Mechanisms by Which Dehydration May Lead to Chronic Kidney Disease

C. Roncal-Jimenez \textsuperscript{a} M.A. Lanaspaa \textsuperscript{a} T. Jensen \textsuperscript{a} L.G. Sanchez-Lozada \textsuperscript{b} R.J. Johnson \textsuperscript{a}

\textsuperscript{a}Division of Kidney Diseases and Hypertension, University of Colorado Denver, Aurora, Colo., USA; \textsuperscript{b}Laboratory of Renal Physiopathology and Nephrology Department, INC Ignacio Chavez, Mexico City, Mexico

Dehydration classically refers to the excessive loss of body water through conditions such as diarrhea, sweating, or urinary losses, but among the lay public dehydration may also refer to the loss of both water and salt leading to a hypovolemic state [1]. Dehydration has multiple effects on the kidney, leading to urinary concentration due to activation of vasopressin that occurs as a result of increase in serum osmolarity due to the loss of body water. Classically dehydration results in a 'pre-renal state' associated with intrarenal vasoconstriction but with relative maintenance of glomerular filtration rate (GFR). If volume depletion is severe, GFR falls, but it has been thought to be completely reversible with hydration, unless ischemia results in acute kidney injury (AKI). Nevertheless, AKI is thought be largely reversible. Hence, dehydration has not been classically considered a risk factor for chronic kidney disease (CKD).

In recent years, the concept that dehydration does not cause CKD has been challenged. This has been highlighted in recent studies investigating a mysterious form of CKD that has been epidemic in Central America [2, 3]. The disease, which has been named Mesoamerican Nephropathy, is being observed at remarkable frequency among male agricultural workers on the Pacific Coast, particularly in Nicaragua and El Salvador. The condition is distinct from other major causes of CKD such as high

Key Words
Dehydration · Chronic kidney disease · Vasopressin · Fructose · Uric acid

Abstract
Dehydration, a condition that characterizes excessive loss of body water, is well known to be associated with acute renal dysfunction; however, it has largely been considered reversible and to be associated with no long-term effects on the kidney. Recently, an epidemic of chronic kidney disease has emerged in Central America in which the major risk factor seems to be recurrent heat-associated dehydration. This has led to studies investigating whether recurrent dehydration may lead to permanent kidney damage. Three major potential mechanisms have been identified, including the effects of vasopressin on the kidney, the activation of the aldose reductase-fructokinase pathway, and the effects of chronic hyperuricemia. The discovery of these pathways has also led to the recognition that mild dehydration may be a risk factor in progression of all types of chronic kidney diseases. Furthermore, there is some evidence that increasing hydration, particularly with water, may actually prevent CKD. Thus, a whole new area of investigation is developing that focuses on the role of water and osmolarity and their influence on kidney function and health.

Richard J. Johnson
Division of Renal Diseases and Hypertension
University of Colorado Denver
Aurora, CO 80045 (USA)
E-Mail Richard.johnson@ucdenver.edu

© 2015 S. Karger AG, Basel
Published online: June 18, 2015
www.karger.com/anm

This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (www.karger.com/OA-license), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.
blood pressure and diabetes. Most subjects are used to working many hours in sugarcane fields under very hot conditions, and dehydration is common in this group [4, 5]. Renal biopsies, when performed, show chronic tubulointerstitial disease, often with evidence for glomerular ischemia [6]. While the etiology of the disease remains unknown, a favorite hypothesis is that it may relate to recurrent volume depletion and dehydration [2, 3]. It has also been suggested that dehydration and volume depletion play a major role in increasing the risk of kidney injury from pesticides, agrochemicals, heavy metals or other potential exposures that are still under investigation [2, 3].

Our group and others have pursued three major possible mechanisms by which dehydration and volume depletion may cause CKD (figure 1). First, there is increasing evidence that elevations in vasopressin may have a role in causing or exacerbating CKD [7]. Vasopressin is increased in the setting of volume depletion due to the effects of hyperosmolarity to stimulate vasopressin release from the posterior pituitary. Vasopressin is also elevated in laboratory animals with CKD. When increased amounts of water are administered, the vasopressin levels can be suppressed and the progression of renal damage can be slowed. Thus, vasopressin has emerged as a likely mediator of kidney damage [8].

Second, it is known that hyperosmolarity can activate a variety of pathways, including stimulation of vasopressin, the central sympathetic nervous system, and the aldose reductase pathway. Recently, our group showed using laboratory rats that dehydration-associated hyperosmolarity can activate the aldose reductase pathway in the renal cortex, resulting in the generation of sorbitol that can then be converted to fructose [9]. The endogenous fructose that is generated can then be metabolized by fructokinase, an enzyme present in the proximal tubule [10]. The fructose is metabolized to fructose-1-phosphate, but in the process there is marked intracellular ATP consumption, leading to intracellular phosphate depletion, activation of AMP deaminase, and the production of chemokines [10]. The local oxidative stress results in tubular injury and stimulates fibrosis [9]. Indeed, animals recurrently exposed to heat and water restriction developed chronic kidney disease, but this was not observed in mice genetically lacking fructokinase [9]. Thus, activation of the aldose reductase-fructokinase pathway is another mechanism by which recurrent dehydration may lead to CKD.

Third, heat-associated dehydration may result in hyperuricemia, both due to increased production (associated with low-grade, subclinical rhabdomyolysis from strenuous exertion) and reduced urate excretion associated with renal vasoconstriction [11]. Hyperuricemia is common in subjects with Mesoamerican Nephropathy. In turn, hyperuricemia has been
recognized as a risk factor for both acute and chronic kidney injury [12, 13]. The mechanism may involve uric acid-induced vasculopathy with the development of glomerular hypertension [14], as well as direct tubular effects resulting in epithelial mesenchymal transition [15].

Research on Mesoamerican nephropathy has led to renewed interest in the role of dehydration as a potential causative factor in CKD. More recently, patients suffering from conditions that appear similar to Mesoamerican nephropathy have been reported from other countries, including Brazil, Sri Lanka, and Australia [16, 17]. Thus, it is possible that recurrent dehydration may be a general cause of CKD, which is being recognized only in recent days.

Furthermore, provocative epidemiological studies suggest that increasing fluid intake can slow the progression of CKD. Indeed, some epidemiological studies suggest that a urinary output of 3 liters per day provides significant renal protection compared to subjects excreting 1 to 1.5 liters per day [18, 19]. If true, this suggests that, while dehydration may be a risk factor for CKD, increasing water consumption to a level that is more than what is considered normal intake may provide superior protection. Indeed, a clinical trial is in process to test this fascinating possibility.

A caveat is that not all fluids should be considered equal. Soft drinks and sugary beverages, for example, might be expected to worsen kidney disease due to their high fructose content that can directly provide substrate to the fructokinase pathway. Indeed, experimental studies show fructose can induce renal injury and accelerate CKD in laboratory animals [20, 21]. Furthermore, some clinical studies also suggest that the intake of sugary beverages may increase the risk for kidney disease [22].

In conclusion, for decades the prevention and treatment of kidney disease has been directed primarily toward good blood pressure management and tight control of diabetes. New studies, initiated from research on Mesoamerican nephropathy, have identified dehydration as another likely risk factor. More recent studies are investigating whether protection can occur not only by preventing dehydration but also by encouraging increased intake of water. Clinical studies are now in progress, but these discoveries may help shepherd new approaches to prevent and slow the progression of kidney disease.

**Financial Support**

Supported by a grant from Danone Research.

**Disclosure Statement**

RJJ, CRJ and LGS have received research funding from Danone Research to explore mechanisms by which dehydration may cause CKD. RJJ, CRJ, LGL and MAL are also members of Colorado Research Partners LLC that is developing inhibitors of fructose metabolism. RJJ also has shares and is on the Scientific Board of XORT therapeutics.

**References**


