

# RISK OF ACUTE KIDNEY INJURY AND HYPONATREMIA IN LONG-DISTANCE RUNNERS

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## Abstract

Long-distance running has gathered some momentum among health-conscious participants. However, some studies have revealed association between long-distance running and development of acute kidney injury. Although the impact usually lasts only for a few days after the event, some participants have been admitted for severe acute kidney injury, the minority of which require dialysis treatment. The mechanisms underlying the injury may include dehydration, development of rhabdomyolysis, heat stroke and concomitant use of NSAIDs. Unfortunately, there is no long-term follow-up study to determine the long-term effect on kidney function.

Acute hyponatremia may develop in a significant proportion of long-distance runners. Majority of them were asymptomatic but a few fatal cases which were supposedly due to cerebral oedema have been reported. Excessive intake of hypotonic drinks, excessive sweating and secretion of non-osmotic antidiuretic hormone have been postulated to be the causes of hyponatremia. This mini review will discuss the pathophysiology of the development of acute kidney injury and hyponatremia. It will also discuss the prevention and treatment of both conditions.

**Keywords:** Long-Distance, Marathon, Kidney Injury, Hyponatremia, Rhabdomyolysis

## Introduction

*"I had run for 3 years, 2 months, 14 days and 16 hours."*  
– Forest Gump

Inspired by the run made by the Greek man Pheidippides from Marathon, to Greece then to Athens in 490BC, long-distance running became one of the major sport events at the 1896 Olympic Games (1). Regular physical activity has been shown to have a positive impact on cardiovascular risk factor, and improved exercise capacity was associated with reduced mortality (2, 3). Observational studies have also shown a positive correlation between higher physical activity levels and slower progression of chronic kidney disease (4). However, randomised trials have not shown consistent results regarding improvement of kidney function with exercise (5, 6). Long-distance runners represent quite a different cohort, when compared to

those who do regular moderate intensity exercise. Healthy effect of exercise was associated with moderate amount of regular physical activity involving energy consumption of 2000-3000 kcal/week (3), while long-distance endurance exercise like marathon requires rigorous training with potential myocardial adaptation due to significant increase in skeletal muscle oxygen demand (1). Two specific complications related to the field of nephrology for long-distance runners are the risk of acute kidney injury (AKI) and development of hyponatremia (7). In other fields, AKI despite clinical recovery has still been associated with greater future risk of developing chronic kidney disease and cardiovascular complications (8, 9). Acute hyponatremia may induce seizure and coma and carries a significant risk of mortality. Hence, it is important for healthcare professionals to be familiar with this condition and its treatment.

## **Risk Of Acute Kidney Injury**

### **1. Does running long distance increase risk of kidney damage?**

In a small study of 22 marathon runners, blood samples were taken before and after a marathon. The average age of participants was 44 years old, BMI was 22.4 kg/m<sup>2</sup> and 41% of participants were men. All runners completed 26.2 miles of running with average time of 4.02 hours. There was a significant increase in serum creatinine post marathon from 0.81 mg/dl (71.6 umol/L) to 1.28 mg/dl (113.2 umol/L). The level then normalised 24 hours later. Other biomarkers of intrinsic kidney damage such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) were also significantly elevated, suggesting that the kidney damage is probably real, and not because of a sudden surge of creatinine (10). The incidence of AKI in 100 km ultramarathon can be as high as 85%, although all of these were mild cases and the subjects recovered shortly later (11, 12). Many similar studies have shown consistent outcome of elevation in the markers of kidney damage as well (13-15).

Other studies using cystatin C as a marker also showed significant decline in kidney function, but returned to baseline within 2 weeks (15). Cystatin C is a small 13-kDa protein with constant rate of production. There is no tubular secretion or reabsorption. Factors like age, gender and body composition that may affect creatinine level do not seem to affect cystatin C value (except for thyroid problem) (16). It may be a more reliable marker for kidney injury after intensive exercise (17). Solid organ transplant recipients who were involved in long distance running also showed similar trend of temporary elevation of creatinine (18). Recent systematic review across 21 studies (n=800) that included half-marathon, marathon and ultra-marathon showed temporary elevation of serum Creatinine after the events was 25.7 umol/L (19).

Data from Comrades Marathon in South Africa showed that over an 18-year period, only 19 significant cases of renal failure were reported, even though the yearly participants were in the range of 2000-10000 per year (14). A recent systematic review identified only 27 cases of severe AKI requiring hospital admission after an endurance event (19). Therefore, although it seems that long-distance running causes temporary kidney damage, it is very rare for it to be significant enough for the runners to be hospitalised.

### **2. What are the risk factors for acute kidney injury post running?**

Apart from the physical act of running itself, other factors that may predispose to acute kidney injury include running in higher temperature environment (20, 21), taking nonsteroidal anti-inflammatory drug (NSAID) before or during running (22-25), dehydration and concomitant infection (14). Injuries are more common in novice runners than the experienced runners (26). In studies looking at the effect of NSAIDs, between 13-30% of runners admitted to

have taken an NSAID in the 24 hours period prior to the race and their serum creatinine level were significantly higher compared to runners who did not take NSAID (24, 25). In fact, 18 out of 27 (67%) case reports of AKI post endurance events requiring hospitalisation mentioned NSAID uses (19). Whether COX-2 inhibitor possess similar characteristic in causing AKI post endurance race is yet to be seen, but studies comparing NSAID and COX-2 inhibitor in other setting showed similar effect on renal function (27).

### **3. Is this kidney damage permanent?**

Available studies showed that kidney function return to normal within a brief period. However, we know from other studies that studied patients who suffered from acute kidney injury, the risk of long term mortality and development of chronic kidney disease were increased, even when they recovered completely from the acute episodes (8, 28). Unfortunately, so far, there is no long-term study for marathon runners in terms of kidney damage. Repetitive damage potentially may have long term impact.

One could also argue that running marathons can improve cardiovascular function, hence lowering the risk of long-term kidney injury. In the study of 26 women marathon runners matched to 28 women with sedentary lifestyles, marathon runners have lower triglyceride and higher high-density lipoprotein (HDL) level, with lower coronary plaque prevalence based on coronary CT angiogram (29).

### **4. What are the potential mechanisms of kidney injury in long-distance runners?**

The exact mechanism is unknown, but we know that there are reports of marathon runners who suffer severe muscle injury. Muscle breakdown causes release of myoglobin, and myoglobin can block the tubules and causes direct toxicity to the kidney. This condition is called rhabdomyolysis. Exercise-induced rhabdomyolysis is usually associated with high-force eccentric (lengthening) contractions and produces a very high level of creatinine kinase (CK). Endurance-type exercise such as marathon typically produces CK level of less than 5000 U/L (30). Although many marathon runners have detectable levels of urinary myoglobin and high CK levels (suggestive of muscle damage), not all of them have significant increase in creatinine (31). Creatine and statin use were associated with increased risk of rhabdomyolysis (32, 33).

The other possible mechanism of acute kidney injury in strenuous exercise involves ischaemic injury to the kidney due to reduction of renal blood flow by 25%, despite an overall increase in cardiac output (34). Volume depletion from severe sweating could contribute further to ischaemic injury.

Another postulated mechanism is through the increase in core body temperature, which may induce heat stress that can lead to kidney injury (35). It has been shown that rectal temperature of the runners can go up to 40°C in a

hot climate (21). Severe heat stroke is usually accompanied by rhabdomyolysis (36).

### **5. How to treat rhabdomyolysis?**

Rhabdomyolysis usually develops a few days after strenuous exercise. When muscle damage is significant, creatinine kinase, lactate dehydrogenase (LDH) and myoglobin appears in the blood. Urine typically will turn dark due to excretion of myoglobin. Acute kidney injury develops when myoglobin precipitates in the kidney tubules thereby causing oxidative damage to the surroundings (33).

The mainstay of treatment will be early and aggressive fluid therapy to increase renal blood flow and helps in secretion of toxic compound. Sodium chloride (0.9%) or lactate-ringer solution may be used. Daily fluid infusion may reach up to 8L per day. Caution must be exercised if hyponatremia is present together with rhabdomyolysis. Alkalinisation of urine with bicarbonate therapy may be tried as acidic urine environment may promote myoglobin cast formation. However, there is no randomised trial to compare infusion of sodium bicarbonate and other isotonic fluids (37). In severe AKI cases, especially with oligo-anuria, renal replacement therapy may be used. Dialysis reduces myoglobin level thereby reducing hospital stay (38).

### **6. What can be done to prevent acute kidney injury for long-distance runners?**

Common sense dictates that minimising the concomitant risk factors for kidney damage may reduce the incidence of acute kidney injury. This includes regular practice before the actual events, good hydration and cautious use of NSAIDs peri-long-distance-running. Precautions to prevent heat stroke include wearing proper attire to promote dissipation of heat, acclimatisation with hot climate (which may take a few days) and adequate hydration (39). Randomised trial of using branched-chain amino acid supplement in ultra-marathon runners did not show significant difference in parameters of muscle damage and kidney function, compared with control group (40). At the end of the day, knowing one's limitation and seeking early medical intervention may prevent worsening of kidney injury.

## **Development of Acute Hyponatraemia**

### **1. What is hyponatremia?**

Hyponatremia is defined as serum sodium concentration of less than 135 mmol/L. It is primarily a disorder of relative excess of body water as compared to total body sodium. Anti-diuretic hormone or vasopressin plays an important role in governing water balance. True changes in serum sodium concentration will affect serum osmolality. Symptoms can vary from feeling unwell, headache and nausea to confusion, vomiting, seizures and coma. These symptoms usually occur when hyponatremia develops rapidly. Sudden shift in osmolality causes brain oedema and raises intracranial pressure. Over 24-48 hours, brain

cells reduce the number of osmotically active particles to reduce the swelling. Hence, acute or chronic hyponatremia is defined by the 48-hour threshold (41). True hypotonic hyponatremia can be further divided, based on possible causes, into hypovolemic, euvolemic and hypervolaemic hyponatremia.

### **2. How significant is hyponatremia in long-distance runners?**

Acute hyponatremia in long-distance runners was described initially as water intoxication due to hyperhydration with hypotonic solution and excessive sweat sodium chloride losses, in ultra-marathoners (42). In 2002 Boston marathon, 13% of the finishers had serum sodium level <135 mmol/L and 0.6% had level <120 mmol/L. Fortunately, they were all asymptomatic (43). Fatal cases with cerebral oedema attributed to hyponatremia have been reported in marathon runners (44). Apart from the usual symptoms of hyponatremia mentioned above, there were reported cases of non-cardiogenic pulmonary oedema associated with hyponatremia (45).

### **3. What is the mechanism for development of hyponatremia?**

Large volumes of hypotonic solution ingestion during long-distance running may contribute to acute hyponatremia. Excessive sodium chloride losses through sweating may also play an important factor. Hypotonic sweat loss may cause hyponatremia by triggering antidiuretic hormone (ADH) release from volume depletion or through ingestion of fluids that are more hypotonic than the losses (46, 47). Large ingestion of hypotonic solution would usually give maximally diluted urine (<100 mOSM). However, investigation of 2 fatal cases of hyponatremia showed urine osmolality >100 mmol/kg/H<sub>2</sub>O and urinary sodium greater than 25 mEq/L. The biochemical results suggested that overhydration with hypotonic solution is not enough to explain the severe hyponatremia. Hence, it was postulated that there is a component of non-osmotic secretion of ADH, possibly due to skeletal muscle injury, as the cause of severe hyponatremia and cerebral oedema (44).

Seven cases of non-cardiogenic pulmonary oedema have been reported, with 1 fatality from brain stem herniation. It was postulated that pulmonary oedema can be a manifestation of cerebral oedema. Most patients were healthy and had low pulmonary capillary wedge pressure, indicating non-cardiogenic causes (45). Subsequently, many other cases of non-cardiogenic pulmonary oedema have been reported in swimmers, divers, triathletes and cyclists (48). This condition is called Ayus-Arieff syndrome.

### **4. What are the risk factors to develop hyponatremia?**

Menstruant women seem to be more prone to develop hyponatremia, probably due to oestrogen-mediated impairment of cerebral adaptation to rapid osmotic swelling (47). Marathon runners who develop hyponatremia were

more likely to be associated with weight gain (possibly due to excessive water ingestion), longer racing time and body mass index below 20 kg/m<sup>2</sup> (43). NSAIDs may potentiate hyponatremia due to its water retention via inappropriate arginine-vasopressin secretion, but this mechanism is not consistently demonstrated (25, 49). Few studies have shown the association between NSAID use during endurance race and development of hyponatremia (24, 25). Runners who follow the strategy “to drink as much as possible” may also be at risk of developing hyponatremia.

### 5. How can runners minimise the risk of hyponatremia?

The belief that long-distance runners should drink as much as possible is unfounded and may cause hyponatremia. It has not been shown to decrease development of fatigue, muscle cramping or exertional heat stroke. A safer method is to drink according to thirst level. Weight loss of 3% of normal body mass is well tolerated. Reduction of the availability of fluids along the route helps to reduce incidence of hyponatremia (47).

An observational study has shown that drinking sports drink containing 18 mmol/L of sodium as compared to water helps to attenuate fall in plasma sodium, despite being a hypotonic drink (50). This has led to the development of sodium supplementation during endurance race. Although it may minimally help in the prevention of hyponatremia (51), it cannot prevent exercise-induced hyponatremia in the setting of excessive fluid intake.

### 6. How should hyponatremia be treated?

Long-distance runners who developed symptoms suggestive of hyponatremia such as headache, nausea and vomiting, should have their sodium level checked. On many occasions, these symptoms may also be attributed to dehydration. However, wrongly administered 0.9% sodium chloride or worse, 5% glucose solution, will further worsen patients with hyponatremia.

In severe cases of encephalopathic hyponatremia, such as in patients who develop seizure or collapse after marathon, intravenous administration of hypertonic sodium chloride solution is the most effective treatment. This can be achieved by giving bolus 100 mls of 3% saline. The dose can be repeated after 10-20 minutes, until symptoms resolve (41, 47). Using Androque-Madias formula, 100mls of 3% saline would increase serum sodium level to not more than 1.5 mmol/L in 50-70 kg person. There have been no reported cases of central pontine myelinolysis to date.

Once the symptoms have resolved, hypertonic saline infusion should be stopped. Infusion of a small feasible volume of 0.9% saline can be tried, provided patients do not have hyponatremia-related pulmonary oedema. Serum sodium level should be checked regularly, with targeted increase of not more than 10 mmol/L during the first 24 hour, and an additional 8 mmol/L over the 24 hour thereafter (41).

### Conclusion

Exercise has been known to be an important factor for good cardiovascular outcome. Long-distance runners however have some risks related to acute kidney injury, which in short term, does not seem to cause any harm. NSAID should be used with caution. More studies are needed to examine the long-term effect of repetitive kidney injury in long-distance runners. More importantly for runners, severe hyponatremia may develop, and fatal cases have been reported. They should take precautions to prevent hyponatremia by taking such measures as adequate hydration and avoiding NSAID use. Management of severe hyponatremia requires proper attention to any increase in the rate of sodium.

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