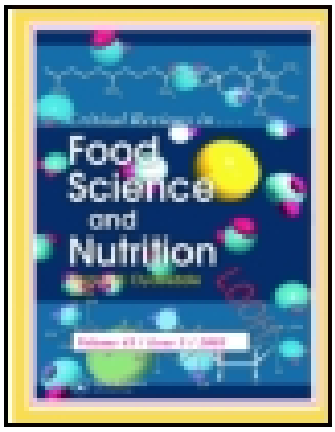

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Water and other fluids in nephrolithiasis: state of the art and future challenges

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Water and other fluids in nephrolithiasis: state of the art and future challenges

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Key words: kidney stones, urolithiasis, prevention, water, urinary volume, fruit juices, soft drinks, hydration, beverages

ABSTRACT

Adequate hydration, as to maintain urinary volume over 2 litres/day, has long been considered as the cornerstone medical prescription for preventing nephrolithiasis. However, scientific evidence about what kind of water stone formers should drink and about the effects of other beverages on urinary stone risk factors is sometimes unclear. Moreover, the recommendation that water therapy prevents kidney stone recurrence relies on only one randomized controlled trial, even if more epidemiologic and basic science studies seem to support this assumption. Therefore, in this review we analyze current evidence that support water therapy in nephrolithiasis and we highlight the possible effects of different types of water and other beverages on lithogenic risk, giving some practical recommendations for what stone formers should be advised to prevent recurrence.

BACKGROUND

Nephrolithiasis is a disease with a high prevalence among the general population, estimated at about 8% in the United States in 2007-2010, most frequent among the 20-40 and over 60 age groups, with a well-established increase trend in females (Croppi et al., 2012; Curhan, 2007; Stamatelou et al., 2003; Trinchieri, 2008). Idiopathic calcium nephrolithiasis is by far the most frequent type, accounting for about 75% of all cases of kidney stones, while secondary causes of calcium nephrolithiasis, such as primary hyperparathyroidism and uric acid nephrolithiasis, are less frequent (Osther, 2012). Approximately 35% to 50% of all newly-diagnosed calcium stone formers relapses within 5 years if an adequate preventive strategy is not issued (Goldfarb, 2003). Recurrent idiopathic calcium nephrolithiasis is therefore a relevant healthcare burden. A survey carried out in France has actually demonstrated that each episode of recurrent renal colic has an average total cost of € 4267 (about 5800 US dollars), 60% of which are direct healthcare-related costs (Lotan et al., 2012).

Nutrition has a central role in all strategies of nephrolithiasis prevention. Nowadays a low-salt, low-protein, normal-calcium diet with a high intake of fruit and vegetables is widely recommended for idiopathic calcium stone formers (Fink et al., 2009), since it has proven to be more effective for prevention of recurrences than the traditionally prescribed dietary calcium restriction (Borghi et al., 2002). Other preventive strategies may address specific metabolic risk factors: for example, subjects with hypocitraturia may benefit treatment with potassium or potassium-magnesium citrate, subjects with hypercalciuria may be treated with thiazide diuretics, and subjects hith hyperuricosuria or uric acid nephrolithiasis may benefit allopurinol (Fink et al., 2013).

However, it is also widely accepted that no preventive strategy for nephrolithiasis recurrence should lack an adequate fluid therapy as to maintain urine as much diluted as possible (Borghi et al., 1999b; Fink et al., 2009). A low urine volume is actually one of the most powerful risk factors for kidney stone formation and, on the other side, a high urinary volume is a strong protective factor. These concepts are known in medical practice since Hippocrates and Galen's times, and have eventually been confirmed by scientific studies (Borghi et al., 1999b). However, there are many points about fluid therapy in nephrolithiasis, including the effects of specific

types of waters and other fluids on lithogenic risk factors, that are far from being completely understood. The aim of this review is therefore to evaluate the current state of art in scientific literature about fluid therapy in nephrolithiasis, addressing potential pitfalls and areas of uncertainty and giving some pearls for everyday clinical practice.

IS FLUID THERAPY EFFECTIVE FOR NEPHROLITHIASIS PREVENTION?

The first, indirect evidence that fluid therapy is protective against kidney stone onset came from observations that the prevalence of nephrolithiasis is higher in geographical areas with a hotter climate (Curhan et al., 1994; Frank et al., 1959; Prince and Scardino, 1960; Soucie et al., 1996). For example, a large nation-wide epidemiologic study carried out in United States in 1982 on 1,167,009 stone formers revealed that people residing in South-Eastern states of the U.S., such as Florida, have a 1.9-fold increased risk of developing kidney stones than people residing in North-Western states such as North Dakota. This increased risk was confirmed after adjustment for other risk factors such as diet. Authors supposed that these data can be explained with climatic differences (mean yearly temperature is 22°C in Florida and 5°C in North Dakota) that may induce people who live in hotter areas to have a worse state of hydration due to higher sweating (Soucie et al., 1996).

According to this hypothesis, a rise in prevalence of nephrolithiasis may occur in future years, due to the global warming phenomenon, as highlighted by an epidemiologic model developed for the United States (Brikowski et al., 2008).

Other observations among workers exposed to high temperatures seem to confirm that nephrolithiasis is linked to environmental temperature. As shown in Table 1, soldiers serving in hot-climate areas, lifeguards, long-distance runners, machinists in iron factories and workers in steel industry have actually a higher risk for nephrolithiasis than general population (Atan et al., 2005; Better et al., 1980; Borghi et al.,1993; Milvy et al., 1981; Pierce and Bloom, 1945). Also workers who must limit their drink intake to avoid frequent urination, such as taxi drivers, teachers, and even surgeons, have been reported to be at high risk for stone formation (Chang and Goldfarb, 2004; Linder et al., 2013; Nygaard and Linder, 1997).

The rise of number of Emergency Department visits in days and seasons with high temperatures is also a well-established worldwide phenomenon, demonstrated both in the United States and in Europe (Cervellin et al., 2011; Chauhan et al., 2004; Fletcher et al., 2012). Therefore a dehydration status following increased sweating and insufficient fluid intake may be a risk factor also for kidney stone mobilization and renal colic onset.

A more direct evidence however comes from large epidemiological studies carried out in the United States, prospectively investigating the influence of dietary habits, including total fluid intake and type of preferred beverages assessed through a food-frequency questionnaire, on the incidence of kidney stones in healthy subjects of various ages. For example, a total fluid intake > 2.5 litres/day was associated to an incidence of nephrolithiasis of 192 cases/100000 person-year, while a total fluid intake < 1.2 litres/day resulted in an incidence of 372 cases/100000 person-year in a cohort of 45,619 healthy men 40 to 75 years of age prospectively followed-up for 4 years, making a 29% decrease in relative risk ($p=0.003$) after adjustment for age, profession, use of thiazide diuretics, intake of alcohol, calcium, animal protein and potassium (Curhan et al., 1993). The same authors also carried out a similar epidemiological survey in a cohort of 91,731 healthy women aged between 34 and 60, finding that a daily fluid intake > 2.5 litres was associated to an incidence of nephrolithiasis of 116 cases/100000 persons-year, while a daily fluid intake < 1.4 litres resulted in an incidence of 232 cases/100000 persons-year after a 8-year follow-up, making a 39% decrease in relative risk ($p=0.03$) in a multivariate model including age, alcohol consumption, body mass index, dietary intake of calcium, animal protein, potassium, sodium, sucrose and intake of supplemental calcium (Curhan et al., 1997). Similar results were obtained in further epidemiological studies carried out with the same methodology in following years, both in men and women. Hydration as to maintain urinary volume > 2.5 litres per day actually resulted in an average 30% relative risk reduction for kidney stone onset, compared with subjects with a poor hydration status (Curhan et al., 2004; Taylor et al., 2004). Diets with a high fluid content, such as those adhering to the principles of the DASH (Dietary Approaches to Stop Hypertension) diet, have proven to be effective in reducing the incidence of kidney stone formation in the same large cohorts of the studies cited above (Taylor et al., 2009). However, DASH-style diet encompasses low salt and animal protein and high fruit and vegetable

intake and, although it does result in a higher fluid intake, it is difficult to separate the effects of every single dietary modification (Taylor et al., 2010). Protective effects may be as well more related to high alkaline citrate, potassium and magnesium content of fruit and vegetables rather than to higher fluid intake.

Even though all these epidemiologic studies give a large amount of evidence that favors the role of hydration in kidney stone prevention, it must also be noted that they are all based on food frequency questionnaires for detecting dietary habits, which have demonstrated in literature to lack accuracy in estimating the quantity of every single food or beverage taken (Prentice et al., 2011). Moreover, these studies did not take into account possible changes in drinking habits during the long follow-up period.

However, a global review of a case-series of 1270 kidney stone formers carried out in the United States from 1977 to 1991 revealed that the only urinary stone risk factor in 194 subjects (15%) was low urinary volume (Levy et al., 1995). Therefore an insufficient fluid intake alone may explain kidney stone formation in a relevant number of patients, highlighting a condition of "chronic dehydration stone disease" without significant serum and urinary metabolic predisposing factors (Embon et al., 1990).

It has been demonstrated that stone formers, even when they have no significant comorbidities, have different dietary habits and lifestyle than non-stone-forming subjects (Al Zahrani et al., 2000; Meschi et al., 2012b). These differences affect mainly salt, meat, fruit and vegetable intake, but a significantly lower fluid intake has been reported in female stone formers aged less than 30 compared to age- and sex-matched controls (Meschi et al., 2012b). An Italian study carried out in mid 1990s compared 199 newly-diagnosed kidney stone formers with 101 healthy stone-free subjects, demonstrating that stone formers had a lower fluid intake (urinary volume 1057 ± 238 vs 1401 ± 562 ml/day, $p<0.001$, in males and 990 ± 230 vs 1239 ± 440 ml/day, $p<0.001$, in females) (Borghi et al., 1996).

There are many reasons why stone formers do not drink adequate amounts of fluids. Many of them have a high thirst threshold and forget to drink or are not aware of benefits of this behavior. Others do not like the taste of water or feel abdominal discomfort after ingesting high quantities of fluids. There are also some stone formers who must limit their fluid intake because the need to

void frequently is incompatible with their job activity (McCauley et al., 2012). However, a recent revision of a large case-series of Italian stone formers revealed that average fluid intake has actually increased in the last decades, possibly as a result of a higher availability of medical information through the media (Nouvenne et al., 2014).

Despite this large amount of epidemiological and observational data about the role of fluids in nephrolithiasis onset and prevention, only a few prospective intervention studies have demonstrated that fluid therapy is effective in diminishing kidney stone incidence. Frank & De Vries in 1960s carried out a prospective study in two Israeli towns in a desert area with a similar incidence of kidney stone disease: in one town they simply observed the trend of incident nephrolithiasis for 3 years, while in the other they issued a wide door-to-door health campaign to promote the benefits of water intake against kidney stones. At the end of the 3-year follow-up period, the incidence of nephrolithiasis was 0.8% in the first town and 0.07% in the second town. This 11-fold decrease in incidence was obtained even if the mean urinary volume of inhabitants at the end of the study was only 267 ml/day higher in the second town (804 vs 1071 ml/day) (Frank and De Vries, 1966).

The first randomized controlled trial to assess the effectiveness of adequate amount of water ingestion on the prevention of nephrolithiasis recurrence was carried out in Italy in 1990s. 199 newly-diagnosed (i.e. at their first renal colic) calcium stone formers were randomized to receive either water therapy as to maintain daily urine output above 2 l/day or no treatment. Patients in the treatment group were taught to monitor their 24-hour urine output once every 2-3 months at home to verify compliance with prescriptions. Yearly follow-up visits were carried out in both study arms with concomitant 24-hour urinary collection for determination of full profile of lithogenic risk. Subjects in both groups were advised to drink the preferred type of water, provided that it was with a low mineral content. After a mean follow-up of 5 years, the incidence of new episodes of renal colic was 12% in the treatment group vs 27% in the control group ($p=0.008$). Moreover, the mean time for recurrence was significantly longer in the treatment group than in the control group (38.7 ± 12.2 vs 25.1 ± 16.4 months, $p=0.016$) (Borghi et al., 1996). This is still nowadays the only randomized controlled trial published in literature to demonstrate that water ingestion as to maintain daily urine volume above 2 l/day is an effective

strategy for nephrolithiasis secondary prevention (Bao and Wei, 2012). There are actually other studies that have addressed this matter, but they also investigated the effects of other treatment combined with fluid therapy, such as dietary manipulations (Fink et al., 2009). However, one study clearly demonstrated that the persistence of a low urinary volume, index of a poor fluid intake, in follow-up visits is a major determinant of recurrence, together with 24-h urinary calcium excretion and length of the interval between the first and the second episode of renal colic in personal history (Strauss et al., 1982).

These results, although unconfirmed by other studies in different settings, have made water therapy the cornerstone medical prescription for every patient with nephrolithiasis. Nowadays it is considered unethical to deny water therapy prescription in kidney stone management and all intervention studies in this field must provide adequate information to patients on how and how much to increase urinary volume. However, it is still unclear whether the relationship between urinary volume and stone formation risk has a threshold level and if a high water intake can be detrimental for other aspects of renal physiology, especially in patients who also have some other chronic comorbidities.

However, increasing water intake is really effective also from an economical point of view. A mathematical model developed in France, based on the assumption that water therapy alone can prevent 55% of kidney stone recurrences in subjects with an insufficient hydration, has demonstrated that water therapy would be a cost-effective preventive strategy, possibly leading to fewer 11,572 episodes of renal colic per year in the whole country and thus to a 49 million euros of savings per year both in direct and indirect costs (Lotan et al., 2012; Lotan et al., 2013).

HOW DOES WATER THERAPY PREVENT KIDNEY STONE FORMATION?

There are at least four different mechanisms by which sufficient water intake influences lithogenic risk preventing stone formation. They are summarized in Table 2.

The simplest and most intuitive mechanism is the dilution of pro-lithogenic substances in urine. Even if the total 24-hour urinary excretion may remain high for dietary or metabolic reasons, a water load diminishes the absolute concentration of calcium, oxalate, phosphate and uric acid in urines, thus making crystal precipitation and nucleation less probable. In the 1980s a complex

algorithm (Equil™) was developed to calculate the relative supersaturation indexes for each lithogenic salt (calcium oxalate, calcium phosphate, struvite and uric acid) for any given level of urinary volume and total urinary excretion of promoters and inhibitors. This algorithm is strongly influenced by urinary volume, since mild increases in urinary volume result in massive decreases of supersaturation indexes, irrespective of other factors (Werness et al., 1985). Computerized simulations have demonstrated that even subjects with no metabolic derangements in other urinary factors may develop high levels of supersaturation indexes, and thus a high lithogenic risk, when their urinary volume is below 1 liter/day. On the other hand, if urinary volume is kept above 2,5 litres/day, supersaturation indexes are normal or only mildly elevated even if the patient has strong metabolic risk factors such as hypercalciuria or hyperuricosuria. The validity of this algorithm has been confirmed by in-vitro analysis, even if there are some concerns about its capacity of estimating the real calcium oxalate saturation (Pak et al., 2009). More recently, other methods have been proposed and validated to estimate lithogenic risk, but they anyway give a primary role to urinary volume (Rodgers et al., 2006).

The beneficial effect of urinary dilution on lithogenic salts has also been demonstrated, both in vitro and in vivo, by studies that have directly assessed the activity product ratio and formation product ratio of every lithogenic salt in stone formers and controls (Pak et al., 1980).

However, some researchers in the past have argued against water therapy in nephrolithiasis. As a matter of fact, they supposed that the decrease of concentrations of anti-lithogenic substances, due to urine dilution, would impede or even delete the beneficial effects of lower concentrations of pro-lithogenic factors (Ljunghall et al., 1988). Low concentrations of lithogenesis inhibitors are actually sufficient to induce stone formation even in absence of other metabolic abnormalities (Kok et al., 1986). However, as highlighted above, water load has been associated to a decrease in indexes of kidney stone formation virtually in all reports. In fact, complex in-vitro urinary manipulations have demonstrated that urinary dilution maintains anti-lithogenic properties of urinary inhibitors unaltered. The addition of purified inhibitors from both concentrated and diluted urine to urine samples treated with an oxalate load actually demonstrated that their inhibitory power is unmodified by the state of dilution (Borghi et al, 1999a).

The same experimental study demonstrated that a mild overnight water intake increases the urinary tolerance to an oxalate load, so that the more urine is diluted, the higher quantity of oxalate excretion is needed to reach calcium oxalate supersaturation index values sufficient to cause crystal precipitation and nucleation (Borghi et al., 1999a). Urine dilution also reduces the capacity of aggregation of calcium oxalate crystals once they have formed (Guerra et al., 2005). It has also been demonstrated that water load promotes citrate excretion, with an adjunctive inhibitory effect on stone formation (Hess et al., 1994). A high filtrate flow in the renal proximal tubule is actually able to stimulate a flow-dependent secretion of H+ ions from tubular cells to filtrate, so that citrate reabsorption, which is somewhat stimulated by a state of intracellular acidosis, is less effective, and thus a higher proportion of citrate is excreted in urine (Hamm, 1990).

Moreover, water load has proven to be effective in preventing the formation of Randall's plaques, which are hydroxyapatite crystal deposits below urothelial layer in renal papilla, which have demonstrated to have a role in formation of calcium oxalate stones (Coe et al., 2011). The dimensions of plaques and the area of hydroxyapatite deposits in histologic sections of renal papilla of stone formers are actually inversely correlated with the habitual hydration status of the subject (Kuo et al., 2003).

WHAT ARE THE EFFECTS OF DIFFERENT TYPES OF WATER ON LITHOGENIC RISK?

From a medical point of view, waters for human nutrition can be generally classified according to their mineral content in mineral waters, oligo-mineral waters and waters with a very low mineral content. However, commercially-available waters exhibit a wide variety of different compositions, so that a further classification may be based on their dry residue at 180°C (356°F), on their hardness (which depends on calcium and magnesium content) and on their ion composition (bicarbonate waters, sulphate waters, saltwater sulphorous waters) (Petraccia et al., 2006). Some waters have well-established, although mild, biological effects, so that cathartic waters, diuretic waters and anti-inflammatory waters can be distinguished (Evandri and Bolle, 2001). Several studies have assessed the possible role of specific kinds of water in modifying

lithogenic risk and preventing kidney stone formation, but no conclusive evidence is nowadays available.

Epidemiologic studies carried out in the 1970s in the United States have tried to link the quality of tap water in different geographical areas to the different incidence of nephrolithiasis. Researchers surprisingly found that South-Eastern regions of the United States, the so-called "stone belt area" due to the high incidence of kidney stones, had significantly lower mineral content in tap waters than other areas of the nation. Thus they hypothesized that nephrolithiasis onset may be linked with particular mineral composition of water and that a hard water may be protective against kidney stone onset (Sierakowski et al., 1979). Other researchers carried out similar studies in other countries and found similar correlations (Churchill et al., 1978; Juuti and Heinonen, 1980; Rose and Westbury, 1975). They supposed that hard waters may have a favorable content in bicarbonate and alkaline load and an inhibitory effect on the intestinal absorption of calcium and oxalate. It was also speculated that the high content in iron, typical of hard mineral waters, might act as a direct lithogenesis inhibitor. However, none of these mechanisms was demonstrated.

It was instead showed that the correlation between the level of hardness of the water actually drunk by stone formers and controls was poorly correlated with nephrolithiasis onset. After dividing a population of 3270 stone formers into deciles according to the hardness of water drunk, only a very small decrease in stone risk was observed between patients in the lowest decile and patients in the highest decile of water hardness (stone rate 3.0 vs 3.4, p=0.0017) (Shuster et al., 1982). Thus water hardness may influence overall stone risk, but the effect for single patients is of very low clinical importance.

Hard water has both anti-lithogenic and pro-lithogenic effects, which are however not significantly different in comparison with a soft water, provided that the overall urinary volume is the same. Hard waters in fact have a high content in calcium, which may enhance calciuria, but they also have a high magnesium content and alkaline load, which in turn raises urinary pH and promotes urinary citrate excretion (Schwartz et al., 2002). It must also be remembered that the quantity of magnesium and calcium introduced with water in a normal diet is trivial (respectively

12% and 7%) if compared to the intake related to other foods, so that calciuria and magnesiuria are much more influenced by dietary habits than by the type of water drunk (Hankin et al., 1970).
The problem of calcium content in mineral waters has been addressed by several studies, that demonstrated a direct correlation between calcium intake with water and urinary calcium excretion (Caudarella et al., 1998; Karagulle et al., 2007; Marangella et al., 1996; Nappi et al., 1987; Rodgers, 1997; Siener et al., 2004). However, drinking mineral waters with high calcium load was associated to a rise in urinary relative supersaturation indexes only in one study, where the administration of a bicarbonate alkaline water with high calcium content (370 mg/L) resulted in a significantly higher supersaturation index for calcium phosphate than the administration of an oligomineral water with low calcium content (< 20 mg/L) (Coen et al., 2001). Compared to oligomineral waters, the ingestion of a mineral water load resulted in a higher urinary calcium excretion, but also in a higher citrate excretion due to alkalinization of urine (Caudarella et al., 1998). Moreover, the effect of increase in urinary volume was similar in every type of water, thus driving similar modifications in supersaturation indexes for every lithogenic salt (Siener et al., 2004). Thus, the rise in calciuria induced by mineral waters may be of little clinical significance, provided that the calcium and alkali content of water is not too high, influencing a possible higher risk for calcium phosphate stone formation.
However, the calciuric effect of mineral waters may be more accentuated in stone formers than in controls (Mirzazadeh et al., 2012), so that some experts claim caution in advising a patient with calcium oxalate or calcium phosphate stones to drink waters with a high calcium content (Karagulle et al., 2007). Moreover, the bioavailability of calcium in mineral waters depends on many factors that are also related with the ionic composition of water, such as sodium, magnesium and chloride content. For example, an Italian mineral water rich in calcium has proved not to raise calciuria in a significant way in healthy subjects (Vezzoli et al., 2010).
The anti-lithogenic effect of oligo-mineral waters is instead mainly due to their effect on diuresis promotion and on their low calcium content. Oligo-mineral waters have traditionally been linked to a higher urinary volume than mineral waters with equal intakes (Simeoni et al., 1998). However, this concept has been contested by some pharmacologic studies (Evandri and Bolle, 2001). Nevertheless, there are some oligo-mineral waters that carry a significant alkali load and

can thus induce a rise in pH and an increase in lithogenesis inhibitor excretion (Bren et al., 1998; Simeoni et al., 1998).

A prospective study carried out in Italy on 384 stone formers enrolled after an extracorporeal lithotripsy intervention and randomized to drink either an oligomineral water with a low sodium and calcium content or a calcium-rich mineral water demonstrated that oligomineral water was associated to a significantly lower recurrence rate (17% vs 23%, $p<0.001$) after a median follow-up period of 19 months (Di Silverio et al., 2000). This is the only fair-quality study published up to date to have prospectively demonstrated significant benefits from one specific type of water on the clinical course of nephrolithiasis, beyond simple modifications of urinary parameters of lithogenic risk.

It should also be noted that most studies comparing one water with another in nephrolithiasis, cited above, have consistent limits that somewhat reshape the validity of their results. First, they generally considered low numbers of subjects, mostly healthy volunteers and not stone formers. Secondly, the protocols were carried out in extremely controlled conditions (fixed amount of water drunk every day, controlled and balanced diet, controlled amount of physical activity and exposure to heat) that are very different from everyday life. Moreover, they focused mainly on the changes in urinary parameters of lithogenic risk, avoiding to follow-up subject for long periods of time. Therefore, with only one exception (Di Silverio et al., 2000), they did not identify the possible long-term effects of specific types of waters on lithogenicity and stone formation. The waters studied were themselves very heterogeneous from one study to another, and sometimes even not well characterized in their specific composition and mineral content. Thus, despite a large amount of papers published, there is still uncertainty about what is the best water to advise to stone formers.

WHAT IS THE EFFECT OF OTHER DRINKS ON KIDNEY STONE FORMATION?

The lithogenicity or protective effect of beverages other than water has been much debated in literature and a full consensus has not been reached yet. The problem was initially dealt with epidemiological studies, trying to connect the habitual amount of different beverages drunk with the incidence of kidney stones. A case-control study carried out on 2,295 subjects from two

different geographical areas of the United States revealed that tea and soda consumption as primary beverages was associated with an increased risk of stones, while beer and coffee were instead protective. The risk was particularly high for habitual soda consumers, who had a 2-to-3-fold risk of developing stones than subjects who mainly drunk water (Shuster et al., 1985). However, this study considered as habitual drinkers of a particular beverage only subjects who had daily intake of that beverage superior to water intake, without detailing the actual intake. Further epidemiologic surveys carried out on even larger cohorts of healthy subjects prospectively followed up for 6 years to detect incident cases of nephrolithiasis revealed that the risk of kidney stones was increased in habitual male consumers of apple juice and grapefruit juice and in habitual female consumers of grapefruit juice. Habitual intake of coffee, tea and wine was protective in both genders, while habitual intake of beer was protective only in males. Soda was found to be unrelated to lithogenic risk, even if a possible positive correlation was speculated in males (Curhan et al., 1996; Curhan et al., 1998). However, a further analysis of data coming from the same cohorts with a longer follow-up revealed that habitual soda consumption is actually associated to a higher number of incident kidney stones in both genders (Ferraro et al., 2013). The possible protective role of habitual beer consumption was also demonstrated in a large cohort of Finnish male smokers (Hirvonen et al., 1999). In these surveys habitual intake of a certain beverage was defined as a daily consumption of more than 240 milliliters or more than one can. However, it must be noted that dietary and drink habits were collected through a food-frequency questionnaire, which, as noted above, is not completely reliable in estimating the precise amounts of every food or drink (Prentice et al., 2011).

The role of fruit juices on lithogenic risk has been further evaluated by clinical studies. For example, there are some reports stating that lemon juice is protective against calcium oxalate and uric acid stone formation through an effect of urine alkalinization and promotion of citrate excretion (Mazdak et al., 2006; Penniston et al., 2007; Touhami et al., 2007). Lemon juice supplementation has even been studied as a possible substitute for potassium citrate therapy in stone formers who have a low compliance to this medication, resulting somewhat protective against stone formation but less effective than potassium citrate (Kang et al., 2007). A similar study has actually found that the only mechanism by which lemonade reduces lithogenic risk is

increasing urinary volume, since it is ineffective even in raising citrate excretion (Koff et al., 2007).

A randomized cross-over study carried out on both stone formers and controls has compared the urinary effects of a fixed supplementation (400 ml/day) of lemon juice and orange juice, demonstrating that, even if these two juices have similar content in citrate, they have very different effects on urinary parameters of lithogenic risk, with orange juice raising urinary pH, citrate, magnesium and alkali load and lemon juice diminishing urinary pH without influencing citrate excretion in a significant way (Odvina, 2006). The author argued that this difference depends on the cation accompanying citrate, which is hydrogen in lemon juice and potassium in orange juice. Thus orange juice may have higher anti-lithogenic properties due to its elevated alkali load.

Cranberry juice has been evaluated in some studies with conflicting results. Some researchers have found that it might have weak anti-lithogenic properties, together with plum and blackcurrant juice, due to its low citrate content and its effect of lowering urine pH, thus promoting a rise in uric acid relative supersaturation index (Kessler et al., 2002). Others instead have demonstrated that a cranberry juice load may induce a rise in urinary citrate and a decrease in urinary oxalate excretion, thus resulting protective against calcium oxalate stones (McHarg et al., 2003). Moreover, it must be noted that cranberry juice has well-established anti-infective properties that give some benefits in urinary tract infections and thus in infectious nephrolithiasis (Vasileiou et al., 2013).

The role of carbonated industrial beverages, commonly referred to as soda, on the lithogenic risk is still unclear. Protective effects may be induced by their high citrate content, especially when they contain fruit juices, and by their tasty flavor, that can make people drink larger quantities and thus produce a higher urinary volume. On the other side, there are many concerns due to their high content in oxalate and simple carbohydrates such as fructose. For example, a high cola intake has been associated with elevated oxalate excretion (Rodgers, 1999), but there are also reports stating that cola may be protective against kidney stones inducing an increase in urinary volume (Herrel et al., 2012).

As a matter of fact, there are many differences in the specific compositions of all commercially available sodas and their effect on urinary stone risk is largely dependent on the quantity of citrate contained in alkaline form (i.e. coupled with K+ ions and not with H+ ions) (Eisner et al., 2010). In a prospective intervention study published two decades ago, 1,009 stone formers who reported a daily average intake of soft drinks > 160 ml were randomized to receive either the prescription of avoiding every intake of this beverages or no dietary prescription. After a median follow-up of 3 years, the prevalence of stone recurrence was 33% in the intervention group (soft drink avoidance) vs 42% in the control group (usual soft drink consumption), p=0.023. Moreover, the risk of recurrence in the control group was significantly higher in subjects who habitually consumed phosphoric acid-supplemented soft drinks than in subjects who drank citric acid-supplemented beverages (Shuster et al., 1992). This data may also be explained by the high sugar content of these beverages, since carbohydrates, especially polyol sweeteners and fructose that are generally added in industrial processes, have proved to induce a significant rise in urinary calcium excretion, thus raising lithogenic risk (Nguyen et al., 1993; Taylor and Curhan 2008). A high fructose load has also been associated to gout onset in both genders, so that an increased risk of uric acid nephrolithiasis cannot be excluded if these beverages are drunk in large amounts (Choi and Curhan 2008; Choi et al., 2010).

This effect is particularly accentuated for sport drinks, which have a high content of sugars to meet the needs of people who have extreme fluid and electrolyte losses due to intense physical exercise (Cohen, 2012; Nguyen et al., 1993). However, there are also reports stating that sport drinks may be protective against kidney stone onset, due to their high alkaline citrate content (Sweeney et al. 2009). Moreover, these beverages have in many cases a high content in sodium. A 16-oz (473 ml) portion of some “energy” drinks may even contain as much as 16% of reference daily intake of sodium (Higgins et al., 2010). A high sodium intake is well known to be detrimental for nephrolithiasis, although in these beverages sodium is mainly present in alkaline form (sodium citrate and sodium bicarbonate) and not as sodium chloride, which is perhaps far more lithogenic (Ticinesi et al, 2014; Muldowney et al., 1994). This is probably the reason why no significant differences have been reported in sodium excretion and overall lithogenic risk after shifting from a fixed amount water regimen to a sport drink regimen in healthy volunteers

(Goodman et al., 2009). However, the lack of specific studies and the large number of commercially available sport drinks with different compositions claim caution for consumption of these beverages in stone formers.

The lithogenic effect of coffee and tea has been less investigated in clinical studies. Coffee has traditionally been considered pro-lithogenic because of its high content in glycolate, which is a precursor of oxalate. However, caffeine has a diuretic effect mimicking thiazide mechanism that might outweigh this factor by increasing urinary volume and diminishing calcium excretion (Curhan et al., 1998). It can also stimulate diuresis and natriuresis through more complex pathways, by blocking hepatic adenosine-mediated sensory nerves that regulate hepato-renal reflex (Ming and Lautt, 2010). However, Ferraro et al interestingly found that habitual consumption of coffee is protective against kidney stones even when it is decaffeinated (Ferraro et al., 2013), thus suggesting that other compounds may be involved, such as polyphenols and chlorogenic acids with strong antioxidant properties (Samanidou et al., 2012). The high content of oxalate and its precursors has been claimed as a pro-lithogenic mechanism also for tea, even if it has been demonstrated that oxalate in tea has a poor bioavailability (Brinkley et al., 1990). Studies in animal models of nephrolithiasis have instead suggested that tea could have a protective effect against kidney stones, both through its diuretic effect and through its high anti-oxidative power (Itoh et al., 2005).

Milk has long been considered detrimental for kidney stone onset, based on the observation that increasing the intake of dairy products, notoriously rich in calcium, may lead to a rise in urinary calcium excretion (Lemann et al., 1979). However, many subsequent evidences have demonstrated that dietary calcium intake is associated to a better profile of lithogenic risk, since calcium can impair oxalate absorption (Martini and Heilberg, 2002). Evidence comes from both epidemiological (Curhan et al., 1993; Curhan et al, 1997; Taylor and Curhan, 2013) and clinical studies (Borghi et al., 2002), so that nowadays a restriction of milk consumption is no longer recommended in patients with nephrolithiasis, provided that the amount is not excessive (Borghi et al., 2006).

The complex amount of sometimes conflicting evidence on the lithogenic effects of beverages other than water is summarized in Table 3.

FINAL CONSIDERATIONS AND PRACTICAL PEARLS

The preventive role of an adequate hydration for all types of nephrolithiasis is well established in almost all medical literature. Water intake has proven to be an effective and economical way to prevent kidney stones, so that it is nowadays considered the cornerstone prescription for every patient with nephrolithiasis, irrespective of its type and causes. Water should actually be considered as a nutraceutical for stone formers, except for selected cases where abundant hydration can precipitate concurrent chronic comorbidities, such as congestive heart failure or advanced chronic renal insufficiency.

Stone formers should drink as much as to maintain daily urinary volume around 2 litres per day. In some specific types of nephrolithiasis, such as cystinuria, urinary volume should be over 3 litres per day (Barbey et al., 2000). Therefore hydration should vary according to climate and physical activity of every subject, according to the level of sweating. Motivational issues are critical to make patients modify their drinking habits and maintain an effective preventive behavior over time.

Given the sometimes conflicting and incomplete scientific evidence on the effects of beverages other than water on lithogenicity, stone formers should be advised to drink preferably water. However, some subjects may not tolerate large amounts of still water, either for perceived bad taste or for gastrointestinal discomfort. In such cases, they might be advised to interchange water with some fruit juices, especially those with a high alkaline load, such as orange juice. The intake of industrial soft drinks or sport drinks should be sporadic. The protective effect of wine, beer and coffee intake on stone risk should be weighed against their other beneficial and detrimental health effects. Milk consumption should be permitted in normal amounts.

Many stone formers may ask physicians what kind of water is more appropriate for prevention of their condition. Clinicians should be aware that the influence of different types of water on lithogenicity is probably negligible if compared to the influence of diet. However, for patients with calcium nephrolithiasis we favor oligo-mineral waters since they have a low calcium content and may improve diuresis, while for patients with uric acid nephrolithiasis waters with a high alkali load, either mineral or oligo-mineral, should be preferred for their action of urinary

alkalinization. Some researchers have also claimed that sparkling waters should be avoided, since they can reduce thirst by anesthetizing nerve endings of tongue and palate and by inducing gastric discomfort, thus ultimately leading to lower overall intake (Petraccia et al., 2006). However, if the patient does not tolerate still water and prefers sparkling water, then it should not be denied, since the main endpoint is increasing urinary volume, irrespective of the way it is obtained.

Further practical recommendations that should be given to stone formers are reported in Table 4 (Meschi et al., 2012a). It is important to highlight that dietary and drinking prescriptions for patients should not be standardized, but tailored to every single subject and his/her previous habits, clinical and metabolic risk factors.

From a clinical research point of view, it should be noted that, despite the large amount of medical papers published on this topic, no conclusive evidence has been reached yet. The preventive value of hydration for kidney stone recurrence has actually been clearly demonstrated by only one randomized controlled trial (Borghi et al., 1996). Moreover, evidence on the effect of specific types of waters and other beverages on lithogenicity comes from studies carried out on little numbers of subjects, mostly healthy controls, and in artificial conditions (strictly controlled diet, high and controlled beverage load) that are difficult to find in normal patients. Therefore more research is needed to clarify some contradictory results and to give more conclusive answers on what stone forming patients should drink for prevention.

CONFLICT OF INTEREST STATEMENT

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The authors also declare that this paper has not been submitted and is not being considered for publication elsewhere.

REFERENCES

Al Zahrani, H., Norman, R.W., Thompson, C., and Weerasinghe, S. (2000). The dietary habits of idiopathic calcium stone-formers and normal control subjects. *BJU Int*. **85**: 616-620.

Atan, L., Andreoni, C., Ortiz, V., Silva, E. K., Pitta, R., Atan, F. and Srougi, M. (2005). High kidney stone risk in men working in steel industry at hot temperatures. *Urology*. **65**: 858-861.

Bao, Y., and Wei, Q. (2012). Water for preventing urinary stones. *Cochrane Datab Syst Rev*. **6**: CD004292.

Barbey, F., Joly, D., Rieu, P., Méjean, A., Daudon, M., and Jungers, P. (2000). Medical treatment of cystinuria: critical reappraisal of long-term results. *J Urol*. **163**: 1419-1423.

Better, O. S., Shabtai, M., Kedar, S., Melamud, A., Berenheim, J., and Chaimovitz, C. (1980). Increased incidence of nephrolithiasis (N) in lifeguards (LG) in Israel. *Adv Med Exp Biol*. **128**: 467-472.

Borghi, L., Guerra, A., Meschi, T., Briganti, A., Schianchi, T., Allegri, F., and Novarini, A. (1999a). Relationship between supersaturation and calcium oxalate crystallization in normals and idiopathic calcium stone formers. *Kidney Int*. **55**: 1041-1050.

Borghi, L., Meschi, T., Amato, F., Briganti, A., Novarini, A., and Giannini, A. (1996). Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol*. **155**: 839-843.

Borghi, L., Meschi, T., Amato, F., Novarini, A., Romanelli, A., and Cigala, F. (1993). Hot occupation and nephrolithiasis. *J Urol*. **150**: 1757-1760.

Borghi, L., Meschi, T., Maggiore, U., and Prati, B. (2006). Dietary therapy in idiopathic nephrolithiasis. *Nutr Rev*. **64**: 301-312.

Borghi, L., Meschi, T., Schianchi, T., Briganti, A., Guerra, A., Allegri, F., and Novarini, A. (1999b). Urine volume: stone risk factor and preventive measure. *Nephron*. **81**: 31-37.

Borghi, L., Schianchi, T., Meschi, T., Guerra, A., Allegri, F., Maggiore, U., and Novarini, A. (2002). Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med*. **346**: 77-84.

Bren, A., Kmetec, A., Kveder, R., and Kaplan-Pavlovic, S. (1998). Magnesium hydrogen carbonate natural mineral water enriched with K-citrate and vitamin B6 improves urinary abnormalities in patients with calcium oxalate nephrolithiasis. *Urol Int*. **60**: 105-107.

Brikowski, T. H., Lotan, Y., and Pearle, M. S. (2008). Climate-related increase in the prevalence of urolithiasis in the United States. *Proc Natl Acad Sci*. **105**: 9841-9846.

Brinkley, L. J., Gregory, J., and Pak, C. Y. (1990). A further study of oxalate bioavailability in foods. *J Urol*. **144**: 94-96.

Caudarella, R., Rizzoli, E., Buffa, A., Bottura, A., and Stefoni, S. (1998). Comparative study of the influence of 3 types of mineral water in patients with idiopathic calcium lithiasis. *J Urol*. **159**: 658-663.

Cervellin, G., Comelli, I., Comelli, D., Meschi, T., Lippi, G., and Borghi, L. (2011). Regional short-term climate variations influence on the number of visits for renal colic in a large urban Emergency Department: results of a 7-year survey. *Intern Emerg Med*. **6**: 141-147.

Chang, M. A., and Goldfarb, D. S. (2004). Occupational risk for nephrolithiasis and bladder disfuction in a chauffeur. *Urol Res*. **32**: 41-43.

Chauhan, V., Eskin, B., Allegra, J. R., and Cochrane, D. G. (2004). Effect of season, age, and gender on renal colic incidence. *Am J Emerg Med*. **22**: 560-563.

Choi, H. K., and Curhan, G. C. (2008). Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. **336**: 309-312.

Choi, H. K., Willett, W., and Curhan, G. (2010). Fructose-rich beverages and risk of gout in women. *JAMA*. **304**: 2270-2278.

Churchill, D., Bryant, D., Fodor, G., and Gault, M. H. (1978). Drinking water hardness and urolithiasis. *Ann Intern Med*. **88**: 513-514.

Coe, F. L., Evan, E., and Worcester, E. (2011). Pathophysiology-based treatment of idiopathic calcium kidney stones. *Clin J Am Soc Nephrol*. **6**: 2083-2092.

Coen, G., Sardella, D., Barbera, G., Ferrannini, M., Comegna, C., Ferazzoli, F., Dinnella, A., D'Anello, E., and Simeoni, P. (2001). Urinary composition and lithogenic risk in normal subjects following oligomineral versus bicarbonate-alkaline high calcium mineral water intake. *Urol Int*. **67**: 49-53.

Cohen, D. (2012). The truth about sport drinks. *BMJ*. **345**: e4737.

Croppi, E., Ferraro, P. M., Taddei, L., Gambaro, G., and GEA Firenze Study Group. (2012). Prevalence of renal stones in an Italian Urban population: a general prectice-based study. *Urol Res*. **40**: 517-522.

Curhan, G. C., Rimm, E. B., Willett, W. C., and Stampfer, M. J. (1994). Regional variation in nephrolithiasis incidence and prevalence among United States men. *J Urol*. **151**: 838-841.

Curhan, G. C., Willett, W. C., Knight, E. L., and Stampfer, M. J. (2004). Dietary factors and the incidence of kidney stones in younger women: Nurses' Health Study II. *Arch Int Med*. **164**: 885-891.

Curhan, G. C., Willett, W. C., Rimm, E. B., Spiegelman, D., and Stampfer, M. J. (1996). Prospective study of beverage use and the risk of kidney stones. *Am J Epidemiol*. **143**: 240-247.

Curhan, G. C., Willett, W. C., Rimm, E. R., and Stampfer, M. J. (1993). A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med*. **328**: 833-838.

Curhan, G. C., Willett, W. C., Speizer, F. E., Spiegelman, D., and Stampfer, M. J. (1997). Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med*. **126**: 497-504.

Curhan, G. C., Willett, W. C., Speizer, F. E., and Stampfer, M. J. (1998). Beverage use and risk for kidney stones in women. *Ann Intern Med*. **128**: 534-540.

Curhan, G. C. (2007). Epidemiology of stone disease. *Urol Clin North Am*. **34**: 287-293.

Di Silverio, F. R., Ricciuti, G. P., D'Angelo, A. R., Fraioli, A., and Simeoni, G. (2000). Stone recurrence after lithotripsy in patients with recurrent idiopathic calcium urolithiasis: efficacy of treatment with Fiuggi water. *Eur Urol*. **27**: 145-148.

Eisner, B. H., Asplin, J. R., Goldfarb, D. S., Ahmad, A., and Stoller, M. L. (2010). Citrate, malate and alkali content in commonly consumed diet sodas: implications for nephrolithiasis treatment. *J Urol*. **183**: 2419-2423.

Embon, O. M., Rose, G. A, and Rosenbaum, T. (1990). Chronic dehydration stone disease. *Br J Urol*. **66**: 357-362.

Evandri, M. G., and Bolle, P. (2001). Pharmaco-toxicological screening of commercially available Italian natural mineral waters. *Il Farmaco*. **65**: 475-482.

Ferraro, P. M., Taylor, E. N., Gambaro, G., and Curhan, G. C. (2013). Soda and other beverages and the risk of kidney stones. *Clin J Am Soc Nephrol.* **8**: 1389-1395.

Fink, H. A., Akornor, J. W., Garimella, P. S., MacDonald, R., Cutting, A., Rutks, I. R., Monga, M., and Wilt, T. J. (2009). Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. *Eur Urol*. **56**: 72-80.

Fink, H. A., Wilt, T. J., Eidman, K. E., Garimella, P. S., MacDonald, R., Rutks, I. R., Brasure, M., Kane, R. L., Ouellette, J., and Monga, M. (2013). Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. *Ann Intern Med*. **158**: 535-543.

Fletcher, B. A., Lin, S., Fitzgerald, E. F., and Hwang, S. A. (2012). Association of summer temperatures with hospital admissions for renal diseases in New York state: a case-crossover study. *Am J Epidemiol*. **175**: 907-916.

Frank, M., De Vries, A., Atsmon, A., Lazebnik, J., and Kochwa, S. (1959). Epidemiological investigation of urolithiasis in Israel. *J Urol*. **81**: 497-505.

Frank, M., and De Vries, A. (1966). Prevention of urolithiasis. Education to adequate fluid intake in a new town situated in the Judean desert mountains. *Arch Environ Health*. **13**: 625-630.

Goldfarb, D. S. (2003). Increasing prevalence of kidney stones in the United States. *Kidney Int.* **63**: 1951-1952.

Goodman, J. W., Asplin, J. R., and Goldfarb, D. S. (2009). Effect of two sport drinks on urinary lithogenicity. *Urol Res*. **37**: 41-46.

Guerra, A., Allegri, F., Meschi, T., Adorni, G., Prati, B., Nouvenne, A., Novarini, A., Maggiore, U., Fiaccadori, E., and Borghi, L. (2005). Effects of urine dilution on quantity, size, and aggregation of calcium oxalate crystals induced by an in vitro oxalate load. *Clin Chem Lab Med*. **43**: 585-589.

Hamm, L. L. (1990). Renal handling of citrate. *Kidney Int*. **38**: 728-735.

Hankin, J. H., Margen, S., and Goldsmith, N. F. (1970). Contribution of hard water to calcium and magnesium intakes of adults. *J Am Diet Assoc*. **56**: 212-224.

Herrel, L., Pattaras, J., Solomon, T., and Ogan, K. (2012). Urinary stone risk and cola consumption. *Urology*. **80**: 990-994.

Hess, B., Michel, R., Takkinen, R., Ackermann, D., and Jaeger, P. (1994). Risk factors for low urinary citrate in calcium nephrolithiasis: low vegetable fibre intake and low urine volume to be added to the list. *Nephrol Dial Transplant*. **9**: 642-649.

Higgins, J. P., Tuttle, T. D., and Higgins, C. L. (2010). Energy beverages: content and safety. *Mayo Clin Proc*. **85**: 1033-1041.

Hirvonen, T., Pietinen, P., Virtanen, M., Albanes, D., and Virtarno, J. (1999). Nutrient intake and use of beverages and the risk of kidney stones among male smokers. *Am J Epidemiol*. **150**: 187-194.

Itoh, Y., Yasui, T., Okada, A., Tozawa, K., Hayashi, Y., and Kohri, K. (2005). Preventive effects of green tea on renal stone formation and the role of oxidative stress in nephrolithiasis. *J Urol*. **173**: 271-275.

Juuti, M., and Heinonen, O. P. (1980). Incidence of urolithiasis and composition of household water in Southern Finland. *Scand J Urol Nephrol*. **14**: 181-187.

Kang, D. E., Sur, R. L., Haleblian, G. E., Fitzsimons, N. J., Borawski, K. M., and Preminger, G. M. (2007). Long-term lemonade based dietary manipulation in patients with hypocitraturic nephrolithiasis. *J Urol*. **177**: 1358-1362.

Karagulle, O., Smorag, U., Candir, F., Gundermann, G., Jonas, U., Beker, A. J., Gehrke, A., and Gutenbrunner, C. (2007). Clinical study on the effect of mineral waters containing bicarbonate on the risk of urinary stone formation in patients with multiple episodes of CaOx-nephrolithiasis. *World J Urol*. **25**: 315- 323.

Kessler, T., Jansen, B., and Hesse, A. (2002). Effect of blackcurrant-, cranberry- and plum juice consumption on risk factors associated with kidney stone formation. *Eur J Clin Nutr*. **56**: 1020-1023.

Koff, S. F., Paquette, E. L., Cullen, J., Gancarczyk, K. K., Tucciarone, P. R., and Schenkman, N. S. (2007). Comparison between lemonade and potassium citrate and impact on urine pH

and 24-hour urine parameters in patients with kidney stone formation. *Urology*. **69**: 1013-1016.

Kok, D. J., Papapoulos, S. E., and Bijvoet, O. L. M. (1986). Excessive crystal agglomeration with low citrate excretion in recurrent stone-formers. *The Lancet*. **1 (8489)**: 1056-1058.

Kuo, R. L., Lingeman, J. E., Evan, A. P., Paterson, R. F., Parks, J. H., Bledsoe, S. B., Munch, L. C., and Coe, F. L. (2003). Urine calcium and volume predict coverage of renal papilla by Randall's plaque. *Kidney Int*. **64**: 2150-2154.

Lemann jr, J., Adams, N. D., and Gray, R. W. (1979). Urinary calcium excretion in human beings. *N Engl J Med*. **30**: 535-541.

Levy, F. L., Adams-Huet, B., and Pak, C. Y. (1995). Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. *Am J Med*. **98**: 50-59.

Linder, B. J., Rangel, L. J., and Krambeck, A. E. (2013). The effect of work location on urolithiasis in health care professionals. *Urolithiasis*. **41**: 327-331.

Ljunghall, S., Fellstrom, B., and Johansson, G. (1988). Prevention of renal stones by a high fluid intake? *Eur Urol*. **14**: 381-385.

Lotan, Y., Buendia-Jimenéz, I., Lenoir-Wijnkoop, I., Daudon, M., Molinier, L., Tack, I., and Nuijten, M. J. (2013). Increased water intake as a prevention strategy for recurrent uroliothiasis: major impact of compliance on cost-effectiveness. *J Urol*. **189**: 935-939.

Lotan, Y., Buendia-Jimenéz, I., Lenoir-Wijnkoop, I., Daudon, M., Molinier, L., Tack, I., and Nuijten, M. J. (2012). Primary prevention of nephrolithiasis is cost-effective for a national healthcare system. *BJU Int*. **110**: e1060-e1067.

Marangella, M., Vitale, C., Petrarulo, M., Rovera, L., and Dutto, F. (1996). Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis. *Clin Sci*. **91**: 313-318.

Martini, L. A., and Heilberg, I. P. (2002). Stop dietary calcium restriction in kidney stone-forming patients. *Nutr Rev*. **60**: 212-214.

Mazdak, H., Ardestani, P. M., and Nejadnik, H. (2006). Effect of lime juice consumption on urine pH value. *Saudi Med J*. **27**: 1923-1924.

McCauley, R. L., Dyer, A. J., Stern, K., Hicks, T., and Nguyen, M. M. (2012). Factors influencing fluid intake behavior among kidney stone formers. *J Urol*. **187**: 1282-1286.

McHarg, T., Rodgers, A., and Charlton, K. (2003). Influence of cranberry juice on the urinary risk factors for calcium oxalate kidney stone formation. *BJU Int*. **92**: 765-768.

Meschi, T., Nouvenne, A., and Borghi, L. (2012a) The importance of water and other fluids in the prevention of stone recurrence. **In** Urolithiasis: basic science and clinical practice, pp 745-749. Talati, J. J., Tiselius, H. G., Albala, D. M., and Ye, Z., Eds., Springer-Verlag, London.

Meschi, T., Nouvenne, A., Ticinesi, A., Prati, B., Guerra, A., Allegri, F., Pigna, F., Soldati, L., Vezzoli, G., Gambaro, G., Lauretani, F., Maggio, M., and Borghi, L. (2012b). Dietary habits in women with idiopathic calcium nephrolithiasis. *J Transl Med*. **10**: 63.

Milvy, P., Colt, E., and Thornton, J. (1981). A high incidence of urolithiasis in male marathon runners. *J Sports Med Phys Fitness*. **21**: 295-298.

Ming, Z., and Lautt, W. W. (2010). Caffeine-induced natriuresis and diuresis via blockade of hepatic adenosine-mediated sensory nerves and a hepatorenal reflex. *Can J Physiol Pharmacol*. **88**: 1115-1121.

Mirzazadeh, M., Nouran, M. G., Richards, K. A., and Zare, M. (2012). Effects of drinking water quality on urinary parameters in men with and without kidney stones. *Urology*. **79**: 501-507.

Muldowney, F. P., Freaney, R. and Barnes, E. (1994). Dietary chloride and urinary calcium in stone disease. *QJM*. **87**: 501-509.

Nappi, G., Ruoppolo, M., De Bellis, M., Rega, V., Minicapilli, G., and Pisani, E. (1987). Efficacia della idropinoterapia in pazienti portatori di calcoli e in soggetti sani trattati con tre tipi di acque diverse. *Giorn Med Term*. **30**: 32-41 [Italian language].

Nguyen, N. U., Dumoulin, G., Henriet, M. T., Berthelay, S., and Regnard, J. (1993). Carbohydrate metabolism and urinary excretion of calcium and oxalate after ingestion of polyol sweeteners. *J Clin Endocr Metab*. **77**: 388-392.

Nouvenne, A., Ticinesi, A., Allegri, F., Guerra, A., Guida, L., Morelli, I., Borghi, L., and Meschi, T. (2014). Twenty-five years of idiopathic calcium nephrolithiasis: has anything changed? *Clin Chem Lab Med*. **52**: 337-344.

Nygaard, I., and Linder, M. (1997). Thirst at work – an occupational hazard? *Int Urogynecol J Pelvic Floor Dysfunct*. **8**: 340-343.

Odvina, C. V. (2006). Comparative value of orange juice versus lemonade in reducing stone-forming risk. *Clin J Am Soc Nephrol*. **1**: 1269-1274.

Osther, P. J. S. (2012). Epidemiology of urolithiasis in the European Union. **In** Urolithiasis: basic science and clinical practice, pp 3-12. Talati, J. J., Tiselius, H. G., Albala, D. M., and Ye, Z., Eds., Springer-Verlag, London.

Pak, C. Y., Maalouf, N. M., Rodgers, K., and Poindexer, J. R. (2009). Comparison of semi-empirical and computer-derived methods for estimating urinary saturation of calcium oxalate. *J Urol*.**182**: 2951-2956.

Pak, C. Y. C., Sakhaee, K., Crowther, C., and Brinkley, L. (1980). Evidence justifying a high fluid intake in treatment of nephrolithiasis. *Ann Intern Med*. **93**: 36-39.

Penniston, K. L., Steele, T. H., and Nakada, S. Y. (2007). Lemonade therapy increases urinary citrate and urine volumes in patients with recurrent calcium oxalate stone formation. *Urology*. **70**: 856-860.

Petraccia, L., Liberati, G., Masciullo, S. G., Grassi, M., and Fraioli, A. (2006). Water, mineral waters and health. *Clin Nutr*. **25**: 377-385.

Pierce, L. W., and Bloom, B. (1945). Observations on urolithiasis among American troops in a desert area. *J Urol*. **54**: 466-470.

Prentice, R. L., Mossavar-Rahmani, Y., Huang, Y., Van Horn, L., Beresford, S. A., Caan, B. Tinker, L., Schoeller, D., Bingham, S., Eaton, C. B., Thomson, C., Johnson, K. C., Ockene, J., Sarto, G., Heiss, G., and Neuhouser, M. L. (2011). Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. *Am J Epidemiol.* **174**: 591-603.

Prince, C. L., and Scardino, P. L. (1960). A statistical analysis of ureteral calculi. *J Urol*. **83**: 561-565.

Rodgers, A., Allie-Hamdulay, S., and Jackson, G. (2006). Therapeutic action of citrate in urolithiasis explained by chemical speciation: increase in pH is the determinant factor. *Nephrol Dial Transplant*. **21**: 361-369.

Rodgers, A. L. (1999). Effect of cola consumption on urinary biochemical and physicochemical risk factors associated with calcium oxalate urolithiasis. *Urol Res*. **27**: 77-81.

Rodgers, A. L. (1997). Effect of mineral water containing calcium and magnesium on calcium oxalate urolithiasis risk factors. *Urol Int*. **58**: 93-99.

Rose, G. A., and Westbury, E. J. (1975). The influence of calcium content of water, intake of vegetables and fruit and of other food factors upon the incidence of renal calculi. *Urol Res*. **3**: 61-66.

Samanidou, V., Tsagiannidis, A., and Sarakatsianos, I. (2012). Simultaneous determination of polyphenols and major pure alkaloids in Greek Sideritis species, herbal extracts, green tea, black tea, and coffee by high-performance liquid chromatography-diode array detection. *J Sep Sci*. **35**: 608-615.

Schwartz, B. F., Schenkman, N. S., Bruce, J. E., Leslie, S. W., and Stoller, M. L. (2002). Calcium nephrolithiasis: effect of water hardness on urinary electrolytes. *Urology*. **60**: 23-27.

Shuster, J., Finlayson, B., Scaeffer, R., Sierakowski, R., Zoltek, J., and Dzegede, S. (1982). Water hardness and urinary stone disease. *J Urol*. **128**: 422-425.

Shuster, J., Finlayson, B., Schaeffer, R. L., Sierakowski, R., Zoltek, J., and Dzegede, S. (1985). Primary liquid intake and urinary stone disease. *J Chron Dis*. **38**: 907-914.

Shuster, J., Jenkins, A., Logan, C., Barnett, T., Riehle, R., Zackson, D., Wolfe, H., Dale, R., Daley, M. and Malik, I. (1992). Soft drink consumption and urinary stone recurrence: a randomized prevention trial. *J Clin Epidemiol*. **45**: 911-916.

Siener, R., Jahnen, A., and Hesse, A. (2004). Influence of a mineral water rich in calcium, magnesium and bicarbonate on urine composition and the risk of calcium oxalate crystallization. *Eur J Clin Nutr*. **58**: 270-276.

Sierakowski, R., Finlayson, B., and Landers, R. (1979). Stone incidence as related to water hardness in different geographical regions of the United States. *Urol Res*. **7**: 157-160.

Simeoni, P. G., Barbera, G., Battisti, A., Battisti, P., Frascaro, E., Fassino, V., Guzzetti, P., Sardella, D., Scuderi, A., Vinciguerra, A., and Coen, G. (1998). Oligomineral versus bicarbonate alkaline water on urinary excretion of solutes in normal subjects. *Ital J Mineral Electrolyte Metab*. **12**: 87-89.

Soucie, J. M., Coates, R. J., McClellan, W., Austin, H., and Thun, M. (1996). Relation between geographic variability in kidney stone prevalence and risk factors for stones. *Am J Epidemiol*. **143**: 487-495.

Stamatelou, K. K., Francis, M. E., Jones, C. A., Nyberg, N. M., and Curhan, G. C. (2003). Time trends in reported prevalence of kidney stones in the United States 1976-1994. *Kidney Int*. **63**: 1817-1823.

Strauss, A. L., Coe, F. L., Deutsch, L., and Parks, J. H. (1982). Factors that predict relapse of calcium nephrolithiasis during treatment: a prospective study. *Am J Med*. **72**: 17-24.

Sweeney, D. D., Tomaszewski, J. J., Ricchiuti, D. D., and Averch, T. D. (2009). Effect of carbohydrate-electrolyte sport beverages on urinary stone risk factors. *J Urol*. **182**: 992-997.

Taylor, E. N., and Curhan, G. C. (2013). Dietary calcium from dairy and nondairy sources, and risk of symptomatic kidney stones. *J Urol*. **190**: 1255-1259.

Taylor, E. N., and Curhan, G. C. (2008). Fructose consumption and the risk of kidney stones. *Kidney Int*. **73**: 207-212.

Taylor, E. N., Fung, T. T., and Curhan, G. C. (2009). DASH-style diet associates with reduced risk for kidney stones. *J Am Soc Nephrol*. **20**: 2253-2259.

Taylor, E. N., Stampfer, M. J., and Curhan, G. C. (2004). Dietary factors and the incidence of kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol*. **15**: 3225-3232.

Taylor, E. N., Stampfer, M. J., Mount, D. B., and Curhan, G. C. (2010). DASH-style diet and 24-hour urine composition. *Clin J Am Soc Nephrol*. **5**: 2315-2322.

Ticinesi, A., Nouvenne, A., Maalouf, N. M., Borghi, L., and Meschi, T. (2014). Salt and nephrolithiasis. *Nephrol Dial Transplant*. doi: 10.1093/ndt/gfu243.

Touhami, M., Laroubi, A., Elhabazi, K., Loubna, F., Zrara, I., Eljahiri, Y., Oussama, A., Grases, F., and Chait A. (2007). Lemon juice has a protective activity in a rat urolithiasis model. *BMC Urol*. **7**: 18.

Trinchieri, A. (2008). Epidemiology of urolithiasis: an update. *Clin Cases Min Bone Metab*. **5**: 101-106.

Vasileiou, I., Katsargyris, A., Theocharis, S., and Giaginis, C. (2013). Current clinical status on the preventive effects of cranberry consumption against urinary tract infections. *Nutr Res*. **33**: 595-607.

Vezzoli, G., Arcidiacono, T., Puzzovio, M., and Mora, S. (2010). Studio comparativo dell'effetto a breve termine di due acque minerali sul metabolismo del calcio. *Giorn Ital Nefrol*. **27**: 391-395. [Italian language]

Werness, P. G., Brown, C. M., Smith, L. H., and Finlayson, B. (1985). Equil 2: a basic computer program for the calculation of urinary saturation. *J Urol*. **134**: 1242-1244.

TABLE 1

Workers who are exposed to a high risk of nephrolithiasis due to insufficient fluid intake / low urinary volume.

Professional cathegory	**Authors**	**Year**	**Prevalence**
Soldiers	Pierce LW et al	1945	35%
Lifeguards	Better OS, et al	1980	24%
Marathon runners	Milvy P, et al	1981	15%
Machinists	Borghi L, et al	1993	9%
Teachers	Nygaard I, et al	1997	13%
Taxi drivers	Chang MA, et al	2004	Case report
Surgeons	Linder BJ, et al	2013	17%

TABLE 2

Mechanisms by which adequate water intake prevents the formation of kidney stones.

Mechanism	References
Reduction of the urinary concentration of prolithogenic substances without affecting the properties of inhibitors of lithogenesis	Werness PG, et al – J Urol 1985 Pak CY, et al – J Urol 2009 Borghi L, et al – Kidney Int 1999
Promotion of urinary citrate excretion	Hess B, et al – Nephrol Dial Transplant 1994
Reduction of the formation of interstitial calcium renal deposits (Randall plaques)	Kuo RL, et al – Kidney Int 2003
Increase in urinary tolerance to an oxalate load	Borghi L, et al – Kidney Int 1999 Guerra A, et al – Clin Chem Lab Med 2005

TABLE 3

Evidence of the role of beverages other than water on lithogenic risk. (Number of participants or study type in square brackets).

BEVERAGE	EPIDEMIOLOGIC STUDIES		CLINICAL STUDIES		ANIMAL / BASIC SCIENCE STUDIES		COMMENT
	Pro-lithogenic / no anti-lithogenic effect	Anti-lithogenic	Pro-lithogenic / no anti-lithogenic effect	Anti-lithogenic	Pro-lithogenic / no anti-lithogenic effect	Anti-lithogenic	
Apple juice	Curhan 1996 [45289 males]						Mechanism unknown. Never confirmed by clinical studies.
Grapefruit juice	Curhan 1996 [45289 males] Curhan 1998 [81093 females]						Mechanism unknown. Never confirmed by clinical studies.
Orange juice		Ferraro 2013		Odvina 2006 [9			High load of alkaline

		[>280000 subjects]		controls and 4 stone formers]			citrate (i.e. potassium citrate).
Lemon juice			Odvina 2006 [9 controls and 4 stone formers] Koff 2007 [21 stone formers]	Mazdak 2006 [30 healthy subjects] Kang 2007 [22 stone formers] Pennisto n 2007 [100 stone formers]		Touhami 2007 [ethilen glycol-induced nephrolithiasis in rats]	High citrate content, but with low alkali load.
Cranberry juice			Kessler 2002 [12 healthy subjects]	McHarg 2003 [20 healthy subjects]			Possibly useful in infection-related nephrolithiasis.
Blackcurrant juice			Kessler 2002 [12 healthy subjects]				Acts only mildly rising urinary pH.

Plum juice			Kessler 2002 [12 healthy subjects]				No significant effect on urinary citrate.
Soft drinks (carbonated industrial beverages)	Shuster 1985 [1633 stone formers and 1339 controls] Curhan 1996 [45289 males] Ferraro 2013 [>280000 subjects]				Eisner 2010 [comparison of 10 soft drink compositions]		High oxalate load; high acid load (especially for beverages with phosphoric acid)
Cola			Rodgers 1999 [45 healthy	Herrel 2012 [3 stone formers			High oxalate load; may promote a

			subjects]	and 10 controls]			high urinary volume.
Sport drinks			Nguyen 1993 [10 healthy subjects]	Sweeney 2009 [12 stone formers and 12 controls]			High citrate load; high polyol content that may enhance calcium excretion.
Tea	Shuster 1985 [1633 stone formers and 1339 controls]	Curhan 1996 [45289 males] Curhan 1998 [81093 females] Ferraro 2013 (37) [>280000 subjects]				Itoh 2005 [ethilen glycol-induced nephrolithiasis in rats]	High oxalate content; possible favorable anti-oxidant effect.
Coffee		Shuster 1985 [1633					Possible pro-lithogenic

		stone formers and 1339 controls] Curhan 1996 [45289 males] Curhan 1998 [81093 females] Ferraro 2013 [>280000 subjects]					effect due to high content in glycolate (never clearly demonstrated).
Wine		Curhan 1996 [45289 males] Curhan 1998 [81093 females					Mechanisms unknown (anti-oxidant effect?).

		] Ferraro 2013 [>280000 subjects]					
Beer		Shuster 1985 [1633 stone formers and 1339 controls] Curhan 1996 [45289 males] Hirvonen 1999 [27001 males] Ferraro 2013 [>280000 subjects					High diuretic effect; supposed pro-lithogenic activity due to uric acid load (never demonstrated).

		]					
Punch	Ferraro 2013 [>280000 subjects]						Effect possibly due to high sugar content.
Milk		Curhan 1993 [45619 men] Curhan 1997 [91731 women] Taylor 2013 [30762 men and 195865 women]		Borghi 2002 [120 male idiopathic calcium stone formers, investigated a composite dietary regimen]			Studies investigated not only milk but dairy products intake in general.

TABLE 4

Practical advices for water therapy that should be given to stone formers.

Consider water as a medicine for preventing further renal colics
Drink 2 liters of water per day (excluding meals): 2 glasses at wakeup, 2 glasses before sleep and 1 glass every hour of work
Keep a bottle of water in all places where you spend your time, especially at work, and drink one glass every hour.
Avoid mineral waters that are rich in chloride
Drink your water cool but not cold
Eat foods with high water content, especially fruits and vegetables
Involve your family in this habits
Change your brand of water at least once a year
Collect 24-h urine at home once a month so that you can check the results of your hydration therapy
Avoid to drink large amounts of water altogether but divide your water portions over the day

