



# Impact of fluid intake in the prevention of urinary system diseases: a brief review

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We are often told that we should be drinking more water, but the rationale for this remains unclear and no recommendations currently exist for a healthy fluid intake supported by rigorous scientific evidence. Crucially, the same lack of evidence precludes the claim that a high fluid intake has no clinical benefit. The aim of this study is to describe the mechanisms by which chronic low fluid intake may play a crucial role in the pathologies of four key diseases of the urinary system: urolithiasis, urinary tract infection, chronic kidney disease and bladder cancer. Although primary and secondary intervention studies evaluating the impact of fluid intake are lacking, published data from observational studies appears to suggest that chronic low fluid intake may be an important factor in the pathogenesis of these diseases.

## Keywords

bladder cancer, chronic kidney disease, fluid intake, urinary tract infection, urolithiasis

## INTRODUCTION

Although our requirement for water and its distribution throughout the body changes with age, homeostatic control of the body fluid balance at any given age remains a tightly controlled process in which the kidneys play a crucial role [1]. Our bodies compensate rapidly for small losses of water through the activation of renal water-saving mechanisms that aim to maintain plasma osmolality within the normal range of 285–295 mOsm/kg [1,2]. As plasma osmolality increases, transient receptor potential vanilloid (TRPV) channels from neurons from the organum vasculosum of the lamina terminalis are activated [3]. This stimulates the hypothalamic release of arginine vasopressin (AVP), a hormone involved in the body's retention of water and, secondarily, in the regulation of systemic blood pressure [1]. By acting to increase water absorption in the collecting ducts of the kidney nephron, AVP promotes water conservation and decreases urine volume [1]. The urinary system, and especially the kidneys, is therefore at the frontline for adverse effects of insufficient hydration and dehydration [2].

Current recommendations for total daily fluid intake (including water from all beverages and moisture content of foods) vary widely between different countries and organizations. In 2010, the European Food Safety Agency (EFSA) recommended a daily total water intake of 2.5 l for men and 2.0 l for

women (with around 20% coming from foods) [4]. Both the EFSA guidelines and the 2008 D-A-CH (Germany–Austria–Switzerland) joint nutrition guidelines recommend that urine osmolality in adults should be maintained around 500 mOsm/l [4,5]. This is equivalent to achieving urine volume of 1.6 l and 2.0 l, respectively, in women and men with an average potential renal osmolytes load [4].

What these guidelines have in common is that, unlike for other nutrients, the recommendations for total daily fluid intake are not based on a clear health rationale. Indeed, few intervention studies have assessed the long-term impact of total fluid intake on the urinary system, and no data from randomized clinical trials (RCTs) are available [2].

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There is some evidence to suggest that chronic low fluid intake/low urine output is associated with the occurrence of urinary tract infection (UTI) [6,7], and ensuring a high urine output with increased fluid intake has been shown to prevent recurrent urolithiasis over 2–5 years [8,9]. Higher fluid intake or daily urine volume is also associated with slower progression of chronic kidney disease (CKD) [10,11] and bladder cancer [12–14].

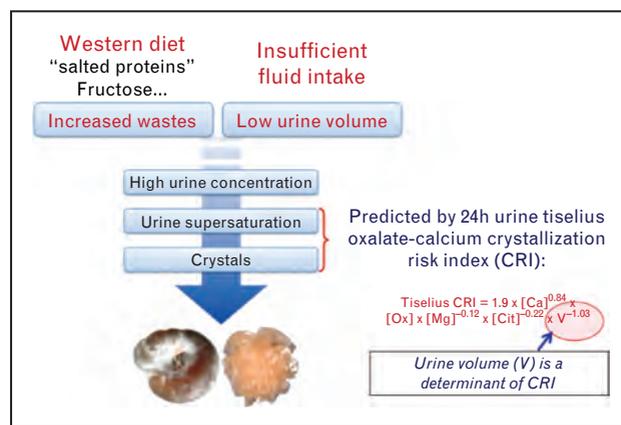
The aim of this study is to provide an overview of the epidemiology and pathophysiology of urolithiasis, UTI, CKD and bladder cancer, and to describe how chronic low fluid intake may play a critical role in their development. It is a narrative review based on the discussions of a panel of experts and is not intended to be a comprehensive review of the urinary system or the individual pathologies.

## UROLITHIASIS

### Epidemiology and pathophysiology of urolithiasis

Urolithiasis, or urinary stone disease, is highly prevalent worldwide with rates ranging from 7 to 13% in North America, 5 to 9% in Europe, and 1 to 5% in Asia. The estimated prevalence of urolithiasis reported in individual countries ranges from 4% in Argentina [15] to 20% in Saudi Arabia [16]. The varying rates between countries can be partly explained by the uptake of imaging. The widespread use of computed tomography scanning has increased identification of small stones, especially in the US and Europe. An analysis of an estimated 1 013 621 discharges for stone disease among the US Nationwide Inpatient Sample population found that inpatient treatment for nephrolithiasis and ureterolithiasis in women had increased by 22.0% ( $P=0.001$ ) and 14.5% ( $P=0.005$ ), respectively, between 1997 and 2002, even when adjusting for population changes [17]. Rates of stone disease also vary with ethnicity; a US population study in men found that Caucasians had the highest prevalence of stone disease, followed by Hispanics, Asians and African-Americans [18].

The processes by which stones form in the urinary system are complex and multifactorial, and remain incompletely understood [19]. Factors that favour the formation of stones include lower volume of water, low citrate levels and increases in solutes such as calcium, oxalate, uric acid and phosphate; factors that inhibit stone formation include urinary inhibitors such as citrate. The initial step of stone formation involves urine that becomes supersaturated with respect to stone-forming salts such as calcium oxalate (CaOx), the most common



**FIGURE 1.** Primary mechanisms associated with urinary calcium oxalate (CaOx) stone formation in Western countries [20–22]. The risk of CaOx crystallization can be predicted using a formula based on urinary calcium, oxalate, citrate and magnesium excretion. As indicated by the circled part of the formula, urine volume is a significant determinant of the risk.

stone composition (Fig. 1). A higher concentration of CaOx is held in solution until it exceeds the limit where urine is considered to be metastable with respect to the salt [23]. Beyond this point, dissolved ions or molecules precipitate out of solution and form crystals or nuclei, which can then aggregate with other crystals and grow to produce a kidney stone [19,24]. In normal human urine, the concentration of CaOx is four times its solubility in water. In supersaturated urine, CaOx can rise to as much as 11 times its solubility [23].

Other factors that can impact stone formation include the time taken for urine to travel through the nephron. There is some controversy over the concept of free crystal particle growth versus fixed particle growth. In some cases, adhesion between free crystals and the luminal cells of the renal tubules, and subsequent renal cell damage, results in the formation of fixed deposits that act as nuclei for crystal growth [19,24]. In supersaturated conditions, these deposits can grow to obstruct the nephron and, ultimately, lead to intratubular calcification [19,24].

Dietary factors associated with increased risk of stone formation include high or excessive intake of animal protein, vitamin C, dietary sodium, refined sugars and foods rich in oxalate [22,25]. Lifestyle factors can also contribute to stone formation. Obesity may result in increased urinary excretion of calcium, oxalate and uric acid, thereby increasing the risk for urolithiasis [22]. Obesity may also lead to low urine pH through insulin resistance, which, along with diabetes, can predispose to uric acid stones [26].

## Fluid intake and urolithiasis risk

Increased fluid intake is a mainstay of prevention for recurrent stone formation, with the aim of avoiding supersaturation through dilution of urine. Borghi *et al.* [9] conducted the first prospective randomized controlled trial of increased fluid intake in patients with a history of urolithiasis. Patients in the intervention group ( $n=99$ ) were instructed to drink enough water to achieve urine volume of at least 2l/day without any further dietary change. Over a 5-year follow-up period, 12% (12/99) had recurrent stone formation compared with 27% (27/100) patients who received no intervention [relative risk (RR) 0.45, 95% confidence interval (CI) 0.24,0.84;  $P=0.008$ ]. Relative supersaturations of CaOx, brushite and uric acid decreased sharply in the intervention group but not in the control group, and mean time to stone recurrence was 39 and 25 months, respectively ( $P=0.016$ ).

These findings suggest that a large daily intake of water can be recommended for effective secondary prevention of urolithiasis (level Ib evidence) [9]. As suggested by a long-term follow-up study in calcium stone formers, urine volume is of critical importance [27]. Patients who experienced stone recurrence despite medical advice to increase water intake had a median urine volume of 1.7l/day (range 0.7–2.8l/day) compared with 2.1l/day (range 1.2–4.0l/day) for patients free of recurrence over a mean follow-up of 6.8 years.

Environmental conditions predisposing to chronic fluid loss can also increase urolithiasis risk. Pronounced changes in ambient temperature can result in rapid development of stones; in a study of US healthy military personnel deployed to Kuwait, symptomatic urinary calculi formed within a mean of 93 days (SD 42 days) from deployment [28]. Studies of regional variations in ambient temperature across the US have identified a prominent 'stone belt' with a two-fold higher prevalence in the southeast than in the northwest [18]. Seasonal changes in stone disease have also been well described ('stone season') [29]. Physical exercise without increasing fluid intake to compensate for body water lost through sweating leads to reduced urine volume and urine acidification that promotes crystalluria and increases the risk of urolithiasis [30].

Although large observational studies exist to support this effect [31,32], the only primary prevention study dates back to 1966 when Frank *et al.* [8] investigated the effects of increased habitual fluid intake on stone formation in healthy inhabitants (no previous stone disease) of two desert towns in Israel with a high incidence of urolithiasis. Inhabitants of one town participated in an education programme to increase fluid intake as a preventive

measure, whereas inhabitants of the second town acted as a control group and did not participate in the programme. After 3 years, urine output was higher and incidence of urolithiasis was lower in the intervention group compared with control group (level IIb evidence) [8].

Given the availability of level I evidence that increased water intake can reduce the risk of stone recurrence by up to 50% [9,33], and that urolithiasis qualifies as a highly prevalent condition with significant morbidity, it is surprising that little effort has been made to consolidate the case for primary prevention set out by Frank *et al.* [8]. A recent economic analysis modelled on the French healthcare system suggests that a primary prevention strategy (fluid intake  $\geq 2$ l/day) could be cost-effective compared with no prevention. At an estimated per-person cost of 4237 Euros per episode of urolithiasis, compliance with increased fluid intake recommendations was found to have a major impact on cost savings, which ranged from 49 million Euros assuming 100% compliance to 10 million Euros assuming 25% compliance [34]. Further studies in the context of primary prevention should therefore be encouraged.

Additional cost-effectiveness analyses of improved hydration in low drinkers at risk of recurrent nephrolithiasis should also be conducted. Such analyses should take into account compliance and the unequal distribution of stone formation with respect to geography, sex, obesity, ethnicity and occupation, and the perspective (healthcare payer/social) of the analyses should be carefully considered in line with this.

## URINARY TRACT INFECTIONS

### Epidemiology and pathophysiology of urinary tract infection

Urinary tract infections result from a bacterial contamination of the genitourinary tract [35]. They are highly prevalent in both men and women of all age groups, but their frequency is about 50 times higher in adult women. More than half of them (50–60%) present with at least one UTI at some stage during their lives [36]. The estimated global incidence of UTIs is at least 250 million cases per year [37]. Accurate assessment of the prevalence and incidence of community-acquired UTIs is complicated by the fact that UTI is not a single clinical entity, and, in countries such as France and the US, is not a reportable disease [38]. Moreover, in most outpatient settings, the diagnosis of UTI is made solely on the basis of symptoms (e.g. difficult, painful and frequent urination, haematuria, supra-pubic

pressure) rather than with the added accuracy of urine culture (e.g. white blood cell count) [38].

Pathogens implicated in UTIs come from the enteric flora and involve mostly *Escherichia coli* (>70–95%) and *Staphylococcus saprophyticus* (<10%) [34]. As the bacteria increase in number they start to destroy the antimicrobial peptides lining the epithelium of the urinary tract, disrupting its integrity [35]. This, coupled with other factors, favours bacterial adherence to the epithelium, where, once anchored, the pathogens are phagocytosed into the cytoplasm of epithelial cells [35]. Infection occurs when a critical mass is reached, eventually resulting in cell exfoliation. Bacterial adherence is therefore an important risk factor for UTIs.

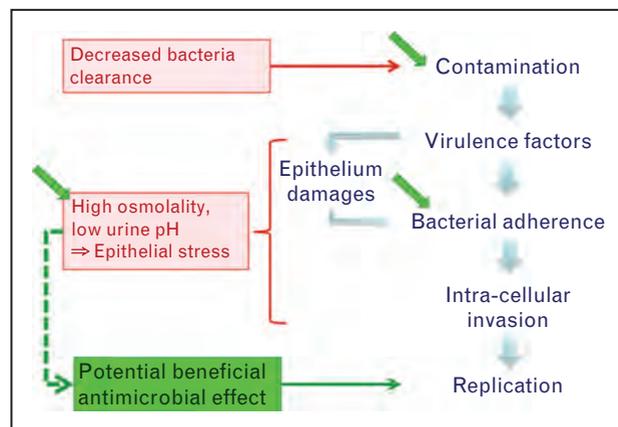
The presence of asymptomatic bacteriuria has been established as a reliable predictor for the development of symptomatic UTI [39]. In the US, the prevalence of asymptomatic bacteriuria ranges from 5 to 6% in women aged 18–40 years up to 20% in older, ambulatory adults [39], following a J-shaped distribution [40]. Higher prevalence of asymptomatic bacteriuria and UTIs has been reported in lower-income countries [41].

The high recurrence rate of UTI may derive from persistent bacterial residence within the mucosa of the urinary tract. One proposed mechanism for this is the formation of biofilm-like communities resistant to immune-system assaults and antibiotic treatments [35], and these have potential for serious complications such as pyelonephritis, septicaemia and foetal mortality [42]. Other factors that increase susceptibility to UTIs can be genetic, biological or behavioural. Subpopulations with greater susceptibility to UTI include children, pregnant women, older adults and patients who require long-term catheterization [42]. Patients with diabetes, multiple sclerosis or HIV/AIDS, and those with underlying urological abnormalities, are also more susceptible to UTIs than the general population [42].

### Fluid intake and urinary tract infection risk

Several factors could explain the potential role of fluid intake on prevention of UTIs. Firstly, increasing diuresis has a diluting effect on contaminating bacteria and virulence factors (Fig. 2) [43]. Secondly, consecutive to increased diuresis, is the flushing effect that occurs with each void, washing out contaminants and cleaning the epithelia. Thirdly, increasing the frequency of voiding has a shrinking effect on the bladder, effectively reducing the available surface area on which bacteria can thrive.

Currently, however, empirical evidence for any relationship between UTI and voiding characteristics (frequency of micturition, delayed voiding



**FIGURE 2.** Impact of a low urine volume on the risk of urinary tract infection (UTI) [42]. Red arrows and text: factors that increase the risk of UTI; green arrows and text indicate the potential beneficial effects of increasing urine volume on the risk of UTI.

and postvoid residual urine volume) is contradictory. An association between infrequent voiding of the bladder with UTI was first described in the 1960s, but studies continue to produce conflicting results: some show no effect of frequency of micturition on the incidence of UTI [44,45], whereas others report a protective effect of frequent voiding [46,47]. A 1-year prospective surveillance study in Norwegian nursing homes found no association between postvoid residual volume at least 100 ml and UTI ( $P=0.59$ ) [48], whereas other studies in older adults have found a strong association with recurrent UTI [49,50].

A fourth potential role for fluid intake in the prevention of UTI involves the maintenance of optimal urine pH. Low fluid intake is associated with an increase in urine osmolality and acidity. As a consequence, the epithelium is indirectly predisposed to bacterial adhesion, and therefore to an increased risk of UTI. Self-monitoring of urine osmolality, using either a probe or a urine colour chart, can alert people with recurrent UTIs when they are not drinking enough fluids [6]. A secondary prevention crossover study in premenopausal women who had been treated for at least two idiopathic UTIs in the previous 6 months found that self-monitoring urine osmolality using a handheld ‘traffic light’ probe was associated with a significant reduction in incidence of UTIs compared with the period in which the probe was not used. Of the 17 patients who completed both 4-month periods, 14 felt that the probe had helped them to prevent infection [6]. There is, however, some in-vitro evidence that an overnight increase in urine osmolality acts as a natural defence mechanism against the growth of isolated *E. coli* strains [51].

Most studies directly investigating the effect of fluid intake in the pathogenesis of UTI are low-quality observational studies, although some evidence of moderate quality is available from case-control studies. Certain subpopulations, such as teachers [7], are known to deliberately limit their fluid intake to avoid micturition during working hours, and may therefore be useful to study. A nonrandomized, multivariate analysis comparing 791 women teachers who deliberately restricted their fluid intake (25% voided only once during working hours, or not at all) with women able to drink without restrictions found that women in the former group were at significantly higher risk of UTI than were women in the latter group (RR 2.21, 95% CI 1.45–3.38) [7].

Given the scarcity and inconsistency of the available experimental and clinical data, it is not possible to draw any firm conclusions on the utility of UTI prevention (primary or secondary) as a basis on which to make recommendations about daily fluid intake. Well designed randomized controlled trials are needed to adequately establish whether maintaining adequate fluid intake contributes to the prevention of UTIs in healthy and recurrent populations. Even a simple, pragmatic study design comparing antibiotics and high water intake with antibiotics alone, could provide evidence of an effect over a short timeframe and in a small number of patients. Assessments could include 24-h urine output with a variety of hard (documented UTI, symptoms of UTI) and soft (patient-defined outcomes) endpoints. Procedures should be put in place to ensure compliance (for example, quarterly spot urine samples) and to avoid contamination.

A primary prevention study of UTI through improved hydration should also be considered, in a selected group of patients at risk for UTI. In this case, first UTI may not necessarily provide a clinically meaningful outcome in terms of hydration as almost all women have at least one UTI by the age of 30. Instead, measures of UTI frequency and recurrence may be considered. With this in mind, a suitable population could be young women followed up over a 5-year period. The number of patients required to adequately power the study in this selected group would be substantially smaller than in the general population.

## CHRONIC KIDNEY DISEASE

### Epidemiology and pathophysiology of chronic kidney disease

Chronic kidney disease is an inevitably progressive, serious condition associated with impaired quality

of life and early mortality, and its prevalence is increasing constantly. According to the National Health and Nutrition Examination Survey (NHANES), CKD affects 14.0% of the adult population in the US alone [52]. The prevalence is higher in subpopulations with hypertension (>20%) or diabetes (>35%) [53]. In the 2009 Health Survey for England, prevalence of CKD stage 3–5 was 5% in men and 7% in women (31% of men and 36% of women aged 75 years and over) [54].

Whereas CKD is more common among women, men with CKD are 50% more likely than women to progress to end-stage renal disease (ESRD), defined as kidney failure requiring dialysis or transplantation [53]. The worldwide prevalence of ESRD is thought to be more than 2 million [55], with an estimated 1.77 million receiving dialysis in 2008 [56]. In the US, 44% of people with ESRD have a primary diagnosis of diabetes and 28% of hypertension [53]. Because of its high prevalence, CKD represents a considerable cost burden. In the US alone, the healthcare costs associated with CKD, and particularly ESRD and renal replacement therapy, were estimated to be around \$28 billion in 2010 [57].

Regardless of the underlying cause, the development of CKD involves sclerosis of the glomeruli and fibrosis of the tubulointerstitial compartment. Due to the structure and function of the renal system, damage to one part of the kidney necessarily affects the other, triggering a negative cycle that leads to a gradual decline in renal function to ESRD [58].

Despite the available interventions to reduce cardiovascular morbidity and mortality, as well as the progression of kidney disease associated with risk factors such as smoking, diabetes, hypertension or hyperlipidaemia, the prevalence of CKD and its associated outcome burden continues to grow. This raises the question of whether these risk factors are as important as first thought. In recent years, there has been a significant research effort to explore and identify non-traditional risk factors for cardiovascular and other chronic diseases [10]. Nutritional patterns and intake of selected nutrients in higher or lower quantities may be one such non-established risk factor. In the context of CKD, most studies have focused on nutrients obtained from food, though some have also considered total fluid intake from both beverages and food.

### Fluid intake and chronic kidney disease risk

A potential mechanism by which a high fluid intake may prevent the development of CKD in healthy people can be proposed, based on works focusing on renal protection against polycystic kidney disease

[59,60]. These works stress the role of AVP, which modulates tubular cell growth, affects the renal microcirculation causing vasoconstriction of the efferent arteriole and renal blood flow redistribution [61,62]. By extension, a permanent increase in AVP concentration could contribute to the progression of tubulointerstitial damage during CKD [62]. Chronic increase of water intake determines a reduction in endogenous AVP levels, leading to lower blood pressure, less proteinuria and potentially reducing the severity of renal damage [62] (Fig. 3).

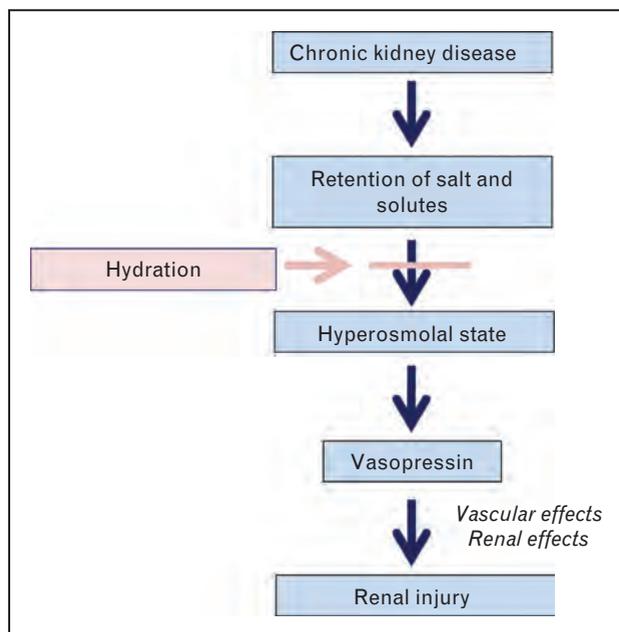
Clinical evidence for a beneficial role of water in CKD is controversial but there are a number of interesting hypothesis-generating studies that warrant the conduction of a properly designed randomized trial. Some studies have suggested that a high urine volume has a deleterious effect in people with established CKD, accelerating the rate of renal function loss [61,63]. Other studies have suggested that increased fluid intake/urine output is associated with a delay in the onset or progression of CKD [10,11].

In 2011, Strippoli *et al.* [10] published results from a cross-sectional study conducted in people

living in the Blue Mountains region of Australia, providing clinical evidence for the association between fluid and nutrient intake and moderate CKD. The study consisted of two surveys: the first in 1992–1994 ( $n=3654$ ) and the second in 1997–1999 ( $n=2335$ ). Mean daily fluid intake was 2.5 l (range 1.7–3.3 l). The prevalence of CKD was 12.4–23.5% in men and 14.9–28.7% in women. A comparison between participants who had the highest quintile of fluid intake (3.2l/day) with those who had the lowest quintile (1.8l/day) indicated a decreased risk for developing CKD in those with the highest water intake [odds ratio (OR) 0.5, 95% CI 0.32, 0.77] [10].

The association of higher fluid intake with lower glomerular filtration rate (GFR) is further supported by the findings of Clark *et al.* [11], who analysed data from 2148 patients over 6 years of follow-up. An inverse, graded relationship between urine volume (categorized according to 24-h samples as <1l/day, 1–1.9l/day, 2–2.9l/day and  $\geq 3$ l/day) and decline in estimated GFR was observed. Annual estimated GFR (eGFR) decline was progressively slower for each 24-h urine volume category increase. Comparison between the effects of excreting 1–1.9l/day and at least 3l/day demonstrated a significant benefit of high urine volume on the prevention of mild-to-moderate eGFR decline [11].

Ad-hoc prospective cohort studies and additional post-hoc analyses should be undertaken to evaluate the potential associations of fluid intake with CKD, death, major adverse cardiac events and other hard endpoints. Ultimately, a randomized controlled interventional study will be necessary to compare high fluid intake with standard behaviour to evaluate the benefits and harms of such an approach. If fluid intake is to be taken seriously as a potential novel protective factor against progression of CKD, it is essential to explore this possibility with adequate scientific methods.



**FIGURE 3.** Chronic kidney disease and hydration. Chronic kidney disease is associated with retention of salt and solutes and a hyperosmolar state that can result in the stimulation of vasopressin release. Vasopressin may have a role in renal injury via its ability to engage V1 receptors on the vasculature leading to hypertension and vascular injury. Hydration may confer benefit by reducing the hyperosmolarity and thereby decreasing endogenous vasopressin concentration.

## BLADDER CANCER

### Epidemiology and pathophysiology of bladder cancer

Bladder cancer is the fourth most common cancer in men and fifth most common cancer overall [64]. In 2008, there were an estimated 139 500 new cases in Europe and 51 300 bladder cancer-related deaths (75% men) [65]. The high prevalence of the disease and costs of intervention make bladder cancer one of the most expensive cancers to treat per patient from diagnosis to death [66].

Evidence suggests that increased exposure of the bladder lining to carcinogens, such as tobacco,

aromatic amines (e.g. benzidine) or other chemicals found in the chemical and rubber industries, is an important cause of bladder cancer [67]. The pathway to neoplasia from exposure to carcinogens is supported both by prospective studies and by inference. Given that almost all known carcinogens bind to DNA (dioxin is one exception) [68], exposure of the bladder wall to toxins inevitably results in some binding with epithelial DNA and the formation of DNA adducts. Each adduct has a low probability of inducing the critical mutations needed for progression through to neoplasia (there may only be a few hundred or thousand critical target bases per genome), but the probability increases with increases in DNA binding.

The highest population risk factor for bladder cancer comes from cigarette smoking, which is implicated in 50–75% of bladder cancer diagnoses in men and 14–35% in women. Compared with non-smokers, bladder cancer risk is three-fold higher in current smokers and two-fold higher in former smokers [69]. Successfully quitting smoking before 50 years of age reduces the risk of bladder cancer by about 50% after 15 years [13]. Second-hand or environmental tobacco smoke is also a risk [70,71]. The presence of the carcinogen 4-aminobiphenyl (one of the many toxins found in cigarette smoke) increases risk for developing butanol-enhanced DNA adducts and mutations at hotspots of the p53 gene [72].

By comparison, the population risk of bladder cancer associated with occupational exposures is less than 10% [73,74]. However, in certain highly exposed populations, bladder cancer rates of more than 50% have been reported [75]. A study of male Indian dye workers studied the long-term impact of benzidine exposure following the ban on industrial use of the compound in 1977. Four DNA adducts were identified at a significantly higher rate in exposed workers, but only N-(3'-phosphodeoxyguanosin-8-yl)-N'-acetylbenzidine was significantly associated with total benzidine metabolites in the urine ( $r=0.68$ ;  $P<0.0001$ ) [76].

### Fluid intake and bladder cancer risk

Given the probabilistic nature of the progression to neoplasia in the bladder from the formation of DNA adducts, there are ample opportunities to intervene and disrupt the process and several studies have shown that adduct levels respond to exposure reduction. It seems logical that increasing fluid intake would result in a rapid dilution of urinary metabolites and flushing out of carcinogens from the bladder through increased voiding, thereby reducing contact between carcinogens and bladder

urothelium [77,78]. However, no consensus has yet emerged from the available literature on the utility of increased fluid intake in reducing bladder cancer risk. There is more compelling evidence for the role of dietary interventions in the modification of bladder cancer risk. A meta-analytical review of epidemiological studies found that low fruit intake (RR=1.40), low vegetable intake (RR=1.16) and high fat intake (RR=1.37) were associated with an increased risk of bladder cancer [79]. Diets high in meat or low in retinol or beta-carotene were not associated with an increase in risk. These results suggest that a diet high in fruits and vegetables and low in fat may help prevent bladder cancer, but the individual dietary constituents that reduce the risks remain unknown [79].

A review of several case-control studies that evaluated the association of fluid intake and bladder cancer found mixed results; seven studies identified an increased risk and three showed no association [13]. Results from the Health Professionals Follow-up Study, in which 252 cases of bladder cancer were prospectively diagnosed among the 47 909 participants, showed that daily fluid intake was inversely associated with the risk of bladder cancer when comparing the highest quintile of total fluid intake with the lowest (>2531 versus <1290 ml; RR 0.51, 95% CI 0.32, 0.80) [12]. This study was based on food-frequency questionnaire given to the participants that recorded the frequency of consumption of the 22 types of beverages. Meanwhile, the European Prospective Investigation into Cancer and Nutrition (EPIC) also used a food frequency questionnaire and found no association between total fluid intake and risk of bladder cancer (513 newly diagnosed cases among 233 236 patients with a mean follow-up of 9.3 years). No associations were observed between risk of bladder cancer and intake of water, coffee, tea/herbal tea, milk and other dairy beverages [80].

One hypothesis for why increased fluids may lead to bladder cancer is presence of water pollutants such as trihalomethanes. One review evaluated six case-control studies of bladder cancer (2729 cases and 5150 controls) with using questionnaires with detailed information on fluid intake and water pollutants [81]. The study controlled for fluid consumption and adjusted for age, sex, study, smoking status, occupation and education. They found that total fluid intake was associated with an increased risk of bladder cancer in men but not women. Interestingly, the increased risk was associated with intake of tap water but not for non-tap water, which suggests that carcinogenic chemicals in tap water may explain the increased risk.

In terms of further research, the existing evidence for an impact of improved fluid intake on bladder cancer is too inconsistent to support a prevention study. Nevertheless, a 'proof-of-concept' study run in a high-risk population and assessing the impact of fluid intake on the DNA-adducts formation may strengthen the evidence. Tobacco smoking is a clear risk factor for increased adduct formation and bladder cancer; an ideal patient group might therefore include all smokers who are also low drinkers with highly concentrated urine. Studies are currently underway to try and identify other biomarkers for bladder cancer, for example, precancerous cell pathology which may predict recurrence.

## **DISCUSSION**

Urinary tract pathologies are a major global public health issue. As the prevalence and cost of these pathologies continue to increase, the need for a better understanding of their underlying mechanisms becomes more urgent. As we have seen, these are complex and multifactorial disorders, and there is growing interest in the roles of nutrition and fluid intake in their development.

Previous reviews on the purported health benefits of a high fluid intake have all pointed towards a lack of evidence to support the widely cited recommendation that we should all be drinking at least eight 8 oz glasses (1.9 l) of water per day (excluding caffeinated or alcoholic drinks) [82,83]. Indeed, historically, there has been little empirical scientific evidence to support any of the claimed public health and cosmetic benefits of a high fluid intake, and high-quality primary and secondary prevention studies are lacking [82]. Importantly, however, the same lack of evidence applies to claims of no benefit. Although we may not yet be able to conclude that drinking extra water reduces the risk of some urinary tract pathologies, we have seen in this review that data, albeit not scientifically rigorous, do exist to support the hypothesis. From these studies, inadequate fluid intake appears to be an important factor in several chronic diseases of the urinary tract.

In many countries worldwide, a significant proportion of the population have a fluid intake below the levels of current recommendations. For example, in France, where an estimated 7% of the population will develop a UTI in a given year (equivalent to 5 million UTIs annually), mean fluid intake is just 1.85 l/day (median 1.72 l/day) [84]. Crucially, population data show that one in four people in France have a fluid intake less than 1.05 l/day. The challenge is to identify similar groups of 'low

drinkers' in other populations, understand the reasons for their restricted fluid intake and investigate the impact of improved fluid intake on the incidence of urinary tract pathologies in these individuals. If these investigations support the preliminary evidence, simply increasing fluid intake may reduce the risk for developing urinary tract pathologies and, consequently, the overall cost to the healthcare system.

When identifying groups of 'low drinkers' using fluid intake surveys, one should be aware of the challenges and limitations of literature related to fluid intake. Many factors such as potential misreporting, the large between and within-individual variation, the way of reporting on the results and environmental conditions need to be taken into consideration when high quality fluid intake data want to be collected [85,86]. Errors in reporting can occur when studies use food frequency questionnaires or 24-h dietary recall to assess fluid intake. As these methods rely on the respondent memory, there is a potential for recall bias and misreporting [87]. Moreover, when these two methods are used to record fluid intake or when mean fluid intakes are reported, the variations in fluid consumption existing between days and within the day are left out of perspective [87]. This, however, could be relevant to the previously described pathologies. For example, one day a person could consume 3 l of fluid and the next day only 1 l. The overall mean of 2 l might be protective, yet the intermittent day of low fluid intake could be adequate to contribute to a pathology. Even within 1 day, the night is such an intermittent period during which most people do not drink and as such are relatively dehydrated. A limited number of studies used a 7-day fluid record to address among others the limitation of within-day variation [88–91]; however, different methodologies to assess fluid intake have also been used [86]. Future studies will need to work to standardize methodologies to collect data.

The task then would be to promote improved fluid intake habits at the population level, which may not be easy. Asking a habitual low drinker to increase their daily fluid intake to, say, 2 l is likely to cause difficulties and non-compliance, and as we have seen from smoking cessation programmes, immediate rewards often win out over long-term health benefits. Another potential issue is that some patients who successfully screen for studies will spontaneously increase their fluid intake immediately upon learning the purpose of the trial, which may confound results. It is important, therefore, that carefully planned, high-quality clinical trials – ideally in the context of primary prevention, where supported by observational and secondary

prevention data – are undertaken to strengthen the existing evidence and convey a compelling enough message to alter fluid intake behaviour.

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### Conflicts of interest

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