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Renal dysfunction in general overheating (literature review)

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Abstract. Over the past 30 years, climate change has taken one of the leading places among the ten main causes of death due to natural disasters. Rising temperatures have been shown to increase emergency department admissions for a wide range of kidney diseases, including acute kidney injury (AKI), chronic kidney disease, kidney stones, and urinary tract infections. The occupational effect of heat stress is also associated with AKI, which can quickly progress to acute kidney failure with high mortality. The basis of the pathogenetic mechanisms of heat-induced AKI is a decrease in the circulating blood volume and electrolyte disturbances due to increased perspiration. Water evaporation from the surface of the skin contributes to dehydration with an increase in serum osmolality. In response to this, vasopressin is activated, the specific gravity of urine increases, and the amount of urine decreases. The glomerular filtration rate progressively decreases. Hypokalemia develops, which changes to hyperkalemia within 12 hours. Tubular endothelium is damaged, which leads to microthrombosis of afferent and efferent renal arteries, the development of an inflammatory response, and exhaustion of the renal interstitium. Possible rhabdomyolysis and myoglobinemia with subsequent tubular obstruction worsen existing kidney damage. According to the leading mechanism of damage, there are two types of acute heat damage to the kidneys: classical rhabdomyolysis and acute interstitial nephritis. Although modern medical advances have contributed to the development of effective treatment and management strategies (rapid cooling, extracorporeal detoxification methods, etc.), mortality in kidney damage due to general overheating has decreased slightly over the past decades. For health care and industry researchers, it is necessary to identify the harmful occupational conditions that lead to heat stress nephropathy and to develop certain occupational safety strategies.

Keywords: climate change; general overheating of the body; heat damage to the kidneys; nephropathy; nephrolithiasis

Global warming is an extremely important problem today. In European countries, including Ukraine, this process progresses almost twice as fast as in other countries, that is, today we are on the edge of a climate crisis. According to the results of numerous modern studies, it has been proven that the average temperature increase throughout the world during the last 50 years is approximately 0.8 °C, while it is expected that it will increase by another 3–4 °C by the end of this century [1–3]. There is an assumption that over the next decades in Ukraine, the temperature term “winter” will lose its previous meaning. Over the past 30 years, climate change has taken one of the leading places among the ten main global causes of death due to natural disasters [4, 5]. In the sum-

mer of 2022, the UNIAN news agency reported on abnormal heat in European countries, a state of emergency was introduced in some places, and more than a thousand deaths were registered [6]. Thermal damage is becoming an increasingly common phenomenon in the world and represents a certain problem of military medicine [7, 8], limiting the safety of people who live and work in hot climates [5], workers of hot workshops, stokers, glassblowers, cooks, etc. [9].

Classic heat stress occurs without physical exertion when heat production and gain exceed output, and exertional heatstroke in healthy young and physically active people is usually caused by significant mechanical work [10, 11]. Military, athletes and agricultural workers mostly experience

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heat stress due to physical exertion. However, temperature damage can occur even in a state of rest due to the indirect infrared radiation from the massive metal surfaces of the vehicle [12]. The threat of excessive professional overheating also exists in developing countries and in formal labor sectors. Occupational hazards reach a high level in tropical countries with low- or middle-income levels, where informal sectors of the population are common, often working with high physical load in hot, densely populated regions with a disregard for safety rules [5, 9, 13]. Elderly people, people who use alcohol, non-steroidal anti-inflammatory drugs, psychodysleptics, etc. are most vulnerable to heat injury and its most frequent complication, acute kidney injury (AKI). In neuroleptic malignant syndrome, AKI occurred in 30 % of patients, of which 8 % required renal replacement therapy. Women are more prone to functional oligoanuria than men due to dehydration [9, 14].

In heat injury, AKI can rapidly progress to acute renal failure with high mortality. Although modern medical advances have contributed to the development of effective treatment and management strategies (rapid cooling, extracorporeal detoxification methods, etc.), mortality in AKI due to general overheating has decreased slightly over the past decades [15–17].

The kidneys play a unique role in protecting the body from dehydration in the heat, but as a result they themselves most often suffer in case of heat injury. The kidneys perform the most important function of stabilizing blood volume to maintain blood pressure, as well as extracellular and intracellular osmolality (“internal environment”), which ensures normal metabolism. One of the most important functions is the concentration of urine, when the kidneys minimize fluid loss, ensuring the excretion of nitrogenous waste. Unfortunately, the high metabolic rate, as well as the concentrated excretion of waste, make the kidneys very susceptible to damage due to climate change. Rising temperatures have been shown to increase emergency department admissions for a wide range of kidney diseases, including AKI, chronic kidney disease (CKD), kidney stones, and urinary tract infections [18]. The occupational effect of heat stress is also associated with a higher incidence of kidney failure and a decrease in the workplace productivity of people with impaired kidney function [19]. Thus, the potential influence of global warming and extreme temperatures on the frequency of AKI is a certain problem of our time [2, 3]. Renal dysfunction of various severity is a documented symptom that occurs in approximately 25–35 % of cases of general overheating [10, 11, 20–23]. During the abnormal heat in the city of Chicago in 1995, 53 % of patients with heatstroke were diagnosed with acute renal failure [2, 14, 24].

An analysis of the results of a multicenter study indicates a 30% increase in the incidence of AKI at high temperatures [25]. The existing situation became the basis for the formation of a hypothesis according to which kidney damage can proceed as a “heat stress” nephropathy [5, 13].

Thermal injury-induced AKI can be related to many factors, such as direct heat stress, prerenal injury (caused by hypovolemia), renal failure, rhabdomyolysis, and inflammatory responses. Disseminated intravascular coagulation

(DIC) due to the heat stress can lead to multiple organ dysfunction, including AKI and electrolyte imbalance [26]. The combination of AKI with DIC is accompanied by an increase in mortality by 50–70 % and requires dialysis treatment and a long stay in a hospital [10, 11, 17, 26, 27].

The main pathogenetic mechanisms of AKI include a decrease in blood volume, microthrombosis of afferent and efferent renal arteries, obturation of renal tubules, direct nephrotoxic effect, and renal interstitial exhaustion [28]. Evaporation of water from the surface of the skin contributes to dehydration with an increase in serum osmolality. Due to the activation of vasopressin, the specific gravity of urine increases (> 1.020 g/l). At the beginning of the process, the glomerular filtration rate remains at an acceptable level, but with the progression of dehydration, it decreases. Until recently, it was believed that such kidney dysfunction is completely reversible, but if ischemia has not already led to acute renal failure. Hyperthermia causes a temporary change in kidney function and, accordingly, in the scintigraphic picture during radionuclide renography. Radionuclide renography is recommended at normothermia, as the analysis at a higher body temperature can lead to false results [29]. Electrolyte abnormalities and renal dysfunction often develop in severe cases of hyperthermia. Upon admission to the hospital, hypokalemia (which after 12 hours was replaced by normo- or hyperkalemia in 56.4 % of patients), hypophosphatemia, hyponatremia, hypocalcemia, and hypomagnesemia were observed in most victims [26]. In the future, the development of the following electrolyte and biochemical disorders is possible: hypernatremia, hyper-/hypocalcemia, hyperphosphatemia, coagulopathy, oliguria, myoglobinuria with the development of acute renal failure. Heatstroke usually leads to stupor and multiple organ failure, and the degree of kidney damage directly depends on the central body temperature [5]. A drop in blood pressure and hypokalemia lead to a sharp decrease in glomerular filtration rate and damage to the endothelium of the renal tubules. Tubular dysfunction can also be associated with myoglobinuria (tubular obstruction) and DIC [23, 27].

High metabolic work, as well as concentrated removal of waste products make the kidneys very sensitive to damage due to climatic anomalies [2, 3]. Glomerular filtration rate decreases by 15–25 % after a temperature increase of 2 °C and changes even more as the central temperature increases. Concentrations of serum creatinine and urea increase, and the albumin/creatinine ratio decreases [29]. Stimulation of the renin-angiotensin system during hyperthermia inhibits renal blood flow [30].

Heat stress causes destabilization of the intestinal barrier that leads to the release of endotoxins from the intestinal lumen into the interstitium and blood flow, which triggers a cytokine cascade and ultimately leads to a systemic inflammatory response syndrome [16, 31]. In addition, the results of several studies also proved that the course of AKI is associated with an increase in myeloperoxidase level, the effect of tumor necrosis factor α against the background of early expression of interleukin-6 [16, 26, 32].

AKI is closely related to the morpho-functional state of macrophages [33, 34] and remodeling of the renal inter-

stitium [35]. Multivariate analysis indicated that increased levels of laboratory markers of inflammation such as lymphocytes and neutrophils and coagulation dysfunction (D-dimers) correlated with the degree of overheating. An increase in hematocrit by 15–20 % was mostly observed in women (69.4 %) [9, 36]. With overheating, induced microthrombosis, aggregation and the process of consumption/use of platelets lead to thrombocytopenia. The exact mechanism of thrombocytopenia development in hyperthermia with AKI has not been fully elucidated [16]. The results of separate studies prove that the platelet count $< 90 \cdot 10^9/l$ is recognized as an independent predictor of AKI in patients with heatstroke. The immune response in victims was mostly strong, and excessive activation of inflammatory cells and damage to the endothelium led to the development of AKI [37, 38]. Serum creatinine levels were significantly higher 24 hours after admission to the intensive care unit, and 18 % of patients required renal replacement therapy. Renal failure was more severe in those who died than in those who survived [14].

Rhabdomyolysis is a syndrome characterized by leakage of muscle cell contents into the bloodstream. Repeated heat stress and analgesia combined with muscle overexertion can lead to mild or overt rhabdomyolysis, hyperosmolarity, hyperthermia, and extracellular fluid depletion. Rhabdomyolysis due to general overheating and physical overload is accompanied by a sharp increase in blood and urine of uric acid with crystalluria, extracellular fluid volume deficit and, as a result, renal hypoperfusion, hypokalemia and hyperosmolarity-mediated mechanisms that trigger the activation of the intrarenal polyol-fructokinase pathway and affect vasopressin [2, 9, 23].

As a complication of rhabdomyolysis, AKI occurs quite often and accounts for about 8–15 % of all cases of kidney damage in the United States, and the frequency of AKI in rhabdomyolysis can reach 55 %. The highest frequency of rhabdomyolysis is determined in patients with classic heatstroke. Classic manifestations of rhabdomyolysis include myalgias, limb weakness, and pigmenturia due to myoglobinuria without hematuria. Mortality in these cases can reach 70 %, especially in cases of delayed treatment and the presence of multiple organ failure [39–41]. Massive rhabdomyolysis can follow physical exertion, especially in combination with other risk factors, such as extremely hot and humid conditions, poor physical condition, and hypokalemia. In addition to severe dehydration and fluid sequestration in damaged muscles, AKI in case of rhabdomyolysis is the result of direct tubular toxicity caused by circulating vasoconstrictor ischemia, activation of the renin-angiotensin and sympathetic nervous systems, and hyperproduction of antidiuretic hormone. By itself, myoglobin practically does not have a noticeable nephrotoxic effect on the tubules, but until the moment when the urine acquires an acidic reaction. In the pathogenesis of AKI during rhabdomyolysis against the background of an acidic reaction of urine, myoglobin is deposited in the lumen of the tubules in the form of granules and lumps, causing obstruction of the convoluted tubules that leads to a direct nephrotoxic effect, resulting in vasoconstriction and impaired renal microcirculation.

Pigment myoglobinuric nephrosis develops, hemodynamic disorders by the “shock kidney” type and filtration of myoglobin through the walls of the nephron are observed [42, 43]. When the serum myoglobin level reaches 100 mg/dL, the color of the urine becomes reddish brown. When making a differential diagnosis of myoglobinuria, other causes of pigmenturia (prolonged compression syndrome, poisoning, etc.) should also be taken into account [10, 44]. In this case, it is advisable to consider urine alkalization as a therapeutic and preventive measure, especially in patients with metabolic acidosis [40, 45].

The muscle cell is affected by direct damage to the membrane or as a result of depletion of energy substrates, then calcium enters the intracellular space, activating proteases and stimulating apoptosis. Hyperproduction of reactive oxygen species causes mitochondrial dysfunction. Edema, ischemia, and cell necrosis aggravate metabolic acidosis, with electrolyte disturbances perpetuating an intracellular vicious cycle that in the end leads to cytolysis [26, 41, 46].

The main regulators of internal body temperature are mitochondrial function and metabolism, and almost 50 % of energy expenditure is directed to maintain internal body temperature. When mitochondria make adenosine triphosphate, they also make heat; these processes occur in opposition as follows: the more efficient the oxidative phosphorylation, the more adenosine triphosphate is formed and the less heat is produced. However, if the proton gradient created by the mitochondrial electron transport chain is leaky, the distributive gradient leads to a decrease in adenosine triphosphate production and an increase in heat production (“uncoupling” phenomenon) [29].

There are 2 types of acute heat damage to the kidneys. One form is classical rhabdomyolysis (usually with a creatine phosphokinase (CPK) level $> 1,000 \mu\text{g/L}$), often associated with hyperuricemia and signs of dehydration. This form may be most common in heatstroke with physical exertion. Another form is associated with a normal or slightly elevated level of CPK and is more common in epidemic heatstroke. Indeed, in contrast to rhabdomyolysis, in which the injury is more similar to an acute tubular injury, the second form of AKI presents clinically as acute interstitial nephritis with leukocytosis in the urine and hematuria, and renal biopsy reveals acute tubulopathy. This condition is believed to result from temperature-induced ischemia, oxidative stress, and depletion of intracellular energy stores [2].

The risk of AKI in rhabdomyolysis is usually low when the level of CPK at the time of admission to the medical institution is less than 20,000 units/l. Nevertheless, AKI, as before, remains in the risk group even with such low values of CPK as 5,000 units/l in the presence of other accompanying conditions (sepsis, severe dehydration, acidosis). In addition to rhabdomyolysis, all three risk factors can coexist with severe heat injury. Usually, the cause of rhabdomyolysis is obvious from the patient’s history or from the circumstances immediately preceding the disease, the provoking factor is not determined only in isolated cases [41].

The results of many studies have also shown that plasma methemoglobin $\geq 1,000 \text{ ng/ml}$, CK $> 1,000 \text{ IU/L}$ (which is 5 times the upper limit of normal) and serum creatinine

above 1.5 mg/dL should be considered independent risk factors of AKI in heat injury. In some cases, at the beginning of the process development, the creatinine clearance may be elevated that leads to a false assessment of the course of AKI; in this case, the study of glomerular filtration rate will be more informative [17, 26, 41, 47, 48].

The following can also be used as metabolic markers of AKI in thermal injury: increased biosynthesis of unsaturated fatty acids (may contribute to the progression of AKI), increased activity of calsequestrin-1, a new marker of malignant hyperthermia [16, 49].

An increase in serum creatinine and oliguria combined with rhabdomyolysis and coagulopathy increase the frequency of AKI and mortality [10, 41, 50]. The results of research by military medics suggest that one in six victims of heat damage ($> 40^{\circ}\text{C}$) will develop an AKI [12].

The KDIGO criteria and classification of the AKI severity have an important role in predicting mortality and risk of CKD. Numerous studies have shown that AKI is associated with an increase in the short- and long-term risks of the end-stage CKD and the fatal outcome [47]. Some studies reported that the level of CPK $> 10,000$ IU/L (50 times higher than the norm) is valuable in predicting renal failure in patients with heat injury [19, 48], but in our opinion, this characterizes the patient's condition, which a priori requires the use of extracorporeal detoxification methods [42, 43, 51].

Persistent oliguria that persists after a patient is brought out of shock should warn about the risk of developing acute renal failure. When the latter occurs, hypokalemia always changes to hyperkalemia [27].

Complications of heat injury can also be acute tubular necrosis, chronic progressive interstitial nephritis with impaired kidney function [5], nephrolithiasis, renal colic, kidney tumors, etc. [25].

The morphological manifestation of AKI is often acute tubular necrosis, which develops as a result of dehydration, pigment load, and urate nephropathy. Morphological studies demonstrate dilatation of glomerular capillaries, hemorrhages into the interstitium, and vascular stasis in small and large vessels [52]. Histologically, glomerular edema, inflammatory cell infiltration, vacuolar dystrophy of endothelial cells and the presence of erythrocytes in the tubular lumen are visualized, which is a characteristic sign of hyperemic inflammation and indicates a high risk of hemorrhage [16]. The morphologic state in cases of heat injury is not mediated by common causes such as glomerulonephritis, hypertension, or diabetes, but is histologically characterized by a predominant pattern of chronic interstitial damage and inflammation, often with some shrinkage of glomerular basement membranes and glomerulosclerosis [53].

Acute renal failure due to acute tubular necrosis develops in 5–25 % of cases. Laboratory changes include low plasma osmolarity, hyperkalemia, hypocalcemia, hyponatremia, high CPK levels (over 10,000 IU/L), moderate proteinuria, presence of sediment and fat droplets in urine [22, 23].

It is assumed that bleeding, and not apoptosis, may be the characteristic trigger for hyperthermic-associated AKI. Moreover, the induced systemic inflammatory response syndrome and secondary hyperfibrinolysis can become

other causes of kidney hyperemia and edema, which is morphologically somewhat different from the picture of usual acute tubular necrosis [16].

It should be noted that the forecast until 2050, based on the climate model of warming, predicts an increase in the incidence of urolithiasis by 30 % during life in some climatic zones [9].

Heatstroke is also usually associated with electrolyte imbalance. One study of 66 patients with heatstroke during exercise reported AKI in 91 %, hyponatremia in 53 %, hypokalemia in 71 %, hypophosphatemia in 59 %, hypocalcemia in 51 %, and hypomagnesemia in 35 % of cases [26]. In particular, low serum potassium, phosphate, and magnesium levels were associated with increased urinary excretion of these electrolytes, suggesting a tubular defect. Other possible causes include the loss of sodium and potassium through sweat.

Some subjects also have respiratory alkalosis, which is known to lower serum phosphate levels, although metabolic acidosis appears to be more common [2]. Heat stress and dehydration also play a role in the formation of kidney stones, and inadequate drinking can increase the risk of recurrent urinary tract infections. The resulting social and economic consequences include disability or loss of productivity and employment.

Given an increase in global temperatures, it is necessary to better understand how heat stress can cause kidney disease, how to best ensure optimal rehydration, and find ways to prevent the negative consequences of chronic exposure to high temperatures [2, 3]. In people who suffered from the effects of high temperatures for a short time, nephrolithiasis was observed more often than other damage to the urinary system, but had a faster course. General overheating statistically significantly increased the risk of nephrolithiasis by 32 % [25, 54]. In addition, clinical studies show that heat exposure and dehydration cause concentrated and acidic urine, which can lead to urate crystallization in the urine with tubular damage. Nephrolithiasis is becoming widespread; it is assumed that one of its causes is an increase in temperature associated with climate change. In the United States, for example, the “stone belt” that characterizes the hotter regions of the southern United States is projected to shift northward as the climate continues to warm. Experimental studies show that the main substance of kidney stones associated with heat stress is uric acid due to its increased formation after muscle damage caused by physical exercises and acidification of urine, which occurs during an increase in its density [2]. Chronic or repeated episodes of heat stress with dehydration ultimately lead to abnormal repair mechanisms, renal fibrosis, vascular refinement, and glomerulosclerosis [9]. Recently, epidemics of CKD have been observed worldwide, which have been documented in agricultural communities in Central America, southern Mexico (Veracruz), India (Andhra Pradesh), Sri Lanka (North Central Province), central Florida and the Central Valley of California [2, 55–57]. The frequency of CKD in these regions is almost 9 times higher than in other populations. High incidence rates are observed among sugarcane pickers in the hottest lowlands of the Pacific in Nicaragua

and El Salvador, where the prevalence of CKD is 18 % compared with 1 % in cooler conditions. The suspicion of the toxic effect of pesticides was refuted [9].

The underrepresentation of these workers in social security systems, as well as the inability to create organized public health systems in these countries make community-level incidence studies extremely necessary [10, 41, 50]. Since the risk of AKI increases with high temperatures, it would be appropriate to inform the public and study kidney diseases, primarily nephrolithiasis, in hot conditions [25]. For researchers in the field of health care and industry, it is necessary to identify harmful occupational conditions that contribute to nephropathy during heat stress, and to develop certain strategies for occupational health issues [9].

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Ниркова дисфункція при загальному перегріванні (літературний огляд)

Резюме. За останні 30 років глобальне потепління посіло одне з провідних місць серед десяти основних причин летальності внаслідок стихійних лих. Відомо, що підвищення температур збільшує кількість невідкладних госпіталізацій з приводу широкого спектра захворювань нирок, включаючи гостре пошкодження нирок (ГПН), хронічну хворобу нирок, сечокам'яну хворобу та інфекції сечовивідних шляхів. Виробнича діяльність у спекотних умовах також часто супроводжується ГПН, що може швидко перейти до гострої ниркової недостатності з високою летальністю. В основі патогенетичних механізмів індукованого перегрівання ГПН лежать зменшення об'єму циркулюючої крові й електролітні порушення внаслідок збільшення перспірації. Випаровування води з поверхні тіла призводить до дегідратації та підвищення осмолярності плазми. У відповідь на це активується вазопресин, збільшується питома вага сечі, зменшується кількість сечі. Прогресивно знижується швидкість клубочкової фільтрації. Розвивається гіпокаліємія, що протягом 12 годин змінюється на гіперкаліємію. Відбувається ушкодження ендотелію

канальців, яке призводить до мікротромбозів аферентних та еферентних ниркових артерій, розвитку запальної відповіді та виснаження ниркового інтерстицію. Можливий рабдоміоліз та міоглобінемія з наступною обструкцією канальців погіршують існуюче пошкодження нирок. Відповідно до провідного механізму пошкодження виділяють два типи теплового ГПН: класичний рабдоміоліз та гострий інтерстиціальний нефрит. Хоча сучасні медичні досягнення сприяли розробці ефективних стратегій лікування й менеджменту (швидке охолодження, екстракорпоральні методи детоксикації тощо), за останні десятиліття летальність при ураженні нирок унаслідок загального перегрівання знизилася незначно. Дослідникам у сфері охорони здоров'я та промисловості необхідно визначити шкідливі професійні умови, що призводять до нефропатії при тепловому стресі, та розробити певні стратегії з питань охорони праці.

Ключові слова: глобальне потепління; загальне перегрівання організму; теплове ушкодження нирок; нефропатія; нефролітіаз