies gave calcium and oxalate together.*

⁴⁵⁵ *So much time is wasted over minutiae of diet oxalate! I cannot understand the cause of this behavior. Fluids, sodium, potassium from food, diet calcium, all these have major health implications. Once one identifies and removes the main oxalate food sources, and eats a high calcium diet, can we all agree to reduce our fanatic obsession over tiny differences in food oxalate?*

The Food Effect

It would appear that all people respond to a range of nutrients (sugar, protein, alcohol) with a fall in tubule reabsorption of calcium and magnesium even though no calcium has been ingested. As best we can tell, the food effect is the same for stone formers as with normal seeming people in general.

Though well established in human experiments many decades ago, its importance has not been widely recognized. It is not my place here to comment on calcium free food components as snacks and their potential for bone mineral loss, except in passing⁴⁵⁶.

Our Drugs Do What Diet Can (almost) Do

Thiazide creates the functional equivalent of a low sodium diet. It is true that by acting on the DCT NaCl cotransporter it specifically increases calcium reabsorption, and lowers urine calcium below what a given 24 hour urine sodium level accomplishes. It lowers fasting urine calcium - the patient effect. But it is also true that an even lower diet sodium intake would do the same without need for a drug. Thiazide increases bone mineral balance, but so does low diet sodium combined with high diet calcium.

Potassium Citrate is nothing more than a substitute for sufficient fruits and veggies. A standard dose is 40 - 60 mEq of potassium as the citrate salt which is added to our usual 40 - 60 mEq of diet potassium. A diet potassium of 100 - 120 mEq from foods will be equivalent, tastier, and cheaper. Effects of alkali on fasting and overnight urine calcium are not known, nor if they affect the food effect.

In both cases, the reason for pills is inconstancy. Not everyone, all the time, can eat contrary to usual norms, and our diet norms promote stones. When stones are of clinical import and diet cannot or will not work, drugs are the right thing to use as they do work in trials and have served many patients well in my long experience⁴⁵⁷.

DISEASES ARE SPECIAL CASES

Diet may not raise the low urine pH that causes uric acid stones. Primary hyperparathyroidism requires surgical cure. Bowel diseases cause stones⁴⁵⁸ and diet is often not an answer. There are hoards of inherited rare stone forming diseases beyond the reach of diet. Diet change is

⁴⁵⁶ *However well established, the food effect has been dormant as an element in medical practice, so I am circumspect in my comments.*

⁴⁵⁷ *Here at the end we must contemplate the limits of clinical medicine and of patient driven behavior against the power of contemporary diet fashions. Simply put, in many ways we eat poorly, in my view and - more importantly - in the view of scholars and scientists whose focus is human nutrition. Yet, with all out wealth, few persist against culture.*

⁴⁵⁸ *By way of referencing this, Ileostomy is one unique example. Small bowel disease is another*

preeminent for the common calcium stone sans systemic disease 'idiopathic' calcium stone formers⁴⁵⁹.

Among the vast numbers of common calcium stone formers for whom diet will prove a good treatment lurk the rare exceptions. There is no formula to discover them, only Informed and sharp eyed physicians will do. I have oftimes rightly suspected rare exceptions here and there, and not rarely wasted time and money on futile testing. I should mention as I pass by that these diseases would have been prejudicial during evolutionary time; they mainly persist as recessive carrier traits rarely expressed except by an unfortunate coupling.

A LAST GOODBYE

Diet

What I have meant to say is that common stones seemingly arise as incidental consequences of modern diet driving to extremes the great physiological regulating systems that maintain terrestrial life among mammals. Within limits diet can reduce stone risk as judged by urine saturation and by the very small amount of diet trial data we have available to us. That very same diet is accepted universally as leading to better health for everyone in the US.

One might say that such a diet should be a universal goal instead of burdensome means for preventing disease. Is it not a paradox that what experts in diet have recognized as better for us is more expensive to shop for and contrary to the mass of products readily available everywhere?

Is it not also paradox for physicians to burden patients with very high fluids as sole treatment? In so doing they distort everyday life, depend on will as against an inexorable fluid balance physiology, and deprive patients of advice for healthier diet⁴⁶⁰.

The same for excessive dependence on a low oxalate diet⁴⁶¹. Given a high calcium intake oxalate lists can be abridged to include only foods in the higher ranges, and safely judged by 24 hour urine repeats. So many patients have come to me obsessed by their oxalate lists and entirely untreated otherwise.

The same for immediate leap to thiazide or potassium citrate. Perhaps the diet will make such unneeded.

Why not aim at a low sodium, low sugar, high potassium, high calcium diet then add fluids or oxalate constraints of medications as needed?

Why is that not the starting point?

⁴⁵⁹ *As a corollary, systemic diseases must be recognized, including genetic traits. Diet works in the absence of disease because it is the cause of disease - stones. But when something else causes stones, diet may be beside the point.*

⁴⁶⁰ *Obviously I do not mean to ignore 24 hour urine volumes that confer immediate risk - below 1.25 liter/d.*

⁴⁶¹ *I do not mean to ignore high oxalate excretions, merely that one might want to see what 1000 mg/d of diet calcium accomplished before judging the need for diet restrictions.*

Why would we all not wish to eat that way?

Thiazide and Potassium Citrate

Effective in trials, one needs these agents. I generally favor adding them to diet change when stones will not stop. How one uses them is obvious from the detailed analyses of their effects which we have reviewed together.

As a clinical point, I sometimes begin with them, especially thiazide. It is when I encounter many stones forming in an active way, or when stones are brushite - my special foe - , or when underlying medical issues make stone prevention urgent⁴⁶².

Clinical Practice

There are clinical decisions I cannot write about, for my pen lacks fluency and precision enough to picture the reality of medical practice. Better to say stone prevention is essentially clinical, despite all of my emphasis on physiology, and graphs, and science.

Better to say, in every history I have taken from a stone forming patient there exist obvious periods of extremes that attract suspicion as causes, and as places to attempt change. As numerous as the sands of seashore or desert, one cannot tell of them. They are what medicine is really about, when all is said: the strangeness and wonderful variety of the human condition.

At least for me, stone prevention calls on all I have from my many years of doctoring. For it is to change habits and behaviors, which people will not do merely on order, or from fear, or respect. It is something else, some usually unspoken relationship between physician and patient as obvious when encountered as it is beyond my words to describe.

Perhaps, at the end, one must say it arises from our very name - doctor, from docere, “to show, teach, cause to know”, “make to appear right”.

Is this not a graceful way for us to part?

⁴⁶² *One cannot do without clinical medicine, howsoever much physiology predicts behavior and stone risk. There are patients for whom one must act with all possible vigor, and I cannot tell another physician exactly why - or would wish to.*