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Heat-related chronic kidney disease mortality in the young and old: differing mechanisms, potentially similar solutions?

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Global warming is the single biggest threat to the future of the planet according to World Health Organisation.[1] Climate change has contributed to higher rates of weather-related disasters over the last 10 years, including exposure to heatwaves.[2] An increased prevalence of chronic kidney disease (CKD)-related mortality in young people who do not have the usual risk factors for the same has raised concern. The problem is particularly concentrated in areas such as Central America, India, Sri Lanka and Egypt,[3] where young working men are exposed to excessive heat on a regular basis. This is sometimes dubbed Mesoamerican nephropathy or CKD of unknown origin (CKDu). Working indoors, which affects more female workers, including kitchen work with ovens, smelters and steel manufacturing are also implicated.[4] Approximately 40% of the world's population inhabit areas subject to excessive heat throughout the year. Increasing prevalence of early-onset CKD has been noted worldwide, with El Salvador, in particular, recording the highest mortality rates.[5]

Meanwhile, CKD is emerging as a leading cause of mortality particularly in patients suffering from hypertension, diabetes mellitus and obesity. Worldwide, kidney disease is now reported as the 12th most common cause of death.[6] While debate persists regarding the diagnosis and actual prevalence of CKD in those of advanced age, the majority of these patients are derived from the older age groups.[7] Moreover, age-related reductions in renal reserve, plasma renin and aldosterone responses, glomerular filtration rate, as well as a predisposition to hyperkalaemia and haemoconcentration with hypernatraemia render older patients particularly susceptible to kidney injury and death when exposed to excessive heat.[8 9] Other particularly vulnerable demographic subgroups include young children, disabled, isolated individuals and those who are socioeconomically disadvantaged.[10]

The possible mechanisms of the escalation in heat-related kidney failure-associated mortality in younger patients have not been fully elucidated. First, in a hot environment, increased insensible loss of body water and salt occurs. With prolonged heat exposure this leads to substantial fluid deficit which, if not replaced, may result in vasoconstriction and associated kidney injury.[11] Moreover, with exertion in a state of chronic dehydration, subclinical rhabdomyolysis can occur due to chronic low-grade muscle injury, which can in turn also contribute to hyperuricaemia.[12 13] This has been postulated to lead to glomerular hypertension and renal tubular injury. A pilot study performed on sugar cane workers in El Salvador demonstrated higher mean end-of-work serum levels of uric acid versus morning levels (428 µmol/L vs. 387 µmol/L), with the vast majority demonstrating concurrent glomerular filtration rates <60 mL/min.[13] Resultant activation of the aldose reductase pathway within the kidney leads to increased levels of glucose and fructose. Fructose is then metabolised by fructokinase in the proximal tubule, which can lead to inflammation and fibrosis of the renal parenchyma as evidenced by Roncal-Jimenez *et al.*, who demonstrated that mice without fructokinase were spared renal injury despite similar exposure to dehydration.[14]

The aetiology of this enhanced susceptibility to CKD appears to be multifactorial.[15] For example, water 'hardness' may play a role. With high levels of calcium, magnesium and other metal cations, endemic areas with harder water in Sri Lanka correlate positively with those areas where CKDu is most prevalent.[16] It is suggested that these cations can combine with substances in herbicides such as glyphosate. Glyphosate is an aminophosphonic acid analogue of the natural amino acid, glycine, which can be absorbed by inhalation, transdermally, or ingested either in food sprayed by herbicide or contaminated water supplies.[16 17] A study of 500 species of juvenile *Clarias gariepinus* fish which were fed with commercial pellets containing glyphosate demonstrated tissue evidence of renal necrosis and degenerated kidney tubules versus control fish without toxicant exposure.[18]

A recently published systematic review and meta-analysis of epidemiological studies on CKDu suggested positive associations with male gender, family history of CKD, water intake and lowland altitude.[19] Meanwhile, in a cross-sectional study of sugar cane workers, Kupferman *et al.* reported that reduction of kidney function occurred commonly and almost half of those affected had CKD after 1 year.[20] Moreover, in a longitudinal study examining rates of decline of kidney function in high-risk populations for CKDu, rapid decline occurred more commonly in men and was associated with outdoor agricultural work and lack of shade during work breaks.[21]

It is difficult to identify consistent risk factors isolated to affected areas but poorer economic areas generally do not provide equal access to healthcare, clean water, toilet facilities (with particularly female workers drinking less to avoid the need to urinate while working), and appropriate screening or diagnostics.[4]

Increased exposure of new populations to heat stress appears inevitable beyond the borders of currently identified countries, thus further enhancing the numbers at risk of CKD. Furthermore, in the presence of traditional risk factors for CKD, such as hypertension and diabetes mellitus, with associated increased rates of ischaemic heart disease, it is reasonable to assume that the increase in heat stress will result in further increases in mortality. Indeed, increased rates of heat-related myocardial infarction have already been reported in a cross-sectional study.[22]

Prevention is the best approach to addressing heat-related CKD-associated mortality. In older patients, this includes anticipatory implementation of simple measures such as maintenance of adequate fluid intake combined with minimising insensible loss using tepid sponging and relocating affected people to a cooler environment. Adjusting doses of medications such as diuretics, monitoring electrolytes and renal function, followed by early intervention to optimise electrolyte abnormalities will minimise progression to acute kidney injury. Regional heat plans and robust social programmes are helpful.[9] In previous heatwaves, a report indicates that those people who met in public places had less morbidity and mortality than those who retreated indoors.[23]

Recent evidence indicates that implementing similar basic interventions in younger susceptible individuals, such as provision of portable water reservoirs, scheduled rest periods and mobile shaded tents to sugar cane workers, resulted in improvements in markers of dehydration and increased GFR.[24 25] However these findings derived from small studies, with many methodological problems and thus lacks external validity. Guidelines recommend replacing fluid frequently when working in conditions that may lead to heat stress, for example, 250 mL water every 20 min with or without weight monitoring.[26] Other interventions such as self-monitoring of early morning body weight, urine colour and thirst perception lack evidence. Education of workers regarding heat illness risks and preassessment of workers' serum creatinine levels may highlight at-risk individuals, but workers may avoid such testing for fear of resultant loss of income. Employers need education to emphasise that time lost with regular hydration breaks should result in increased productivity, less illnesses, workplace accidents and absenteeism.

While the mechanisms of heat-related kidney disease may differ between young and older individuals, simple anticipatory interventions could ameliorate deleterious renal consequences for all age groups.

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