Incidence and Prevalence of Acute Kidney Injury During Multistage Ultramarathons

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Objective: Determine prevalence, incidence, and risk factors of acute kidney injury (AKI) during multistage ultramarathons.

Design: Prospective observational cohort study.

Setting: Jordanian Desert 2012; Atacama Desert, Chile 2012 and 2013; and Gobi Desert 2013 RacingThePlanet 250 km, 6-stage, ultramarathons.

Participants: One hundred twenty-eight participants (384 measurements) from the Jordan (25, 19.5%), Gobi (35, 27.3%), 2012 Atacama (24, 18.8%), and 2013 Atacama (44, 34.4%) races.

Interventions: Blood samples and weights were gathered and analyzed immediately after stage 1 (40 km), 3 (120 km), and 5 (225 km).

Main Outcome Measures: Changes in serum creatinine (Cr), cumulative incidence, and prevalence of AKI were calculated for each stage with "risk of injury" defined as 1.5 × baseline Cr and "injury" defined as 2 × Cr.

Results: Cumulative incidence of AKI was 41.4%. Stage 1 had 56 (43.8%) with risk of AKI and 24 (18.8%) with injury; in stage 3, 61 (47.7%) were at risk, 41 (32%) had injury; in stage 5, 62 (48.4%) runners were at risk and 36 (28.1%) had injury. Acute kidney injury was significantly associated with females [odds ratio (OR), 4.64; 95% confidence interval (CI), 2.07–10.37; $P < 0.001$], lower pack weight (OR, 0.71; 95% CI, 0.56–0.91; $P < 0.007$), and percentage weight loss (OR, 0.87; 95% CI, 0.78–0.97; $P < 0.015$). Lowest quintile of finishers was less likely to develop AKI (OR, 0.18; 95% CI, 0.04–0.78; $P < 0.022$).

Conclusions: Prevalence of AKI was 63%–78% during multistage ultramarathons. Female sex, lower pack weight, and greater weight loss were associated with renal impairment.

Key Words: acute kidney injury, ultramarathon, multistage, risk factors, incidence, prevalence

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INTRODUCTION

Ultramarathon endurance events, defined as any race longer than a marathon (26.2 miles), are increasing in popularity,[1] with a 10% increase in annual participants, and more than 69 000 finishers worldwide in 2013.[2] Considerable literature has documented alterations in serum biochemical profiles of these endurance athletes, with consistent evidence of elevated serum creatinine (Cr) in healthy race finishers[3–5] and those seeking medical care.[6–8] The etiology of renal injury is believed to be multifactorial, with contributions from myoglobinema, increased sympathetic tone, and reduced renal perfusion,[9] compounded by dehydration.[7,10] Although acute renal failure in ultramarathon runners is a rare occurrence,[11–15] acute kidney injury (AKI) is common, ranging from 34% in a single-stage ultramarathon[16] to 55% to 80% in multistage ultras.[17]

Multistage ultramarathons have competitors race up to seven days, often carrying their own food and gear throughout the course, while traversing canyons, mountains, and deserts in wide-ranging conditions. These multiday events often have several stages, providing the opportunity for rest and potential recovery between periods of exertion, and the potential for cumulative injury.[18] Previous studies have examined competitors' degree of renal injury during a single-stage ultramarathon,[5,19,20] but only one small study has examined multistage events.[17] We hypothesized that a similar incidence of AKI would be observed during a multistage ultramarathon as a single-stage, with similar associated factors.

METHODS

Setting and Selection of Participants

The RacingThePlanet events are 7-day, 6-stage 155-mile (250 km) ultramarathon foot races through wilderness terrain, held in various locations throughout the world. Participants in these events are usually experienced runners who have completed multiple endurance events as self-reported in their race applications. At each race, competitors

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complete four stages of approximately 40 km (25 miles), a fifth stage of approximately 80 km (50 miles), and a sixth stage of approximately 10 km (6 miles) through diverse terrain. Participants are mandated to carry all their personal items for the duration of the race, including gear, food (minimum of 2000 calories/day), emergency items, and clothing. All participants are offered the same amount of water each day (1.5 L per 10–12 km along the course of the stage) and start the race at the same time with a given allotment of time for completion of each stage. The study venues included the Jordanian Desert, Jordan (2012), the Atacama Desert, Chile (2012 and 2013), and Gobi Desert, China (2013).

All participants competing in a RacingThePlanet event were given the opportunity to enroll in the study. Participants were excluded if they were currently taking cardiac medication, had a history of cardiac arrhythmia or myocardial infarction, were pregnant, believed to be pregnant, were younger than 18 or older than 75 years, had any level of cognitive impairment, language impairment in reading/speaking English, or had hearing impairment not alleviated by the use of a hearing aid. At the time of race registration, interested healthy participants reviewed the study and informed consent was obtained. Approval was obtained from the institutional review boards at Stanford University School of Medicine and University of Washington Medical Center.

Research Design

Participants were enrolled the day before the race start with informed consent, weigh in, and documentation of demographics. Each participant was weighed in his or her running gear and shoes without a pack, using a calibrated battery-operated digital scale (SC-505 HoMedics; Commerce Tsp, Michigan) placed on a solid level surface. At the finish line of stages 1, 3, and 5, or on removal from competition, weights were measured and fingertip blood samples were obtained by lancet and capillary collection tube (Mock, Morrison, and Yatscoff, 1995) and then analyzed onsite immediately after collection using an iSTAT point-of-care analyzer (Abbott; East Windsor, New Jersey). Any participant who did not complete all stages was removed from the competition and the study. Both the point-of-care device and the digital scale were calibrated for each stage of the race before taking measurements.

A baseline expected glomerular filtration rate (GFR) of 100 mL/min was used when participant age was less than 40 years, and 140 minus age when than 40 years or older.[21] This estimated GFR was then used in the "modification of diet in renal disease" equation[22] to back-calculate expected baseline Cr. Established RIFLE criteria for qualification of AKI[23,24] were used to assess renal function with "risk of injury" being defined as 1.5 × Cr and "injury," defined as 2 × Cr. Measured Cr values at the end of stage 1 were used for comparisons with stage 3, and serum Cr levels from the end of stage 3 compared to the finish of stage 5.

Statistical Analyses

A descriptive analysis evaluated the age, sex, height, baseline body weight, pack weight, body mass index (BMI), and race site. Serum Cr, AKI, body weight, their cumulative changes, and race rank quintile were described for males and females after stages 1, 3, and 5. We calculated the cumulative incidence of AKI and prevalence of AKI per stage. Missing data were excluded when estimating the incidence and prevalence. The relationship between AKI and percent weight change was estimated with a Pearson correlation coefficient. We used generalized estimating equations with a logistic link function to estimate the association between AKI over the duration of the race and the predictors: race stage, age, sex, BMI, baseline pack weight, baseline body weight, stage percent weight change, cumulative percent weight change, nonsteroidal anti-inflammatory drugs (NSAID) use, and race ranking. We adjusted all models for stage, age, sex, BMI, and pack weight. All statistical significance was set at $\alpha = 0.05$. All analyses were performed using Stata IC version 12.1 (College Station, Texas).

RESULTS

Three hundred eighty-four measurements representing 128 study participants (28% women, mean age 39.6 ± 9 years) were obtained (Table 1). Because all 4 races had equivocal distances, caloric, and logistical demands, all the participants were combined into one cohort for analysis. Table 2 shows Cr by stage, with an estimated baseline and measured stage 1, 3, and 5. Table 3 has AKI status by stage; the cumulative incidence of AKI was 41.4%. Table 4 presents the descriptive results of participants per stage and level of AKI. Body weight decreased over the course of the race with men losing an average of 3.4% body weight (2.8 Kg ± 2.7 Kg) and women losing an average of 2.4% (1.5 Kg ± 12.3 Kg) by the completion of stage 5.

Multivariate analysis found AKI significantly associated with stages 3 and 5, females, lower pack weight, and percentage weight loss, with a nonsignificant association in those using NSAID. Finishers in the lowest quintile were found to be significantly less likely to develop AKI (Table 5). Significant paired correlations ($P < 0.001$) were found between percent change in weight and changes in serum creatinine between stages 1 and 3 and between stages 3 and 5 (Figure 1).

DISCUSSION

This is the largest study to date to examine the rates of AKI and associated factors during a multistage ultramarathon foot race. The observed cumulative incidence of 41.4% was greater than the reported incidence in both marathons[25] and single-stage ultramarathons.[16] The per stage prevalence of AKI ranged from 62.5% to 79.7%, validating observations from our previous study where at least 50% of analyzed runners encountered some form of AKI.[17] Although usually self-limited,[4,5,7,26] elevated creatinine values are concerning as the renal insult may be compounded by dehydration and rhabdomyolysis, a common occurrence with average creatinine kinase (CK) levels in ultramarathoners ranging from 20 000 U/L[27] to more than 40 000 UL,[28] although elevated serum CK levels have not been found to be predictive of injury progression or renal failure.[12,29]

Our study found increased odds of developing AKI associated with weight loss, both per stage and cumulatively. This is similar to the directional trend seen in single-stage

ultramarathons.[5,16] Body weight decreased in both men and women, with men losing more weight over the course of the race, with > 3% body weight loss commonly used to diagnose dehydration in ultraendurance events.[30] Although women lost less weight than men, a female runner was found to be 4 times more likely to have AKI. This directional trend is similar to the increased rate of exercised-induced hyponatremia seen in women.[30,31] As this is the first time an association has been seen between females and AKI, further research is necessary to elucidate this relationship.

Lower pack weight was found to be strongly associated with increased odds of developing AKI. Anecdotally, the fastest and most competitive RacingThePlanet entrants have the lightest packs, so a relationship was explored between better finishing times and the study outcome of AKI. Only one study to date has examined the relationship of weight, AKI, and ultramarathon performance; however, they were unable to correlate if the dehydrated runners developed AKI or what the impact was on overall performance.[5] A strong inverse relationship has been seen between greater weight loss and improved performance in marathons,[32] endurance cyclists,[33,34] triathletes,[35] and ultramarathons.[36] It is theorized that weight loss <3% represents physiologic euhydration, as water is released with the oxidization of stored glycogen and is reasonable that greater glycogen stores are being used in those generating greater speed and better finishing times. Although percentage of weight loss in our study participants was strongly associated with increased serum creatinine levels, it was the slowest race finishers who were less likely to develop AKI, 82% less likely than those who finished in the top 10%. This may have been due to the prolonged exposure of these individuals allowing greater hydration and mitigating dehydration-induced kidney insult, but this is hypothetical as we were unable to quantify the amount of fluid ingested in all finishers. Slower finishers in ultraendurance events have been associated with lower levels of myoglobin,[37] and this may explain our findings as this population may have had less myoglobinemia-induced renal damage, although this relationship was not evident in another study.[27]

TABLE 1. Baseline Characteristics of Study Participants

	Males (n = 92)	Females (n = 36)	All Participants (n = 128)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)	39.9 (9.3)	38.9 (7.9)	39.6 (8.9)
Height (m)	1.81 (0.13)	1.68 (0.73)	1.78 (0.13)
Weight (Kg)	79.5 (9.9)	61.9 (9.5)	74.5 (12.6)
BMI	24.3 (2.6)	21.8 (2.3)	23.6 (2.8)
Pack weight (Kg)	9.9 (1.6)	9.1 (1.6)	9.7 (1.6)
Event	**n (%)**	**n (%)**	**n (%)**
Atacama 2012	17 (18.5)	7 (19.4)	24 (18.8)
Jordan	16 (17.4)	9 (25.0)	25 (19.5)
Gobi	25 (27.2)	10 (27.8)	35 (27.3)
Atacama 2013	34 (40.0)	10 (27.8)	44 (34.4)

BMI = body mass index.

TABLE 2. Creatinine by Stage

Stage	Mean	SD	Mean Change	SD Change
Baseline	0.72 (0.49 to 0.89)	0.13	—	—
Stage 1	1.20 (0.70 to 2.30)	0.28	0.49 (0.02 to 1.54)	0.26
Stage 3	1.33 (0.70 to 2.90)	0.37	0.12 (−0.50 to 1.50)	0.26
Stage 5	1.28 (0.70 to 2.70)	0.34	−0.05 (−1.0 to 0.50)	0.24

creatinine in mg/dL.

The use of NSAID was compared between those with AKI and those not meeting criteria, with a trend toward significance seen with an overall use rate of 29 (22.7%) during some point in the study. It has been reported that as many as 75% of ultraendurance athletes ingest NSAID during competition,[38] and concurrent use has been associated with greater creatinine levels than matched controls,[39] and hospitalization and acute renal failure.[15] This is in contrast to a marked lack of difference of elevated creatinine levels between NSAID users and nonusers,[4] and also lack of association with subsequent development of AKI.[16] Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase, which prevent the breakdown of arachidonic acid to prostaglandins that contribute to renal vasodilation. Without these prostaglandins, there is reduced renal perfusion leading to impaired GFR; ranging from mild elevations in renal function laboratory parameters to acute renal failure.[40] The effects of NSAID use in endurance athletes remain controversial and unresolved. The only randomized trial to date on this subject found no difference in serum creatinine at ultramarathon race end versus matched controls, but conclusions were limited by the lack of blinding, small sample size, and NSAID dosages that were likely subtherapeutic.[39] Further prospective studies are needed to better understand the impact of NSAIDs on the ultramarathon runner.

Our baseline values and subsequent criteria of AKI in stage 1 were based on the accepted assumption that the healthy ultramarathon runners had normal renal function at the start of a race.[16] Estimated GFR has been shown to be accurate compared with calculated GFR under rest conditions in healthy subjects.[40] As stages 3 and 5 used direct measurements to calculate creatinine and subsequent AKI, and both showed greater prevalence than stage 1, the algorithm may have overestimated baseline Cr values, which would have resulted in a smaller delta Cr in stage 1 and underestimation of AKI prevalence and incidence.

TABLE 3. AKI Status by Stage

	Stage 1	Stage 3	Stage 5
AKI Status	**n (%)**	**n (%)**	**n (%)**
Normal	48 (37.5)	26 (20.3)	30 (23.4)
Risk of injury	56 (43.8)	61 (47.7)	62 (48.4)
Injury	24 (18.8)	41 (32.0)	36 (28.1)

AKI, acute kidney injury; injury, 2 × baseline creatinine; risk of injury, 1.5 × baseline creatinine.

TABLE 4. Descriptive Results by AKI Status and Stage

Stage 1	Normal		Risk of Injury		Injury	
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %
Age	39.4	10.2	39.9	8.7	39.4	6.4
Sex (female)	3	6.3	18.0	32.1	15.0	62.5
Prerace weight (kg)	77.5	9.7	73.8	12.5	70.5	16.4
BMI	24.2	2.0	23.6	2.6	22.2	3.8
Stage % weight change	−0.1	2.9	−1.1	2.9	−1.2	2.4
Creatinine	1.06	0.12	1.22	0.24	1.46	0.38
Change in creatinine	0.27	0.08	0.52	0.14	0.85	0.28
Finishing rank, %						
Top 10	4	9.3	2	3.9	3	13.6
11–25	4	9.3	9	17.7	1	4.6
26–50	17	39.5	14	27.5	11	50.0
51–75	7	16.3	15	29.4	5	22.7
>75	11	25.6	11	21.6	2	9.1
Stage 3						
	Normal		**Risk of Injury**		**Injury**	
	Mean or n	**SD or %**	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**
Age	40.8	10.7	39.0	9.7	39.9	6.1
Sex (female)	1	3.9	17	27.9	18	43.9
Prerace weight (kg)	75.2	9.4	73.2	11.7	76.1	15.4
BMI	23.8	2.2	23.4	2.1	23.6	3.8
Stage % weight change	−1.8	1.9	−1.6	2.4	−1.9	2.0
Creatinine	1.06	0.12	1.24	0.23	1.62	0.44
Change in creatinine	0.00	0.10	0.08	0.15	0.26	0.39
Finishing rank, %						
Top 10	1	4.2	6	10.7	2	5.6
11–25	4	16.7	6	10.7	4	11.1
26–50	9	37.5	15	26.8	18	50.0
51–75	3	12.5	17	30.4	7	19.4
>75	7	29.2	12	21.4	5	13.9
Stage 5						
	Normal		**Risk of Injury**		**Injury**	
	Mean or n	**SD or %**	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**
Age	40.2	10.7	38.9	9.6	40.4	5.6
Sex (female)	2	6.7	18	29.0	16	44.4
Prerace weight (kg)	76.7	10.0	73.2	11.7	75.0	15.6
BMI	24.2	1.9	22.9	2.5	24.1	3.5
Stage % weight change	−0.1	1.2	−0.3	1.7	−1.4	1.6
Creatinine	1.02	0.15	1.24	0.24	1.61	0.38
Change in creatinine	−0.14	0.20	−0.06	0.24	0.04	0.24
Finishing rank, %						
Top 10	2	6.7	3	5.2	4	14.3
11–25	1	3.3	11	19.0	2	7.1
26–50	9	30.0	18	31.0	15	53.6
51–75	8	26.7	15	25.9	4	14.3
>75	10	33.3	11	19.0	3	10.7

AKI, acute kidney injury; BMI, body mass index; injury, 2 × baseline creatinine, creatinine in mg/dL; risk of injury, 1.5 × baseline creatinine.

There was no control for variables, including electrolyte supplementation type or amount, NSAID amount, quality or maximum quantity of caloric intake, and the athletes' option to stop at an aid station on stage 5 for rest and/or rehydration. All which may have effected results. Other factors possibly altering outcomes included ambient temperature differences

TABLE 5. Adjusted Odds Ratios of AKI for Predictor Variables

Variable	Odds Ratio	95% CI		*P*
Stage 1	Reference	—	—	
Stage 3	2.26	1.46	3.48	<0.001
Stage 5	1.82	1.11	2.98	0.017
Age	1.02	0.98	1.05	0.34
Female	4.64	2.07	10.37	<0.001
BMI	1.17	0.99	1.38	0.062
Pack weight	0.71	0.56	0.91	0.007
Stage % weight change	0.87	0.79	0.96	0.003
Cumulative % weight change	0.87	0.78	0.97	0.015
NSAID use (yes)	2.00	0.93	4.28	0.075
Finishing rank, %				
Top 10				
11–25	0.51	0.13	2.01	0.337
26–50	1.34	0.43	4.20	0.614
51–75	0.48	0.13	1.73	0.262
>75	0.18	0.04	0.78	0.022

AKI, acute kidney injury; BMI, body mass index; CI, confidence intervals; NSAID, nonsteroidal anti-inflammatory drugs.

between the different races (causing increased/decreased sweating and hydration) and actual fluid intake (we presumed all drank the allotted 1.5 L between aid stations). Interrace data were combined for analysis as each race was of similar design, length, and logistical demands; as the environmental and race conditions varied between the study locations, this assumption may have led to disparate results. Our cohort grouping was similar to other studies that have combined athletes from different races for analysis.[30,36] Obtaining baseline values either before a race or at stage start on multiple days throughout, a competition held in wilderness conditions is logistically challenging and is unfeasible when attempting to gather large data. This approach has been attempted and likely contributed to the high rate of participant attrition seen in our previous research.[17]

CONCLUSIONS

Acute kidney injury has a high cumulative incidence and stage prevalence in multistage ultramarathoners. Observed rates of AKI were markedly higher than those reported in marathons and single-stage ultramarathons.

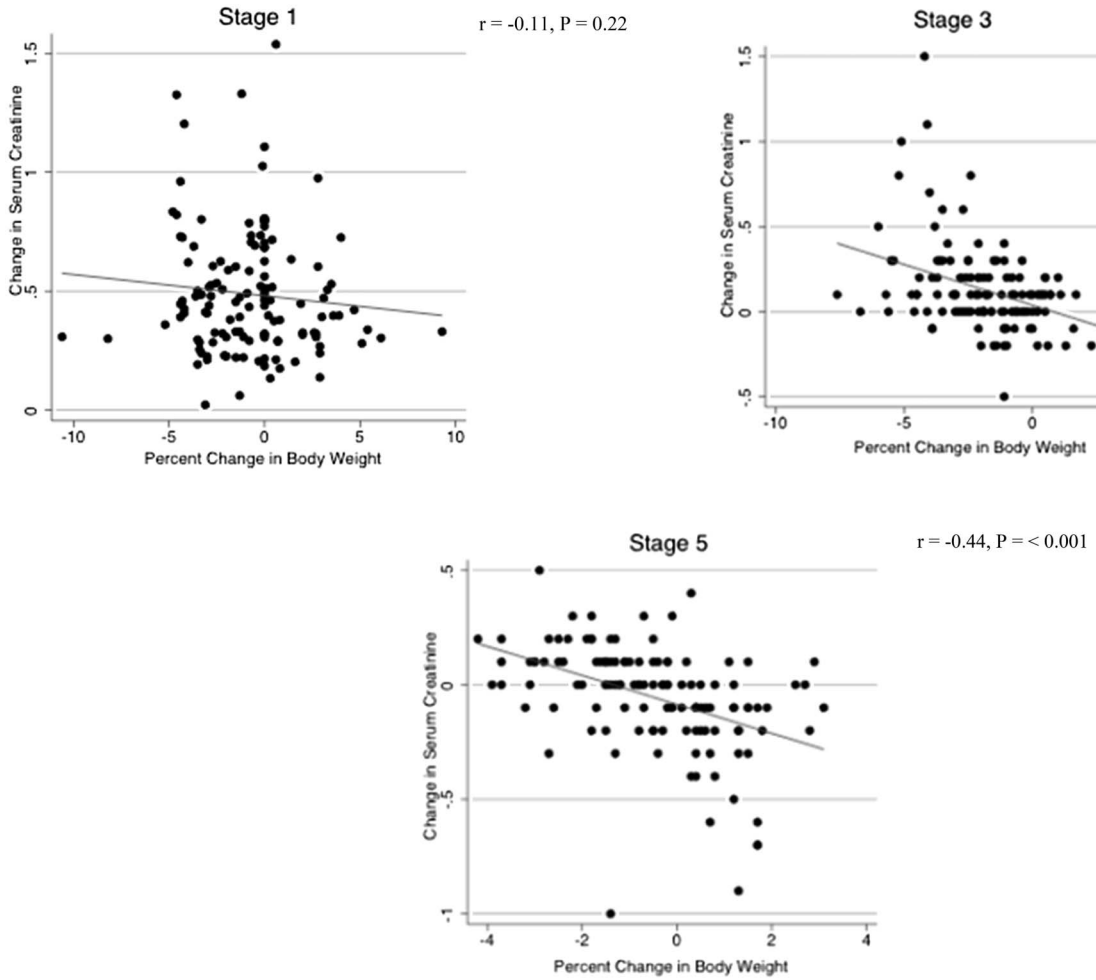

FIGURE 1. Paired correlation between stage change in serum creatinine and % weight change.

Multivariate analysis found AKI was significantly associated with females, lower pack weight, and percentage weight loss. These finding may represent "at risk" individuals who could benefit from increased education and awareness by medical providers. Slower finishers were less likely to develop AKI, a novel finding that along with females as an independent risk factor for increased odds of having impaired renal function needs to be explored. Although NSAID use was not significantly associated with AKI, future studies examining this controversial relationship are necessary. Whether the observed increase in runners' creatinine levels are representative of renal injury or an adaptive response to the physiologic stressors remains to be seen.

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