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The Impact of Ultramarathon Running on Acute Kidney Injury Risk: A Review of Current Evidence

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Introduction

The popularity of ultramarathons has increased significantly in recent decades. Surveys assessing the number of athletes participating in such runs have seen a significant increase since the 21st century. These are runs defined as longer than a standard marathon (> 42,195 meters) or longer than 6 h, and are often set in unfavorable conditions such as deserts or mountains. Ultramarathons can take the form of continuous one-day events or runs divided into multiple days, where 50 km, 80 km, 161 km are often established running distances, as well as multi-day runs divided into stages that total 3 to 7 days and are longer than 250 km[1]. While it is known that sport activity is beneficial to health, having multiple health positives, improving cardiovascular, respiratory, excretory and other system functions, as well as prolonging life, it is postulated that excessive physical activity can have adverse health effects. It is believed that extreme physical exertion, which can occur during ultramarathons, can become harmful as a result of exceeding the compensatory capacity of the human body[2]. Among the risks of such exercises are the acute kidney injury described in this paper. Acute kidney injury is a significant medical problem; it is characterized by deterioration of renal function, which can lead to a wide range of complications, from minor changes in renal function to severe renal failure requiring serious medical intervention. The pathophysiology of AKI in the context of ultramarathons is multifactorial, involving inadequate hydration, exercise-associated hyponatremia, exertional rhabdomyolysis, use of non-steroidal anti-inflammatory drugs (NSAIDs), inadequate nutrition during exercise and gastrointestinal complaints, and others. The incidence of acute renal failure in ultramarathon runners has not been established with much accuracy. A systematic review published in 2022 pooled data involving 1113 ultrarunners participating in running over the past 15 years and found an overall incidence of mild AKI of 42%, but only 1 case (0.01%) met criteria for severe kidney injury but did not require a dialysis[3].

Material and Methods

We reviewed available literature from The PubMed database, Scopus and ScienceDirect in order to assess the risk factors of AKI affecting ultramarathon runners. Key factors included combinations of ultramarathon, acute kidney injury, rhabdomyolysis, exercise-associated hyponatremia and hydration. Publications from 2000 to 2024 were considered with a focus on peer-reviewed articles, clinical trials, observational studies and systematic reviews.

Keywords: ultramarathon, acute kidney injury (AKI), rhabdomyolysis, non-steroidal anti-inflammatory drugs (NSAIDs), hydration

1. Acute kidney injury

Participation in ultramarathons places an unusually high burden on the body, due to the prolonged and demanding physical exertion[4]. As a result, in addition to other health risks, AKI is a frequently found abnormality in ultra athletes, although the reported prevalence varies significantly between studies: it ranges from 0 to 85%. Such large discrepancies between reported prevalence are due to different and inconsistent methodologies depending on changes in serum creatinine (SCr) and also due to different variables of races[5]. Classically, AKI is diagnosed based on SCr (an increase of >=0.3mg/dl within 48h or >=1.5x increase within 7 days) or urine output (<0.5 ml/kg b.w./h for 6h)[6].

Creatinine clearance is commonly used in medicine as an indicator of kidney function, using creatinine as a product of muscle metabolism excreted by the kidneys. Creatinine is formed as a product of a metabolic pathway, the initial step of which is the formation of creatine; glycocyamine formed in the kidneys from the amino acids: glycine and arginine is then transported to the liver, where it is methylated by S-adenosyl methionine to creatine; creatine is then transported by blood to other organs, among others, to the muscles, where it is phosphorylated to high-energy phosphocreatine; creatinine is the product of this reaction and is produced at a relatively constant rate; it is then moved from the muscles via the bloodstream to the kidneys[7]. The amount of creatinine filtered in the glomeruli is proportional to GFR, so it can serve as a tool for assessing kidney function. In addition to those mentioned above, there are many factors that affect plasma creatinine concentration. These include muscle mass (with greater muscle mass, plasma creatinine concentrations are higher), diet (large amounts of meat in the diet increase plasma creatinine concentrations), medications (can affect secretion and overestimate SCr), hydration status (dehydration increases SCr)[8]. As mentioned above, AKI is diagnosed based on changes in SCr and diuresis. SCr standards were developed based on studies on hospital patients who have a relatively constant rate of creatinine production. In athletes, during prolonged and strenuous exercise, there is increased creatinine production; for this reason, increased creatinine levels do not necessarily indicate deteriorated renal function. To avoid misdiagnosis of AKI, renal function can also be assessed using other parameters such as cystatin C, NGAL or KIM[5]. Cystatin C, unlike creatinine, is independent of muscle mass or diet; changes in its concentration are less sensitive to changes in renal blood flow associated with sports or muscle damage[9]. It has been detected that changes in NGAL and KIM1 concentrations are more reliable in assessing the actual deterioration of renal function resulting from renal tissue damage[10]. NGAL glycoprotein, part of the innate immune system, is released in the early stages of the response to renal ischemia, oxidative stress and inflammatory response[11]. It is an early indicator of ischemic kidney injury and can be used for early detection of AKI and prediction of kidney disease progression5,10. Among 120-km runners, NGAL-based AKI prevalence was found to be 12.5%, whereas GFR-based AKI prevalence was found to be only 0-4.2%[12]. Further studies are needed to assess the usefulness of indicators other than creatinine clearance for the diagnosis of AKI in ultrarunners[13,14].

2. Hydration

As mentioned above, ultramarathons are often held in places with extreme climatic conditions: hot, humid, tropical, deserts, mountains; in such places, participants are particularly vulnerable to inadequate hydration[4,15]. It is known that inadequate hydration is a factor in kidney damage[16]. Too little fluid intake causes reduced renal flow leading to renal ischemia, which results in accumulation of metabolic products, including creatinine and myoglobin. Although dehydration alone does not lead to elevated blood creatinine levels[17], the combination of dehydration, increased energy expenditure and heat strain can elevate blood creatinine levels and can lead to AKI[18]. Assessment of dehydration can be estimated from the difference in body weight before and after a run, considering lost weight as water that has been excreted through various routes from the body.

However, studies have described that the change in body weight is not only due to water loss, but also to altered body composition; a study based on athletes participating in a 24-hour run detected a significant decrease in body weight, but this is correlated with a decrease in body fat percentage and is also due to remodeling of body fat[19]. In a study describing runners completing a 100-kilometer run, the average weight loss was 2.6%, with runners completing the run faster having a greater weight loss than those running slower[20]. It is believed that losing > 2% of body weight during exercise should be avoided to avoid hyperthermia, but the study described that a weight loss of 3-4% during prolonged exercise of 23-30 h in hot conditions was well tolerated and did not lead to hyperthermia. This indicates that the recommendation to replenish fluids enough not to lose more than 2% of body weight is not supported[21]. However, it was shown that athletes with greater weight loss had a more severe reduction in GFR[22]. Other methods of assessing hydration may include plasma osmolality measurement, urinary ketone presence, fluid intake monitoring, urine specific gravity or presence of dehydration symptoms[23]. There is evidence that sufficient hydration can be achieved by drinking water or other hypotonic fluids. When drinking in accordance with guidelines that say to drink enough to keep weight loss below > 2% during exercise, there is a significant risk of overhydration. It is the most common cause of another dangerous condition affecting ultrarunners, which is exercise-associated hyponatremia[24].

3. Exercise-associated hyponatremia

Exercise-associated hyponatremia (EAH) is a condition when the plasma sodium concentration falls below 135 mmol/L during or immediately after physical activity; it most often results from excessive fluid intake and impaired urinary water excretion, caused by excessive secretion of AVP[25]. The hyponatremia effects in an influx of water into cells to equalize osmotic pressure, leading to cell swelling and facilitated cell membrane damage and disruption. The breakdown of many muscle cells leads to increased release of metabolic products and poses a risk of exertional rhabdomyolysis and acute kidney injury. AVP is also produced in response to polydipsia, intense exercise, hypoglycemia, vomiting, and nausea. Under normal conditions, the body's response to excessive fluid intake and the other mentioned factors is to reduce AVP secretion, resulting in the production of large amounts of dilute urine, whereas in endurance athletes such a response does not occur[26]. It is not yet established whether the loss of electrolytes with sweat is relevant to the development of EAH. It has been shown that the sweat of endurance athletes contains far less electrolytes than the sweat of people who do not engage in intense exercises[27]. The secretion of hypotonic sweat should result in an increase in plasma sodium concentration, while it is known that sweating can lead to hyponatremia if water loss with sweat is so significant that it stimulates AVP secretion, or if fluids taken in are more hypotonic than the excreted sweat[28]. Before starting a treatment, EAH has to be differentiated from other exertional illnesses such as heat exhaustion, heatstroke, and exercise collapse associated with sickle cell trait, as their treatments are often contradictory. Treatment is dictated by the presence or absence of symptoms; the goal of treatment is to achieve a normal plasma sodium concentration and resolve or relieve symptoms. If the patient does not exhibit neurological symptoms, EAH is considered mild and restriction of oral fluid intake is recommended.

Concentrated oral sodium repletion can be given, although it may be poorly tolerated due to taste or nausea and vomiting. Oral administration may be preferable to intravenous administration. In cases of severe EAH, when neurological symptoms (e.g., seizures, coma) are present, intravenous hypertonic saline is administered. Upon admission to the hospital, patients with suspected EAH should have their sodium and other electrolytes measured immediately. In preventing EAH, it is important to prevent overhydration. The risk of EAH in endurance runners is about 8.5%[29]. Guidelines for the amount of water athletes should take in during exercise are not clear. In the past, it was recommended to take in as much fluid as one can, but these guidelines have been proven wrong because they increase the risk of EAH. Some researchers recommend aiming for drinking rates of 500-1000 mL per hour, adjusted according to individual losses, to prevent dehydration and optimize performance. Others believe that drinking enough water to satisfy thirst is sufficient[30]. It is suggested that salt supplementation of 1-2 grams per hour may be beneficial, particularly when combined with carbohydrate intake. A daily sodium intake of up to 3 grams prior to a race has been shown to positively affect athletic performance[21]. Lopez de Lara published a study describing runners of the 114-kilometer Gran Trail de Peñalara ultramarathon (GTP) and the Vitoria Gasteiz Ironman triathlon (VGI, in which participants had to cover 3,800 meters by swimming, 180 kilometers by bicycle and 42.2 kilometers by running). Ultrarunners were advised to drink fluids according to their own sense of thirst and 83,3% of the finishers of the GTP run and 77.6% of the finishers of the latter race had normal blood sodium levels (range 135 - 145 mmol/L) after the run. These recommendations not only prevented hyponatremia, but also did not lead to hypernatremia or negative effects on race performance[31].

The response to low sodium levels has been found to vary between sexes. In a comparison of male and female triathletes, certain clinical variables display distinct patterns of association with hyponatremia. For instance, altered mental status shows an inverse relationship with low sodium in men, but no such correlation in women. Similarly, abdominal pain, muscle cramps, hypotonia, and tachycardia are directly related to hyponatremia in men, while no such connection is observed in women. Conversely, vomiting and hypokalemia are inversely associated with low sodium in women but do not show any relationship in men[32]. Coaches should be on the lookout for symptoms of EAH which, however, can be problematic due to the fact that these are nonspecific. Women are more likely to develop EAH than men[32,33]. The higher incidence of EAH in women may be explained by Varon-Ayus syndrome, which is characterized by severe hyponatremia, pulmonary and cerebral edema; this syndrome was first observed in female marathon runners and indicates that the two sexes have different resistance to exercise of this type[34]. Plasma sodium levels before running are not a predictor of post running levels, while there is a significant negative association between change in body weight and sodium levels after running[35]. It has been suggested that there is a connection between EAH and exertional rhabdomyolysis (ER) - hyponatremic athletes are more likely to develop ER than normonatremic athletes[36], while it is important to remember that EAH and ER need to be treated in opposite ways; with EAH, water supply should be limited in most cases, and with ER, the patient should be intensively hydrated.

4. Exertional rhabdomyolysis

Exertional rhabdomyolysis (ER) is characterized by significantly elevated creatine kinase levels, with an average creatine kinase level of 31,481 IU/L at presentation and reaching as high as 38,552 IU/L in some cases. Stahl et al. put forward a definition of rhabdomyolysis as a clinical syndrome of acute muscle weakness, myalgia, and muscle swelling combined with a creatine kinase cut-off value of > 1000 IU/L or more than 5 times upper limit of normal value for the standard definition of a mild rhabdomyolysis. Additionally measured myoglobinuria and AKI indicate a severe type of rhabdomyolysis[37]. ER is initially caused by intense, repetitive exercise or a sudden increase in the intensity of exercise, especially in people who have not previously trained at this intensity. However, it can also occur in trained athletes, as in the case of ultrarunners. It then leads to symptoms such as muscle damage, pain, weakness, localized swelling, dark urine, reduced range of motion in particularly trained muscle parts. Rhabdomyolysis leads to the release of myoglobin into the bloodstream, potentially leading to kidney damage[38]. Damage to muscle cell membranes also leads to the release of myoglobin, as well as CK, LDH, AST, electrolytes. Severe ER can result in renal failure, compartment syndrome, and dysrhythmias in the absence of proper diagnosis and treatment; for this reason, it is important to recognize the initial signs of ER to prevent complications. ER is diagnosed on the basis of elevated plasma creatine kinase levels. Myoglobin can be utilized as a marker of an ER and can be measured with a positive urine dipstick for myoglobin. However, myoglobin is rapidly eliminated from the bloodstream, making CK which persists longer in the blood a more reliable indicator[39]. Yet, not all described cases of renal failure in ultramarathoners were connected to profoundly elevated levels of creatine kinase or myoglobin, which indicates that other factors may be involved in the development of acute renal failure[40]. Myoglobin and other metabolites released in rhabdomyolysis can damage the kidneys in several ways - tubular obstruction, toxic reaction, and decreased oxygen supply due to vasoconstriction of renal tissues. Hyperkalemia due to the potassium leakage increases the risk of dysrhythmias, for which reason it is important to monitor this parameter[41]. Isotonic fluid therapy is the most commonly used treatment for rhabdomyolysis[42] Prevention of ER is proper hydration, gradual increase in training intensity and adequate intervals[43]. Hyponatremic ultra athletes were more likely to develop ER than normonatremic ultra athletes, which draws attention to proper hydration and electrolyte levels in athletes before running[44]. Risk factors for ER are male gender, younger age, lower education, lower chronic physical activity, and physical activity in warmer months[45]. As shown by Juan et al. the risk of ER depends largely on the genetic profile. Athletes with lower CK response after running had a more favorable polygenic profile than those with high serum concentrations, suggesting a significant role for genetic polymorphisms in the levels of exertional muscle damage and rhabdomyolysis[46]. In 2006, 39 athletes who completed a 246-kilometer run with a 36-hour time limit were studied. Significant elevations in markers of muscle and liver damage (CK, LDH, AST, ALT) were detected, while despite significantly elevated levels, none of the athletes showed signs of damage to the organs and required hospitalization[47]. The presence of asymptomatic rhabdomyolysis, which is harmless and transient in trained athletes, was demonstrated.

Though ER is relatively rare, in combination with AKI it is a dangerous condition. ER can lead to hyperkalemia, hypernatremia, acidosis and kidney damage. ER in combination with AKI can result from dehydration, hyperthermia and high muscle strain, especially in the hot and humid conditions typical of many ultra-endurance competitions. Prolonged exercise under such conditions increases the severity of both ER and AKI [48].

5. Non-steroidal anti-inflammatory drugs (NSAIDs)

The use of non-steroidal anti-inflammatory drugs is very common among ultra runners. Martinez et al. showed that 60.3% of participants admitted to taking NSAIDs before, during or just after ultra running[49]. These drugs have an analgesic effect, alleviating muscle and joint pain during and after exercise. They also exhibit anti-inflammatory effect, counteracting the inflammation that develops in muscles and joints due to prolonged physical activity. Additionally, some athletes believe that these drugs enhance their performance, facilitate quicker recovery following a run. Sometimes they are used prophylactically before a run to prevent pain during physical exertion[50]. The longer the run, the more frequent the intake of NSAIDS. The study found that among marathon runners (who complete a 42,195-meter run), the use of NSAIDs occurs in 35.5%, while in ultra-runners it is as high as 60.3%; other studies have found similarly high use of NSAIDs, e.g. Nieman et. al. showed an incidence of NSAIDs usage as high as 72%[51]. Regarding the timing of drug use, the majority of participants (65.7%) indicated that they take these medications exclusively during the run, rather than before or after. The most frequently cited reason for taking the drug was pain prevention (56.4%), followed by pain relief (30.9%), and injury treatment (9.1%). It is noteworthy that athletes most often took these drugs deciding on their own, without consulting a doctor. The same study described that a third of the athletes taking the drugs were unaware of the side effects of the drugs, especially in such an extreme setting as ultra running. This is a concerning fact, bearing in mind that NSAIDs usage by ultramarathoners has been shown to be a risk factor for AKI[52]. NSAIDs inhibit cyclooxygenase, what prevents the breakdown of arachidonic acid into prostaglandins, which are involved in renal vasodilation; this leads to reduced renal flow and thus reduced GFR. The use of NSAIDs is an identified risk factor for AKI[16], so their intake should be monitored and under the care of the medical team.

6. Gastrointestinal disorders

Gastrointestinal symptoms (GIS) are common in ultramarathon runners. In runners of the 60-kilometer run, 73% of runners reported such complaints, with 20% having severe discomfort[53]. During the multi-stage ultramarathon, 85% of runners reported GIS, which were linked to reduced energy and macronutrient intake. Additionally, 89% had affected carbohydrate and protein intake. This indicates that gastrointestinal disorders are an important and common problem among athletes in this endurance sport. Such symptoms can cause discomfort, impaired performance, failure to complete a run, and the need for medical attention[54]. Severity of GIS during an ultrarace is associated with lower energy, and worsened macronutrient and water intake throughout the event. During competition, common complaints typically include nausea (the most common symptom), the urge to urinate, muscle cramps, belching, bloating, flatulence, side ache, and dizziness[55].

The above complaints were much more common in ultramarathon runners than marathon runners, indicating that longer exercise time and longer running length exacerbates symptoms[56]. There was a positive correlation between the severity of nausea and the level of endotoxemia, suggesting that as nausea worsened, endotoxemia levels also increased[57]. A marker that can assess gastrointestinal injury is intestinal fatty-acid binding protein (I-FABP), as it detects early mucosal damage preceding clinical symptoms and its level increases in a patient with mesenteric ischemia[58]. Niek et al. showed that there was no direct relationship between gastrointestinal (GI) complaints and gastrointestinal injury as measured by intestinal fatty-acid binding protein (I-FABP) response, suggesting that the severity of GI symptoms does not correlate with GI damage, emphasizing the complex interplay of factors influencing gastrointestinal health during strenuous physical activity[59]. Energy intake during the race showed an inverse relationship with the I-FABP response, indicating that higher energy intake may help prevent exercise-induced GI injury. Biomarkers of inflammation significantly increased from pre- to post-race among the ultramarathon runners. This suggests that participating in an ultrarace can lead to an inflammatory response in the body, which may be influenced by factors other than GI complaints or injury[54]. A method that may prove beneficial in ultrarunners is to follow a low-FODMAP diet. It is a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) and it is proven to be beneficial for alleviating gastrointestinal symptoms during ultra-endurance activities[60]. It can reduce the severity of gastrointestinal symptoms in individuals with irritable bowel syndrome, potentially improving their overall race experience and performance[61].
As shown, most ultrarunners did not meet the recommended carbohydrate intake of 90 g/h. Those who consumed more carbohydrates, such as 120 g/h, had a reduced internal exercise load, have limited exercise-induced muscle damage, and had improved post-exercise recovery; higher intake can positively impact performance during ultra-trail races[62]. It was shown that runners with GIS had lower rates of fluid consumption compared to asymptomatic runners, which suggests that higher fluid intake is beneficial[63]. During intense runs, blood is redistributed from the central organs to the muscles and skin, reducing blood flow through the kidneys and spleen. Severe intestinal ischemia can cause mucosal damage, leading to endotoxemia, which impairs kidney function[64]. Endotoxins, entering the circulation due to increased gastrointestinal permeability, trigger immune reactions and inflammation. NSAIDs can further increase cytokine levels and impair renal function[5]. GIS must be considered when taking care for ultramarathon runners with AKI.

Conclusions

The lifetime of elite ultra-marathon runners is greater than that of the general population. The long lifespans of elite athletes completing 50-mile races suggests the long-term health benefits of ultra-marathon participation outweigh the risks[65]. However, as outlined in the article above, there are risks associated with participating in extreme sports such as ultramarathon running. The risk of acute kidney injury that would require significant medical intervention or lead to the development of chronic kidney disease among ultramarathoners is not high, but it is medically significant enough to keep in mind.

Factors such as exertional rhabdomyolysis, exercise associated hyponatremia, the use of NSAIDs, gastrointestinal problems, the issue of adequate hydration and the provision of food must be addressed by the medical staff caring for the athletes and the ultrarunners themselves to avoid adverse health effects.

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