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RESEARCH ARTICLE

Hypohydration augments the acute increase in urinary biomarkers of kidney injury following the 100-mile Western States Endurance Run

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Abstract

Ultraendurance races may transiently increase acute kidney injury (AKI) risk, yet data on contributing factors are sparse. Therefore, we examined the acute effects of the Western States Endurance Run [WSER (100 miles; 161 km)] on urinary AKI biomarkers and kidney blood flow, while also assessing the influence of race pace and hydration status. Blood and urine samples were collected to assess urine specific gravity (USG), creatinine, and AKI risk [nephrin, neutrophil gelatinase-associated lipocalin (NGAL), insulin-like growth factor binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinase 2 (TIMP2), and IGFBP-7·TIMP-2]. Renal blood velocity and conductance were measured via Doppler ultrasonography. Pre and post measures were obtained from 36 runners (29 males/7 females, age: 44 ± 9 yr, mean finish time: 25:45:55). Urinary AKI biomarkers increased postrace, with nephrin, IGFBP7, and IGFBP7·TIMP-2 remaining elevated after indexing to creatinine (Ps $<$ 0.008). Hydration status declined, with only 8 of 35 runners remaining euhydrated postrace. Finishing euhydrated attenuated increases in urinary creatinine and creatinine-indexed IGFBP-7·TIMP-2 (Ps $\leq$ 0.006). Faster race pace correlated with increases in USG (rho, $\rho = 0.338$, $P = 0.048$) and urinary creatinine (rho, $\rho = 0.443$, $P = 0.010$), but not with creatinine-indexed AKI biomarkers (Ps $\geq$ 0.382). Kidney blood velocity and conductance were unchanged (Ps $\geq$ 0.186). Finishing hydrated appears to help mitigate the transient increase in kidney injury following an ultraendurance race.

NEW & NOTEWORTHY Urinary concentrations of several acute kidney injury (AKI) biomarkers increased after completing the 2023 Western States Endurance Run; however, there were no changes in renal blood flow in a subset of runners. When normalized to creatinine, several AKI biomarkers, including IGFBP7·TIMP2 (an FDA-approved biomarker of AKI), remained elevated. Notably, finishing the race euhydrated appeared to have a protective effect, mitigating increases in IGFBP7·TIMP2.

acute kidney injury; hydration; performance; renal blood flow; ultramarathon

INTRODUCTION

Ultramarathons (i.e., footraces over 42 km) have become increasingly popular, with interest and participation rising exponentially over the past decade (1). Beyond prolonged physical exertion, ultramarathon runners often face extreme temperatures, hypohydration, and altitude changes, contributing to a relatively high incidence of mild-to-moderate acute kidney injury (AKI) (2). Importantly, findings from epidemiological and experimental studies suggest that AKI may serve as a trigger for the development of chronic kidney disease (3, 4).

Prolonged exercise transiently increases serum creatinine (proxy for decreased kidney function) and urinary AKI biomarkers (2, 5–13). Indeed, data from marathon (6, 14–16) and ultramarathon finishers (5, 9, 13, 17–19) indicate that up to 80% of finishers experience transient elevations in AKI biomarkers. The clinical significance of elevated AKI biomarkers and whether repeated participation predisposes runners to long-term sequelae remains unclear (5, 9, 20). Nonetheless, many studies have not accounted for hydration status or race intensity (i.e., running pace) when assessing postrace AKI. Given the rise in popularity of ultra endurance footraces, it is important to investigate strategies, such as maintaining euhydration, to mitigate AKI risk. Regarding potential mechanisms of AKI, blood flow is redistributed during exercise, thus reducing renal perfusion seven- to

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eightfold during maximal exertion (21, 22). The reduction in renal perfusion during exercise, mediated mainly by renal sympathetic nerve activity (21) and catecholamine release (23), can be exacerbated by heat stress and hypohydration (24–26), which are common during ultramarathons. Specifically, shifts in blood flow toward working muscles for oxygen delivery (27, 28) and skin for cooling (29) and reduced blood volume with exercise and heat-induced hypohydration lead to reduced kidney perfusion. Thus, adequate hydration, which can help prevent blood volume reductions, may attenuate AKI risk during ultramarathons. Another concern with these events is postrace increases in circulating creatine kinase (CK) (30, 31), a biomarker of muscle damage and exertional rhabdomyolysis, both of which are linked to AKI in endurance athletes (32). However, their role in AKI development during ultramarathons is uncertain.

The purpose of this study was to examine whether completing the 161 km (100.2 mile) Western States Endurance Run (WSER) ultramarathon *1*) increases AKI risk, evaluated using a comprehensive panel of urinary biomarkers and *2*) reduces renal perfusion. We also investigated whether maintaining euhydration blunts increases in AKI biomarkers or reductions in renal perfusion, and whether race pace influences these changes. We indexed urinary AKI markers to creatinine and osmolality to account for variations in urine concentration and dilution. We hypothesized that runners with a postrace urine specific gravity (USG) $\leq$ 1.020, whom we presumed maintained euhydration during the WSER (33), would experience smaller increases in urinary AKI biomarkers (34). We also hypothesized that a faster race pace would correlate with greater changes in AKI biomarkers (21, 23).

METHODS

Participants were recruited from athletes entered to run the 2023 WSER, an ultraendurance event traversing the Sierra Nevada mountains that includes 5,486 m of ascent and 7,010 m of descent (35). As we have described (31), the race is held annually in the last week of June, with typical ambient temperatures ranging between 4 and 37°C. The race begins at 0500 Pacific time, and runners have 30 h to complete the distance. There are 20 aid stations on the course, all supplied with beverages, and runners are encouraged to maintain ad libitum food and fluid intake for the duration of the event. We collected information on environmental conditions within our field data collection laboratory using a Davis Instruments Vantage Vue weather station console (DAVIS 6351 M).

Study Design

The present investigation was conducted in 2023, a year in which 379 runners (296 males/83 females, ~22% female) began the race, of which 328 (260 males/68 females, ~21% female) finished the race (86.5% finish rate) (31). Temperature ranged from 10 to 27°C and relative humidity ranged from 30 to 75%. All athletes were provided written informed consent before participation, and all procedures involving human research participants were approved by the Institutional Review Board at Georgia Southern University (H23253).

Participants were recruited up to 6 mo before the 2023 WSER, all of whom completed virtual questionnaires (training, nutrition, race preparation details) before any testing. Data included in this investigation were collected up to 72 h before the beginning of the event (pre), and within 1 h (30 ± 14 min, max = 59 min) of individuals finishing the race (post). At each time point, renal blood velocity was assessed as an applied measure of kidney perfusion, and spot urine and capillary blood samples were collected.

Urine Collection and Hydration Assessment

Participants were provided sealed, sterilized urine collection cups at the pre- and postrace data collections. From the provided urine samples, we measured USG (ATC 3-in-1 Scale Clinical Refractometer) at our field laboratory and stored aliquots of urine in cryogenic tubes for future analyses on dry ice before longer term storage at −80°C (36, 37). Although freezing can influence stability of certain biomarkers (36, 37), frozen samples were thawed simultaneously to minimize variability and subsequently analyzed at Auburn University School of Kinesiology for electrolyte concentrations (sodium, potassium, and chloride) using a Smartlyte Easylyte Electrolyte Analyzer and osmolality using an Advanced Instruments Advanced 3D3 Osmometer model 3250 (38–41). Notably, USG and urine osmolality are well-accepted biomarkers of hydration status for athletes (33, 42). Changes in urine electrolyte concentrations and ratios (e.g., sodium:potassium) have also been reported after endurance exercise events (43, 44). As we have previously described (38–41), we measured all analytes in triplicate, and using these methods has resulted in a <1% intrasample coefficient for urine electrolytes and urine osmolality (39).

Biomarkers of Kidney Function and AKI

Capillary blood was collected using a Touch-Activated Phlebotomy device (TAP Micro, YourBio Health, Medford, MA). Blood was centrifuged at 735*g* for 10 min to separate serum, which was aliquoted and stored on dry ice before storage at −80°C. Serum CK was measured with a Roche Integra 400+ analyzer at the Indiana University School of Medicine Center for Diabetes and Medical Disease's Translational Core Laboratory. We also measured serum creatinine as a proxy for glomerular function via the University of Alabama at Birmingham Biochemical Genetics Laboratory. Serum and urine creatinine samples were measured using liquid chromatography-mass spectrometry (LC-MS). In brief, LC-MS was performed using tandem mass spectrometry using multiple reaction monitoring and quantified via stable isotope dilution (45). For LC-MS experiments, 20 µL of the sample was deproteinated and diluted with a stable isotope in a single step. The diluted samples were subjected to isocratic HPLC with 10 mM ammonium acetate in 65% acetonitrile. Creatinine and d_3-creatinine were detected by electrospray ionization tandem mass spectrometry. For general kidney function, we also measured pre- and postrace urine cystatin C as measures of glomerular filtration (41, 46).

Urine samples were also shipped to the Indiana University School of Medicine Center for Diabetes and Medical Disease's Translational Core Laboratory for multiplex analysis to assess kidney function. Multiplex assays were performed in duplicate

using Meso Scale Discovery assay kits (Meso Scale Diagnostics, Rockville, MD) according to the manufacturer's instructions. The assays were selected based on the specific analytes of interest, ensuring compatibility with the matrix being tested. The assay plates were precoated with capture antibodies specific to the target analytes. Regarding our selection of specific analytes, nephrin is a protein expressed in the glomerulus and is responsible for maintaining the glomerular barrier, and the excretion of nephrin is associated with glomerular damage (47). As for biomarkers related to the renal tubules, neutrophil gelatinase-associated lipocalin (NGAL) is a protein expressed in the thick ascending loop of Henle and the collecting ducts and is detectable up to 3 h after toxic kidney injury (48). Insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP2) induce cell cycle arrest (49). Although it remains unclear precisely where IGFBP7 and TIMP2 are secreted and what their specific function is surrounding kidney injury, the product of the two urinary biomarkers (IGFBP7·TIMP2) is a sensitive biomarker for the prediction of AKI (25). Indeed, urinary IGFBP7·TIMP2 is the only *United States Food and Drug Administration*-approved biomarker for the clinical screening of AKI risk (proprietary name NephroCheck, Astute Medical, San Diego, CA) (25). We chose this array of analytes based on our experience (38, 41, 48–52), the Indiana University Translation Core's experience measuring them, their relatively high expression along the nephron such as the proximal tubule (26, 48) and ascending loop of Henle (53), as well as their documented effectiveness at representing subclinical kidney injury (26, 48, 53, 54).

Similar to our prior work, we indexed all urinary biomarkers of AKI to urine creatinine concentration (38, 41), which was an important methodological consideration since we collected spot urine samples. We indexed the AKI biomarkers to account for fluctuations in urine concentration and ensure more accurate comparisons across samples (55–58). In clinical populations, elevated spot urine creatinine alone has utility in identifying kidney injury-related risk of all-cause mortality (59) and hospitalization (60). We anticipated that indexing samples to creatinine would attenuate the magnitude of pre- to postrace changes (13). However, we suspected elevations would persist, a finding supported by recent dehydration and endurance race studies (16, 25). Nonetheless, urinary creatinine may be affected by prolonged exercise, where it could be a function of changes in glomerular filtration rate or muscle breakdown. Therefore, we also indexed AKI biomarkers to urine osmolality and urinary cystatin C.

Renal Blood Velocity

Renal and segmental artery blood velocity (RBV) were collected using Doppler ultrasound (GE Logiq e) with a 3–5 MHz phased array transducer (61, 62). Participants were positioned in the decubitus position on a massage table during each collection (pre- and postrace) and familiarized with a brief 10-s breath-holding protocol to minimize the movement of the kidneys (61, 62). The coronal approach was used to visualize both renal and segmental arteries. Color flow was used to confirm the internal structure of the renal vasculature. Once the renal vasculature was confirmed, each measure lasted between three and five cardiac cycles. Measures were collected in triplicate for both renal and segmental arteries for both timepoints. Semiautomated waveform tracing (GE software) within the ultrasound was used to analyze individual mean RBV, and we report the average of replicate measures here.

Regarding a technical limitation, the diameter of the vessel walls of the renal vasculature cannot be accurately measured due to the resolution of Doppler imaging with the relatively deep kidney tissue depth. Using measures such as MRI for a field study would not be feasible; therefore, we used Doppler ultrasound to quantify blood velocity (61). The use of Doppler ultrasound to quantify hemodynamics in the renal and segmental arteries operates under the assumption that vessel diameter does not change during physiologically induced changes in blood flow. This assumption is based on evidence that, during infusion of a vasoconstrictor (adenosine) and vasodilators (isosorbide dinitrate, papaverine, dopamine, and fenoldopam), changes in renal blood flow are dependent on changes in blood velocity rather than changes in the diameter of the renal artery (63, 64). Thus, changes in Doppler ultrasound-derived RBV are often interpreted as changes in renal blood flow (25, 62, 65, 66).

Additional hemodynamic measures were obtained from this study, which we have reported on previously (31, 67). We used estimated aortic blood pressure to calculate renal vascular conductance (velocity ÷ pressure), as this more closely represents the pressure within the renal arteries, as opposed to brachial pressures. During pre- and postrace, aortic blood pressure was estimated via pulse wave analysis (SphygmoCor XCEL, AtCor Medical, Naperville). In brief, brachial artery pressure waveforms were transformed using a validated generalized transfer function to estimate an aortic pressure waveform and derive aortic blood pressure (68, 69).

Statistics

All data were assessed for normality using a Shapiro-Wilk test. If data were normally distributed, paired samples *t* tests were used to determine differences between pre- and postrace measures; if data were not normally distributed, the Wilcoxon ranked test was used. We used Cohen's *d* to assess the effect size for normally distributed data (70) and interpreted effects as small ($d = 0.2$–0.49), medium ($d = 0.5$–0.79), and large ($d > 0.8$). We used the rank-biserial correlation (r_{rb}) to assess effect size for nonnormally distributed data (71), interpreted as small (0–0.19), medium (0.2–0.29), large (0.3–0.39), and very large (0.4–1.0). Creatinine-indexed AKI biomarker change scores were calculated to correlate the relative change in AKI biomarkers, RBV, and performance measures as [$\%\Delta = [(\text{post}-\text{pre}/\text{pre}) \times 100$] and were only calculated in participants with complete AKI and RBV data. Spearman's rho was used for all correlations, as neither pace nor any biomarkers were normally distributed. Finally, participants were split based on hydration status at the end of the race (euhydrated: USG $\leq$ 1.020, hypohydrated: USG $>$ 1.020) (33, 42) to assess whether finishing euhydrated attenuated the effect of the race on elevating urinary AKI biomarker concentrations. Since residuals for AKI biomarkers were not normally distributed, data were natural log-transformed (l_n) before running a mixed model ANOVA (hydration status $\times$ timepoint); however, we visually depict the raw data. We used Fisher's exact test to compare proportions between groups. Since this was a field study, we decided not to screen for outliers unless we observed clear

visual outliers (~3 SD) outside of the range of the data distribution. Specifically, given the exploratory, field-based nature of the study, we did not conduct a formal power analysis (72), and due to the small sample size, we used a deliberately lenient outlier criterion to preserve physiological variability and avoid introducing bias through arbitrary data exclusion, particularly female athletes who are historically underrepresented in this research area (73). There were two data points that were removed with this criterion (one from NGAL/creatinine-pre and one from IGFBP7·TIMP2/creatinine-pre; Supplemental Fig. S1). Post hoc pairwise comparisons with Bonferroni adjustment were completed where appropriate. Statistics were run in jamovi (v2.6.19), and figures were generated in Graphpad Prism (v10.4.1). Significance was set a priori to $P \leq 0.05$. All data are presented as means ± SD for normally distributed data or median (interquartile range) for nonnormally distributed data in the tables or as individual data points superimposed on box and whisker plots in the figures. Interquartile ranges are reported as single numerical values (Q3–Q1) to reflect variability from pre to post race.

RESULTS

Demographics

A schematic of participant recruitment and enrollment is presented as Fig. 1. Thirty-six participants were included in the analyses investigating the effects of completing the WSER on biomarkers of AKI. Twenty-nine (27) of those 36 participants completed RBV for at least one artery and were included in investigating the effects of completing the WSER on RBV. Thirteen participants of the 29 who completed RBV for at least one artery had complete renal (paired; $n = 12$) or complete segmental (paired; $n = 12$) artery velocity data and were included in exploratory correlations between RBV and biomarkers of AKI, as both pre and post measures are needed to calculate change scores. Participant demographics for both subsets of participants can be found in Table 1.

Due to the small number of female participants and unequal sample sizes (F = 7, M = 29), we did not separate participants by biological sex, but we depict them with different symbols in figures. In addition, we did complete a sex comparison for prerace hydration, given a prior study demonstrating sex differences in the change in hydration during an endurance cycling event (42). Nonetheless, we observed no baseline sex differences in USG (male participants = 1.010 ± 0.006, female participants = 1.011 ± 0.008, $P = 0.741$) or urine osmolality (male participants = 460 ± 245, female participants = 421 ± 268 mosmol/kg, $P = 0.667$). Furthermore, we also observed a decrease in aortic mean blood pressure ($P = 0.016$, $d = 0.423$, pre: 93 ± 8 mmHg, post: 89 ± 9 mmHg) and an increase in serum CK concentration ($P < 0.001$, $d = 1.582$, pre: 132 ± 85, post: 13,373 ± 8,414 U/L) in all the runners, similar to our previous findings (31).

Postrace Hypohydration is Associated with Pace

Upon completion of the 2023 WSER, USG (Fig. 2*A*; $P < 0.001$) and osmolality (Fig. 2*B*; $P < 0.001$) were increased. Using USG to classify hypohydration status (USG > 1.020), only 11% of participants (4/35) were hypohydrated at their prerace collections, whereas 77% were hypohydrated (27/35) upon completion Fig. 2*C* (Fisher's exact test $P < 0.001$). Race pace was positively correlated with changes in both USG (Fig. 2*D*; $\rho = 0.34$, $P = 0.048$) and urine osmolality (Fig. 2*E*; $\rho = 0.53$, $P = 0.002$). The larger range in percent change for urine osmolality compared with USG reflects differences in scale. For example, an increase in urine specific gravity from 1.020 to 1.030 represents only a ~1% change, whereas an increase in urine osmolality from 200 to 800 mosmol/kg reflects a 300% change. A more extreme shift from 150 to 950 mosmol/kg represents a 533% increase. These differences explain the broader *y*-axis range for osmolality in Fig. 2, *D* and *E*. Of note, one participant had missing USG data that were not realized until all urine had been used for other measures; hence, $n = 35$ as opposed to $n = 36$.

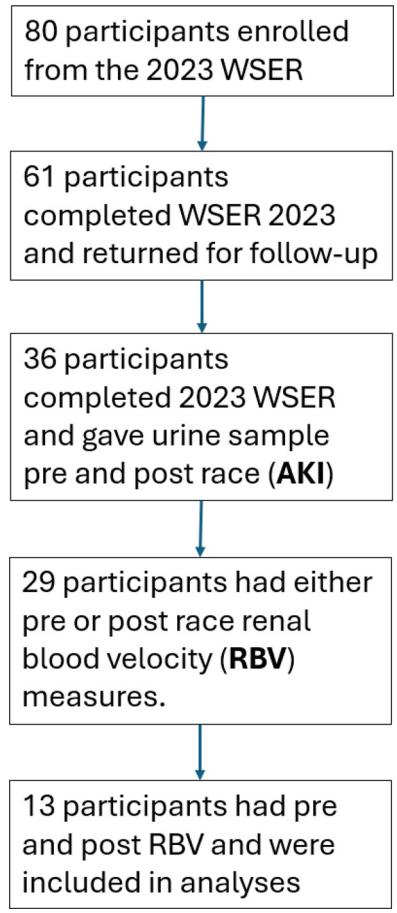

Figure 1. Outline of participant selection.

Postrace Increases in Biomarkers of Hydration, Electrolytes, and AKI

Comparisons between pre- and postrace serum creatinine, urine electrolyte concentrations, and raw urinary AKI biomarker concentrations are reported in Table 2. We observed pre- to postrace increases in urine potassium concentration ($P < 0.001$, $r_{rb} = 0.84$) and all raw urinary AKI biomarker concentrations ($Ps < 0.001$); and decreases in urine sodium ($P < 0.001$, $r_{rb} = 0.75$) and urine chloride concentration ($P < 0.001$, $r_{rb} = 0.97$). As presented in Fig. 3, *A–F*, we also observed significant increases in urine creatinine concentration and all urine AKI biomarkers when indexed to urine

Table 1. *Demographics for urine collections (AKI) and renal blood velocity (RBV) assessments (includes all participants who had this data)*

	AKI	RBV (Total)	RBV (Paired)
n	36	29	13
Sex	29 M/7 F	25 M/4 F	11 M/2 F
Height, cm	175.9 ± 8.8	176 ± 8.2	174.3 ± 7.2
Body mass, kg	70.4 ± 10.0	71.5 ± 9.3	69.1 ± 10.4
BMI, unit	22.6 ± 1.8	22.9 ± 1.8	22.6 ± 2.1
Age, yr	44 ± 9	44 ± 9	45 ± 10
Race	28W/3A/1N/1NW/3PNA	26W/2A/1PNA	12W/1A
Finishing time, h:min:s	25:45:55 ± 3:05:50	25:39:12 ± 3:09:07	24:40:48 ± 3:22:57

Data presented as means ± SD. A, Asian; AKI, acute kidney injury; BMI, body mass index; F, female; M, male; N, American Indian or Alaskan Native; NW, American Indian or Alaskan Native and White; PNA, prefer not to answer; RBV, renal blood velocity; W, white.

creatinine (*Ps* < 0.008), except for creatinine-indexed NGAL ($P = 0.334$) and TIMP2 ($P = 0.287$). Supplemental Fig. S1 depicts the data with outliers included. The only change in interpretation is the interaction term for our mixed model ANOVA for time × hydration status on IGFBP7·TIMP2 (before outlier removal $P = 0.104$; after outlier is removed $P = 0.003$). Respective qq plots have been included in Supplemental Fig. S1 to demonstrate why these outliers were removed, with the data points highlighted by a crossed-out box. In addition to the creatinine-indexed data, we indexed all AKI biomarkers to osmolality and cystatin C as presented in Table 4. These findings were generally consistent with the data presented in Fig. 3. When indexed to osmolality, all AKI biomarkers were elevated from pre- to postrace except NGAL. When indexed to cystatin C, all AKI biomarkers were elevated from pre- to postrace except IGFBP7.

Hypohydration Linked to Greater Postrace Increases in IGFBP7·TIMP2

Comparisons between euhydrated ($n = 8$) and hypohydrated ($n = 27$) finishers are presented in Fig. 4. Urinary creatinine (Fig. 4*A*; $P = 0.006$) and creatinine-indexed IGFBP7·TIMP2 (Fig. 4*F*; $P = 0.003$) exhibited significant time × hydration status interaction terms, but not creatinine-indexed nephrin, NGAL, IGFBP7, or TIMP2 (*Ps* > 0.136). Regarding the creatinine and IGFBP7·TIMP2/creatinine (biomarkers demonstrating time × hydration status interactions), we also observed pre- versus postrace pairwise differences within the hypohydrated finishers' group only (Fig. 4, *A* and *F*). In addition, hypohydrated finishers exhibited higher postrace urinary creatinine and IGFBP7·TIMP2/creatinine than euhydrated finishers (Fig. 4, *A* and *F*). We observed no baseline differences between

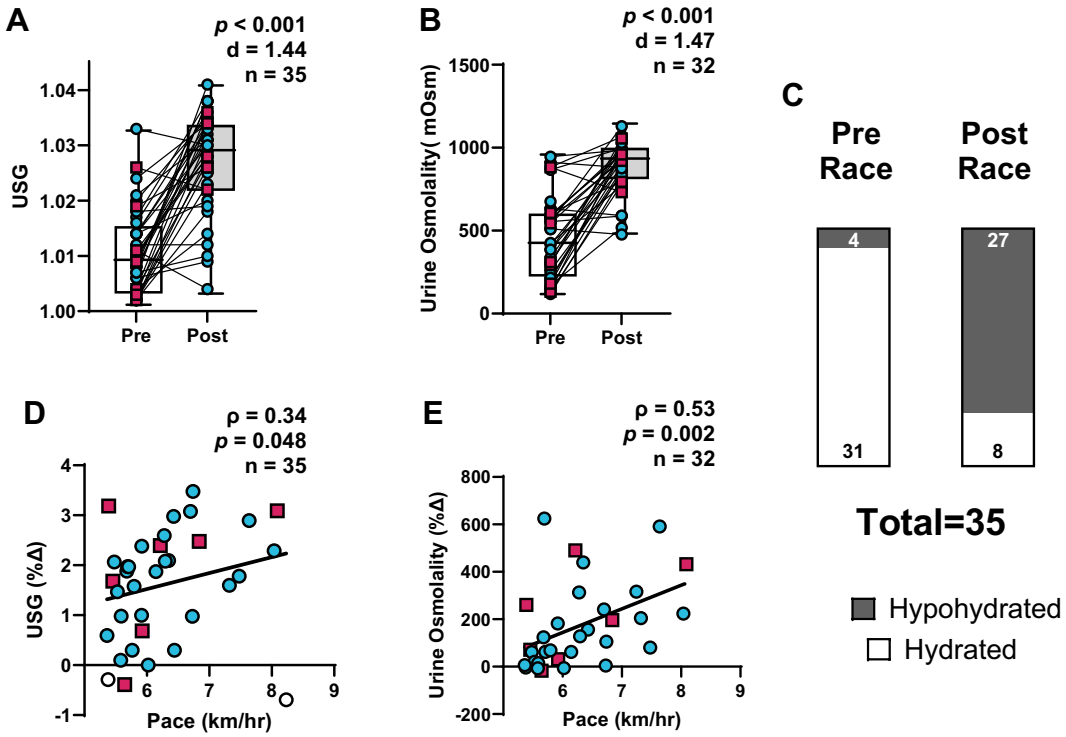

Figure 2. Markers of hydration (*A* and *B*) were compared between pre- and postrace time points. *C*: hydration status (USG > 1.020 is dehydrated; USG ≤ 1.020 is hydrated) of participants at pre- and postrace timepoints. Fisher's exact test results ($P < 0.001$) indicate a significant association between timepoints and spot hydration status. Change in hydration markers (*D* and *E*) correlated with the overall pace of participants who completed the 2023 WSER. Blue circles indicate male participants; pink squares indicate female participants. USG, urine specific gravity; WSER, Western States Endurance Run.

Table 2. *Raw values of serum creatinine, urine point of care measures, and raw AKI biomarker concentrations*

Biomarker	*n*	Pre	Post	*P*	*d*	r_{rb}
Serum						
Creatine kinase, U/L	14	109.5 (61.8)	13,232 (11,216)	**<0.000**		1.00
Creatinine, mg/dL	15	0.74 ± 0.14	0.95 ± 0.23	**<0.001**	1.38	
Urine						
Sodium, mmol	31	62.1 (48.3)	27.4 (23.8)	**<0.001**		0.75
Potassium, mmol	34	41.4 (58.9)	132.8 (71.3)	**<0.001**		0.84
Chloride, mmol	34	95.0 (75.9)	31.4 (25.5)	**<0.001**		0.97
Creatinine, mg/dL	35	42.4 (73.6)	138.5 (79.5)	**<0.001**		0.90
Cystatin C, ng/mL	36	22.7 (39.2)	87.5 (102.9)	**<0.001**		0.87
Nephrin, ng/mL	36	7.2 (17.6)	60.6 (72.4)	**<0.001**		0.88
NGAL, ng/mL	36	4.50 (6.36)	16.60 (18.96)	**<0.001**		0.72
IGFBP7, ng/mL	36	21.9 (24.6)	96.8 (74.7)	**<0.001**		0.84
TIMP2, ng/mL	36	1.03 (1.26)	3.49 (2.51)	**<0.001**		0.87
IGFBP7 × TIMP2, ng/mL	36	23.4 (63.5)	326.6 (518.5)	**<0.001**		0.87
eGFR, mL/min/1.73 m^2	15	112 ± 114	93.6 ± 89.8	**<0.001**	1.22	

Serum creatinine and eGFR were normally distributed and are presented as means ± SD. All urinary biomarkers were not normally distributed and are therefore presented as median (IQR). Bolded *P* values indicate significance. AKI, acute kidney injury; *d*, Cohen's *d*; eGFR, estimated glomerular filtration rate; IGFBP7, insulin-like growth factor binding protein 7; NGAL, nephrin, neutrophil gelatinase-associated lipocalin; r_{rb}, rank-biserial correlation; TIMP2, tissue inhibitor of metalloproteinase 2.

euhydrated and hypohydrated finishers in any AKI biomarker. Interestingly, we noted that all euhydrated finishers were males (0/7 females euhydrated vs. 8/28 males; Fisher's exact test $P = 0.166$).

No Reductions in Renal or Segmental Artery Blood Velocities

As presented in Fig. 5, we did not detect any pre- versus postrace race differences in renal artery blood velocity (Fig. 5*A*; $P = 0.186$, $d = 0.41$), renal artery conductance (Fig. 5*B*; $P = 0.339$, $r_{rb} = 0.33$), segmental artery blood velocity (Fig. 5*D*; $P = 0.483$, $d = 0.21$), nor segmental artery conductance (Fig. 5*E*; $P = 0.622$, $r_{rb} = 0.18$). Representative images of the renal ultrasound assessment of RBV are presented in Fig. 5, *C* and *F*.

Fast Race Pace Associated with Greater Changes in Electrolytes and Creatine Kinase

We present simple bivariate correlations in our variables of interest, primarily correlations between race pace (km/h) and pre- versus postrace race differences in urinary AKI

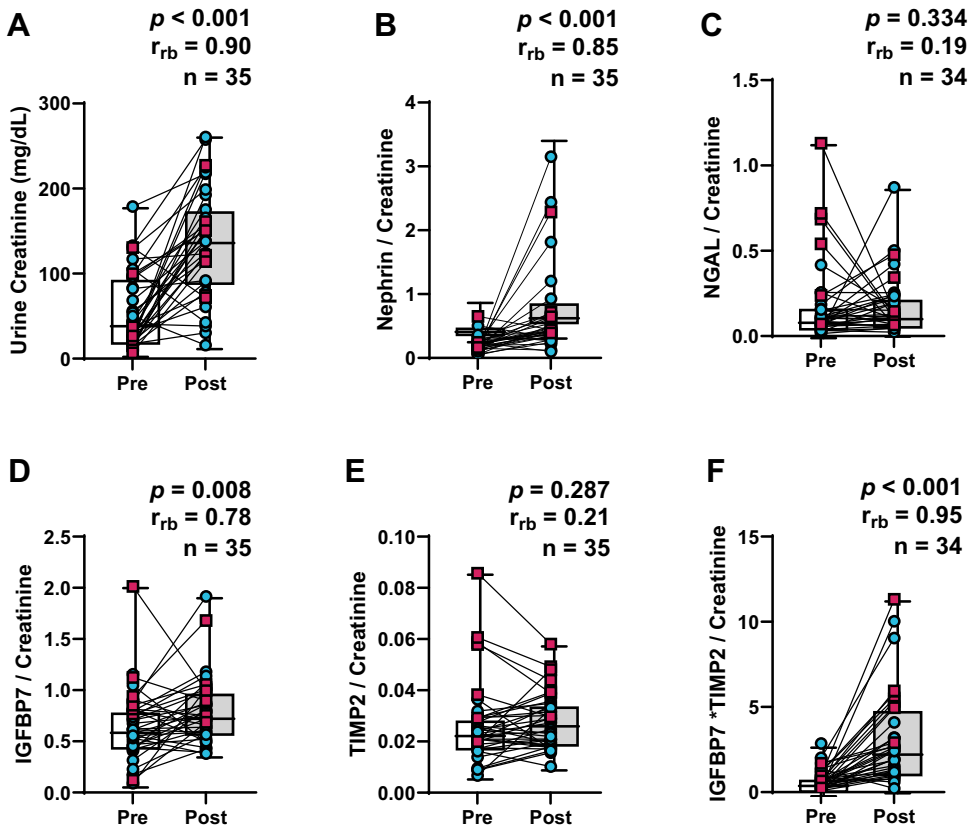

Figure 3. Creatinine-indexed kidney injury markers before and after completing WSER 2023. Urine creatinine concentration (*A*), and creatinine-indexed nephrin (*B*), NGAL (*C*), IGFBP7 (*D*), TIMP2 (*E*), and IGFBP7*TIMP2 (*F*). Blue circles indicate male participants; pink squares indicate female participants. WSER, Western States Endurance Run.

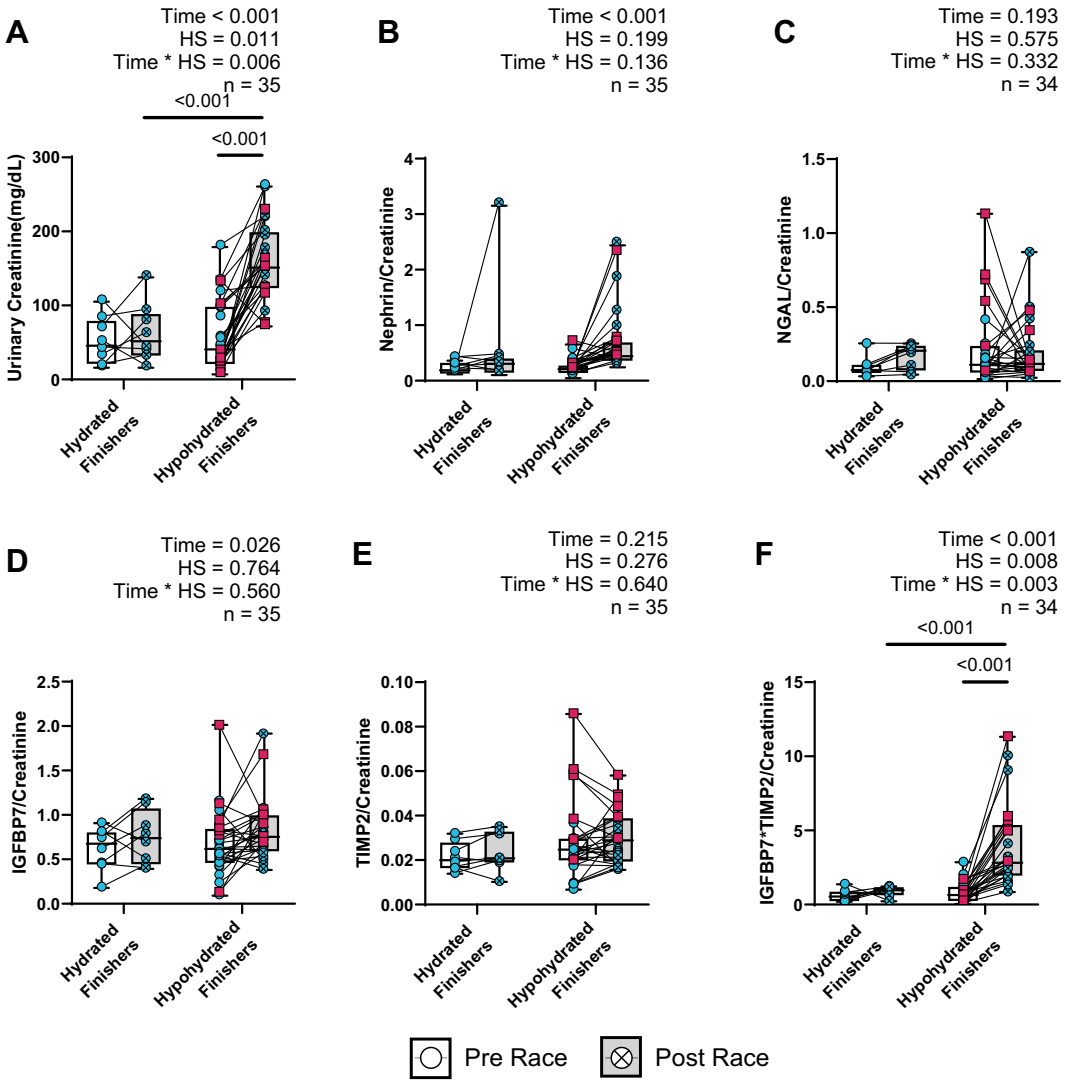

Figure 4. Creatinine-indexed kidney injury biomarker responses on completing the 2023 WSER by postrace hydration status. Urine creatinine concentration (*A*), and creatinine-indexed nephrin (*B*), NGAL (*C*), IGFBP7 (*D*), TIMP2 (*E*), and IGFBP7*TIMP2 (*F*). Blue circles indicate male participants; pink squares indicate female participants. Statistics are reported from the log-transformed data used for ANOVA for all biomarkers; data are plotted as raw values. WSER, Western States Endurance Run.

biomarkers, race pace and pre- versus postrace race differences in hydration, and pre- versus postrace race differences in hydration and urinary AKI biomarkers, in Table 4. We observed correlations between pace and changes in serum CK ($\rho = -0.596$, $P = 0.028$), urine sodium ($\rho = 0.543$, $P = 0.004$), urine potassium ($\rho = 0.341$, $P = 0.049$), urine chloride ($\rho = 0.128$, $P = 0.468$), and urine creatinine concentration ($\rho = 0.433$, $P = 0.010$). We observed no correlations between pace and changes in renal artery blood velocity ($\rho = -0.109$, $P = 0.755$) or conductance ($\rho = -0.027$, $P = 0.946$) or changes in segmental artery blood velocity ($\rho = 0.373$, $P = 0.261$) or conductance ($\rho = 0.382$, $P = 0.248$). There were no correlations between changes in any AKI biomarker and changes in renal artery velocity ($Ps > 0.297$), renal artery conductance ($Ps > 0.366$), segmental artery velocity ($Ps > 0.067$), or segmental artery conductance ($Ps > 0.075$). In addition, changes in serum CK were negatively associated with changes in urine osmolality ($\rho = -0.571$, $P = 0.045$), but there were no correlations between serum CK and any urinary AKI biomarker ($Ps > 0.202$). We were unable to correlate serum CK and measures of RBV due to incomplete data across both measures.

DISCUSSION

We investigated the acute effects of ultraendurance competition on urinary biomarkers of AKI and surrogate measures of kidney blood flow (RBV and conductance). Our main findings were that completing the 161 km footrace increased select urinary AKI biomarkers, with nephrin and IGFBP7·TIMP2 remaining elevated regardless of creatinine, osmolality, or cystatin C indexing. Importantly, finishing euhydrated appeared to attenuate increases in urinary creatinine and creatinine-indexed IGFBP7·TIMP2.

Preliminary reports suggest that completing the WSER ultramarathon may leave participants at a higher risk of needing prolonged dialysis treatment for AKI with exertional rhabdomyolysis compared with other ultramarathons (35).

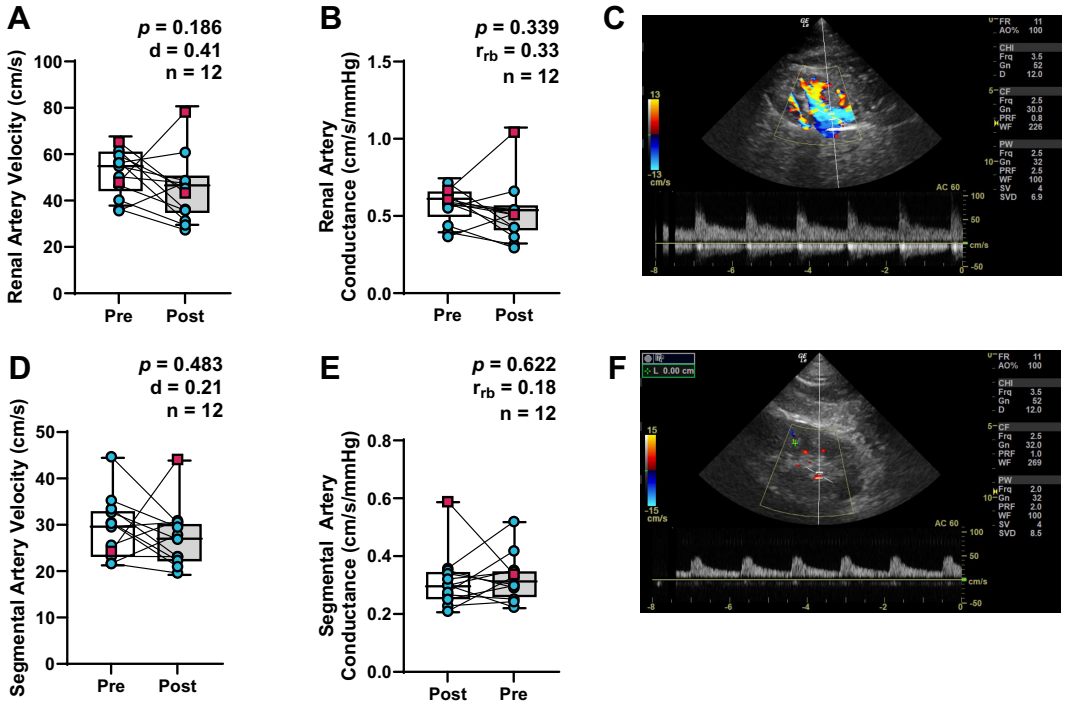

Figure 5. Renal (*A–C*; $n = 12$) and segmental (*D–F*; $n = 12$) blood velocity data. Blue circles indicate male participants; pink squares indicate female participants. Reference image of renal (*C*) and segmental (*F*) artery blood velocity collections.

Similarly, we observed elevations in serum creatinine; however, all changes in AKI biomarkers were of subclinical magnitude and did not require hospitalization (Tables 2 and 4). We observed increases in all unadjusted concentrations of urinary AKI biomarkers, and select creatinine-indexed AKI biomarkers (nephrin, IGFBP7, and IGFBP7·TIMP2), which aligns with the prior work done in competitors in marathons and ultramarathons (Fig. 3). For example, findings from the Boston Marathon indicated transient increases in urinary creatinine and NGAL at the conclusion of the race (14). However, 24 h after the race, the two biomarkers diverged, with NGAL remaining elevated and urinary creatinine decreasing to below prerace concentrations. Another ultramarathon study (80 km race) reported increased urinary creatinine, NGAL, and kidney injury marker-1 (13). In our study, when NGAL was indexed to creatinine or osmolality, the differences were abolished. The NGAL discrepancy may be due, in part, to the runners completing the 80 km race (13) running 1.1 kph faster than the runners in our present study, or differences between the event environments (e.g., changes in elevation, temperature/time of year), although we acknowledge these are speculative reasons. Nonetheless, all biomarkers returned to basal concentrations in a 9-day postrace sample after the 80 km ultramarathon in the prior study. We replicated the transient increases in raw urinary NGAL and creatinine and extended this finding to additional AKI biomarkers that provided a more comprehensive evaluation of kidney injury (Fig. 3). Indeed, the AKI biomarkers we selected enable us to infer that kidney injury occurred within the glomerulus (nephrin) and along the tubules (IGFBP7·TIMP2). Future mechanistic studies may further interrogate specific structures within the nephron that may be most impacted by ultraendurance competition.

Interestingly, changes in creatinine-indexed IGFBP7·TIMP2 were attenuated in the participants who finished the race euhydrated (Fig. 4). These findings align with prior studies demonstrating that maintaining euhydration attenuates changes in urine AKI biomarkers in the context of thermal stress (26, 34). They also support findings demonstrating short-term water restriction, leading to mild-to-moderate hypohydration without concomitant heat stress or exertion, leading to elevation in urine AKI biomarkers (25). These data suggest that maintaining adequate hydration throughout the event, an assumption based on postrace hydration status, is an effective strategy to attenuate the developing acute AKI after ultraendurance competition. Future investigators should aim to capture individual nutrition data to determine patterns of fluid and electrolyte balance that adequately prevent AKI development while not increasing the risk of hyponatremia during ultramarathons.

We observed no correlations between race pace and changes in urine AKI biomarkers, contrary to our hypothesis that faster race pace would be positively correlated with greater changes in urine AKI biomarkers (Table 3). We speculated that running the race faster may create greater renal ischemia and subsequent kidney injury. Relative exercise intensity is likely a better correlate of renal ischemia and subsequent kidney injury (23) than simply using race pace. Although our study was not designed to assess the relative intensity at which runners completed the event, this is an interesting future direction to examine in future ultramarathon races, potentially using heart rate data and metabolomic profiling. However, several factors may explain why our hypothesis was not fully supported. Slower runners are on the course for longer periods, leading to extended exposure to dehydration, electrolyte imbalances, and other environmental stressors. Conversely, the faster

Table 3. *Correlations of applied measures of intensity, kidney function, urine point-of-care measures, and AKI biomarkers*

	Race Pace	Renal Artery Velocity	Segmental Artery Velocity	Renal Artery Conductance	Segmental Artery Conductance	Urine Specific Gravity	Urine Osmolality	Serum Creatinine Kinase
Serum								
Creatine kinase	**−0.596 (0.028)**					−0.473 (0.090)	**−0.571 (0.045)**	
Creatinine	−0.032 (0.913)					0.059 (0.844)	0.055 (0.856)	−0.077 (0.817)
Urine								
USG	**0.338 (0.048)**	−0.109 (0.755)	0.373 (0.261)	−0.027 (0.946)	0.382 (0.248)		**0.815 (<0.001)**	−0.473 (0.090)
Osmolality	**0.533 (0.002)**	0.200 (0.584)	0.233 (0.552)	0.103 (0.785)	0.333 (0.385)	**0.815 (<0.001)**		**−0.571 (0.045)**
Sodium	**0.543 (0.004)**	−0.033 (0.948)	0.381 (0.360)	0.017 (0.982)	0.405 (0.327)	**0.456 (0.018)**	0.292 (0.157)	−0.252 (0.430)
Potassium	**0.341 (0.049)**	−0.182 (0.595)	0.000 (1.000)	−0.127 (0.714)	0.091 (0.797)	**0.780 (<0.001)**	**0.834 (<0.001)**	−0.305 (0.288)
Chloride	**0.128 (0.468)**	0.136 (0.694)	0.436 (0.183)	0.255 (0.451)	0.491 (0.129)	**0.361 (0.037)**	**0.396 (0.031)**	0.068 (0.820)
Creatinine	**0.433 (0.010)**	−0.049 (0.886)	−0.007 (0.991)	0.119 (0.716)	0.021 (0.956)	**0.903 (<0.001)**	**0.819 (<0.001)**	−0.379 (0.202)
Nephrin/creatinine	0.101 (0.562)	0.021 (0.956)	0.175 (0.588)	0.084 (0.800)	0.119 (0.716)	**0.670 (<0.001)**	**0.549 (0.002)**	−0.154 (0.617)
NGAL/creatinine	0.033 (0.855)	−0.118 (0.734)	−0.173 (0.614)	0.118 (0.734)	−0.155 (0.654)	−0.147 (0.411)	−0.154 (0.416)	−0.055 (0.863)
IGFBP7/creatinine	−0.066 (0.706)	0.126 (0.700)	0.378 (0.227)	0.273 (0.391)	0.322 (0.308)	−0.114 (0.519)	0.341 (0.061)	−0.093 (0.765)
TIMP2/creatinine	−0.152 (0.382)	−0.329 (0.297)	−0.035 (0.921)	−0.287 (0.366)	−0.147 (0.651)	−0.151 (0.393)	0.294 (0.109)	0.000 (<0.999)
IGFBP7 × TIMP2/creatinine	0.164 (0.352)	−0.063 (0.852)	0.552 (0.067)	0.084 (0.800)	0.538 (0.075)	**0.549 (0.001)**	0.249 (0.184)	−0.245 (0.444)

Spearman's rho (ρ) was used for all correlations, and correlations were conducted on normalized change scores. Statistics are presented as Spearman's ρ (*P* value). Bolded cells indicate significance. Empty columns indicate measures where there was insufficient sample to investigate relations between variables. AKI, acute kidney injury; IGFBP7, insulin-like growth factor binding protein 7; NGAL, nephrin, neutrophil gelatinase-associated lipocalin; TIMP2, tissue inhibitor of metalloproteinase 2; USG, urine specific gravity.

runners may have been somewhat protected due to greater fitness and/or resiliency from higher training volumes. Indeed, a prior ultramarathon study (100 km) reported that those who experienced AKI after an ultramarathon exhibited slower running velocities over the course of the race (18). These findings highlight the complex interplay between race pace, environmental exposure, and physiological responses in determining AKI risk, while suggesting that faster race pace does not inherently exacerbate this risk.

Understanding that RBV decreases in response to exercise (23), we expected to observe reductions in RBV that may substantiate prior observations of AKI in response to ultraendurance events (5, 9, 13, 17–19). However, we did not observe reductions in RBV or conductance in response to completing the 2023 WSER (Fig. 5). An important methodological consideration is that we measured RBV after the cessation of exercise which reflects postexercise recovery, when RBV would be expected to return to resting values, unlike the more pronounced reductions observed during exercise (65, 66). We suspect RBV returned to baseline values quicker than we were able to capture these measures. We know that there are many mechanisms by which blood flow is redistributed both at the onset and cessation of exercise (27, 28), though this has predominantly been assessed in skeletal muscle.

We observed significant increases in serum creatinine (31), as well as increases in USG and osmolality, reflecting higher urinary solute concentrations that are commonly observed after endurance exercise (43) (Tables 2 and 4). Race pace was correlated with urine osmolality, which corresponds with previous marathon literature reporting race pace to be correlated with fluid loss measured by changes in body mass (74). We also observed the WSER-influenced electrolyte excretion, with urine sodium and chloride concentrations being reduced and potassium concentration being elevated after the race (Table 2). Therefore, the potassium:sodium excretion increased. These findings are consistent with prior reports demonstrating urine potassium:sodium increases after ultraendurance races (44). Although outside the scope of our investigation, others have speculated that this response may be driven by renin

Table 4. *Urinary AKI biomarkers normalized to urine osmolality and urine creatinine*

Biomarker	*n*	Pre	Post	*P*	*d*	r_{rb}
Osmolality normalized						
Nephrin/osmolality	32	0.018 (0.024)	0.076 (0.063)	**<0.001**		0.80
NGAL/osmolality	32	0.011 (0.021)	0.022 (0.020)	0.224		0.25
IGFBP7/osmolality	32	0.065 (0.039)	0.114 (0.070)	**<0.001**		0.75
TIMP2/osmolality	32	0.003 (0.001)	0.004 (0.003)	**<0.001**		0.70
IGFBP7 × TIMP2/osmolality	32	0.065 (0.086)	0.417 (0.509)	**<0.001**		0.80
Cystatin C normalized						
Nephrin/cystatin C	36	0.402 ± 0.135	0.581 ± 0.200	**<0.001**	0.76	
NGAL/cystatin C	36	0.268 (0.303)	0.155 (0.146)	**0.048**		0.38
IGFBP7/cystatin C	36	1.243 (0.844)	1.015 (0.422)	0.119		0.30
TIMP2/cystatin C	36	0.045 (0.020)	0.037 (0.021)	**0.006**		0.52
IGFBP7 × TIMP2/cystatin C	36	1.274 (1.440)	3.365 (4.126)	**<0.001**		0.72

Urinary nephrin/cystatin C is normally distributed and presented as means ± SD. No other urinary biomarkers were normally distributed and are therefore presented as median (IQR). Bolded *P* values indicate significance. AKI, acute kidney injury; *d*, Cohen's *d*; IGFBP7, insulin-like growth factor binding protein 7; NGAL, nephrin, neutrophil gelatinase-associated lipocalin; r_{rb}, rank-biserial correlation; TIMP2, tissue inhibitor of metalloproteinase 2.

angiotensin aldosterone system activation during exercise, resulting in altered electrolyte excretion (44). We did not assess serum electrolytes due to limited blood sample volume. However, prior WSER investigations have examined pre- and postrace blood sodium concentrations to assess exercise-associated hyponatremia (75). Coupling urine and serum electrolyte data is an interesting future direction that could provide additional complementary insight.

There were no correlations between changes in RBV and AKI biomarkers, which we speculate may result from methodological limitations, as our postrace measures of RBV may not accurately reflect the changes in blood flow during the actual exercise (Table 3). Interestingly, race pace was negatively correlated with changes in CK, potentially due to slower runners being on the course longer and therefore accumulating more muscle damage and/or permitting more time for serum CK to accumulate. This finding could also reflect lower training levels among slower runners, which may exacerbate muscle damage during such events. Similarly, the WSER could also have been a greater relative insult for runners with lower training volumes, resulting in greater physiological responses. Furthermore, serum CK concentrations begin to peak between 24 and 48 h after bouts of exhaustive and submaximal exercise (76, 77). Therefore, we may have missed CK peak windows in our participants, though it is worth considering that our participants had been active for over 24 h on average and could have finished as serum CK was starting to peak. There was no correlation between race pace and serum creatinine. The kidneys maintain relatively stable glomerular pressure over a wide range of arterial pressures through autoregulation to reduce the risk of kidney damage (78), and that could be one reason why there was no influence of race pace.

Limitations and Future Directions

We would like to acknowledge the limitations of the present study. First, these data were collected in the field. Specifically, pre (~1,890 m) and post (~385 m) measures were taken at different altitudes due to the spaces provided to collect data near the start and finish lines. Similarly, WSER 2023 was a relatively temperate year and resulted in the highest completion rate on record (per WSER website). Therefore, we hesitate to use our data to compare with other years (e.g., years where temperatures may have been substantially more elevated for the duration of the event) or other ultramarathons where environmental demands can vary widely. In addition, most participants dispersed very shortly after the race; hence, we could not collect recovery samples to determine the timeline of resolution for the increase in AKI biomarkers. In future iterations of the WSER, researchers should attempt to have participants provide a postrace sample perhaps 24 or 48 h after the race and arrange for shipping to complete these measures, as presentation of emergency symptoms may range between 17 and 32 h postrace (35). Finally, it is possible that the timing of the last meal before the urine sampling could have influenced urine concentration of certain biomarkers such as osmolality and creatinine, which are commonly used to assess urine concentration, potentially creating an artifact suggestive of hypohydration despite overall euhydration (79, 80). We asked participants to refrain from eating for at least 3 h before prerace data collection; however, this was not strictly enforced, and adherence likely varied. In addition, we did not control meal timing for the postrace measures.

The field study nature of the investigation also affected our RBV measures. We collected these data as close to immediately after the race as we could. Some participants finished the race in the evening and in the middle of the night, which we consequently collected RBV data at potentially near opposite times of day, resulting in inconsistent light exposure, temperature, control of external stimuli, etc., between collections. In addition, participant fatigue and shivering made obtaining postrace recordings of the renal and segmental artery difficult; hence, the smaller paired sample size for these measures. Finally, to more comprehensively understand the physiological impact of these events, it is important to examine organ cross talk. For instance, exercise is associated with both acute (81–83) and chronic (84) changes to the gut microbiome, which produces metabolites that may contribute to kidney injury (e.g., indoxyl sulfate, p-Cresyl sulfate). Future studies should examine these interactions to provide a more holistic understanding of the effects of ultramarathon on interrelated organ systems.

Conclusions

Taken together, our results suggest that a 161 km footrace increases concentrations of excreted urinary AKI biomarkers and that completing the race euhydrated attenuates increases in creatinine-indexed urinary IGFBP7·TIMP2. With the growing popularity of ultraendurance foot races, monitoring participant health postrace is important. Although endurance competition elevates postrace urinary AKI biomarkers, evidence suggests that transient AKI after an ultramarathon does not necessarily increase the risk of subsequent AKI in future races. Within the select group of competitors in which we were able to collect RBV, we observed no changes in RBV in response to the 2023 WSER and also observed no correlations between changes in RBV and changes in AKI or hydration biomarkers. Nonetheless, the long-term implications of repeated exposures to elevations in AKI biomarkers remain unclear. Our findings suggest that maintaining euhydration may be one strategy to reduce AKI risk, although future controlled hydration studies are needed.

DATA AVAILABILITY

Data will be made available upon reasonable request and shared after completion of a data/material transfer agreement.

SUPPLEMENTAL MATERIAL

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.28761449.v1.

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conflict with APS ethical policies, and the authors take full responsibility for the content.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

J.R.B., J.C.W., M.C.B., G.J.G., and A.T.R. conceived and designed research; B.A.L., S.J., N.L.S., O.B.E., and J.D.V. performed experiments; B.A.L. analyzed data; B.A.L., S.J., N.L.S., O.B.E., J.D.V., A.P., J.R.B., J.C.W., Z.J.S., M.C.B., G.J.G., and A.T.R. interpreted results of experiments; B.A.L. prepared figures; B.A.L. drafted manuscript; B.A.L., S.J., N.L.S., O.B.E., J.D.V., A.P., J.R.B., J.C.W., Z.J.S., M.C.B., G.J.G., and A.T.R. edited and revised manuscript; B.A.L., S.J., N.L.S., O.B.E., J.D.V., A.P., J.R.B., J.C.W., Z.J.S., M.C.B., G.J.G., and A.T.R. approved final version of manuscript.

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