Water intake and kidney stones

Epidemiology, pathophysiology of kidney stones, and water intake for prevention and reduction of health costs in stone disease

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Table of Content

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Introduction

Stone disease is also called lithiasis or urolithiasis, while nephrolithiasis refers more precisely to stones located in the kidney. Kidney stones have been known for centuries and affect around 10% of the global population (*Shah and Whitfield 2002*). Costs of care are considerable, and annual expenses were estimated at more than $2 billion in the United States alone (*Pearle et al. 2005*). Besides, in first stone patients, recurrence rate approaches 50% within five years after the first episode (*Ettinger 1979; Hosking et al. 1983; Sutherland et al. 1985*). Despite high costs and recurrence rate, stone disease is not widely recognized as an important health issue. Yet, many researchers have addressed the question of preventive measures. Nutrition for instance is a key parameter in the process of stone formation, as urine composition reflects mainly our food and fluid intakes. High water intake in particular has long been the only method used by doctors for the prevention of recurrence (*Borghi et al. 1999c; Ramello et al. 2000*). However, scientific evidence of the efficiency of water intake for prevention was limited for many years. In the last two decades, new research brought insights regarding the beneficial impact of a high water intake for primary and secondary prevention of urolithiasis.

This document overviews the current knowledge about the epidemiology and pathophysiology of urolithiasis, and summarizes the state of the art knowledge regarding water intake and kidney stones.

I. Epidemiology of kidney stones

I.1. Prevalence of kidney stones

Lifetime prevalence for kidney stones approaches 10% but it can vary according to geography (*Shah and Whitfield 2002*). **Figure 1** shows values of lifetime prevalence around the world.

Increasing prevalence of kidney stones is a global phenomenon and is particularly observed in developed countries, where kidney stones are the more common (*Daudon et al. 2012; Lopez and Hoppe 2010; Ramello et al. 2000*). It has been attributed to increasing living standards and changes in dietary habits following World War II (*Bartoletti et al. 2007; Daudon et al. 2012*). For instance high calorie content of the diet and high intakes of animal protein and salts, often associated with the consumption of ready-made dishes, may be part of the explanation (*Bartoletti et al. 2007; Daudon et al. 2012*). Increasing prevalence of overweight and obesity may also be correlated to this increase of kidney stone disease as body mass index (BMI) has repeatedly been linked to the risk of stone formation (*Leonetti et al. 1998; Siener et al. 2004*).

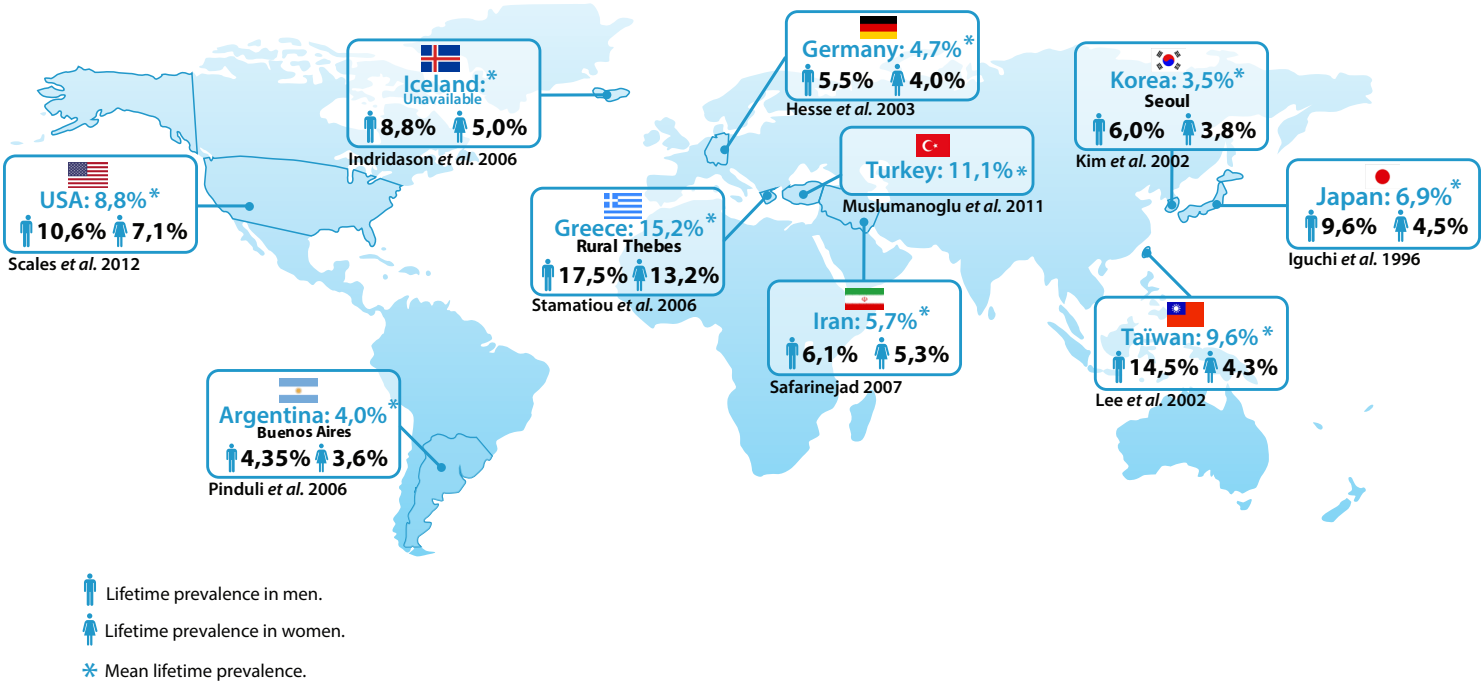

Figure 1. World map of kidney stone lifetime prevalence for the general population, and for men (M) and women (W). *(Hesse et al. 2003; Iguchi et al. 1996; Indridason et al. 2006; Kim et al. 2002; Lee et al. 2002; Muslumanoglu et al. 2011; Pinduli et al. 2006; Safarinejad 2007; Scales, Jr. et al. 2012; Stamatiou et al. 2006).*

I.2. An increasing trend in children

Cases of kidney stones have often been reported in infants and children but are rare and mainly related to urinary tract infections or abnormalities of the urinary tract (*Trinchieri et al. 2008*). In Iran for instance, a recent study performed on 100 children with stone under the age of 14, showed that 54 of them presented with a urinary tract infection (*Sepahi et al. 2010*). Metabolic abnormalities are also common in children with kidney stones, the most common being hypercalciuria (excess of calcium in urine) and hypocitraturia (insufficient citrate in urine) (*Thomas 2010*).

Although it is rare, kidney stones among children are becoming more prevalent (*Clayton and Pope 2011; Lopez and Hoppe 2010; Sas 2011; Thomas 2010*). In Minnesota, a retrospective analysis of childhood incidence of kidney stones showed that, for children under the age of 18, the incidence increased from 13 per 100,000 person-year in the period of 1984-1990 to 36 per 100,000 person-years in 2003-2008 (*Dwyer et al. 2012*). In South Carolina, an increase of childhood incidence of kidney stones was also reported. Among 1,535 children who had had an episode of nephrolithiasis between 1996 and 2007, the incidence increased from 7.9 per 100,000 in 1996 to 18.5 per 100,000 children in 2007. Interestingly, a higher rate of increase was noted among girls (*Sas et al. 2010; Sas 2011*).

This increase in childhood prevalence of urolithiasis is often attributed to changes in habits, and in particular in diet (*Lopez and Hoppe 2010; Sarica et al. 2009*).

II. Pathophysiology of kidney stones

II.1. Lithogenesis

Kidney stones result from complex mechanisms leading to the formation of a stone in the urinary tract. Lithogenesis refers to all these processes and includes several steps (*Daudon et al. 2012; Finlayson 1978*) (Figure 2).

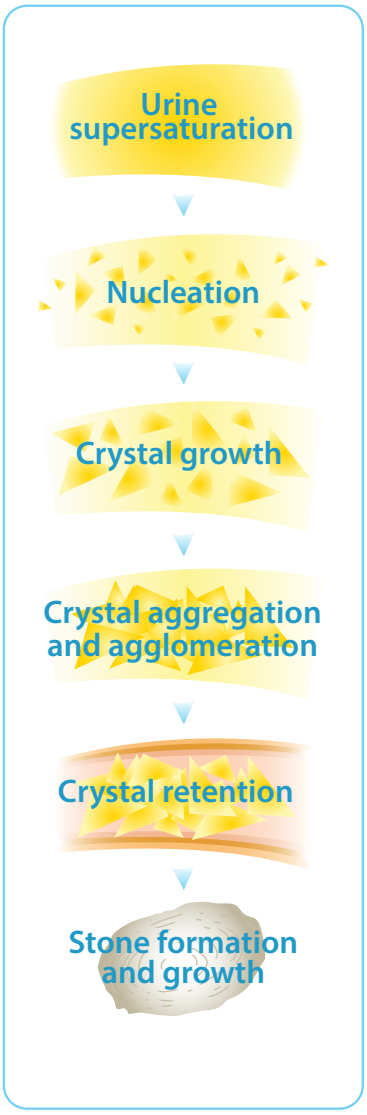

Figure 2. Main steps of lithogenesis.
(adapted from Daudon et al. 2012).

II.1.1. Urine supersaturation : the driving force of crystallogenesis

Urine supersaturation initiates stone formation (*Daudon et al. 2012; Evan 2010*). Moderate urine supersaturation is common in healthy subjects, and doesn't result in crystal formation (*Fleisch 1978*). In this case, urine is described as metastable, existing crystals can grow but new crystals cannot form. When urine supersaturation exceeds a certain threshold, called the Upper Limit of Metastability (ULM), urine becomes unstable and new crystals are more likely to form (*Brenner and Rector 2008; Finlayson 1978*).

These crystals are formed through the nucleation of ions dissolved in urine. There are two types of nucleation. Homogeneous nucleation is rare and corresponds to the spontaneous formation of new crystals in crystal-free urine. In most cases it is the presence of particles or crystals of one substance that will facilitate nucleation of other substances on their surface. This phenomenon is called heterogeneous nucleation. About 90% of urinary stones are composed of several substances and form by heterogeneous nucleation (*Brenner and Rector 2008; Daudon et al. 2012*).

II.1.2. Promoters and inhibitors of stone formation

Stone formation can also be promoted or inhibited by other compounds present in the urine. These components are respectively referred to as promoters and inhibitors (*Coe et al. 2011*).

Promoters are ions which can associate and form larger stone forming molecules. Calcium and oxalate are called promoters because they can associate to form calcium oxalate, which is a stone forming compound. As a result, recommendations state that a balanced intake of calcium is necessary to prevent kidney stones recurrence. An insufficient intake of calcium may actually favor oxalate absorption and therefore also appears to increase the propensity of kidney stones formation (*Curhan et al. 1993*).

Inhibitors include various types of compounds. Some inhibitors (e.g. citrate and magnesium) have a small molecular weight and will associate with promoters to prevent the formation of stone forming compounds. Other inhibitors are macromolecules that associate with crystals and reduce the propensity of crystal growth, aggregation and agglomeration (*Daudon et al. 2012*).

II.2. Urine volume and composition: a necessary balance

Kidney stones formation results from an imbalance in urine composition. This is summarized in **Figure 3**. Observational studies have shown differences between individuals who form stones and control subjects in several urinary parameters. Stone formers often present with high frequencies of excessive urinary concentrations of calcium (hypercalciuria), oxalate (hyperoxaluria) and uric acid (hyperuricosuria), as well as insufficient urinary concentration of citrate (hypocitraturia) and low urine volume (*Curhan et al. 2001; Peres et al. 2003*). Given the mechanism of lithogenesis, all these parameters appear to act on urine supersaturation and on urinary concentrations of promoters and inhibitors of stone formation.

Supersaturation state can be assessed by different methods and formulas among which the Tiselius Crystallization Risk Index (CRIT). This index is calculated from urinary analysis and takes into urinary excretion of calcium (Ca), oxalate (Ox), citrate (Cit), magnesium (Mg) and urine volume (V) (*Tiselius 1991*).

Urine volume is clearly an essential component in the pathogenesis of kidney stones. Borghi *et al.* acknowledged that increasing urine volume is the simplest way to reduce urine supersaturation (*Borghi et al. 1999c*). It was however hypothesized that increasing urine volume could also dilute promoters and inhibitors. The question of how concomitant dilutions of promoters and inhibitors impact the risk of forming a stone has been addressed in several papers. In vitro, urine dilution had no impact on the inhibitory effect of citrate and magnesium on calcium oxalate crystallization (*Guerra et al. 2006*). Similarly, in vivo studies have shown that urine dilution does not impact the inhibitory effect of macromolecules over 10kDa on calcium oxalate crystallization (*Borghi et al. 1999a*). Moreover, it appears that urine dilution can lead to an increase of the upper limit of metastability (*Pak et al. 1980*).

Daudon *et al.* postulated that urine dilution reduces the effect of promoters without any impact on inhibitors. It is actually the product of molar concentrations of oxalate and calcium which drives crystallization. A twofold urine dilution will for instance reduce both calcium and oxalate concentrations, and will result in a fourfold decrease of their product of molar concentrations. The inhibitory effect of compounds such as oxalate is also dependent on the molar ratio between promoters and inhibitors (e.g. calcium and oxalate). This inhibitory effect is thus not affected by urine dilution. They concluded that an increase in urine volume may reduce the risk of forming a stone (*Daudon et al. 2012*).

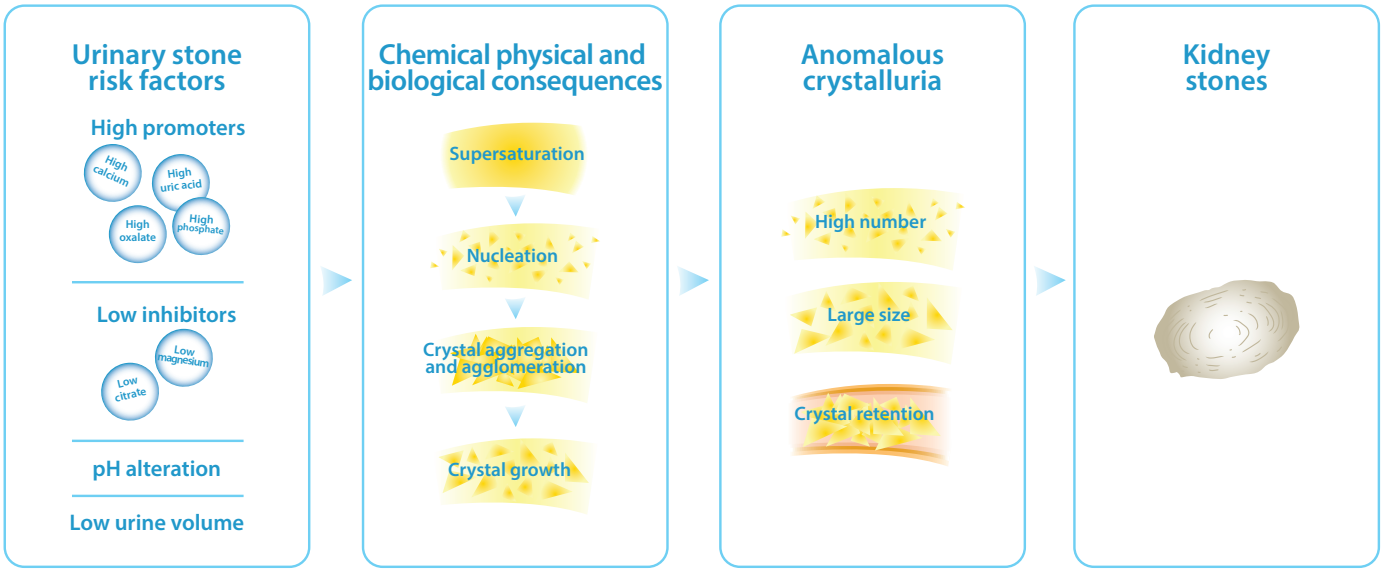

Figure 3. Urinary risk factors leading to stone formation.

Low urine volume contributes to urine supersaturation, which drives stone formation. Increasing urine volume reduces urine supersaturation as it lowers the effect of promoters, with only a small effect on inhibitors.

III. Risk factors for kidney stones

Many factors influence the propensity of forming a kidney stone (*Brenner and Rector 2008; Curhan 2007; Ramello et al. 2000; Trinchieri et al. 2008*), including both individual and environmental factors (**Figure 4**). Main individual risk factors include age, gender and ethnicity, while the most important environmental risk factors are related to geography and climate (*Brenner and Rector 2008; Curhan 2007; Ferrari et al. 2007; Ramello et al. 2000; Trinchieri et al. 2008*). Body Mass Index (BMI) and a family history of kidney stones are also thought to influence the risk for kidney stones (*Curhan 2007; Ramello et al. 2000*). **Figure 4** summarizes these factors.

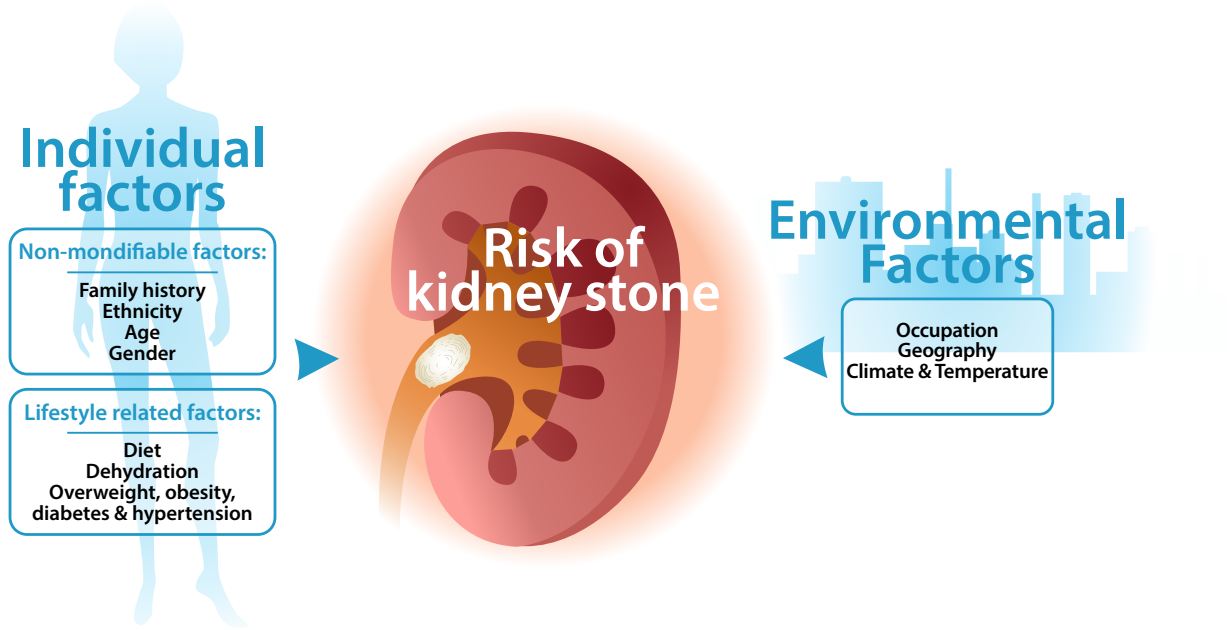

Figure 4. Main risk factors for kidney stones.

III.1. Individual, non-modifiable risk factors

III.1.1 Family history

Family history of stones is a confirmed risk factor and it is actually reported more often among stone formers than among healthy subjects (*Coe et al. 1979; Curhan et al. 1997a; Serio and Fraioli 1999; Trinchieri et al. 2008*). These observations suggest a hereditary predisposition to kidney stones. Main difficulty in addressing this question is that members of a family usually share many environmental factors. Familial inheritance of kidney stones may thus be related to an environmental effect (*Curhan et al. 1997a; Ramello et al. 2000; Trinchieri et al. 2008*). To investigate this point, Curhan *et al.* published in 1997 a cohort study of 37,999 men from the Health Professionals Follow-up Study (HPFS). After adjustment for other potential risk factors (e.g. dietary factors, fluid intake or geography), men with a family history of kidney stones were at greater risk of forming a stone (relative risk of 2.57) as compared to men without a family history (*Curhan et al. 1997a*).

III.1.2. Race and ethnicity

Only a few epidemiological studies have evaluated race and ethnicity as risk factors for kidney stones, however there appear to be race-related differences in prevalence rates. In men, Soucie *et al.* found a higher prevalence among whites than blacks. The prevalence among Hispanic and Asian men was intermediate between whites and blacks (*Soucie et al. 1994*). This was also reported by Stamatelou *et al.* on data from the second and third National Health and Nutrition Examination Survey (NHANES II and III). On 15,364 and 16,115 adult United States residents, they reported a higher prevalence of kidney stones among non-Hispanic Caucasians than among non-Hispanic African Americans, or among Mexican Americans (*Stamatelou et al. 2003*). On data from the 2007-2010 NHANES studies, Scales *et al.* reported lower prevalence of kidney stones among non-Hispanic African Americans and Hispanic individuals than among non-Hispanic Caucasians (*Scales, Jr. et al. 2012*).

III.1.3. Age and gender

Age and gender are established risk factors for kidneys stones; urolithiasis is more prevalent among men than among women (*Brenner and Rector 2008; Ramello et al. 2000; Trinchieri et al. 2008*); observations of male-to-female ratios generally vary between 1.3:1 (*Scales, Jr. et al. 2007*) and 3:1 (*Ferrari et al. 2007*). Gender prevalence of kidney stones is often attributed to differences in diet and to a suggested greater capacity of men to concentrate urine. This may lead to differences in urinary excretion of lithogenesis promoters and inhibitors. Curhan *et al.* have found higher urinary excretion of stone promoters such as calcium, oxalate, uric acid and sodium among men than women. On the contrary, women presented higher urinary excretion of citrate which inhibits stone formation (*Curhan et al. 2001*).

Kidney stones are also more common in middle-aged adults, with the highest prevalence rates occurring in adults aged 30 to 50 years (*Brenner and Rector 2008; Ferrari et al. 2007; Trinchieri et al. 2008*). Incidence peaks vary between gender, with one peak around 35 observed in men, while two peaks are observed in women at 30 and around 55 years, which corresponds to a post-menopause period (*Trinchieri et al. 2008*).

III.1.4. Current change in gender prevalence

During the last two decades, a decrease in male-to-female ratios has however been observed (*Marickar and Vijay 2009; Scales, Jr. et al. 2007; Strope et al. 2010; Trinchieri et al. 2008*). Epidemiological studies show a general increase in the incidence of urolithiasis, however interestingly **Figure 5** shows that it increased at a higher rate among women (*Marickar and Vijay 2009; Scales, Jr. et al. 2007; Strope et al. 2010*).

In their prospective cohort involving 1,091 female and 7,499 male stone patients, Marickar and Vijay highlighted a change in gender prevalence over four decades: as shown in **Figure 6**, the percentage of females among stone formers increased from 8% in the time period of 1971-1975, to 17% in 2003-2008 (*Marickar and Vijay 2009*). Similarly, on 204,594 hospital discharges of urinary stone patients, Scales *et al.* observed a decrease of the male-to-female ratio from 1.7:1 in 1997 to 1.3:1 in 2002 (*Scales, Jr. et al. 2007*). Changes in urinary excretion of various compounds among women could explain this trend: over the years, female excretions of calcium and oxalate increased while excretions of magnesium decreased. These changes in excretions are often attributed to changes in living standards and in dietary habits (*Marickar and Vijay 2009*).

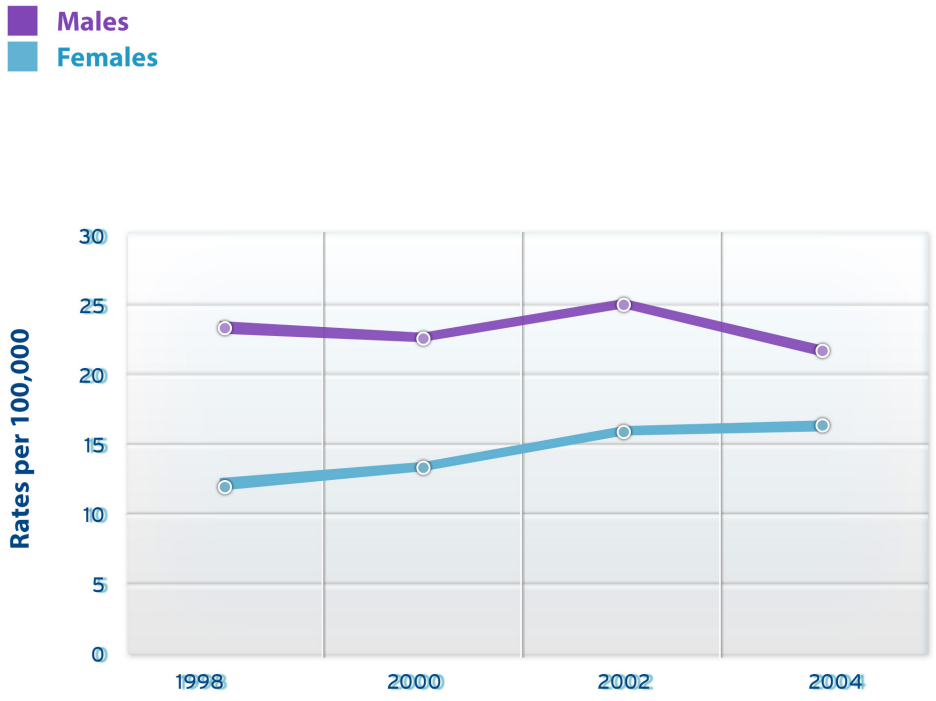

Figure 5. Incidence inpatient admissions for upper urinary stones.
(Strope et al. 2010).

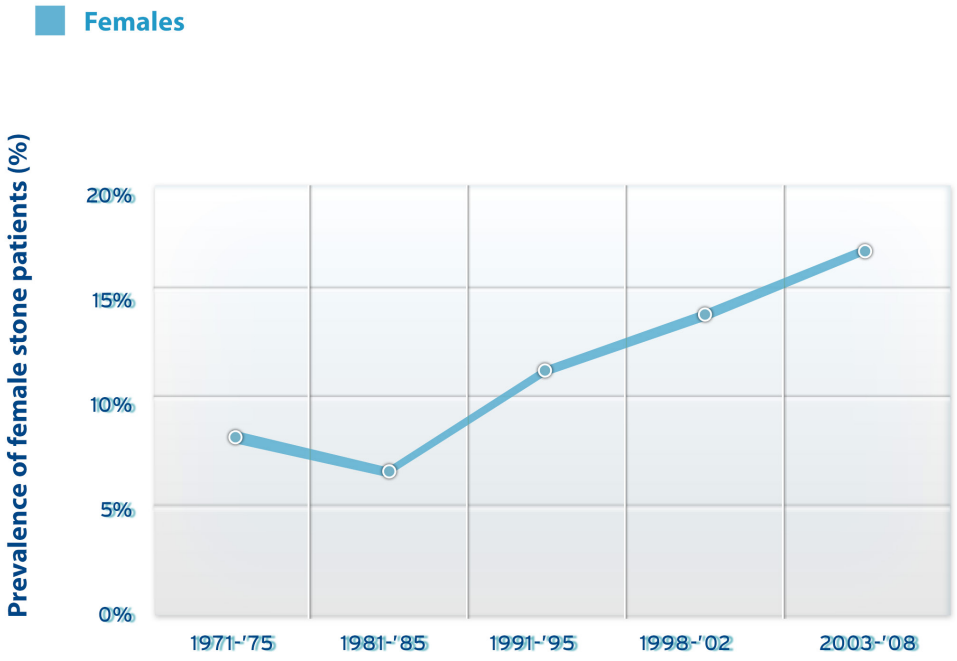

Figure 6. Increasing prevalence of female stone formers.
(Marickar and Vijay 2009).

III.2. Lifestyle related factors

III.2.1. Calcium intake

The impact of nutritional habits on kidney stone risk have been widely studied and reviewed. Diet is known to influence urine composition and to play a major role in kidney stone formation (*Bartoletti et al. 2007; Brenner and Rector 2008; Curhan 2007; Hughes and Norman 1992; Trinchieri et al. 2008*). Specifically, in a study of 91,731 women participating in the Nurses' Health Study I, Curhan *et al.* showed that women who consumed supplemental calcium were at greater risk of kidney stones, with a relative risk of 1.20 compared to women who did not (*Curhan et al. 1997b*).

Many studies have also shown that without supplemental intake of calcium, a low calcium intake was associated with a higher risk of kidney stones. On 108 stone formers and 210 healthy subjects, Leonetti *et al.* observed a significantly lower calcium intake in stone formers (*Leonetti et al. 1998*). In another study involving 45,619 men from the Health Professional Follow-up Study (HPFS) cohort, men in the highest quintile of calcium intake (1,326mg/d) were less likely to develop kidney stones (relative risk of 0.66), as compared to the lowest quintile (516mg/d). This shows that a low calcium intake may increase the risk of kidney stone formation (*Curhan et al. 1993*). A low calcium intake (bellow 400mg/d) is actually associated with an increased intestinal absorption of oxalate. As oxalate is a promoter of kidney stones, this may explain the increased risk of stones. Official guidelines for calcium intake therefore recommend a balanced calcium intake (*Tiselius et al. 2001*).

III.2.2. Emerging dietary risk factors

Fluid intake as a risk factor was long overlooked but Borghi *et al.* found that low fluid intake increases the risk (*Borghi et al. 1999c*). This topic is widely addressed in sections IV, V, VI and VII below.

Other dietary factors such as intakes of animal proteins, purines and sodium are emerging and may be positively correlated to the risk of kidney stones (*Brenner and Rector 2008; Ferrari et al. 2007*). On the contrary, a high potassium intake may decrease the risk (*Curhan et al. 1993*).

III.2.3. Association with other chronic diseases

Epidemiological studies tend to show an association between kidney stones and other chronic diseases such as diabetes, obesity and hypertension (*Bartoletti et al. 2007; Brenna et al. 2013; Daudon et al. 2012; Ramello et al. 2000*).

Overweight and obesity appear to be related to the risk of kidney stones. Using data from 89,376 women and 51,529 men who participated in the Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), Curhan *et al.* showed a positive correlation between BMI and history as well as BMI and incidence of kidney stones (*Curhan et al. 1998*). In a sample of 363 male and 164 female stone formers, Siener *et al.* found overweight and obesity in 59.2% of men and 43.9% of women (*Siener et al. 2004*). BMI was actually linked to several urinary risk factors. Evaluating 807 stone formers and 237 controls from NHS I, NHS II and HPFS, Curhan *et al.* reported a positive correlation between body weight and urinary excretions of calcium, but found no difference in excretions of oxalate and uric acid (*Curhan et al. 2001*). In a study involving 527 idiopathic calcium oxalate stone formers, Siener *et al.* found a positive correlation between BMI and (a) urinary excretion of uric acid in both men and women, (b) urinary calcium in men, and (c) urinary oxalate in women (*Siener et al. 2004*).

Diabetes mellitus is one consequence of obesity and is also thought to be an important risk factor for kidney stones. In a cross-sectional study including more than 200,000 subjects from NHS I, NHS II and HPFS, authors found that subjects with type 2 diabetes were at greater risk of stone disease (*Taylor et al. 2005*). More precisely, on 2464 stone patients (272 with and 2192 without type 2 diabetes), Daudon *et al.* tried to investigate whether this greater risk corresponded to higher rates of calcium stones, uric acid stones, or both. They confirmed that type 2 diabetes was associated with greater risk of stone, and they found that the relative proportion of uric acid stones was higher among diabetic patients than among non-diabetic (*Daudon et al. 2006*). This greater incidence has been attributed to a lower urine pH (*Cameron et al. 2006; Hari Kumar and Modi 2011*). Yet, Daudon *et al.* found that uric acid stone formers with type 2 diabetes presented higher fractional excretion of uric acid, and this excretion was reduced in patients with metabolic syndrome and without diabetes (*Daudon et al. 2006*).

Hypertension was also found to be positively correlated with the risk of kidney stones. Three studies reported a higher risk of nephrolithiasis among hypertensive subjects than among normotensives (*Borghi et al. 1999b; Cappuccio et al. 1999; Madore et al. 1998*). Urinary analysis of hypertensive compared to normotensive subjects showed greater urinary supersaturation of calcium oxalate in women, and of calcium oxalate and calcium phosphate in men (*Borghi et al. 1999b*). In parallel, a higher prevalence of hypertension was noted among stone formers (*Cappuccio et al. 1999*). This strong association between hypertension and nephrolithiasis has been attributed to common risk factors such as overweight and high dietary intakes of animal protein and salt (*Borghi et al. 1999b; Ramello et al. 2000*).

Risk factors for urolithiasis include age, gender and ethnicity, as well as geography, diet and lifestyle. Prevalence of kidney stones approaches 10% worldwide and is increasing. Epidemiological studies have suggested that obesity, diabetes and hypertension may increase the risk of developing kidney stones.

IV. Dehydration: a risk factor for kidney stones

Chronic dehydration is a confirmed risk factor for kidney stones (*Brenner and Rector 2008*). This has been clearly observed in a retrospective study investigating causes of urolithiasis on 708 stone formers. In this study, chronic dehydration was defined as history of exposure to heat (e.g. climate and or occupation), or poor drinking, with normal urine and plasma osmolality. Authors concluded that chronic dehydration was the main cause of 19% of all kidney stones incidents (*Embon et al. 1990*).

IV.1. Low urine volume: a key risk factor for kidney stones

Dehydration or low water intake can lead to low urine volume, which is common in stone formers: A urine volume lower than 1.0L/d was reported in 10% of recurrent stone formers (*Stitchantrakul et al. 2007*), and a urine volume lower than 1.5L/d was found in 40% of recurrent and first time stone formers (*Orakzai et al. 2004*).

Observational studies have identified low urine volume as a risk factor for kidney stones. In a retrospective study published in 2008, all subjects from NHS I, NHS II and HPFS who provided a 24-h urine collection were evaluated. Among a total of 3,350 subjects, 2,237 had already had at least one episode of kidney stone. Results showed that subjects with a urine volume above 2.5L were at lower risk of developing kidney stones than subjects with a urine volume below 1.0L; the corresponding relative risks (RR) were 0.22 for NHS I subjects, 0.33 for NHS II and 0.26 for HPFS. In all three cohorts, a higher urine volume was associated with a reduced risk of kidney stones (*Curhan and Taylor 2008*).

Low urine volume leads to higher concentrations of urinary compounds and may promote urine supersaturation. Studies in general population have shown that a low urine volume increases the risk of forming a stone (*Borghi et al. 1999c; Curhan 2007; Pak et al. 1980; Trinchieri et al. 2008*).

IV.2. Environmental factors predisposing to low urine volume

IV.2.1. Occupational risk of kidney stones

Observational studies have reported higher incidence rates of kidney stones among subjects working in hot environments. In a prospective study from 1993, Borghi *et al.* compared prevalence of kidney stones between machinists working in hot environment and control subjects working at a mild temperature, and observed higher prevalence among machinists (8.4%, compared to a prevalence of 2.5% in controls)(*Borghi et al. 1993*). More recently, a cross-sectional study carried out on a population of workers from a steel factory showed that hot-area workers presented a higher risk of kidney stones and lower urine volumes than employees who were stationed in a mild environment (*Atan et al. 2005*).

Higher incidence rates of kidney stones were also observed in marathon runners. This may be a result of repeated, although short-term episodes of substantial dehydration (*Irving et al. 1986; Milvy et al. 1981*). Authors observed that in marathon runners, crystalluria and urine supersaturation were similar to stone formers, and significantly different from healthy subjects who did not run (*Irving et al. 1986*).

IV.2.2. Climate and temperature as risk factors

Climate and temperature vary greatly between countries and could partly explain how geography influences the risk of developing kidney stones (**Figure 1**). Other factors such as nutritional and lifestyle habits could also explain these variations between countries. Epidemiological studies have shown variations in prevalence within countries (*Soucie et al. 1996*). This was observed in 1963 in a hot arid region of Israel, where the highest incidence of stones were noted in the hottest regions (*Frank et al. 1963*). Variations of prevalence were also observed within the United States: a «stone-belt» was identified after a higher prevalence of kidney stones was observed among the warmest states (*Brikowski et al. 2008*). Boyce *et al.* found that prevalence of kidney stones

was the highest in the southern states of South Carolina and Georgia, and the lowest in Wyoming and Missouri (*Boyce et al. 1956*). Likewise, a retrospective analysis of data from NHANES II and from the Cancer Prevention Study II (CPS II), highlighted that the age-adjusted prevalence of kidney stones increased from north to south and from west to east (*Soucie et al. 1994*). After controlling for other risk factors, prevalence appears to be correlated to ambient temperature and sunlight exposure (*Soucie et al. 1996*). Overall, the higher prevalence in warmer regions is due to high water losses and inadequate water intake leading to low urine volume (*Brikowski et al. 2008; Soucie et al. 1994*).

Incidence of kidney stones appears to vary seasonally, with higher incidences generally recorded in the warmer months of spring and summer (*Bartoletti et al. 2007; Chauhan et al. 2004; Chen et al. 2008*). Yet, in one study carried out in Iran, authors observed the highest incidences in the months of June, July and November (*Basiri et al. 2004*). This was mostly attributed to positive correlation between mean ambient temperatures and incidence of kidney stones (*Chauhan et al. 2004; Chen et al. 2008; Fletcher et al. 2012; Soucie et al. 1994; Soucie et al. 1996*).

Higher temperatures can lead to greater water losses through sweating, resulting in a lower urine volume. This could explain the increased risk of urolithiasis (*Bartoletti et al. 2007; Frank et al. 1963*) (**Figure 7**).

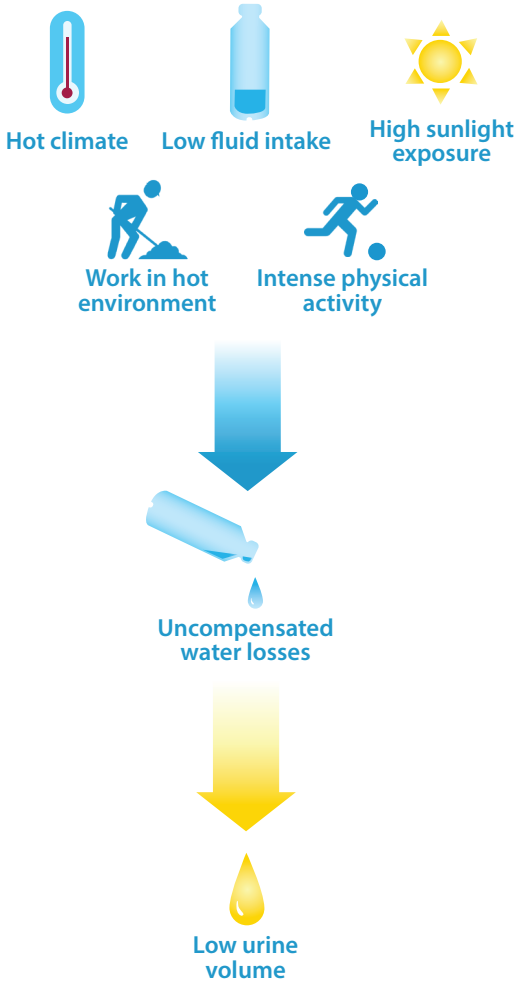

Figure 7. Conditions related to chronic dehydration, predisposing to a low urine volume and thereby increasing the risk of kidney stones.

It is essential to avoid dehydration by maintaining an adequate water intake, particularly in situations of acute water losses. In these situations, insufficient water intake leads to uncompensated water losses, a low urine volume and a higher risk of kidney stones.

V. Prevention of stone recurrence with high water intake

Recurrence rate of kidney stone disease is high: 40 to 60% of stone formers will relapse within 5 years following a first episode (*Ettinger 1979; Hosking et al. 1983; Sutherland et al. 1985*). Current recommendations to prevent stone recurrence involve diet and lifestyle (*Brenner and Rector 2008; Tiselius et al. 2001*). A high water intake had been advised as a preventive measure for stone recurrence since the time of Hippocrates, and was for a long time the only advice given to reduce the risk (*Borghi et al. 1999c; Ramello et al. 2000*). Until a few decades ago, there was little scientific evidence of this preventive effect.

V.1. Reduction of recurrence rate with increased water intake

Prospective cohort studies have shown that recurrence was associated with lower urine volumes. In his study published in 2005, Daudon enrolled 181 stone formers who were advised to follow a particular diet (including a fluid intake sufficient to result in a urine volume of at least 2.0L/d). After a 3-years follow-up, 72 patients experienced at least one episode of recurrence while 109 subjects remained stone free. Urinary analysis showed that patients who remained stone free had increased their urine volume to a greater extent than patients who experienced recurrence: in stone-free patients, mean daily urine volume was 2.26L/d, as compared to 1.74 in patients with recurrence. Actually, a 1.0L/d increase in urine volume was associated with a hazard ratio of 0.32, meaning that an increase in fluid intake leads to a reduced risk of stone recurrence (*Daudon 2005*). Likewise, in a study involving 70 stone patients, 25 were treated with a calcium channel blocker, 25 increased their fluid intake to achieve a urine volume of at least 2.5L/d and 20 received no treatment. A reduction in recurrence from 55% to 40% was observed in subjects who increased their fluid intake as compared to no treatment group; however no information was given regarding mean fluid intake in subjects without any treatment (*Sarica et al. 2006*).

The main research regarding this matter was published by Borghi *et al.* in 1996. They assessed the causal effect of increased water intake and risk of kidney stone recurrence. Authors recruited 199 stone formers right after their first episode of kidney stones. Patients were randomized in two groups: in the first group, 99 patients increased their water intake to achieve a urine volume of at least 2.0L/d, while 100 subjects in the second group didn't receive any particular instructions. After a 5-years follow-up, patients with higher water intake presented a significantly lower recurrence rate (12.1% compared to 27% in controls, p=0.008) (*Borghi et al. 1996*).

V.2. Water intake and urinary parameters in stone formers

Studies performed on stone formers investigated the impacts of an increased urine volume on urinary parameters related to stone formation. Results showed that an increase in urine volume leads to a reduction of urine density (*Amar et al. 2006*), and urine supersaturation for calcium oxalate (*Borghi et al. 1999a; Pak et al. 1980*), calcium phosphate and monosodium urate (*Pak et al. 1980*). Moreover, increasing urine volume also leads to an increase of the upper limit of metastability for calcium oxalate (*Pak et al. 1980*), and to an increase of the permissible increment in oxalate, meaning that a greater level of supersaturation of these compounds is required to initiate crystallization (*Borghi et al. 1999a*). Furthermore, increased urine volume reduced the frequency of crystalluria (*Amar et al. 2006; Kaid-Omar et al. 2001; Rodgers et al. 1991*). Finally, increasing water intake leads to a higher rate of clearance of residual stone fragments (*Sarica et al. 2006*), and to better rates of spontaneous passage of stones (*Kaid-Omar et al. 2001*).

Increasing water intake is an effective measure to reduce the risk of kidney stone recurrence.

VI. Primary prevention of stones with high water intake

Increased water intake is widely recommended for secondary prevention of urolithiasis but only a few investigations have focused on primary prevention.

VI.1. Reduction of stone incidence with increased water intake

Two prospective cohort studies involving 45,619 men and 91,731 women without any history of kidney stones showed an inverse correlation between fluid intake and the risk of nephrolithiasis. Relative risk for the highest quintile of fluid intake compared to the lowest quintile was 0.71 in men, and 0.61 in women. These results show that a higher fluid intake is associated with a lower risk of kidney stones (*Curhan et al. 1993; Curhan et al. 1997b*).

The strongest evidence of primary prevention with increased water intake was an interventional study published by Frank *et al.* in 1966. In this research, authors investigated the effect of a drinking education on urinary output and on the incidence of urolithiasis. Subjects with no history of kidney stones were enrolled in two towns of an arid desert mountain region of Israel. In the newly established town of Arad, subjects received education to high fluid intake, whereas settlers of the neighboring town of Beersheba constituted a control group with no instruction. After a three years follow up, a higher urine output and lower prevalence of urolithiasis existed in the educated citizens of Arad (prevalence of 0.28% in Arad and 0.85% in Bersheeba). This study shows that higher fluid intake achieved by education can prevent urolithiasis in a hot and dry climate (*Frank and De 1966*).

VI.2. Water intake and urinary parameters in healthy subjects

Only few studies have investigated the impact of increased water intake on urinary parameters involved in the process of stone formation. Most of these studies included healthy subjects as well as stone formers, and thus present evidence of a beneficial effect of increased water intake both for secondary and primary prevention of urolithiasis. For instance, Borghi *et al.* observed a beneficial effect of an increased fluid intake on several urinary risk factors in 12 healthy subjects. An additional intake of 500mL before going to bed led to a reduction of calcium oxalate (CaOx) relative supersaturation, and to an increase in the tolerance of oxalate without any modification of the metastability limit for CaOx. Besides, the inhibitory effect of macromolecules on CaOx crystallization was not altered by increased water intake (*Borghi et al. 1999a*). Similar results were reported by Pak *et al.* on 3 subjects with no history of kidney stones: increased water intake to achieve total water intake of 2.3, 2.5, 3.3L/d led to a reduction of urine supersaturation for calcium oxalate, calcium phosphate and monosodium urate, and to an increase of the upper limit of metastability for CaOx (*Pak et al. 1980*). More recently, De La Guéronnière *et al.* studied the effect of an increased water intake on the Tiselius Cristallization Risk Index (CRIT). Forty-eight healthy subjects were divided in a control and a water group, which was asked to drink a 2L/d additional water intake. After a week of intervention, subjects in the water group had increased their urine volume by 1.3L/d. In 24 hour urine, the CRIT was reduced by 33.9% in women and 44.8% in men as compared to controls (*de La Gueronniere et al. 2011*).

There is growing evidence that increasing water intake may help prevent first episodes of kidney stones.

VII. Water intake and health costs of kidney stones prevention

Health costs for kidney stone disease are considerable. For instance in the United States, total care for kidney stone disease was estimated to cost more than $2.1 billion for the year of 2000 alone (*Pearle et al. 2005*). In France, the total cost of one episode of nephrolithiasis was estimated at €4267, which corresponds to an annual budget impact of stone disease of €590 million for the French health care system (*Lotan et al. 2012*).

Prevention may represent a key economic lever. Lotan *et al.* studied the impact of various preventive measures, and mainly of water intake, on the reduction of health costs of kidney stones.. As it appears below, they concluded that high water intake is a cost-effective measure for the prevention of kidney stones.

VII.1. Reduction of stone recurrence costs via adequate water intake

Cost savings through secondary prevention by increased water intake were estimated on a hypothetical cohort of French stone formers. Cost savings were calculated with a Markov statistical model for an adequate water intake of 2.0L/d as compared to the French average water intake of less than 2.0L/d. Results showed that with a compliance of 100%, an adequate water intake could reduce the French health care costs by €49 million every year by preventing 11,572 new stone recurrences. Even with a compliance of only 25%, as much as 2,893 stones could be prevented and €10 million could be saved every year on recurrences (*Lotan et al. 2013*).

VII.2. Reduction of first stone costs with adequate water intake

Lotan *et al.* estimated that prevention of kidney stones through adequate water intake can be cost-effective in healthy subjects as well (see **Figure 8**). They showed that a compliance of 100% could save €273 million every year by preventing 9,265 first stone episodes just in France. With a compliance of 25% cost savings were still estimated at €68 million (*Lotan et al. 2012*).

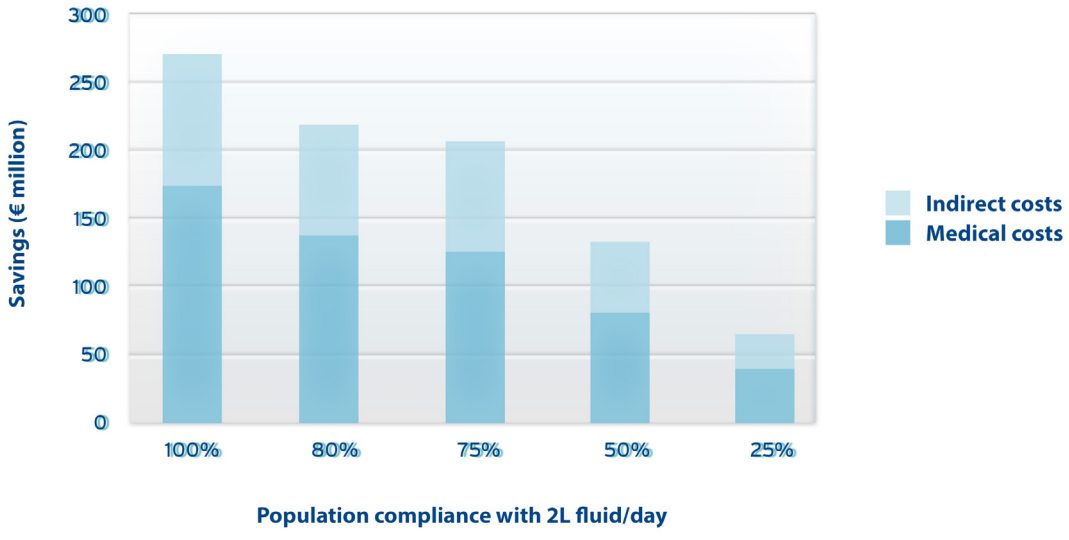

Figure 8. Cost-effectiveness of high water intake to prevent first episodes of kidney stone according to population compliance.
(Lotan et al. 2012).

Prevention of kidney stones with an adequate water intake of 2.0L per day is cost-effective and can reduce the economic burden of urolithiasis.

VIII. Dietary and water recommendations for stone prevention

VIII.1. Guidelines for the prevention of recurrence in patients

Kidney stone formation results from an imbalance in urine composition, which is influenced by food (total osmolar load and chemical composition) and water intakes. Hence, recommendations to prevent kidney stones recurrence mainly involve changes in dietary habits, changes in lifestyle and increased water intake. Depending on the composition of previous stone(s), dietary advice will vary and additional medication may be necessary for patients with a high risk profile. Overall, recommendations also include general preventive measures (e.g. diet, water intake), applicable to every type of stone former (*Kairaitis 2007; Tiselius et al. 2001*).

In Europe, guidelines for the management of stone patients were established by the European Association of Urology (EAU). Main general preventive measures of EAU guidelines are presented in **Figure 9**. They include recommendations related to fluid intake, diet and lifestyle. Dietary recommendations for the prevention of stone recurrence are based on guidelines for the general population: normal calcium intake (1,000-1,200mg/d), low intakes of sodium chloride (4-5g/d) and animal proteins (0.8-1g/kg/d). Recommendations on fluid intake for the prevention of recurrence are based on urine volume. The EAU recommends a fluid intake sufficient to achieve a urinary output of at least 2.0L per day. Lifestyle recommendations also stipulate that excessive fluid loss (e.g. sweating during exercise, diarrhea) should be compensated by an increased fluid intake. (*Tiselius et al. 2001*).

Increased fluid intake	• **Urine volume > 2.0L/d** • Urine Specific Gravity < 1,010
Balanced diet	• **Normal calcium intake** (1,000-1,200 mg/d) • **Limit salt** intake (4-5 g/d) • **Limit animal protein** intake (0.8-1g/kg/d)
Lifestyle	• **BMI** 18-25 • Limit stress • **Adequate physical activity** • Balancing excessive fluid loss

Figure 9. General measures for the prevention of kidney stone recurrence based on European Association of Urology guidelines for nephrolithiasis patients.
(adapted from Tiselius et al. 2001).

In Australia, the organization Caring for Australasians with Renal Impairment (CARI) established guidelines for recurrent calcium stone formers. They also recommend a normal calcium intake (1,000-1,200mg/d), and a fluid intake sufficient to achieve a urine volume of at least 2.0L per day (*Kairaitis 2007*).

VIII.2. Dietary and water guidelines for general population

Dietary guidelines for recurrent kidney stones patients are based on guidelines for the general population and both are thus similar. Recommended intakes are 1.000-1.200mg/d for calcium, 5g/d for sodium and 0.83g/kg/d for protein (*Ross et al. 2011; World Health Organization 2007; World Health Organization 2012*).

Recommendations for water intake in the general population vary between countries. Official guidelines for Europe are presented in **Table 1**. Even though most of these recommendations may be sufficient to achieve a urine volume of at least 2L/d and may thus be similar to recommendations for the prevention of recurrence, they are not based on urinary outputs. They actually state adequate values for Total Water Intake (TWI) which includes both water coming from food and water coming from beverages.

Table 1. Recommendations for Total Water Intake (TWI) in Europe.
(EFSA 2010).

	1-2 years	2-3 years	4-8 years	9-13 years	14-18 years	Adults	Pregnant women	Lactating women
Recommended TWI (EFSA 2010)	1.1-1.2 L/d	1.3L/d	1.6L/d	Girls 1.9L/d	Women 2L/d		2.3L/d	2.7L/d
				Boys 2.1L/d	Men 2.5L/d			

EFSA estimated that around 80% of TWI comes from fluids, and 20% from food (EFSA 2010). This is equivalent to drinking 1.6L/d of water for adult women, 2L/d for adult men, 1.8L/d for pregnant women and 2.2L/d for lactating women.

Dietary recommendations are similar in recurrent stone formers and in the general population. They include a normal calcium intake, limited salt and animal protein intakes, and a high water intake. In case of large water losses it is recommended to increase water intake.

Conclusion

- Lifetime prevalence of kidney stones approaches 10% of all adults worldwide, and has been constantly increasing in the last decades.

- The increase in kidney stone prevalence is associated with other chronic diseases such as obesity, diabetes and hypertension. Changes in diet and lifestyle can partly explain this phenomenon.

- Urolithiasis is a multifactorial disease; many factors can increase the risk of stone formation.

- Chronic dehydration is a major risk factor for kidney stones.

- Chronic dehydration results in a low urine volume and increases urine supersaturation.

- A high fluid intake increases urine volume, promotes urine dilution and reduces urine supersaturation.

- Increased fluid intake is an effective preventive measure for the prevention of kidney stones recurrence and may help reduce the risk of first episodes.

- Adequate water intake is cost-effective and can help reduce the economic burden of kidney stones.

- Water is essential and should be at the core of everyone's daily intake. To prevent recurrence, official guidelines include a fluid intake sufficient to achieve a urine volume of at least 2.0L per day.

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