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# Effects of Exercise on Acute Kidney Injury Biomarkers and the Potential Influence of Fluid Intake

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## Keywords

Acute kidney injury · Chronic kidney disease · Exercise · Neutrophil gelatinase-associated lipocalin · Kidney injury molecule-1 · Hydration · Fructose

## Abstract

Acute kidney injury (AKI) incidence (diagnosed by changes in serum creatinine [Cr]) following prolonged endurance events has been reported to be anywhere from 4 to 85%, and hypohydration may contribute to this. Whilst an increase in serum Cr indicates impaired kidney function, this might be influenced by muscle damage. Therefore, the use of other AKI biomarkers which can detect renal tubular injury may be more appropriate. The long-term consequences of AKI are not well understood, but there are some potential concerns of an increased subsequent risk of chronic kidney disease (CKD). Therefore, this brief review explores the effects of exercise training/competition on novel AKI biomarkers and the potential influence of fluid intake. The increase in novel AKI biomarkers following prolonged endurance events suggests renal tubular injury. This is likely due to the long duration and relatively high exercise intensity, producing increased sympathetic tone, body temperature, hypohydration, and muscle damage. Whilst muscle damage appears to be an important factor in the pathophysiology of exercise-associated AKI, it may require coexisting hypohydration. Fluid intake

seems to play a role in exercise-associated AKI, as maintaining euhydration with water ingestion during simulated physical work in the heat appears to attenuate rises in AKI biomarkers. The composition of fluid intake may also be important, as high-fructose drinks have been shown to exacerbate AKI biomarkers. However, it is yet to be seen if these findings are applicable to athletes performing strenuous exercise in a temperate environment. Additionally, further work should examine the effects of repeated bouts of strenuous exercise on novel AKI biomarkers.

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## Introduction

Following prolonged endurance events, the incidence of acute kidney injury (AKI), defined as a rapid decline in kidney function, has been reported to be anywhere from 4 to 85% [1–5]. This variable, but often high, incidence is likely due to a combination of factors, including muscle damage, sympathetic tone, body temperature, and hypohydration [1]. Of these factors, hypohydration may be of particular interest, as it is commonly seen during prolonged endurance events [6] and is relatively easy to manipulate (i.e., consume fluid to maintain euhydration). If optimizing hydration status is able to reduce the extent of

AKI, then this could have implications for long-term renal function, as there are concerns that repeated AKIs (even subclinical AKIs) could increase the subsequent risk of chronic kidney disease (CKD), which describes irreversibly impaired kidney function [7]. This theory has been proposed to explain the epidemic of CKD seen in Central America among sugarcane workers, who are regularly exposed to factors that increase the risk of AKI [8]. This is of concern because CKD is associated with an increased risk of cardiovascular disease and mortality [9]. This topic, specifically kidney injury caused by working in the heat and the subsequent risk of CKD in labourers, was the focus of a recent comprehensive review by Schlader et al. [10], which will provide an excellent background for this brief, invited review. The present review will focus on the impact of exercise training/competition on AKI biomarkers in athletic populations, as well as exploring the influence of fluid intake.

In 2017, Hodgson et al. [11] conducted a systematic review of the literature observing AKI following endurance events, with a focus on serum creatinine (Cr). They reported that increases in serum Cr concentrations were seen following endurance events, but that the long-term implications were unknown [11]. Serum Cr, the principal biomarker used to clinically diagnose AKI, is a muscle breakdown product filtered by the kidneys and excreted in urine, meaning a rise, in many settings, indicates impaired kidney function. While this impaired kidney function normally indicates renal injury, in the context of prolonged endurance events, the rise in serum Cr concentrations post-exercise may simply be due to increased muscle breakdown (i.e., increased production) [1, 11] and/or a temporary reduction in renal blood flow (RBF) (i.e., reduced clearance) [12]. In this context, the use of other AKI biomarkers may be more appropriate to detect renal tubular injury [13]. Therefore, this brief review will focus on the responses of such biomarkers to exercise training/competition.

### Novel Biomarkers of AKI

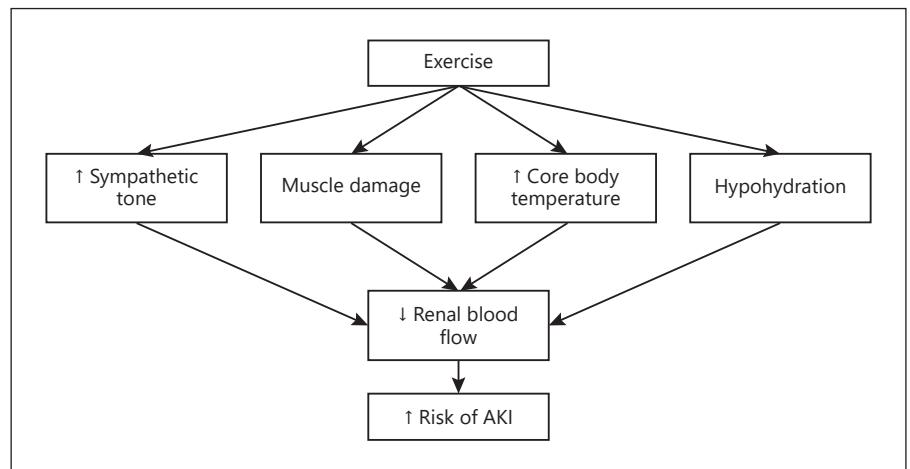
While there are many potential candidate biomarkers of AKI, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18, liver-type fatty acid binding protein, insulin-like growth factor binding protein 7 and tissue inhibitor metalloproteinase 2, NGAL and KIM-1 have received the most attention for exercise-associated AKI, as well as having been studied in a variety of clinical settings [13].

NGAL and KIM-1 expression are upregulated following AKI, which is thought to aid the proliferation of tubular cells [13]. An advantage of using NGAL and KIM-1 over serum Cr is that they may be able to indicate the location of kidney injury, as a rise in urinary KIM-1 (uKIM-1) indicates injury to the proximal tubule [13], whereas a rise in urinary NGAL (uNGAL) indicates injury mainly to the distal nephron [14]. Increases in NGAL and KIM-1 can be detected in blood or urine, but it is thought that the urinary forms may be more specific for determining AKI, as NGAL and KIM-1 are also expressed in organs other than the kidneys [13–15]. Therefore, this brief review will focus on uNGAL and uKIM-1.

An issue for consideration when studying urinary biomarkers is that the concentration of urine itself can vary substantially, and thus a rise in a urinary biomarker may be due to an increase in urine concentration, rather than an increase in biomarker production. To account for this, a variety of corrections have been applied in the literature, including correction for urinary Cr and urine osmolality [5, 16–21]. When measured in close proximity to exercise, it is thought that urine osmolality may be the more appropriate correction, as urinary Cr may be increased due to muscle damage [17, 19].

### Exercise and RBF

The previously mentioned risk factors for exercise-associated AKI may all contribute to AKI by reducing RBF [12, 22, 23]. A reduction in RBF may lead to renal ischaemia and subsequent renal ATP depletion, which can initiate AKI [24]. During exercise, increased sympathetic tone serves to increase blood flow to the skeletal muscles, while increased core body temperature increases blood flow to the skin, both of which may reduce RBF [12, 22]. Indeed, this notion is supported by the finding that RBF decreases as exercise intensity increases [12]. Additionally, if exercise involves repeated eccentric muscle contractions, it can cause skeletal muscle damage [25], which may result in extracellular fluid entering the muscle cells [23]. These effects may decrease plasma volume and activate the renin-angiotensin-aldosterone system (RAAS), which may contribute to reduced RBF during exercise [23]. Damage to skeletal muscle may also lead to leakage of cellular contents into the circulation, including myoglobin, which is thought to scavenge nitric oxide, potentially resulting in renal vasoconstriction [23]. Furthermore, hypohydration, although a modifiable factor, is commonly present towards the end of endurance events



**Fig. 1.** Schematic representing how exercise may reduce renal blood flow and thus increase the risk of AKI. AKI, acute kidney injury.

[6]. Typically, hypohydration decreases plasma volume (resulting in subsequent RAAS activation), increases circulating vasopressin, and increases core body temperature during exercise, all of which may further reduce RBF [22, 23, 26–29]. During exercise, these factors may combine to reduce RBF (Fig. 1), which has been reported to fall by as much as 75% during vigorous exercise [12].

### The Effects of Exercise on Novel AKI Biomarkers

In agreement with the often high incidence of AKI (as defined by serum Cr) measured following prolonged endurance events, increases in uNGAL [3, 16, 30] and uKIM-1 [3, 30] have also been reported after these events. These increases appear to be due to increased biomarker production, rather than simply urine concentration, as in one of these studies, urine specific gravity did not change from pre- to post-marathon [3]. Additionally, in another study, the increase in uNGAL from pre- to post-ultramarathon remained significant after correction for urinary Cr [16]. Taken together, these findings suggest that prolonged endurance events may cause renal tubular injury, rather than just muscle damage and/or a temporary reduction in RBF.

Given that uNGAL and uKIM-1 concentrations are sometimes only presented in their uncorrected form [3, 30], and that when they are corrected, it is often only for urinary Cr [5, 16, 17, 21], which may be inappropriate post-exercise [17, 19], this paragraph will compare uncorrected concentrations between studies. Prolonged endurance events, such as marathons and ultramarathons, appear to be the forms of exercise that produce the highest post-exercise uNGAL concentrations [3, 5, 15–21, 30–

32]. This may be due to the combination of long duration and relatively high-intensity exercise. This theory could explain the comparatively lower uNGAL concentrations reported after an 800 m run (high intensity, but very short duration; [17]) and prolonged walking (long duration, but low intensity; [18]). Comparing the response of uKIM-1 to different forms of exercise is more challenging as there is less data available and there appears to be higher variability in baseline readings [3, 18, 19, 30].

Although exercise duration and intensity appear to be important factors determining the extent of kidney injury, the mechanisms are not fully understood. Increases in exercise duration and intensity are likely to align with increases in sympathetic tone, muscle damage and core body temperature. For example, Bongers et al. [19] documented greater rises in uNGAL and osmolality-corrected uNGAL following 107 min of exercise, compared to after the initial 30 min of this exercise, but the lack of a control group meant that no single risk factor could be isolated. Using a crossover design, Junglee et al. [15] demonstrated that uNGAL following exercise in the heat was significantly higher when the exercise was preceded by a bout of downhill muscle-damaging running (compared to flat less-muscle-damaging running). It has also been shown that continuous upper body cooling during exercise in the heat attenuated the increase in uNGAL [32]. The findings from these crossover studies suggest that muscle damage is an important factor in the pathophysiology of exercise-associated AKI and that an increase in core body temperature exacerbates kidney injury. A summary of the studies mentioned in this section of the review that examined the effect of exercise training/competition on uKIM-1 and/or uNGAL concentrations is presented in Table 1.

**Table 1.** A summary of the studies referenced in the body text that examine the effect of exercise training/competition on uNGAL and/or uKIM-1 concentrations

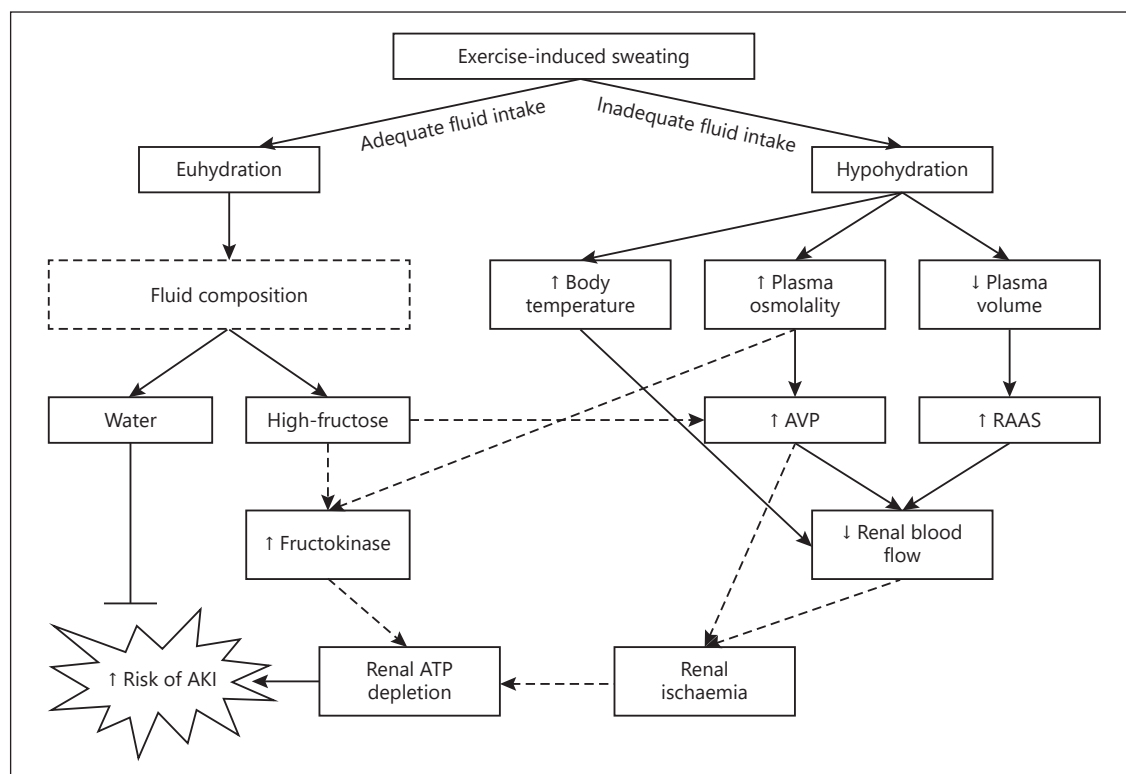
Study	Sample size	Exercise	uNGAL, ng/mL	uKIM-1, ng/mL	AKI incidence, %
McCullough et al. [30]	25	Marathon (1°C)	Pre-EX: (8.2±4.0) Post-EX: (47.0±28.6) 24 h post-EX: (10.6±7.2)	Pre-EX: (2.6±1.6) Post-EX: (3.5±1.6) 24 h post-EX: (2.7±1.6)	40
Lippi et al. [16]	16	60 km ultramarathon (6–8°C)	Pre-EX: [4.4, 0.5–33.9] Post-EX: [35.6, 12.5–86.3]	nr	38
Junglee et al. [17]	20	800 m run	Pre-EX: ~3 25 min Post-EX: [12.8, 6.2–23.2] 2 h post-EX: [0.8, 0.02–3.3]	nr	nr
Junglee et al. [15]	10	40 min HS run (65% VO <sub>2</sub> ; 33°C) preceded by either 60 min run (65% VO <sub>2</sub> ; 20°C) at –10% (MD) or +1% gradient (CON) (crossover)	MD: Pre-EX: [~1.9] Post-HS: [15.0] CON: Pre-EX: [~3.0] Post-HS: [~3.0]	nr	MD: 50 CON: 0
Mansour et al. [3]	22	Marathon (17°C)	Pre-EX: [8.0, 4.2–30.5] Post-EX: [37.6, 19.0–84.6] 24 h post-EX: [18.5, 9.3–33.7]	Pre-EX: [0.1, 0.1–0.2] Post-EX: [0.7, 0.5–2.0] 24 h post-EX: [0.7, 0.1–1.1]	82
Bongers et al. [18]	60	30, 40, or 50 km walks for 3 consecutive days	Pre-EX: [9.2, 5.2–14.7] Post day 1: [20.7, 11.0–37.2] Post day 3: [14.2, 8.0–26.3]	Pre-EX: [2.6, 1.4–6.0] Post day 1: [5.2, 2.4–9.1] Post day 3: [2.9, 1.4–6.4]	Day 1: 10 Day 3: 0
Bongers et al. [19]	35	30-min cycle (acute) (20°C) followed by cycle (25°C) 120 min or until 3% HYP (prolonged)	Δ Pre-EX to post-acute: [1.0, 0.0–8.0] Δ Pre-EX to post-prolonged: [11.1, 0.7–22.6]	Δ Pre-EX to post-acute: [0.7, –0.2–2.1] Δ Pre-EX to post-prolonged [3.0, 0.8–7.6]	nr
Butts [20]	18	Eccentric knee flexions (10×10 repetitions) followed by 60-min run (~60% VO <sub>2</sub> ; 33°C) in EU and HYP conditions (crossover)	EU: Pre-EX: (~5.0) Post-EX: (~6.0) 21.5 h post-EX: (~7) HYP: Pre-EX (~12) Post-EX (~12) 21.5 h post-EX (~7)	nr	nr
Mansour et al. [21]	23	Marathon (18°C)	Pre-EX: nr Post-EX: [44.1, 16.0–100.5]	Pre-EX: nr Post-EX: [2.7, 0.7–3.3]	55
Poussel et al. [5]	24	120-km trail race	Pre-EX: [20.1] Post-EX: [53.1]	nr	4

AKI incidence was defined as a 1.5-fold and/or 0.3 mg/dL increase in serum Cr from pre-exercise. Data are presented as (mean ± SD) or [median, interquartile range]. When a study did not state uNGAL and/or uKIM-1 concentrations, but presented them in a figure instead, these data were estimated and denoted using ~. EX, exercise; nr, not reported; HS, heat stress; VO<sub>2</sub>, maximal oxygen uptake; MD, muscle damaging; CON, control; Δ, change; EU, euhydrated; HYP, hypohydrated; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uKIM-1, urinary kidney injury molecule-1; AKI, acute kidney injury.

## Repeated Bouts of Exercise

An important caveat when interpreting the effect of exercise training/competition on long-term renal function is that exercise training has been suggested to preserve renal function through the improvement of cardiometabol-

ic risk factors [10, 33]. To our knowledge, only one study has examined the effect of bouts of exercise on consecutive days on uNGAL and uKIM-1. Bongers et al. [18] found that uncorrected and osmolality-corrected post-exercise uNGAL and uKIM-1 concentrations did not accumulate after 3 days of prolonged walking. However, the effect of



**Fig. 2.** Schematic representing how fluid intake may influence the risk of exercise-associated AKI. Solid arrows refer to established pathways, dashed arrows refer to potential/conditional pathways and the arrow from water to risk of AKI refers to potential inhibition. Temp, temperature; AVP, arginine vasopressin; RAAS, renin-angiotensin-aldosterone system; ATP, adenosine triphosphate; AKI, acute kidney injury.

repeated bouts of more strenuous exercise, which have been shown to cause higher elevations in novel AKI biomarkers, remains unknown. Serum Cr has been measured after various stages of multistage ultramarathons, but similarly, no accumulation was found [4]. In addition, individuals that developed exercise-associated AKI from an ultramarathon did not experience greater post-exercise renal dysfunction at a following ultramarathon [1]. In this study, pre-exercise blood samples were not taken, and thus pre-exercise serum Cr concentrations were approximated [1]. In this instance, it would have been beneficial to have measured pre-exercise serum Cr values, as Cr is of more use when it is in steady state. This was done by Pryor et al. [34], who showed that 6 days of heat acclimation did not affect baseline serum Cr. A potential explanation for these findings may be that changes in novel AKI biomarkers, such as uNGAL, may precede changes in serum Cr [35]. Therefore, further research is required to determine the effect of repeated bouts of strenuous exercise on novel AKI biomarkers in athletic populations.

### The Potential Role of Fluid Intake in Exercise-Associated AKI

During exercise, the increase in metabolic heat production results in sweating, and as endurance athletes rarely match their sweat losses with fluid intake, hypohydration is commonly present towards the end of endurance events [6]. Not only can hypohydration reduce RBF but it also has the potential to exacerbate exercise-associated AKI via other mechanisms. As sweat losses are hypotonic compared to plasma, failure to replace them with fluid intake typically causes a decrease in plasma volume and a rise in plasma osmolality that draws water out of the intracellular fluid compartment via osmosis [26, 27]. This results in the release of arginine vasopressin, which acts on the kidney to increase water reabsorption [26, 27]. While this process is important for water conservation, it may result in increased renal oxygen consumption [28], which could exacerbate exercise-induced renal ischaemia and subsequent kidney injury. It was recently document-



ed that marathon runners with AKI had higher post-exercise copeptin (a surrogate marker of vasopressin) concentrations than those without [21]. Plasma hypertonicity may also result in the conversion of glucose to sorbitol in the proximal tubule [36]. Sorbitol can then be converted to fructose, which can be metabolized by fructokinase, potentially resulting in renal ATP depletion and subsequent AKI [36].

While it has been suggested that the most common cause of exercise-associated AKI is muscle damage [1], this may require coexisting hypohydration in order to cause AKI [25]. In a study where large rises in markers of muscle damage were caused by maximal eccentric contractions, but hydration status was controlled for with fluid ingestion, there was no incidence of AKI [25]. A potential explanation for this is that both muscle damage and hypohydration may act in concert to increase kidney injury via synergistic reductions in plasma volume and RAAS activation [23]. Furthermore, while Junglee et al. [15] demonstrated that muscle damage increased uNGAL, it is important to note that this was in the presence of hypohydration.

To our knowledge, only two studies have used a cross-over design to investigate the effect of hypohydration during exercise/simulated physical work on novel AKI biomarkers. Butts [20] manipulated hydration status (via fluid ingestion or restriction) before and during exercise in the heat that was preceded by muscle damaging exercise. They showed no rise in uNGAL from pre- to post-exercise in either trial, and while uNGAL concentrations were higher in the hypohydrated trial at these time points, correction for urine osmolality removed this effect [20]. Conversely, Chapman et al. [32] showed, through a panel of novel AKI biomarkers, that maintaining euhydration during simulated physical work in the heat appeared to reduce injury to the proximal tubules. These results may explain the lack of effect of hydration status on osmolality-corrected uNGAL in Butts [20], as a rise in uNGAL is thought to indicate injury mainly to the distal nephron [14].

Whilst maintaining euhydration may be beneficial, it is possible that not all drinks produce the same effect. Compared to water, ingestion of a high-fructose soft drink during and after simulated physical work in the heat caused a large increase in AKI incidence and a small increase in overnight uNGAL [31]. This effect may have been mediated through activation of the vasopressin and fructokinase pathways [31, 36], and thus the disparity between the large rise in AKI incidence and small increase in overnight uNGAL may be because fructose ingestion

is more likely to lead to the injury of the proximal tubules [36]. If uKIM-1 had been measured in this study, we speculate that there would have been a large difference between trials. Therefore, although research is scarce, it is possible that fluid intake (volume and composition) might represent a potential modifiable factor to influence AKI biomarkers/risk (see Fig. 2 for potential effects).

## Conclusion

The increase in serum Cr following prolonged endurance events, such as marathons and ultramarathons, appears to be accompanied by an increase in novel biomarkers of AKI. This suggests renal tubular injury, rather than just muscle damage and/or a temporary reduction in RBF. The large rise in AKI biomarkers often seen following marathons and ultramarathons is likely due to the long duration and relatively high exercise intensity, resulting in an increase in sympathetic tone, muscle damage, core body temperature and level of hypohydration. While it is challenging to isolate the role of these factors, due to their mechanistic interactions, it has been shown that maintaining euhydration with water ingestion during simulated physical work in the heat attenuated rises in biomarkers of AKI [32]. However, ingesting a high-fructose soft drink during simulated physical work in the heat has been shown to exacerbate markers of AKI. Unfortunately, whether these findings regarding fluid intake apply to athletes undertaking strenuous exercise in a temperate environment remains unknown. The long-term effects of exercise-associated increases in AKI biomarkers and the effect of interventions that may attenuate these rises, such as maintaining euhydration with water ingestion, are also not well understood and require further research.

## Conflict of Interest Statement

L.A. Juett received travel expenses and registration fees from Danone Research to attend the 2019 Hydration for Health Scientific Conference. L.J. James has previously received funding for his research from PepsiCo., Inc. and has previously performed consultancy work for Lucozade Ribena Suntory. These previous funding/consultancy activities are in no way linked to the present article and have always been paid directly to L.J. James's employer, not to L.J. James. The authors have no other conflicts of interest to declare.

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