Accepted Date: 12-May-2010

Original Article

Summary at a Glance -

This paper describes that some marathon runners experience a transient rise in serum creatinine that meets criteria of AKI with a parallel elevation of urinary biomarkers (NGAL and KIM-1) that resolve within 24 hours. These data suggest AKI with a transient and minor change in renal filtration function occurs with the stress of marathon running.

CHANGES IN RENAL MARKERS AND ACUTE KIDNEY INJURY AFTER MARATHON RUNNING

Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP, Kavitha M. Chinnaiyan, MD, FACC, Michael J. Gallagher, MD, James M. Colar, RN, Jeffrey M. Gold, MD, Justin E. Trivax, MD

Word Count: 2469

From the Departments of Cardiovascular and Internal Medicine

William Beaumont Hospital, Royal Oak, MI, USA

Address for Correspondence:
Peter A. McCullough, M.D., M.P.H., F.A.C.C., F.A.C.P., F.C.C.P., F.A.H.A.
Departments of Cardiology and Internal Medicine,
Division of Nutrition and Preventive Medicine
William Beaumont Hospital
Beaumont Health Center
4949 Coolidge
Royal Oak, MI 48073
Phone: 248-655-5948
Fax: 248-655-5901

This is an Accepted Article that has been peer-reviewed and approved for publication in the *Nephrology*, but has yet to undergo copy-editing and proof correction. Please cite this article as an "Accepted Article"; doi: 10.1111/j.1440-1797.2010.01354.x

E-mail: peteramccullough@gmail.com

Financial support: The Beaumont Foundation (William Beaumont Hospital, Royal Oak, Michigan) provided funding for the costs of laboratory, exercise testing, and CMR studies

Relationships with industry and/or conflicts: none

ABSTRACT (Word Count: 244)

Background. The impact of marathon running on kidney function has not been previously described.

Methods. From 425 marathon runners, 13 women and 12 men were randomly selected and cardiovascular MRI and blood/urine biomarkers were performed 4 weeks before (baseline), immediately after (peak), and 24 hours after the race (recovery).

Results. Participants were 38.7±9.0 years old and completed the marathon in 256.2±43.5 minutes. A total of 10/25 (40.0%) met the Acute Kidney Injury Network definition of AKI based on a rise in serum creatinine. There were parallel and similar mean rises in serum creatinine and cystatin C from baseline, to peak, and return to normal in recovery. Urine neutrophil gelatinase associated lipocalin (NGAL) rose from 8.2±4.0 to 47.0±28.6 and returned to 10.6±7.2 ng/ml, $p<0.0001$. Likewise, the mean urinary kidney injury molecule-1 (KIM-1) levels were 2.6±1.6, 3.5±1.6, and 2.7±1.6 ng/ml, $p=0.001$. The mean and minimum pre- and post-IVC diameters by MRI were 24.9, 18.8 and 25.3, 17.5 mm, respectively, suggesting that runners were not volume depleted at the first post-race measurement.

Conclusions. Approximately 40% of marathon runners experience a transient rise in serum creatinine that meets criteria of AKI with a parallel elevation of cystatin C, and supportive elevations of NGAL and KIM-1 in the urine. All biomarker elevations resolved by 24 hours. These data suggest AKI with a transient and minor change in renal filtration function occurs with the stress of marathon running. The impact of repetitive episodes of AKI with long-distance running is unknown.

(ClinicalTrials.gov number, NCT00752752.)

INTRODUCTION

Marathon running has increased in popularity over the last three decades with participation in the United States rising from 25,000 runners in 1976 to more than 400,000 in 2007.[1] The potential deleterious effects of prolonged strenuous physical exertion include severe dehydration, electrolyte abnormalities, rhabdomyolysis, acute myocardial infarction, and sudden cardiac death**.** It is estimated that 6 to 8 marathon runners will die while running each year, and many more collapse, due to the combination of occult cardiac disease and superimposed physical and/or environmental stresses including dehydration.[1 2] The degree to which there is organ damage beyond the heart with extreme exertion is not completely known. However, it is widely recognized that severe dehydration can lead to pre-renal azotemia and be a precursor to acute kidney injury (AKI) in a variety of settings.[3] Behrman first reported changes in urine studies of Boston marathon runners in 1941 including myoglobinuria, hematuria, and occasional albuminuria.[4] Thompson has recently summarized the history of 84 publications surrounding the physiologic observations reported from the Boston Marathon.[5] No single paper identified AKI as a potential consequence of marathon running in the absence of rhabdomyolysis. Novel blood and urine biomarkers can detect AKI before a rise in serum creatinine including neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), both secreted by renal tubular cells in the setting of injury.[6] Therefore we set out to evaluate the incidence of AKI in a group of well characterized subjects who participated in a cardiovascular study affiliated with the 2008 Detroit Free Press/Flagstar Marathon in whom serum creatinine and urine measurements were made before and after the race.

METHODS

Subjects

All enrollees in the 2008 Detroit Free Press/Flagstar Marathon received an e-mail communication after registering for the race that described the study and invited their participation. Responses were received from 428 individuals; after verifying age (>18 years) and the absence of signs, symptoms, or medical history of heart disease, including coronary artery disease or structural heart disease, 25 were randomly selected to participate. Additional exclusion criteria included pregnancy and allergy to gadolinium. Written informed consent was obtained from all participants. The study protocol was approved by the Human Investigation Committee at William Beaumont Hospital in Royal Oak, Michigan, USA.

Measurements

One to four weeks prior to the marathon, participants provided a detailed medical and training history and blood samples (baseline). Serum creatinine was measured by the Jaffe method, Siemens Advia 2400, Beaumont Reference Laboratories, Royal Oak, MI. Troponin I and B-type natriuretic peptide (BNP) (normal range 0-100 pg/ml) were measured using chemiluminescence immunoassays (Bayer Diagnostics, Tarrytown, New York). For troponin I, the manufacturer reports the minimum detected concentration 0.03 ng/mL, normal ranges less than 0.06 ng/mL, indeterminate range 0.06-1.19 ng/mL, and suggestive of myocardial infarction >1.2 ng/mL. Serum cystatin C, and urinary NGAL and KIM-1 were quantified by ELISA or western blotting with commercially available kits and antibodies R&D Systems (Minneapolis, MN), Hycult Biotechnology (Netherlands), Cusabio (Newark, DE), respectively. At the finish

line, runners provided blood samples (peak). Twenty-four hours later, each participant provided another set of blood and urine specimens (recovery).

Magnetic Resonance Imaging

Cardiac magnetic resonance imaging was performed using a 1.5T whole-body magnetic resonance imaging scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) before and after the marathon. Cine bright-blood images in the four-chamber, left-sided two-chamber, right-sided two chamber, and three-chamber planes (included the inferior vena cava) were performed using a breath-hold balanced steady-state free precession sequence (true fast imaging with steady-state precession; repetition time 70 ms, echo time 1.2 ms, flip angle 70°, slice thickness 6 mm, matrix size 256 x 126). Gadolinium diethylenetriamine penta-acetic acid (Omniscan, GE Healthcare, Chalfont St. Giles, United Kingdom) 0.15 mmol/kg was injected at a rate of 4 mL/second. Quantitative analysis was performed using dedicated computer software (ARGUS; Siemens Medical Solutions). Electrocardiographically-gated techniques and standard inversion recovery cine images were obtained in short-axis slices as well as three long axes: horizontal long axis, vertical long axis and the three-chamber view. Chamber volumes and LV mass were calculated. All measurements were made by two physicians trained in Level III CMR (KC, MG), blinded to the subject's clinical information and subsequent analysis.

Statistical Analysis

With a sample size of 25, the observed power for detecting paired changes in serum creatinine was >99% using the paired t-test, alpha=0.01 two-tailed. Univariate statistics were reported with means±standard deviation or counts with proportions as appropriate. Comparisons

were made using the paired two-sample t-test or the paired Wilcoxon rank sum test for variables that were not normally distributed (NGAL and KIM-1 in Figures 3 and 4). Pearson correlations were used to evaluate bivariate relationships. A P-value <0.05 was considered statistically significant.

RESULTS

Baseline Parameters

A total of 25 runners, 13 women and 12 men, averaging 38.7±9.0 years of age (range 23-58) participated in the study. Baseline characteristics are reported in Table 1. The average body mass index was 23.0±2.6 kg/m^2. The mean training mileage over the previous five years and over the previous six months was 17.0±11.8 and 30.2±11.4 miles per week, respectively. Of the 25 subjects, 7 were participating in their first marathon and an additional 7 were participating in their second. The remaining 11 runners had participated in three or more previous marathons. A total of 23 (92.0%) ate some food before the race. The mean marathon finishing time was 256.2±43.5 minutes, corresponding to an average pace of 9.8±1.7 minutes per mile. The temperature at the start of the marathon was 33 degrees Fahrenheit (1 degree Celsius). The estimated volumes of water and electrolyte solutions consumed during and in the 24 hours after the race were 28.9±25.4, 25.0±36.0, and 19.3±13.4, 16.0±18.0 ounces, respectively. Eleven (44.0%) urinated one or more times during the race. Twenty three (92.0%) consumed 2 or more glucose/carbohydrate supplements while running, mean 3.3±1.5. The mean total oral fluids in those with and without AKI were 100.0±62.4 and 82.6±69.0 ounces, respectively. There was no relationship between the occurrence or frequency of urination during the race and AKI, p=0.65.

Laboratory Data

Laboratory data are shown in Table 2. Blood urea nitrogen and serum creatinine both increased significantly with baseline and peak values of 15.6±3.1 to 24.0±4.8 mg/dL and 0.9±0.1 to 1.2±0.2 mg/dL, respectively, P<0.0001, for each pairwise comparison. Serum creatinine values rose with 10/25 (40.0%) meeting the Acute Kidney Injury Network (AKIN) definition of AKI (Stage 1) defined as ≥0.3 mg/dl or 50% rise in serum Cr.[5] None of the subjects met criteria for AKIN Stage 2 (>2-3 fold rise) or Stage 3 (>3 fold rise). The median and interquartile ranges of serum creatinine at the three timepoints are shown in Figure 1. There were no statistically significant differences in any of the baseline parameters and the development of AKI including the running time. The correlation between age and the change in serum creatinine was -0.07, p=0.72 There was a nonsignificant rise and fall in mean serum cystatin C, 0.8±0.1 to 1.0±0.2 mg/L, p=0.91. However, the median values for cystatin C were statistically different across the three time points as shown in Figure 2. The correlation between age and the rise in serum cystatin C was -0.14, p=0.61. Changes in the blood urea nitrogen: creatinine ratios are shown in Table 2, indicating a small but sustained rise from baseline to peak lasting into recovery. Urine NGAL rose from 8.2±4.0 to 47.0±28.6 and returned to 10.6±7.2 ng/ml, p<0.0001 (medians with interquartile ranges are shown in Figure 3). Likewise, the mean urine KIM-1 levels were 2.6±1.6, 3.5±1.6, and 2.7±1.6 ng/ml, p=0.001 (medians with interquartile ranges are shown in Figure 4). Serum aldolase also increased from 5.9±1.7 to 15.2±5.0 units/L immediately after the race, p<0.0001. B-type natriuretic peptide more than doubled from mean baseline to peak values (15.3±11.3 to 44.8±31.2 pg/mL), p<0.0001. The maximum paired change in CK and BNP for those with and without AKI was 2576.4±2668.3, 32.8±23.0, and 1248.9±1090.3 units/L, 25.6±27.6 pg/ml, p=0.50 and 0.11, respectively.

There was a rise in potassium levels immediately after crossing the finish line, 4.3±0.2 to 5.5±0.6 mEq/L, $p<0.0001$. The correlations between changes in creatinine and troponin I, CK-MB, and BNP were: r=0.09, p=0.69; r=0.18, p=0.44; and r=0.51, p=0.02, respectively. See Figure 5 for the relationship between maximum change in creatinine and CK. The correlations between changes in CK and elevations of creatinine and cystatin C were r=-0.04, p=0.86 and r=0.03, p=0.95, respectively.

Cardiovascular Magnetic Resonance Imaging

The post-marathon CMR was performed on average of 242.5±97.4 (range 50 to 421) minutes after crossing the finish line in 24 participants. One additional participant was imaged 24.5 hours after completing the race. Pre-marathon left ventricular ejection fraction, end-diastolic volume index, end-systolic volume index and stroke volume CMR were 57.7±4.1%, 79.1±13.7 mL/m^2, 33.5±6.7 mL/m^2, and 83.2±22.2 mL, respectively. No significant differences between the pre- and post-CMRs were seen regarding left ventricular ejection fraction or volumes. Overall, resting cardiac output increased from 5.4±1.8 6.3±1.7 L/min.. The correlation between the increase in right atrial volume and change in creatinine and cystatin C was R=-0.05, p=0.83, and R=0.12, p=0.65, respectively. The mean and minimum pre- and post-IVC diameters by MRI were 24.9, 18.8 and 25.3, 17.5 mm, respectively, suggesting that runners were not volume depleted at the first post-race measurement.[7] The mean paired change in IVC diameter was -0.5 mm, p=0.39. The coefficients of variation for pre- and post-IVC diameter measurements were 11.4% and 14.8%, respectively.

DISCUSSION

In this study, 40% of healthy, well-trained runners had evidence of AKI by AKIN criteria by 24 hours after completing the marathon.[8] The changes in serum creatinine were modestly related to evidence of skeletal muscle injury as seen in Figure 5; however, no subject developed evidence of rhabdomyolysis or hematuria. Changes in cystatin C also supported the finding of an acute reduction in glomerular filtration function.[9] Both novel markers of kidney injury, NGAL, and KIM also showed temporal changes supporting the pathobiologic case for AKI. The blood urea nitrogen: creatinine ratio, urine specific gravity, and the IVC measurements by MRI indicated that runners were not significantly volume depleted at any time point during the study. However, slight increases in albumin and total protein, suggest volume depletion played a minor role. Importantly, there appeared to be no relationship between oral fluid intake, urination, the urinalysis, and evidence of AKI by serum creatinine. We recognize that serum creatinine is a metabolic product of creatine, and thus, can be elevated to some degree due to skeletal muscle size and activity. However, the parallel course observed with cystatin C, which is not dependent on muscle mass, suggests the decreases in renal filtration function observed were real and not a biochemical manifestation of skeletal muscle injury. Thus our data suggest that cardiovascular exhaustion is in some way linked to a systemic, potentially inflammatory injury to the nephron units resulting in the fivefold rise in urine NGAL and a minor rise in urine KIM-1. The result is a transient reduction in renal filtration function and a rise in serum Cr and cystatin C. These changes are unlikely to be due to volume depletion, fluid shifts, or pre-renal azotemia alone.

To date, our study is the first to use blood and urine biomarkers, and CMR to comprehensively evaluate the acute renal and cardiovascular effects of marathon running. There

appears to be evidence of a "cardiorenal syndrome" or a linkage between cardiac and renal function manifested by transient right heart dilatation, elevations in blood BNP and cardiorenal markers of injury, and a transient decrease in renal filtration function. These findings are possibly consistent with marked and sustained activation of the sympathetic nervous system and circulating catecholamines which can have both cardiotoxicity and work to reduce renal blood flow.[10] However, we found no relationship between the marathon time, a proxy of effort, and the rise in renal markers. Our data raise concern that repetitive marathon running and repeated episodes of AKI could cause a persistent decline in eGFR. Since 18 of 25 runners had prior experience and baseline renal function was normal in all, these concerns for the present can be held in check.

Marathon running is known to transiently impair right heart function. Neilan and associates evaluated 60 nonelite marathon runners using similar methodology during consecutive Boston Marathons (2004 and 2005) and documented transient increases in echocardiographically estimated pulmonary artery pressure, RV dilation, and RV dysfunction.[11] A recent confirmatory study (n=14) study by Mousavi and colleagues who also found right sided chamber dilatation in runners after a marathon.[12] These right heart changes also seen in our subjects, however, did not result in dilatation of the inferior vena cava nor did they impact cardiac output, thus, we believe the connection between the recognized cardiac exhaustion of marathon running and the transient changes seen in renal filtration function are more likely due to neurohormonal, inflammatory, or oxidative stress factors rather than hemodynamic influences on renal blood flow.

We recognize several limitations to this small observational study, including the lack of a control group. The temporal relationships to the race suggest it was the marathon effort itself

that induced the evidence of AKI and elevation in blood and urine biomarkers that we observed. Our findings may not necessarily apply to elite marathon runners or individuals participating in shorter or longer distance races or non-running events. None of our patients had significant risk factors for or the presence of chronic kidney disease, thus, we cannot generalize to that important population. Importantly, we did not weigh patients at all three time points, so cannot give any inferences on changes in total body fluid weight.[13] The use of inferior vena cava diameter measurement by MRI has not been validated, thus, we cannot rule out some degree of volume depletion accounting for our results. In addition, we did not measure renal volumes. Since we did not collect urine at the finish line, we were unable to measure urine electrolytes or calculate the fractional excretion of sodium. We also did not measure serum or urine osmolality. Finally, we did not have additional markers of AKI such as fatty acid binding protein, which may have further supported our evidence of acute kidney damage.[14] Nor did we have measures of sympathetic nervous system activity, inflammation, or oxidative stress, all of which may have been helpful in explaining our findings.

Conclusions

Marathon running causes changed in serum creatinine that meet a definition of AKI in 40% of participants based on rises in serum creatinine in the absence of prerenal azotemia, volume depletion, or hemodynamic changes. There is a marked rise in urinary NGAL, and a lesser elevation in urinary KIM-1, both supporting the diagnosis of AKI. Cystatin C, an alternative biomarker of renal filtration function which is not dependent on muscle mass, also elevates immediately after a marathon confirming an acute decline in renal function immediately after a race in the setting of extreme skeletal muscle exhaustion. Future research with advanced blood and urine biomarkers in marathon runners is warranted.

Acknowledgments: We are grateful to The Beaumont Foundation for providing funding for the costs of laboratory, exercise testing, and CMR studies. We recognized Timothy Geddes in his work in obtaining the novel biomarker results. We are also indebted to Ralph Gentry RT for CMR acquisition and image construction and Amy Murawka RN and Barbara Pruetz BS for phlebotomy services at baseline evaluation, finish line, and at the follow-up visit.

Additional information: All of the authors listed in this manuscript substantially contributed to the conception and design, acquisition of data, or analysis and/or interpretation of the data. All of the authors were involved in the drafting of the manuscript and in the final approval of this version. The study protocol was approved by the Human Investigation Committee at William Beaumont Hospital in Royal Oak, Michigan, USA.

Figure 1. Changes in serum creatinine with marathon running, represented by medians (lines) and interquartile ranges (boxes).

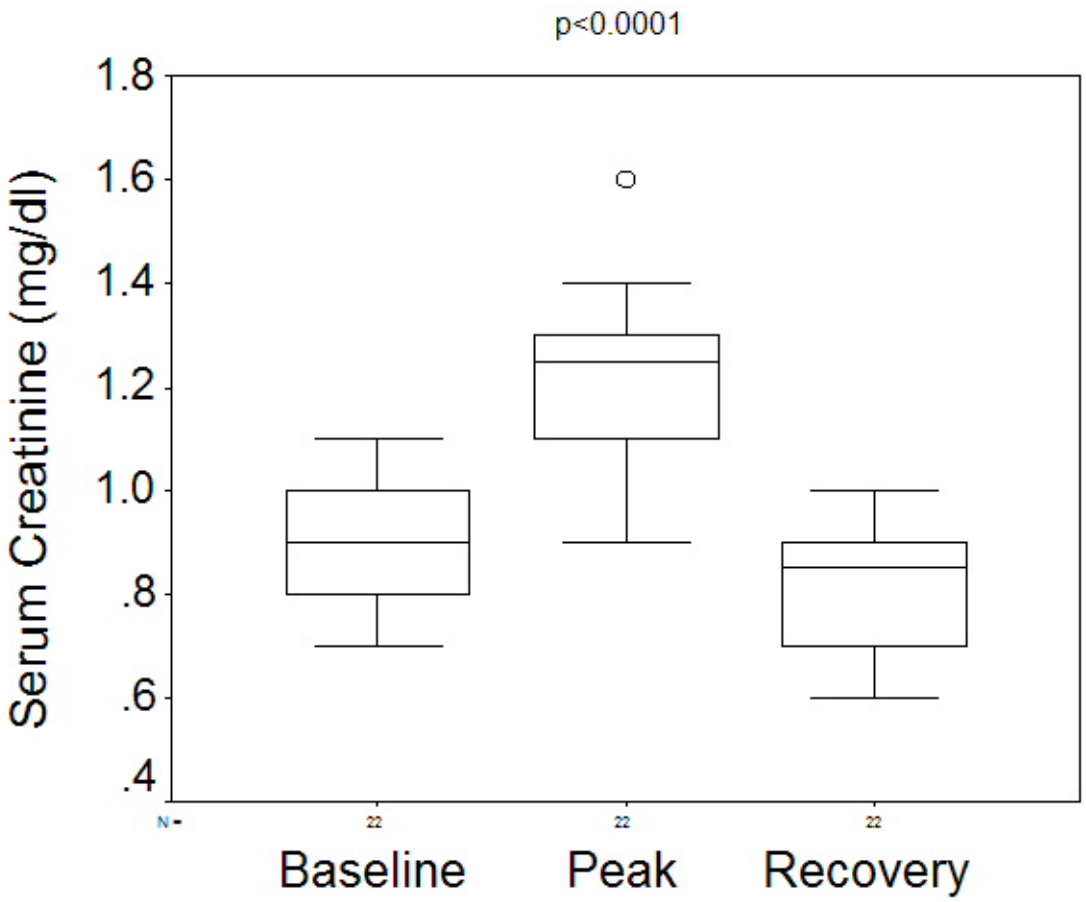

Figure 2. Changes in serum cystatin C with marathon running, represented by medians (lines) and interquartile ranges (boxes).

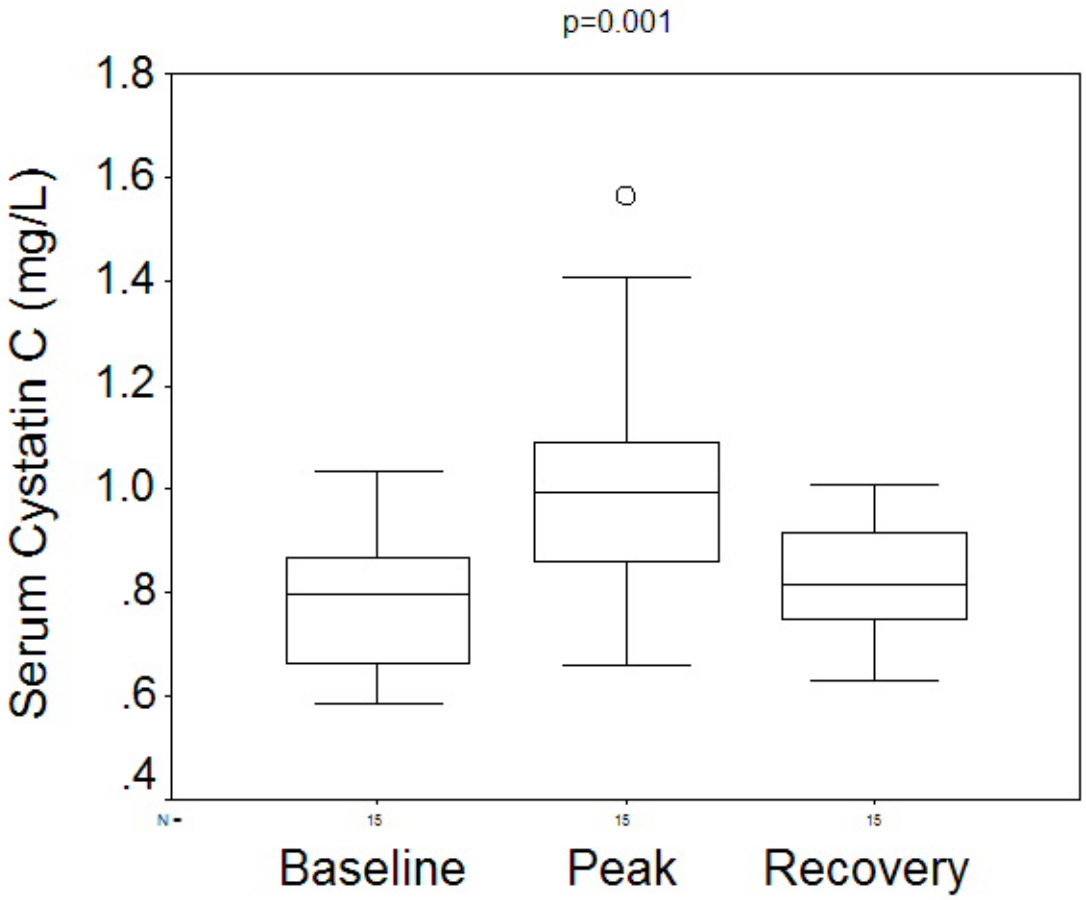

Figure 3. Changes in urine NGAL with marathon running represented by medians (lines) and interquartile ranges (boxes).

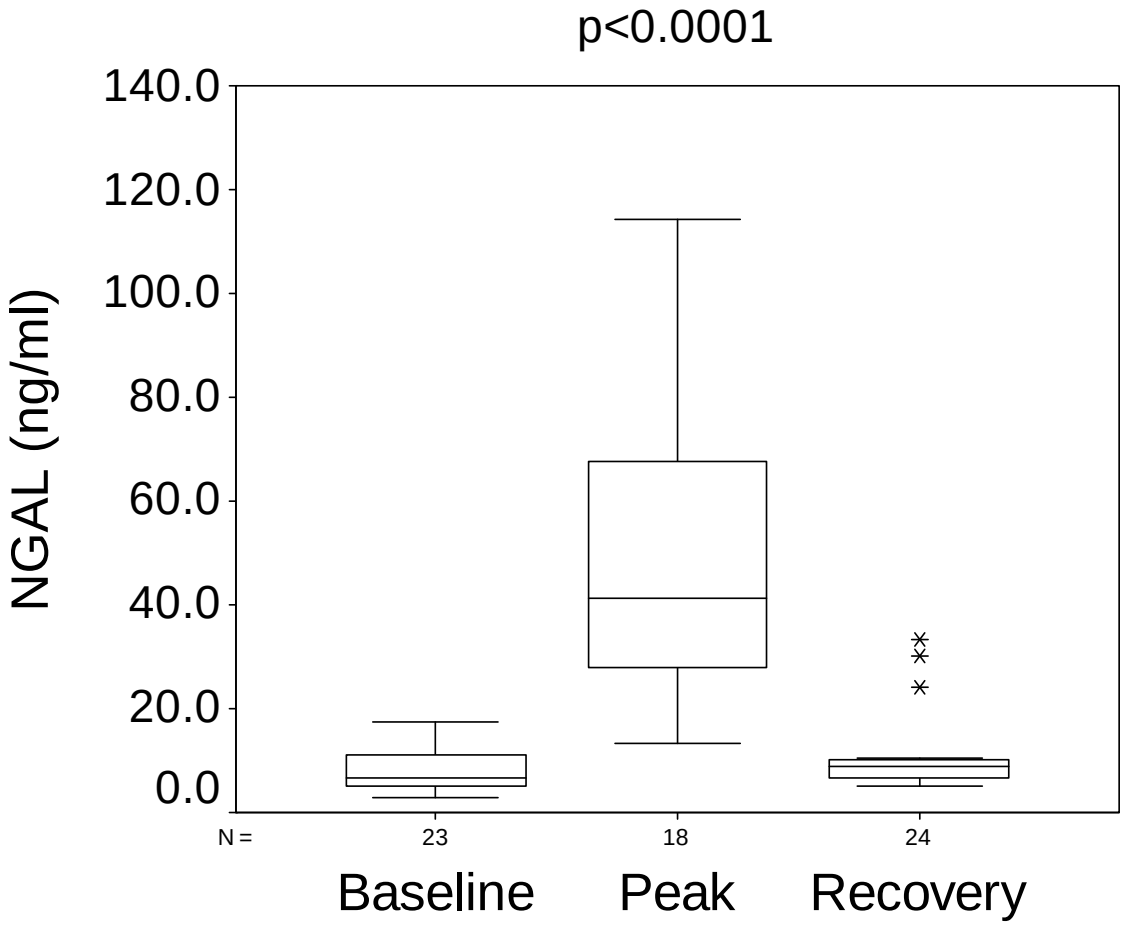

Figure 4. Changes in urine KIM-1 with marathon running represented by medians (lines) and interquartile ranges (boxes).

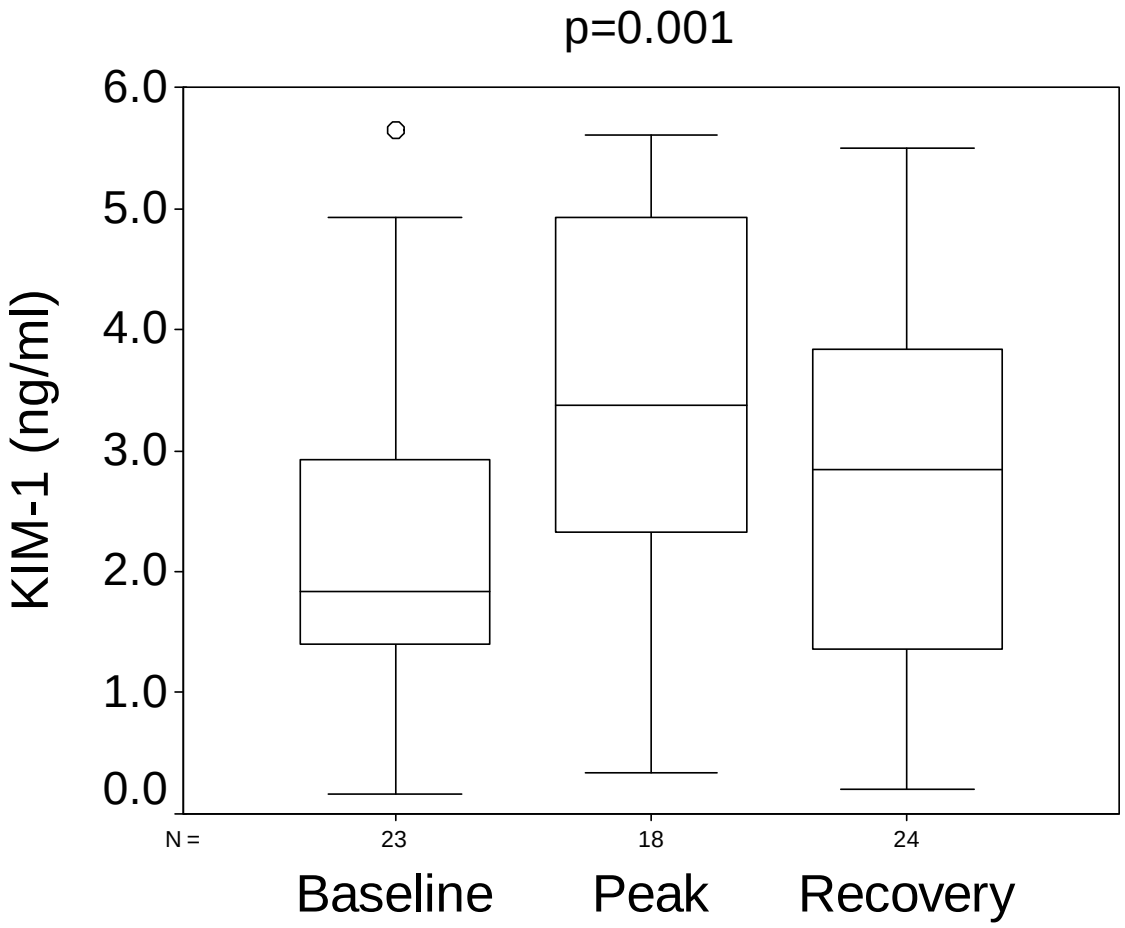

Figure 5. Relationship between the maximum change in CK and the rise in serum creatinine in those with and without AKI.

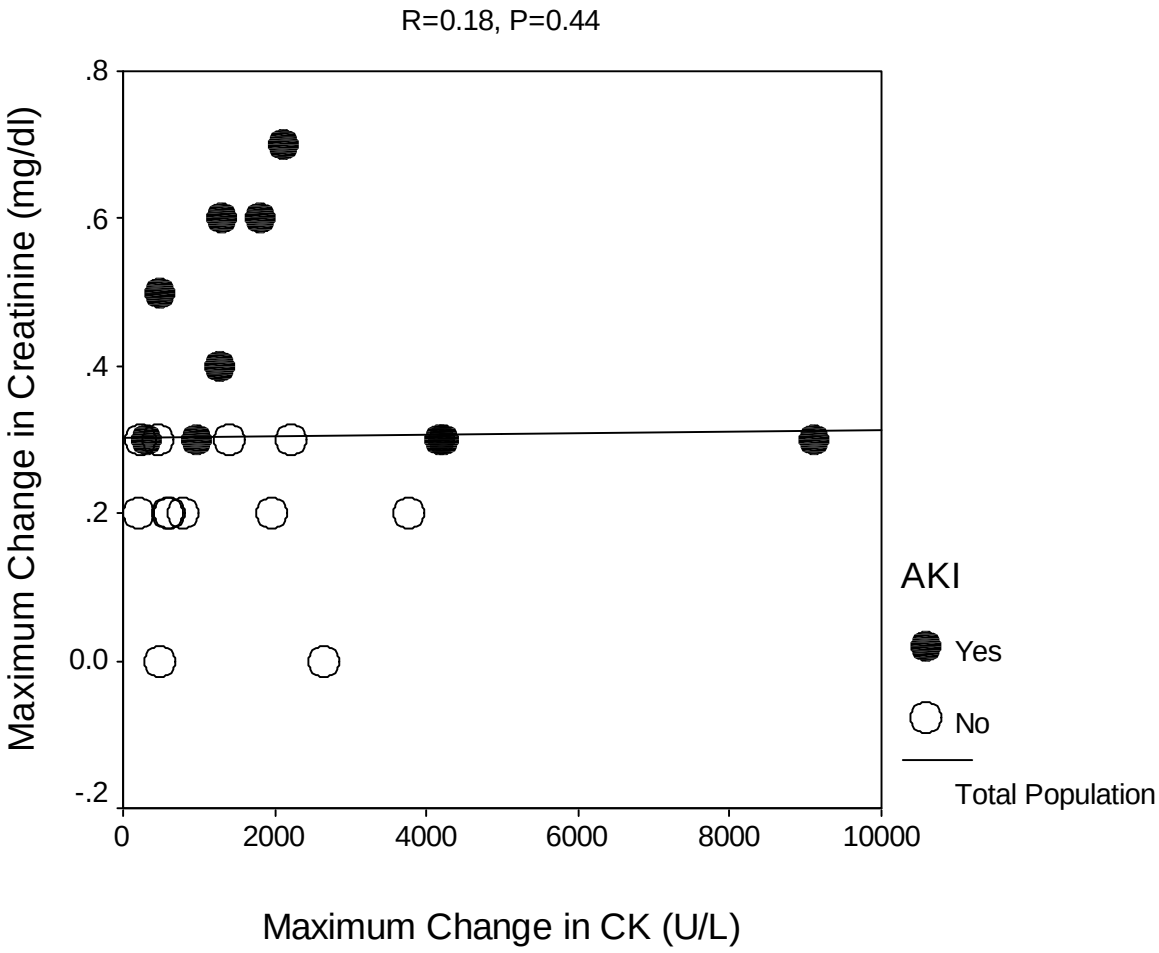

Table 1. Baseline characteristics of the study group (N=25) expressed as means±standard deviations or counts with proportions as appropriate.

Demographics	
Age (years)	38.7±9.0
Male	12 (48%)
Body mass index (kg/m^2)	23.0±2.6
Height (cm)	172.5±0.1
Weight (kg)	68.9±13.7
Hypertension	1 (4%)
Diabetes mellitus	0 (0%)
Prior smoking	1 (4%)
Average training mileage (miles/week over previous 5 years)	17.0±11.8
Number prior marathons	2.3±3.0

Table 2. Biochemical data at baseline, immediately after the marathon, and 24 hours later expressed as means±standard deviations or counts with proportions as appropriate.

Variable	Baseline	Immediately post-marathon	24 hours post-marathon	Greatest paired change in value	P-value
BUN mg/dL	15.6±3.1	24.0±4.8	17.0±3.3	8.4±5.1	<0.0001
(mmol/L)	(5.6±1.1)	(8.6±1.7)	(6.1±1.2)	(3.0±1.8)	
Serum creatinine mg/dL	0.9±0.1	1.2±0.2	0.8±0.1	0.3±0.2	<0.0001
(mmol/L)	(79.6±8.8)	(106.1±17.7)	(70.7±8.8)	(26.5±17.7)	
Serum cystatin C mg/L	0.8±0.1	1.0±0.2	0.8±0.1	0.2±0.2	0.91
(nmol/L)	(59.9±7.5)	(74.9±15.0)	(59.9±7.5)	(74.9±74.9)	
Plasma NGAL ng/ml	8.0±4.1	47.1±27.7	10.7±7.4	38.4±27.4	<0.0001
Plasma KIM-1 ng/ml	2.2±1.5	3.3±1.7	2.7±1.6	0.9±0.9	0.001
Serum sodium mEq/L	140.9±3.4	141.3±3.3	141.2±2.2	0.4±4.3	0.69
(mmol/L)					
Serum potassium mEq/L	4.3±0.2	5.5±0.6	4.3±0.4	1.3±0.6	<0.0001

(mmol/L)					
Blood glucose mg/dL	91.9±11.7	108.9±26.9	91.3±16.7	17.0±24.5	0.004
(mmol/L)	(5.1±0.7)	(6.1±1.5)	(5.1±0.9)	(0.9±1.4)	
Total protein mg/dl	7.3±0.1	7.8±0.1	7.0±0.1	0.5±0.1	0.001
(g/L)	(73.0±1.0)	(78.0±1.0)	(70.0±1.0)	(5.0±1.0)	
Albumin mg/dl	4.6±0.1	5.0±0.1	4.5±0.0	0.4±0.1	0.002
(g/L)	(46.0±10.0)	(50.0±10.0)	(45.0±00.00)	(4.0±1.0)	
Globulin mg/dl	2.8±0.1	2.8±0.1	2.5±0.1	0.0±0.0	<0.0001
(g/L)	(28.0±1.0)	(28.0±1.0)	(25.0±1.0)	(0.0±0.0)	
Alkaline phosphatase units/L	56.5±2.4	61.0±2.8	54.9±2.5	4.9±1.3	<0.0001
Aspartate aminotransferase unit/L	26.3±1.4	63.1±17.8	90.6±12.7	14.8±3.6	0.05
Alanine aminotransferase	26.51.4	28.4±1.8	40.6±3.9	14.6±17.6	0.02
Aldolase units/L	5.9±1.7	15.2±5.0	13.4±7.5	9.3±4.8	<0.0001

CK units/L	186.4±132.7	675.3±497.7	1984.8±2031.0	1802.0±1976.1	<0.0001
CK-MB units/L	2.6±1.6	10.1±5.1	16.4±9.8	13.8±9.6	<0.0001
Troponin I ng/mL	0.03±0.003	0.2±0.3	0.1±0.2	0.2±0.3	0.001
(μg/L)					
BNP pg/mL	15.3±11.3	18.7±15.8	44.8±31.2	28.5±35.6	<0.0001
(ng/ml)					
Urine Specific Gravity	1.0173±0.0002	-	1.0185±0.0010	0.69	0.69
Urine pH	6.4±0.2	-	6.3±0.8	0.28	0.28
Urine blood (dipstick)	2 cases	-	1 case	-	-
Urine protein (dipstick)	1 case	-	1 case	-	-
Urine myoglobin	0	-	0	-	-
Urine ketones	0	-	1 case	-	-

Abbreviations: BNP = B-type natriuretic peptide, BUN = blood urea nitrogen, CK = creatine kinase, CK-MB = creatine kinase MB isoenzyme

[1] USA Marathoning: 2007 Overview. (Accessed December 12, 2008 at http://www.marathonguide.com/features/Articles/2007RecapOverview.cfm)
[2] Kenefick RW, Sawka MN. Heat exhaustion and dehydration as causes of marathon collapse. Sports Med. 2007;37(4-5):378-81.
[3] Powers SR Jr. Renal response to systemic trauma. Am J Surg. 1970 May;119(5):603-5.
[4] Behrman RA. Urinary findings before and after a marathon race. N Engl J Med. 1941;225:801-2
[5] Thompson PD, Venero HC. A History of Medical Reports on he Boston Marathon: 112 Years and Still Running. Med. Sci. Sports Exerc., 2009:41(6) 1341-1348.
[6] Rosner MH. Urinary biomarkers for the detection of renal injury. Adv Clin Chem. 2009;49:73-97.
[7] Yanagawa Y, Nishi K, Sakamoto T, Okada Y. Early diagnosis of hypovolemic shock by sonographic measurement of inferior vena cava in trauma patients. J Trauma. 2005 Apr;58(4):825-9
[8] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
[9] Séronie-Vivien S, Delanaye P, Piéroni L, Mariat C, Froissart M, Cristol JP; SFBC "Biology of renal function and renal failure" working group.Cystatin C: current position and future prospects. Clin Chem Lab Med. 2008;46(12):1664-86.
[10] DiBona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 2005 Sep;289(3):R633-41.
[11] Neilan TG, Januzzi JL, Lee-Lawandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, Lewandrowski KB, Siegel AJ, Marshall JE, Douglas PS, Lawlor D, Picard MH, Wood MJ. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston Marathon. Circulation 2006;114:2325-2333.
[12] Mousavi N, Czarneck A, Kumar K, Fallah-Rad N, Lytwyn M, Han SY, Francis A, Walker JR, Kirkpatrick ID, Neilan TG, Sharma S, Jassal DS. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. Am J Cardiol 2009;103:1467-1472.
[13] Cheuvront SN, Montain SJ, Sawka MN. Fluid replacement and performance during the marathon. Sports Med. 2007;37(4-5):353-7.
[14] Endre ZH. Acute kidney injury: definitions and new paradigms. Adv Chronic Kidney Dis. 2008 Jul;15(3):213-21.

Figure 1. Changes in serum creatinine with marathon running, represented by medians (lines) and interquartile ranges (boxes).

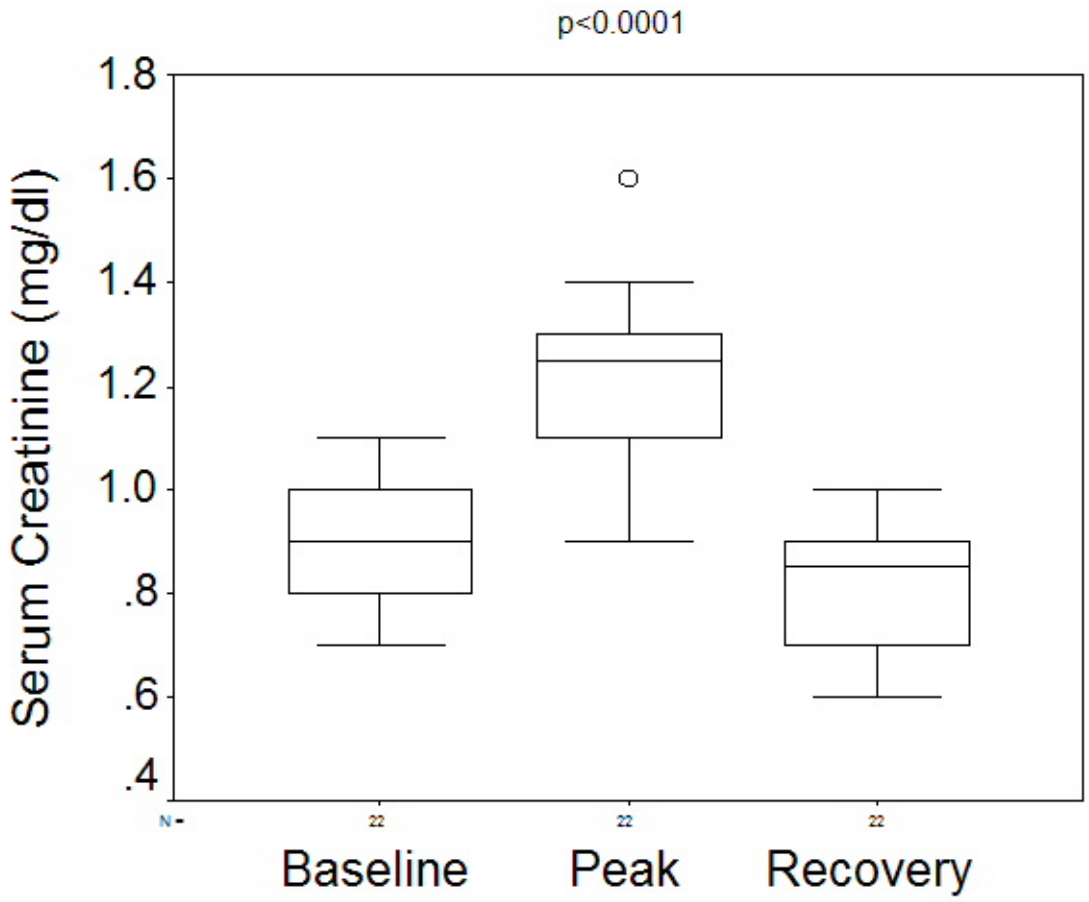

Figure 2. Changes in serum cystatin C with marathon running, represented by medians (lines) and interquartile ranges (boxes).

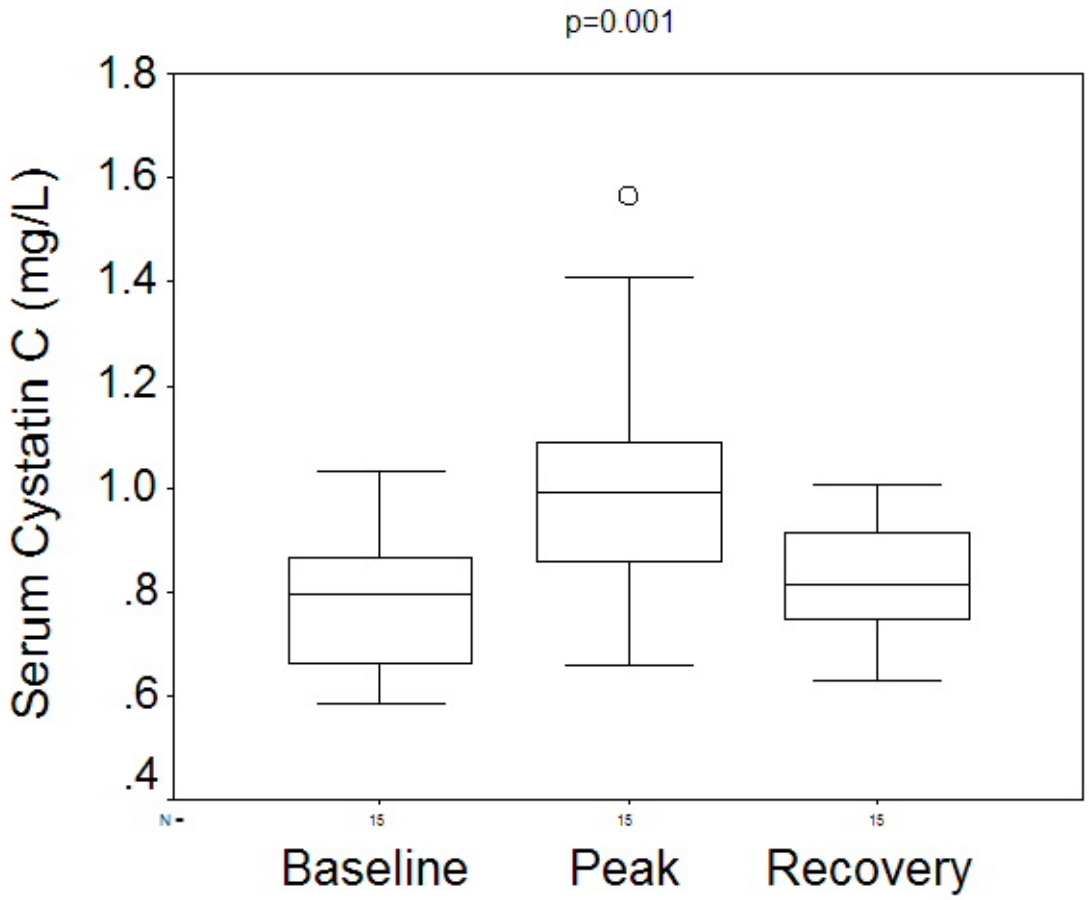

Figure 3. Changes in urine NGAL with marathon running represented by medians (lines) and interquartile ranges (boxes).

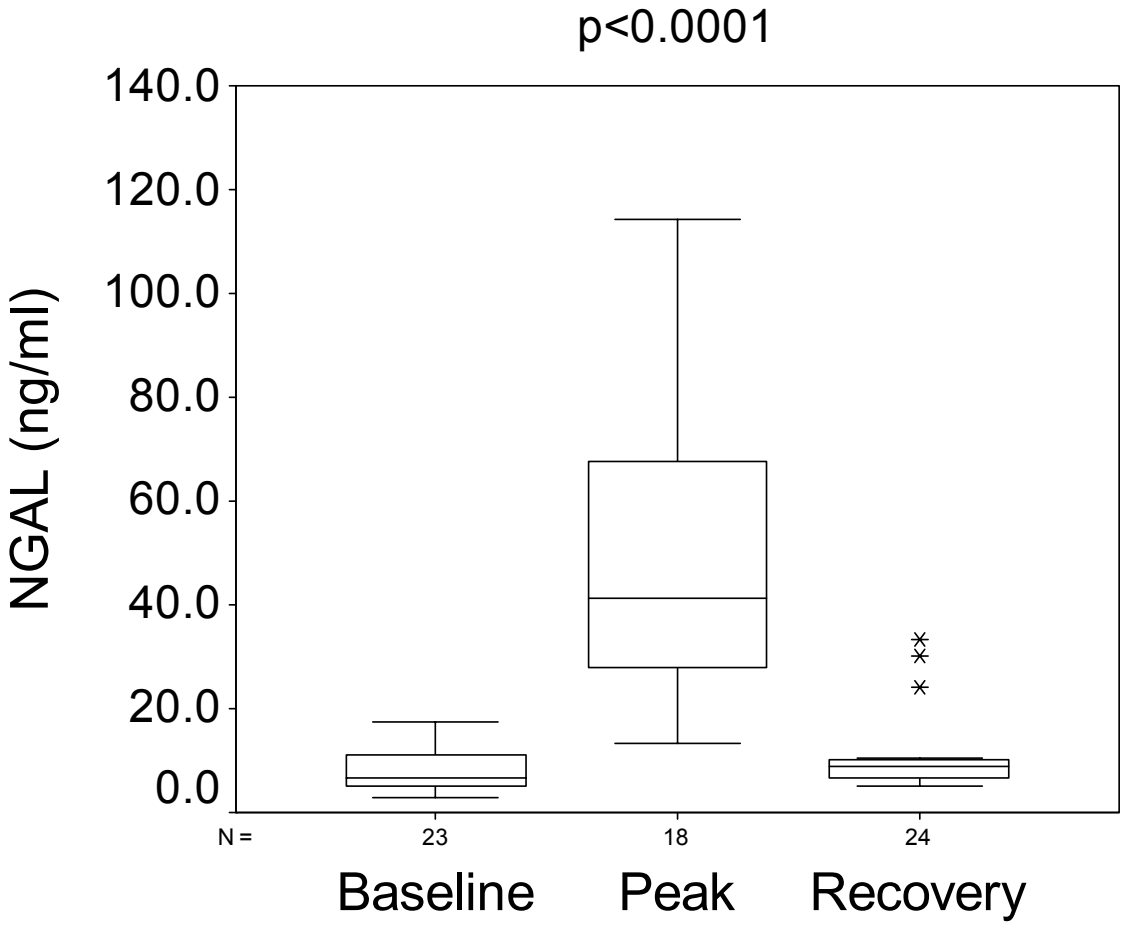

Figure 4. Changes in urine KIM-1 with marathon running represented by medians (lines) and interquartile ranges (boxes).

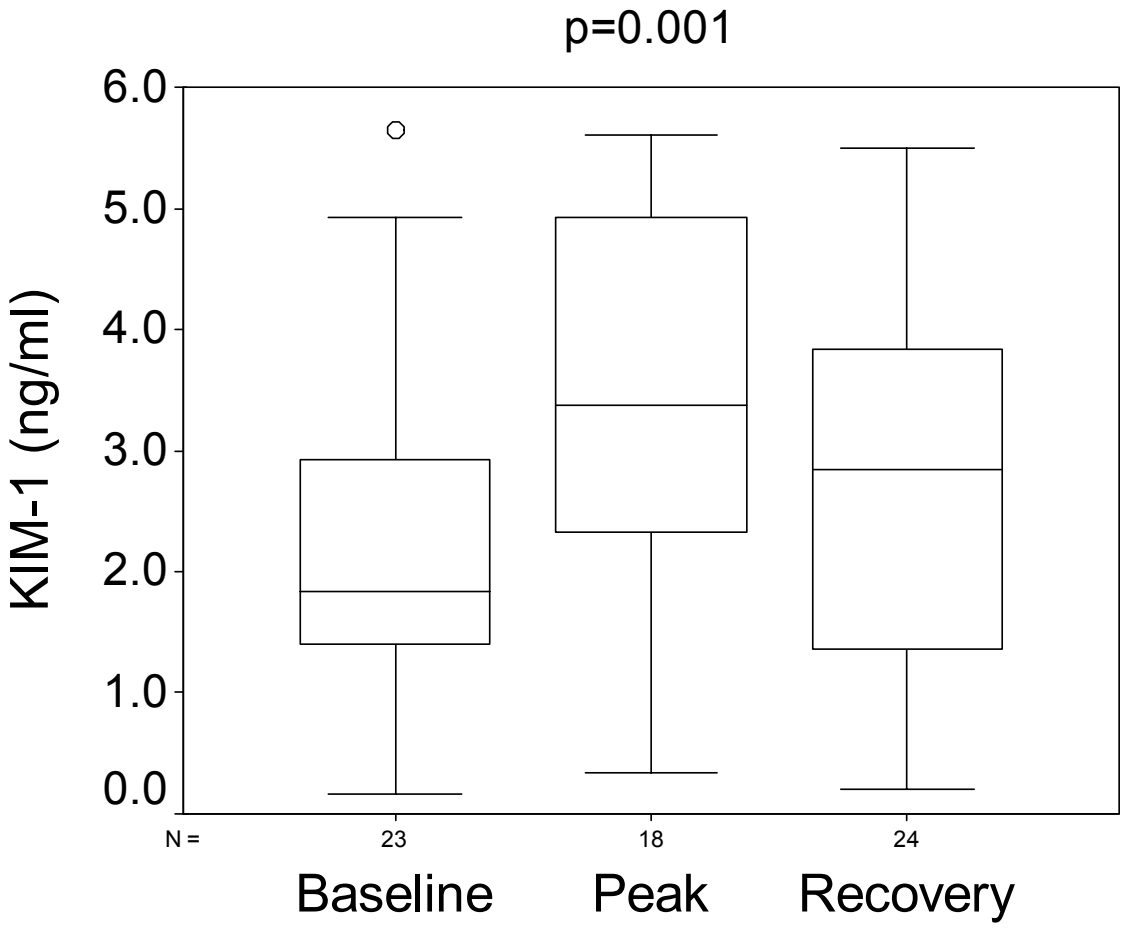

Figure 5. Relationship between the maximum change in CK and the rise in serum creatinine in those with and without AKI.