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Climate Change and the Kidney

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Abstract
The worldwide increase in temperature has resulted in a marked increase in heat waves (heat extremes) that carries a markedly increased risk for morbidity and mortality. The kidney has a unique role not only in protecting the host from heat and dehydration but also is an important site of heat-associated disease. Here we review the potential impact of global warming and heat extremes on kidney diseases. High temperatures can result in increased core temperatures, dehydration, and blood hyperosmolality. Heatstroke (both clinical and subclinical whole-body hyperthermia) may have a major role in causing both acute kidney disease, leading to increased risk of acute kidney injury from rhabdomyolysis, or heat-induced inflammatory injury to the kidney. Recurrent heat and dehydration can result in chronic kidney disease (CKD) in animals and theoretically plays a role in epidemics of CKD developing in hot regions of the world where workers are exposed to extreme heat. Heat stress and dehydration also has a role in kidney stone formation, and poor hydration habits may increase the risk for recurrent urinary tract infections. The resultant social and economic consequences include disability and loss of productivity and employment. Given the rise in world temperatures, there is a major need to better understand how heat stress can induce kidney disease, how best to provide adequate hydration, and ways to reduce the negative effects of chronic heat exposure.

Introduction

Increasing worldwide temperatures are now well documented, and the mean temperature increase in the last 50 years approximates 0.8 °Centigrade. While the absolute rise in temperature may not seem large, it is already having major effects on human health [1]. One of the more striking consequences is a marked increase in extreme heat events, termed heat waves [2–4]. Heat waves are the

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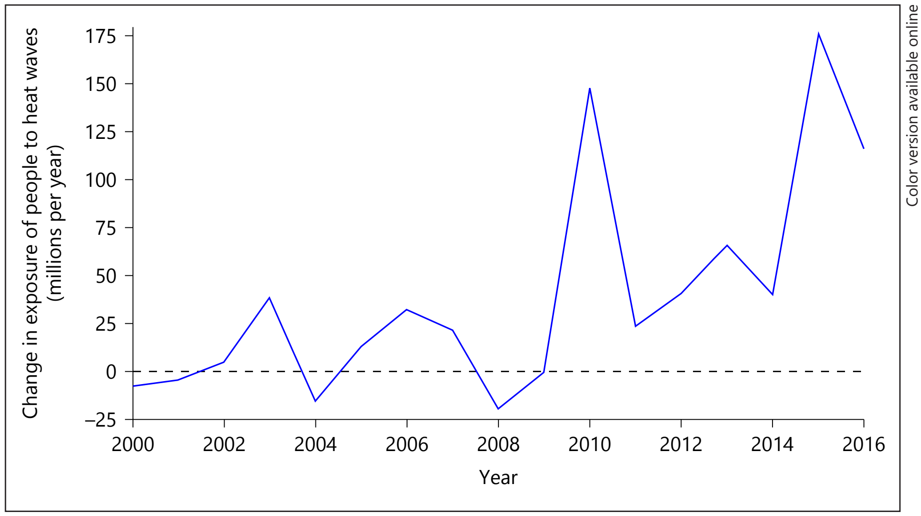

Fig. 1. Change in heat wave exposure (in individuals >65 years old) relative to the 1986–2008 average. Here heat waves are defined as a period of 3 days or more in which the minimal temperature exceeds the 99th percentile of the average temperature between 1986 and 2008, and the population was limited to individuals 65 years or older. Reused with permission from the Lancet [7].

most common cause of mortality of all weather-related events in the United States (including tornados, hurricanes, and lightning strikes) [5]. Heat waves are also among the top 10 worldwide causes of death by natural disasters between 1980 and 2017 (Table 1). Different definitions have been used to classify heat waves, but one of the more common definitions is a temperature that is 5 °C greater than the mean high temperature for a given day, and one that persists for at least 5 days [6]. Numerous studies have reported a dramatic increase in heat waves worldwide [7] (Fig. 1). For example, one estimate suggests that in 2015 alone there were 175 million more people exposed to heat waves as a consequence of climate change [7]. Heat waves are dangerous not only because of the risk of overheating the human body but also due to increased mortality of individuals with cardiovascular and respiratory disorders [6]. One of the worse heat waves was the one that struck Europe in August 2003, resulting in 73,000 deaths [8]. However, heat waves have caused significant mortality throughout the world, including Chicago in 1995 [9], Andhra Pradesh in 2014 and 2015 [10, 11], and Karachi, Pakistan in 2015 [12]. Heat waves and extreme heat also affect labor performance and efficiency [13] and may affect crop performance [14]. Some heat waves have been associated with such extreme temperatures that even wildlife are endangered, and there are predictions that in the future some parts of the world could become so hot that they will become uninhabitable [15–17]. Thus, regulating body temperature is a key to survival. Maintaining a well-hydrated state is critical to this process, but it is of additional concern that the availability of safe water supplies is dwindling worldwide. Indeed, there is now evidence that as much as 10% of the world population faces a serious shortage of water availability [18, 19]. In addition, studies suggest that many individuals, including children and adolescents, who do have access to potable water are considered to be underhydrated [20].

Table 1. The most fatal natural disasters between 1980 and 2017

Event (location, date)	Deaths
Tsunami/Earthquake (Thailand, 2004)	220,000
Earthquake (Haiti, 2010)	159,000
Cyclone, storm surge (Myanmar, 2008)	140,000
Cyclone, storm Surge (Bangladesh, 1991)	139,000
Earthquake (Pakistan, 2005)	88,000
Earthquake (China, 2008)	84,000
Heat wave, Drought (Europe, 2003)	**70,000**
Heat wave (Russia, 2010)	**56,000**
Earthquake (Iran, 1990)	40,000
Earthquake (Iran, 2003)	26,000

Adapted from data published by Münchener Rückversicherungs-Gesellschaft. Heat waves accounted for the 7th and 8th most fatal natural disasters during this period. From: https://www.munichre.com/site/corporate/get/params_E1716525033_Dattachment/1707976/munichre-natural-catastrophes-in-2018.pdf.

In this review, we discuss the effect of climate change on diseases of the kidney. The kidneys have a supreme function in maintaining blood volume to support blood pressure as well as extracellular and intracellular osmolality ("the internal milieu") that allows for normal metabolism. One of their more important functions is urinary concentration, in which it minimizes fluid loss while assuring the excretion of nitrogenous wastes. Unfortunately, the high metabolic work, as well as the concentrated

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excretion of wastes, makes the kidney very susceptible to injury from climate change. Indeed, studies have reported that increasing temperatures translate into increased admissions through the emergency room of a wide range of renal disorders, including acute kidney injury, chronic kidney disease (CKD), kidney stones, and urinary tract infections (UTIs) [21, 22]. Occupational exposure to heat stress has also been linked with higher incidence rates of kidney disease [23] and to a loss in productivity of workers when their kidney function becomes compromised [13]. Here we discuss some of these associations as well as potential links with the epidemics of CKD of unknown origin in hot regions throughout the world.

Heatstroke and Acute Kidney Injury

One of the major health consequences of extreme heat is heatstroke, which results when one cannot adequately control body temperature, resulting in hyperthermia (typically defined as a temperature >40.6 °C, >105°F) that can lead to delirium, coma, seizures, and multiorgan failure [5]. Heatstroke can occur during heat waves (termed epidemic or classic heatstroke) and also in association with exercise or labor in the heat (termed exertional heatstroke) [24].

Exertional heatstroke is especially common among military personnel, marathon runners [25–28], as well as workers in mines or agricultural fields (especially sugarcane) [29]. It is especially common among new workers who are not acclimatized and those that are overweight [29]. Epidemic heatstroke most commonly occurs in association with heat waves and affects those vulnerable to illness, such as the elderly, those with obesity or diabetes, those who are malnourished, individuals who have no air conditioning, and those with underlying cardiovascular or respiratory diseases.

Both classical and exertional heatstroke can be severe, in which case they are characterized by confusion or delirium, often coupled with acute liver and kidney failure. Indeed, acute kidney injury is a common manifestation in individuals presenting with epidemic heatstroke. For example, in the 1995 heat wave in Chicago, over 50% of those presenting with heatstroke had acute kidney injury [9]. While acute kidney injury may accompany severe manifestations with coma and liver failure, milder forms of heatstroke may be only associated with fevers and acute kidney injury.

There appear to be 2 types of acute kidney injury [24]. One form appears to be classical rhabdomyolysis (typically with creatine phosphokinase levels >1,000 μ/L), often associated with hyperuricemia and signs of dehydration. This form may be more common with exertional heatstroke. The other form is associated with normal or only mildly elevated creatine phosphokinase levels and is more common in epidemic heatstroke [24]. Indeed, unlike rhabdomyolysis, in which the injury appears more like an acute tubular injury, the second form of acute kidney injury clinically manifests more as an acute interstitial nephritis, with urinary leukocytosis and hematuria, and with a renal biopsy showing acute tubulointerstitial nephritis. It is thought that this condition results from ischemia, temperature-induced oxidative stress, and decreasing intracellular energy stores [30, 31].

Heatstroke is also commonly associated with electrolyte abnormalities [24, 32]. One study of 66 subjects with exertional heatstroke reported acute kidney injury in 91%, hyponatremia in 53%, hypokalemia in 71%, hypophosphatemia in 59%, hypocalcemia in 51%, and hypomagnesemia in 35% [32]. In particular, the low serum potassium, phosphate, and magnesium were all associated with increased urinary excretion of these electrolytes, suggesting a tubular defect. Other potential causes include loss of sodium and potassium through the sweat. Some subjects also present with respiratory alkalosis, which is known to reduce serum phosphate, although metabolic acidosis appears to be more common.

Some individuals (10–30%) with heatstroke-associated acute kidney injury require dialysis [32]. If the patient survives the acute illness, kidney function usually returns to normal [32]. However, some cases of heatstroke may progress to CKD months later with the presence of chronic tubulointerstitial nephritis on biopsy [33, 34].

Heat Stress Nephropathy as a Cause of CKD

In recent years, epidemics of CKD have been identified in various hot regions of the world where it preferentially affects workers who labor manually under extremely hot conditions [35]. One of the major sites of this disease is along the Pacific Coast of Central America, developing among sugarcane workers and others working in agricultural communities [36]. There is evidence that this epidemic has been progressively increasing since the 1970s [37]. The observation that the disease tends to occur in the hotter regions of Central America, coupled with evidence that the workers are placed under a great deal of heat stress [38, 39], has led to the hypothesis that the disease may be driven by global warming [40]. Indeed, a recent study suggests that working in the sugarcane fields is associated with higher humidity due to the presence of the cane and that heat waves are driven not only by increasing mean temperatures but also by El Niňo events [41].

There is increasing evidence that the development of CKD may result from repeated acute kidney injury driven by subclinical or clinical heatstroke [42]. Specifically, repeated acute kidney injury has been recently reported across work-shifts in sugarcane workers from this region [43–46]. While most cases are asymptomatic, some subjects present with fever, leukocytosis, leukocyturia, and acute kidney injury that may require admission to the local hospital [47–49]. These latter cases resemble heatstroke, as they may present with similar electrolyte abnormalities and also with acute interstitial nephritis on biopsy [47–49]. There is also evidence that some develop CKD over time [48], similar to that which occurs with exertional heatstroke [34].

Experimental studies support this association. Indeed recurrent heat stress and dehydration can induce chronic inflammation and tubular injury in mice and rats [50–52]. The mechanism of the kidney injury is likely related to increased internal body temperatures, the effects of hyperosmolarity to activate the polyol-fructokinase pathway, and the chronic effects of vasopressin to induce tubular and glomerular injury [50–52]. In addition, clinical studies suggest that the effects of heat and dehydration induce a concentrated and acidic urine, which can also lead to urinary urate crystallization with tubular damage [53]. Indeed, some experimental data suggest that lowering uric acid might provide protection [54, 55].

Acute kidney injury is now being reported throughout the world in hot agricultural communities including India (Andhra Pradesh), Sri Lanka (north central province), Mexico (Vera Cruz), central Florida, and the Central Valley of California [56–58]. In many of these areas, epidemics of CKD are also being reported [59–61]. A major concern is that these epidemics may be driven by increasing temperatures and heat waves, and that they may presage epidemics to come.

Other Effects of Heat Stress on the Kidney: Stones and Infections

Kidney stones (nephrolithiasis) are increasing in prevalence [62] and have also been proposed to result from increasing temperatures associated with climate change [63]. Heat stress and dehydration predispose to urinary concentration and low urine volumes that increase the risk for stones [64]. In the United States, for example, the "stone belt" that characterizes the hotter regions in the southern United States is projected to move northward as climate warming continues [63]. Experimental studies show that the primary kidney stone substance associated with heat stress is uric acid, due to its increased generation following exercise-induced muscle damage and the urinary acidification that occurs during the concentrating process [64].

UTIs may also be related to underhydration and potentially affected by climate change. Indeed, a recent study found that increased daily water consumption could increase urine output and reduce the risk for UTIs [65].

Effect of Soft Drinks in Heat Stress-Associated Kidney Damage

Soft drinks contain fructose, a sugar that results in local tubular injury, inflammation, and oxidative stress when metabolized by the kidney [66]. Recent studies suggest that soft drinks may increase the risk for acute and chronic kidney injury [67]. Indeed, experimental studies have shown that rehydration with soft drinks could enhance kidney damage in dehydrated rats [51, 68]. In addition to the injury associated with fructose metabolism, fructose may be able to stimulate vasopressin that can then augment the renal injury [51, 69]. Indeed, a recent clinical study also reported that rehydration with soft drinks could induce markers of kidney damage in healthy subjects following exercise in high temperatures [70], although epidemiologic studies conducted in hot field settings to date have found no association.

Additive Effects of Toxins and Toxicants

A prevailing theory suggests that in the context of heat and dehydration, naturally occurring toxins and man-made toxicants may concentrate in the kidney during periods of recurrent acute kidney injury. Candidates under investigation include potentially nephrotoxic agrochemicals, heavy metals, use of nonsteroidal anti-inflammatory drugs, tobacco, and silica. Further research is ongoing, including environmental risk assessments that include meteorological conditions.

Summary

In summary, while the kidney has a major role in protecting the host from the effects of heat stress, it is also a target for heat stress associated injury. The effects of heat can lead to both acute and CKD, electrolyte abnormalities, and kidney stones and UTIs. As global warming continues, major efforts are required to assure adequate hydration and prevent overheating in vulnerable populations who are at risk for heatstroke. Heat warning systems, changes in occupational practices, and public health initiatives also are needed [71, 72]. Most importantly, scientific investigations should be directed at identifying how to slow, stop, and reverse global warming.

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