Review

# Hydration and Disease

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**Key words: dehydration, hydration, hyperhydration, chronic diseases**

Many diseases have multifactorial origins. There is increasing evidence that mild dehydration plays a role in the development of various morbidities. In this review, effects of hydration status on acute and chronic diseases are depicted (excluding the acute effects of mild dehydration on exercise performance, wellness, cognitive function, and mental performance) and categorized according to four categories of evidence (I–IV).

Avoidance of a high fluid intake as a precautionary measure may be indicated in patients with cardiovascular disorders, pronounced chronic renal failure (III), hypoalbuminemia, endocrinopathies, or in tumor patients with cisplatin therapy (IIb) and menace of water intoxication.

Acute systemic mild hypohydration or dehydration may be a pathogenic factor in oligohydramnios (IIa), prolonged labor (IIa), cystic fibrosis (III), hypertonic dehydration (III), and renal toxicity of xenobiotica (Ib).

Maintaining good hydration status has been shown to positively affect urolithiasis (Ib) and may be beneficial in treating urinary tract infection (IIb), constipation (III), hypertension (III), venous thromboembolism (III), fatal coronary heart disease (III), stroke (III), dental disease (IV), hyperosmolar hyperglycemic diabetic ketoacidosis (IIb), gallstone disease (III), mitral valve prolapse (IIb), and glaucoma (III).

Local mild hypohydration or dehydration may play a critical role in the pathogenesis of several broncho-pulmonary disorders like exercise asthma (IIb) or cystic fibrosis (Ib). In bladder and colon cancers, the evidence on hydration status' effects is inconsistent.

**Key teaching points:**

- Extremes of water intake, severe dehydration, and water intoxication, are known causes of mortality.
- It is now known that even mild dehydration may also account for different morbidity.
- Prolonged labor, urolithiasis, and urinary tract infection are examples of conditions associated with acute or chronic dehydration.

## INTRODUCTION

Many diseases have multifactorial origins. Particularly, differences in lifestyle and environmental impact are implicated in several diseases and constitute risk factors that are currently being evaluated. The extremes of water metabolism, severe dehydration, and water intoxication are well-known causes of mortality. There is increasing evidence, however, that mild dehydration may also account for different morbidity. This review is a follow up to two earlier reviews [1,2] and is based mainly on computer-based literature searches such as Medline. The following markers of hydration status were used: [a] intake (water OR fluid), [b] urine (volume OR osmolality), and [c] hydration. Papers were classified according to the following categories of evidence [3]:

(Ia) evidence from meta-analysis of randomized controlled trials;
(Ib) evidence from at least one randomized controlled trial;
(IIa) evidence from at least one controlled study without randomization;
(IIb) evidence from at least one other type of quasi-experimental study;
(III) evidence from descriptive studies such as comparative, correlation, and case control studies; and
(IV) evidence from expert committee reports, opinions or clinical experience of respected authorities, or both.

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Acute health effects of mild dehydration on exercise performance, wellness, cognitive function, and mental performance will be discussed by other authors in this supplement.

## HYPERHYDRATION AND DISEASE

The short half-life time of water excretion of about 100 min based on a high renal dilution capacity is an effective mechanism to protect healthy subjects from hyperhydration [4].

### Health Effects of Polydipsia and Polyuria

A high water intake may be pathogenic in certain diseases. It is a routine clinical practice to recommend a moderately high fluid intake in patients with cardiovascular disorders, low serum albumin levels, or endocrinopathies (e. g. inappropriate ADH secretion). Patients with chronic renal insufficiency were urged to drink to be well-hydrated. However, a high fluid intake with urine osmolalities below plasma osmolality may accelerate the decline of glomerular filtration rate (category III evidence) [5]. Low urine osmolality is a determinant of cisplatin-induced nephrotoxicity in tumor patients, justifying the use of concurrent intravenous infusion of osmotically active substances (category IIb evidence) [6].

### Water Intoxication

Acute water intoxication with confusion, nausea, fatigue, seizures, and even death has been considered a rare event [7]. In miners, steal workers, and firemen on a boat working in the heat, uncompensated high sodium losses in sweat may result in hyponatremia and non-osmolar vasopressin secretion. An additional high intake of water with low sodium content may decease hyponatremia further provoking convulsions and even death. Water intoxication in infants may result from repeated immersion during swimming [8] or malicious forcing of water on a child [7], in toddlers from near drowning or drowning [9], in marathon runners from an uncontrolled high intake of fluids eventually combined with the intake of anti-inflammatory drugs [10,11], in crash diet potomania from a hypocaloric diet with a low renal osmolar load and a slightly impaired maximum urine dilution capacity [12] and in psychotic patients from forced drinking [13].

Iatrogenic water intoxication may be observed after rapid infusion of high amounts of hypotonic solutions in infants with hypertonic dehydration, during urine concentration test with vasopressin analogues [14] or uncontrolled gastric lavage in children after oral poisoning [15]. Chronic hyperhydration may result in chronic diarrhea [16].

## MILD DEHYDRATIN OR HYPOHYDRATION AND DISEASE

Mild hypohydration or dehydration may favor acute or chronic, systemic, or local health effects.

### Acute Systemic Mild Dehydration or Hypohydration

**Oligohydramnios.** Amniotic fluid is a complex substance essential for fetal wellbeing. Both oligohydramnios and polyhydramnios are associated with a significant increase in perinatal morbidity and mortality. Simple and long-term maternal hydration with oral water or intravenous hypotonic fluid appeared to increase amniotic fluid volume and seemed to be beneficial in the preventing and managing oligohydramnios during labor (category IIa evidence) [17,18]. In pregnancy-induced hypertensive gravidae, the effect on amniotic fluid index was not as pronounced as in normotensive gravidae (category IIa evidence) [19].

**Prolonged Labor.** Little is known about differences in labor progress, birth outcomes, and neonatal status between women who consume food and/or fluid during labor and those who fast during labor [20]. Increasing fluid administration for nulliparous women in labor above rates commonly used was associated with a lower frequency of prolonged labor and possibly less need for oxytocin in a randomized controlled study (category Ib evidence) [21].

Theoretically, hydration may reduce uterine contractility by increasing uterine blood flow and by decreasing pituitary secretion of antidiuretic hormone and oxytocin. In two small studies, however, no advantage of hydration was observed when compared to bed rest alone to stop preterm labor (category IIa evidence) [22].

**Cystic Fibrosis.** Patients with cystic fibrosis show high sodium content in sweat just below plasma sodium concentration. Sweat volume is mainly derived by contraction of extracellular volume during physical activity and in the heat. As losses of functional water are small, plasma osmolality rises very little and there is almost no stimulus to drink [23]. Patients with cystic fibrosis, therefore, are especially prone to heat injury. During the August 2003 heat wave in France, six out of 245 adult patients with cystic fibrosis developed extrarenal dehydration with functional kidney failure, hypokalemia, and hypochloremia. One patient died of malignant hyperthermia (category III evidence) [24].

**Hypertonic Dehydration in Infants.** In infants, high protein and sodium content in formula and weaning food may result in a submaximal urine osmolality, which increases the life-threatening risk of hypertonic dehydration during acute gastroenteritis (category III evidence) [25].

**Dehydration and Toxicity of Xenobiotica.** Contrast agents used in angiography procedures are known to cause contrast-induced nephropathy, especially in patients with mild dehydration. Prehydration is sufficient to prevent contrast-induced nephropathy (category Ib evidence) [26].

## CHRONIC SYSTEMIC MILD HYPOHYDRATION OR DEHYDRATION

### Urolithiasis

There are many descriptive studies relating urolithiasis to low fluid intake or urine volume. However, there is only one randomized controlled study [27]. The study consisted of 199 patients, who were divided into two groups. After the first idiopathic stone episode, one group was instructed to increase its fluid intake to achieve a urine volume of at least 2 L without any further dietetic change, while the other group did not receive any treatment. During the five year follow up periods, patients from the intervention group had higher urine volume (2.1–2.6 vs. 1.0– 1.2 1/24 h), a lower recurrence rate (12 vs. 27%), and a longer time to first recurrence (39 vs. 25 months) (category Ib evidence). In Israel, primary prevention was demonstrated comparing two desert towns with a high incidence of urolithiasis. Inhabitants of one settlement participated in an education program to increase fluid intake as a preventive measure, whereas inhabitants of the second settlement were not informed. Three years later, follow up on the intervention population showed a higher urine output and a lower incidence of urolithiasis (category IIb evidence) [28].

Two prospective studies with large cohorts confirm high fluid intake's preventive effect on symptomatic urolithiasis risk (category IIb evidence) [29,30]. In a study on hot-area workers presenting with low urine volumes had a nine-fold risk of urolithiasis compared to room-temperature workers (category IIb evidence) [31]. Children with urolithiasis rarely comply with high fluid intake recommendations despite their experience of pain during colic [32]. Prolonged exposure to microgravity during spaceflight increases the risk of renal stone formation. Lower body negative pressure chamber treadmill, alkali therapy, and aggressive hydration are recommended countermeasures to decrease urinary supersaturation [33].

### Urinary Tract Infection

Experimental and clinical data on the connection between fluid intake and urinary tract infection risk are conflicting [34]. In two recent descriptive studies, poor fluid intake or low urine output were host-mediated predisposing factors (category III evidence) [35,36]. In two comparative studies, poor fluid intake was much more frequent in females with urinary tract infection than in controls (53% vs. 16%; 50% vs. 9.5%) (category III evidence) [37,38]. Two years after implementing health education and seasonal on-the-job training in 366 qualified female workers, the number of water intakes and urine voids increased and the prevalence of urinary tract infection decreased from 9.8% to 1.6% (category IIb evidence) [39].

### Bladder and Colon Cancer

Two recent literature reviews and two meta-analyses investigating the relationship between total fluid intake and bladder cancer show inconsistent findings (category III evidence) [40–43]. Single studies point to increased bladder cancer risk in patients that regularly consume high quantities of special beverages or tap water (category III evidence) [44]. Consuming high quantities of contaminated water, such as tap water with a high nitrate concentration, may increase colon cancer risk (category III evidence) [45,46]. A high total fluid intake seems not to account for an increased risk. Constipation and laxative use may increase colon cancer risk (category III evidence). However, mild dehydration seems not to be a confounder [47].

### Constipation

A few studies have shown fluid restriction to increase constipation [48]. The beneficial effect of increased fluid intake may perhaps be limited to subjects with dehydration [48]. In a retrospective, multi-center, case-control study, 73% of the children with constipation drank less than four glasses of water per day compared to 47% of those without constipation (category III evidence) [49]. In another study, 94 Japanese patients with Parkinson's disease had a much lower intake of coffee and tea than controls (604 ml/d vs. 910 ml/d) [50]. Constipation severity correlated inversely with the amount of water intake (category III evidence) [50].

### Hypertension

A potent renal vasopressin receptor agonist, dDAVP, markedly reduced both urine flow and sodium excretion in healthy humans [51]. The impact of antinatriuresis by chronic high vasopressin levels in mild dehydration on the pathophysiology of hypertension, however, needs to be delineated. In diabetic patients, lower urine flow and sodium excretion rates are associated with higher blood pressure during the day and a reduced fall in blood pressure at night (category III evidence) [52]. The offspring of prenatally water-restricted ewes exhibit hypernatremia and hypertension, indicating *in utero* programming of an altered set point for systemic osmolality and blood pressure [53].

### Venous Thromboembolism

Hemoconcentration, polycythemia, and the special circumstances of travel-thrombosis are risk factors for thromboembolism that are possibly intensified by dehydration. After an acute ischemic stroke, venous thromboembolism was increased in

patients with serum osmolality values of more than 297 mosm/kg (category III evidence) [54]. Long-distance travel seems to be associated with increased venous thromboembolism risk. Although the causal role of travel-related factors (e.g. sitting in a cramped position, hypobaric hypoxia, low humidity due to climatization, and reduced fluid intake) is not yet proven, several scientific committees recommend maintaining adequate hydration, exercising one's legs, and using compression stockings (category IV evidence) [55]. In vitro tests show that changes in hydration can significantly impact adhesion, causing normal erythrocytes to display adhesive properties similar to those of sickle cells and vice versa [56].

### Fatal Coronary Heart Disease

In the Adventist Health Study, a high water intake was associated with a reduced risk of fatal cardiac heart disease (category III evidence) [57]. In Japanese taxi drivers, low water intake at night might have caused increased blood coagulation, hematocrit, and fatal cardiac heart disease risk [58].

### Cerebral Infarct

Raised plasma osmolality or hematocrit on admission is associated with increased risk of stroke morbidity and mortality (category III evidence) [59,60]. In patients with ischemic stroke, the best discharge outcome is associated with an initial mid-range hematocrit level [61].

### Dental Diseases

Although there is considerable circumstantial evidence to indicate a link between dehydration and dental diseases, this has not yet been proven [62]. Hypohydration reduces salivary excretion. Exercise dehydration may be the main reason for loss of salivary protection of teeth. One aspect of individualized patient-empowering erosion WATCH strategies to combat tooth wear in healthy young Australians, therefore, is the recommendation for an adequate water intake during exercise (category IV evidence) [63]. Salivary protection of teeth may be disturbed not only by quantity and composition of beverage intake, but also by drinking habits. Infant bottle or breastfeeding caries is an example that sipping from a bottle for too long and breastfeeding too frequently favors dental caries [64].

### Hyperosmolar Hyperglycemic Diabetic Ketoacidosis

In patients with diabetes mellitus, dehydration favored hyperglycemia development, whereas fasting resulted in reduced plasma glucose concentrations (category IIb evidence) [65]. Elderly patients with diabetes mellitus are particularly vulnerable to hyperglycemia and dehydration, the key components of hyperosmolar hyperglycemic syndrome, because insulin sensitivity and thirst mechanisms decrease with increased age [66]. In children with diabetic ketoacidosis, the serum osmolality level on admission was the most important predictor of death [67]. In pediatric patients with newly diagnosed diabetes mellitus, high intakes of carbonated carbohydrate fluids favored a more severe presentation of ketoacidosis [68].

### Gallstones

Water ingestion has been shown to induce gallbladder emptying and a high daily water intake could perhaps prevent gallstone formation [69]. In a case control study in a female population, the main risk factors of gallstone disease were age, family history of gallstone disease, fat intake, number of pregnancies, and menopause. Drinking water from a deep well was a protective factor (category III evidence) [70].

### Mitral Valve Prolapse

Mild dehydration induced echocardiographic-visible signs of mitral valve prolapse in approximately 50% of healthy asthenic women with previously normal cardiac findings. In men, only 10% developed dehydration-induced mitral valve prolapse (category IIb evidence) [71].

### Glaucoma

The difference between intraocular pressure and blood pressure of ocular vessels plays a dominating role in the pathogenesis of glaucoma. The combination of a high intraocular pressure and a low blood pressure is especially unfavorable. Oral intake of water transiently increases intraocular pressure while dehydration decreases it. In a retrospective analysis of the eyes of 76 open-angle glaucoma patients, mean intraocular pressure peak and percentage of intraocular pressure variation were significantly higher during a water drinking test in patients with visual field progression compared to patients without progression (category III evidence) [72]. Eyes with higher glaucomatous visual field damage presented with higher intraocular peaks and fluctuations after water ingestion [73]. In patients with low-tension glaucoma and visual field defects, emotional stress or cooling one hand in cold water may lead to ocular vasospasms with low blood pressure and increased eye sensitivity to intraocular pressure [74]. In a case control study, subjects with vasospastic syndrome reported a reduced desire to drink, a lower estimated quantity of daily fluid intake, and more episodes of low blood pressure (category III evidence) [75].

## LOCAL MILD HYPOHYDRATION OR DEHYDRATION

### Bronchopulmonary Disorders

Improvement of systemic hydration status has not been demonstrated to be clinically effective in disorders of the lungs and airways [76]. However, local water transport and hydration status of mucus play a critical role in the pathogenesis of

several of these disorders. In exercise asthma, inhaling warm, humidified air or medicaments that stabilize mucus hydration status rapidly ameliorate the clinical picture (category IIb evidence) [77]. During exercise, the evaporative water loss from the airway surface triggers mast cells to release inflammatory mediators that stimulate bronchoconstriction [78]. Persistent inflammation leads to excessive production of mucus with high viscoelasticity and adhesiveness. Inhaling hypertonic saline or mannitol increased the clearance of mucus and improved the quality of life in patients with mild asthma, bronchiectasis, and cystic fibrosis [79]. In patients with cystic fibrosis, the clinical benefit of inhaled hypertonic saline was impeded by amiloride inhibiting the osmotically-driven water transport (category Ib evidence) [80]. In 10 asthmatic patients and 10 controls, a dry-air tachypnea challenge in the laboratory caused dehydration in the expired air in all subjects and bronchoconstriction in half of the asthmatics but none of the controls (category IIb evidence) [81]. Humidifying the inspired air prevented bronchoconstriction. In 19 healthy subjects, the net water loss in expired air increased by 42% when the breathing mode was switched from nasal to oral expiration [82]. In a randomized crossover study, aerosol administration of hyaluronic acid, a substance with a unique capacity to link and to retain a particularly relevant number of water molecules, reduced the bronchial hyper-reactivity to exercise in asthmatics [83].

**Table 1.** Relationships of Acute, Chronic and Local Mild Dehydration on Various Disease or Body States and Category of Evidence Classification

| | Category of Evidence | | | | | |
|---|---|---|---|---|---|---|
| | Ia | Ib | IIa | IIb | III | IV |
| Acute Systemic Mild Dehydration | | | | | | |
| Oligohydramnios | | | X | | | |
| Prolonged labor | | | X | | | |
| Hypertonic dehydration in infants | | | | | X | |
| Cystic fibrosis | | | | | X | |
| Renal toxicity of xenobiotics | | X | | | | |
| Chronic Systematic Mild Dehydration | | | | | | |
| Urolithiasis | | X | | | | |
| Urinary tract infections | | | | X | | |
| Constipation | | | | | X | |
| Hypertension | | | | | X | |
| Venous thromboembolism | | | | | X | |
| Coronary heart disease | | | | | X | |
| Stroke | | | | | X | |
| Dental Disease | | | | | | X |
| Hyperosmolar hyperglycemic diabetic ketoacidosis | | | | X | | |
| Gallstones | | | | | X | |
| Mitral valve prolapse | | | | X | | |
| Glaucoma | | | | | X | |
| Local Mild Dehydration | | | | | | |
| Bronchopulmonary disorders: | | | | | | |
| Exercise asthma | | | | X | | |
| Cystic fibrosis | | X | | | | |

## CONCLUSION

There are conditions where an individual may need to limit fluid intake and they include cardiovascular disorders, end stage chronic renal failure, hypoalbuminemia, and treatment with cisplatin. Acute systemic mild hypo- or dehydration may be a pathogenic factor in other conditions including oligohydramnios, prolonged labor, patients with cystic fibrosis, hypertonic dehydration in infants and renal toxicity of xenobiotics. Chronic systemic mild- hypo- or dehydration also may be a pathogenic factor in urolithiasis, urinary tract infection, constipation, hypertension, venous thromboembolism, fatal coronary heart disease, stroke, dental disease, hyperosmolar hyperglycemic diabetic ketoacidosis, gallstone disease, mitral valve prolapse and glaucoma. Local mild hypo-or dehydration may be a pathogenic factor in bronchopulmonary disorders such as exercise asthma or cystic fibrosis.

Table 1 summarizes the conditions described herein and the level of evidence supporting the associations. Few randomized controlled trials exist. Most available evidence is from descriptive studies, such as comparative studies, correlation studies, and case control studies.

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