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Recovery of Inflammation, Cardiac, and Muscle Damage Biomarkers After Running a Marathon

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Abstract

Bernat-Adell, MD, Collado-Boira, EJ, Moles-Julio, P, Panizo-González, N, Martínez-Navarro, I, Hernando-Fuster, B, and Hernando-Domingo, C. Recovery of inflammation, cardiac and muscle damage biomarkers after running a marathon. *J Strength Cond Res* XX(X): 000–000, 2019—Physical endurance sports conditions the increase of blood biomarkers responsible for the acute inflammatory response. The purpose of this study was to observe the impact of intense physical exercise on these biomarkers and detect their recovery pattern. This is an experimental study of repeated measures (pre-post marathon). The biomarkers lactate dehydrogenase (LDH), creatine kinase (CK), high-sensitivity troponin T (hs-TNT), and C-reactive protein (CRP) were analyzed in a total of 86 runners, 24 hours before the marathon, immediately after finishing the race and at 24, 48, 96, and 144 postrace hours. The comparative analyses were performed using the Friedman and Wilcoxon tests. The correlations between dependent and independent variables were analyzed using Spearman correlations. The data were processed through the IBM SPSS package, version 23. Significant value was $p \leq 0.05$. The LDH increased and showed significant differences ($p \leq 0.001$) for all times, compared with the initial LDH value, normalizing after 192 hours ($p = 0.667$) (effect size [ES], $r = 0.807$). The CK increased and showed significant differences ($p \leq 0.001$) (ES, $r = 0.975$) up to 96 hours afterward, normalizing after 144 hours. The hs-TNT presented an increase and showed significant differences ($p \leq 0.001$) between the pre-post race times, 24 and 48 hours, normalizing after 96 hours, although it showed a new significant value at 192 hours ($p \leq 0.001$) (ES, $r = 0.519$). The CRP increased and showed significant differences ($p \leq 0.001$) between the pre-post race times, at 24, 48, 96, 144, and 192 hours after race. The recovery after alterations produced by the marathon varies according to the biomarker. Blood levels of biomarkers decrease with longer race times. Greater energy expenditure increases the blood levels of LDH, CK, and hs-TNT.

Key Words: physical activity, energy expenditure

Introduction

In the past 2 decades, there has been a considerable increase in the number of individuals who, as amateurs, practice endurance sports, such as marathon and ultramarathon races (10,24). Most amateur athletes are not subject to medical monitoring, and the literature on this regard, although not conclusive, indicates that this sport is not free of risks. In adults younger than 35 years, cases of hypertrophic cardiomyopathy are described, and in those older than 35 years, cases of coronary heart disease, increased arterial wall stiffness, and increased arrhythmias have been described, highlighting cases of atrial fibrillation (25,27,28). Schnohr et al., comparing a sample of 1,098 runners with a sample of 3,950 sedentary adults, found that runners who performed light or moderate sport had a lower mortality than sedentary adults (HR: 0.51; 95% confidence interval [CI]: 0.24–1.10); however, those who practiced endurance or highly demanding sports had a mortality rate that was not statistically different from that of the sedentary group (HR: 0.94; 95% CI: 0.40–2.18) (39).

Physical activity is related to the level of well-being and is a component of a healthy lifestyle. It is recommended for weight control, to delay onset of chronic disorders and to prevent various diseases (4,31). The American College of Sports Medicine and the American Heart Association, in 2007, advised healthy adults to perform, at least, aerobic physical activity at a moderate intensity for a duration of 30 minutes 5 days a week or vigorous exercise during 20 minutes 3 times a week or the combination of both types of activity (14).

Physical exercise induces changes in the immune system and metabolic changes, with upregulation of certain enzymatic and protein factors. When this physical exercise is intense or extreme, the immune response is similar to that caused by other stressors, causing effects that are not beneficial for the athlete (11,19). Whether or not systemic damage is caused, the levels of myoglobin, troponin, creatine kinase (CK), lactate dehydrogenase (LDH), and C-reactive protein (CRP), among other biomarkers that are part of the acute inflammatory response, considerably increase their blood level concentration after endurance or highly demanding sport (21,32).

Therefore, the purpose of this study was to explore the physiological impact of intense physical exercise on the biomarkers of cell damage and inflammation, explain the postmarathon recovery pattern, and study possible correlations with the different study variables: biological sex and age of the runners, race time, and energy expenditure.

Material and Methods

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Subjects and Design

This is a pre-experimental study of repeated measures (pre-post marathon) of a single group without control group. Data were extracted from the Trinidad Alonso EDP Marathon, held in the city of Valencia on November 20, 2016, with a flat, 42,195-km circuit on asphalt (average temperature of 19° C and average relative humidity of 61%).

All registered subjects (18,800) previously received a communication through email describing the study and requesting their participation. A total of 456 runners responded (nonprofessional athletes). Two informative sessions were held to explain the study's protocol.

All runners who signed an informed consent form and met the following inclusion criteria were included:
- Not suffering heart or kidney disease.
- Not taking medication on a continuous basis.
- Having a previous registered marathon mark of between 3 and 4 hours for men and between 3 and a half and 4 and a half hours for women.
- Being aged between 30 and 44 years.
- Having a body mass index between 16 and <25 kg·m^{-2}.

The initial sample obtained was $n = 103$ runners, of which 88 completed the 42,195 km. One runner did not go to the place where they were taking the samples, and another one arrived after 1 hour after the race, so he was excluded from the study. Finally, 86 runners completed the study ($n = 86$).

Procedure

Subjects completed an online survey on their medical history and provided blood samples at different times before and after the race.

The first blood sample was taken 24 hours before the marathon (initial sample at the beginning of the study with baseline results). The following samples were obtained immediately after finishing the marathon and at 24, 48, 96, and 144 postrace hours.

All blood samples were collected from antecubital veins, transported in cold medium within 2 hours after their extraction, and processed on arrival to the laboratory of the Vithas Nisa 9 de Octubre Hospital (Valencia), using the modular platform Roche/Hitachi clinical chemistry analyzer cobas c 311.

Variables. As dependent variables, the following biomarkers were identified:
- Lactate dehydrogenase is a nonspecific marker of tissue damage. Normal reference values for healthy adult men are 135 –225 UI·L^{-1} and 135–214 UI·L^{-1} for women (42).
- Creatine kinase is an indicator of acute muscle damage. Normal reference values for healthy adults are <190 UI·L^{-1} (men) and <170 UI·L^{-1} (women) (42).
- High-sensitivity troponin T (hs-TNT) is an indicator of acute myocardial damage. Normality ranges in healthy individuals are <14–30 ng·L^{-1} (26).
- C-reactive protein is an indicator of acute inflammatory reaction. Normality ranges in healthy individuals are <0.5 mg·dl^{-1} (7).

In the blood sample obtained immediately after the race, the values of the aforementioned biomarkers were corrected because of changes in plasma volume and the hemoconcentration caused by dehydration, based on the hemoglobin and hematocrit values according to the Dill and Costill method (8).

Age, sex, race time, and energy expenditure were considered as independent variables.

The energy expenditure was measured by GENEActiv accelerometer (Activinsights, Ltd., Kimbolton, Cambridgeshire, United Kingdom). The cutpoints established to measure the intensity of the race were those established by Hernando et al. (15).

Statistical Analyses

The descriptive analysis of the continuous variables is reported by mean values and SDs, minimum and maximum values. Categorical variables were expressed in absolute frequencies and percentages. The Kolmogorov-Smirnov test (K-S test) was applied to check the normality of the variables, obtaining values of $p \leq 0.05$ in all cases. The result of the K-S test motivated the analysis of the variables through nonparametric tests.

To compare the results according to each time points, the Friedman and Wilcoxon tests were used, according to the normality of the variables. According to Cohen's recommendations for nonparametrical test, the magnitude of effect sizes was explored by (r value). The meaning of the r value is 0.10, small effect, 0.030, medium effect, and 0.50, great effect.

Subsequently, the correlation between the biomarker values and the independent variables (age, sex, race time, and energy expenditure) was verified through Spearman correlations. Statistical analyses were performed using the IBM SPSS version 23 statistical package. A p value less than <0.05 was accepted as significant.

Ethical Considerations. In compliance with the Declaration of Helsinki (v. 2013) and respecting the Organic Law 15/1999 on the Protection of Personal Data, the anonymization of data was performed. Random numbers were assigned to the runner's race identification number assigned by the organization; bar codes were used to identify the samples. All subjects were informed of the study and signed an informed consent form. The Deontological Commission of the Universitat Jaume I approved the study's protocol in May 2016.

The study was registered in the database of Clinical Trials of the U.S. National Library of Medicine (code NCT03155633).

Results

For a sample of $n = 86$, 86% (74) were men and 14% (12) were women: The mean age was 38.62 years ($\pm$3.62 years). The value of the mean body mass was 69.98 ($\pm$8.95) kg with a range of 45.60–89.70 kg. The value of the mean height was 174.69 ($\pm$8.44) cm with a range of 151–191 cm. As for the time invested in the race, a mean value of 03 hours:34 minutes:32 seconds ($\pm$0 hours:20 minutes:49 seconds) was obtained, ranging between 02 hours:58 minutes:25 seconds and 04 hours:36 minutes:03 seconds. The mean energy expenditure value was 2,953.02 ($\pm$393.48) kcal.

The K-S test for dependent variables (CK, LDH, hs-TnT, and PCR) skewed no normality for such variables for all the analyzed times. The same occurred when checking for sphericity by means of the Mauchly W test; therefore, the nonparametric Friedman test was used for contrasts of more than 2 dependent samples. Table 1 shows [T1] the descriptive results, and the contrast statistic results indicate the existence of significant differences with value $p \leq 0.001$ between the evaluated times for the variables LDH, CK, hs-TnT, and CRP.

The results of the Wilcoxon test for LDH analysis and its recovery point showed statistically significant differences with

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Table 1

Results of the descriptive analyses (mean, *SD* and range) and Friedman's test for the biomarkers: LDH, CK, hs-TnT, and CRP.*

	Mean (*SD*)	Range	Chi-squared	*p*
LDH (UI·L^{-1}) baseline	190.26 ± 71.59	119–650	376.20	≤0.001§
LDH (UI·L^{-1}) finish line	318.36 ± 61.40	227.48–583.92		
LDH (UI·L^{-1}) 24 h	240.76 ± 57.12	161–503		
LDH (UI·L^{-1}) 48 h	253.36 ± 54.21	169–474		
LDH (UI·L^{-1}) 96 h	225.00 ± 45.06	147–373		
LDH (UI·L^{-1}) 144 h	215.91 ± 42.75	142–351		
LDH (UI·L^{-1}) 192 h	182.30 ± 30.47	131–299		
CK (UI·L^{-1}) baseline	158.48 ± 77.11	53–502	398.83	≤0.001§
CK (UI·L^{-1}) finish line	396.74 ± 244.94	132.12–1805.39		
CK (UI·L^{-1}) 24 h	1,443.36 ± 1,533.78	165–11.287		
CK (UI·L^{-1}) 48 h	825.59 ± 1,078.98	88–6,534		
CK (UI·L^{-1}) 96 h	386.59 ± 691.09	66–5,359		
CK (UI·L^{-1}) 144 h	235.74 ± 296.79	49–1928		
CK (UI·L^{-1}) 192 h	166.39 ± 119.08	57–788		
hs-TnT (ng·L^{-1}) baseline	5.63 ± 5.12	0–30	390.88	≤0.001§
hs-TnT (ng·L^{-1}) finish line	48.36 ± 51.05	9.16–419.36		
hs-TnT (ng·L^{-1}) 24 h	15.42 ± 13.71	0–92.80		
hs-TnT (ng·L^{-1}) 48 h	11.31 ± 13.41	0–112.60		
hs-TnT (ng·L^{-1}) 96 h	5.07 ± 4.58	0–35		
hs-TnT (ng·L^{-1}) 144 h	4.85 ± 4.51	0–35		
hs-TnT (ng·L^{-1}) 192 h	4.41 ± 4.48	0–35		
CRP (mg·dl^{-1}) baseline	0.08 ± 0.24	0–1.75	445.07	≤0.001§
CRP (mg·dl^{-1}) finish line	0.08 ± 0.27	0–2.35		
CRP (mg·dl^{-1}) 24 h	1.29 ± 0.54	0.20–2.88		
CRP (mg·dl^{-1}) 48 h	0.68 ± 0.30	0.18–2.06		
CRP (mg·dl^{-1}) 96 h	0.29 ± 0.16	0.07–0.96		
CRP (mg·dl^{-1}) 144 h	0.17 ± 0.15	0.01–1.14		
CRP (mg·dl^{-1}) 192 h	0.12 ± 0.15	0.02–1.26		

*LDH = lactate dehydrogenase; CK = creatine kinase; hs-TNT = high-sensitivity troponin T; CRP = C-reactive protein.

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†$p \leq 0.05$.

‡$p \leq 0.01$.

§$p \leq 0.001$.

[F1] values ($p \leq 0.001$) for all times, compared with the initial prerace value, except for the value obtained at 192 hours after race, as can be observed in Figure 1.

[F2] The Wilcoxon test for CK indicated significant differences ($p \leq 0.001$) between prerace and postrace times, at 24, 48, and 96 hours. No significant differences were observed at 144 hours after the race, as can be seen in Figure 2.

In the case of the hs-TNT, statistically significant differences were found with $p \leq 0.001$ values between prerace and postrace times, at 24 hours, and at 48 hours. No significant differences were found at 96 and 144 hours. However, a new significant difference was observed between the prerace sample and the one [F3] taken at 192 postrace hours. See results in Figure 3.

The Wilcoxon test for CRP showed significant differences at all times analyzed with respect to the sample taken before the race. At 192 hours after race, it continued to show significant differences, [F4] as can be observed in Figure 4.

Spearman's rho statistic did not reveal any correlation between biomarker values, age, and sex for any of the analyzed times. However, a negative and significant correlation between race time and the values of the analyzed biomarkers was observed [T2] (Table 2).

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Discussion

The evidence highlights a transient increase in the biomarkers responsible for the inflammatory response during and after intense physical exertion. Although, in healthy athletes, this

increase is explained as a physiological response to intense physical exercise rather than as indicators of tissue damage (37), it is not clear whether these transient increases could, in the future, induce illness (30). In this study, none of the runners required medical help after the race.

The 4 analyzed biomarkers show significant changes after the race and during the recovery period. The peak value for LDH is reached just after finishing the race, and from this point onward, it begins to decrease, achieving normalization values at 192 hours (8 days) after race. This result coincides, in part, with the pattern presented by Arakawa et al. (1), who indicate that LDH continues to rise on day 2 after race, and after 48 hours, it starts to decrease. However, these authors did not indicate the time of normalization.

In this study, we have observed that the levels of CK increase significantly after the marathon and reach a peak at 24 hours. These values start to decrease after 24 hours; yet, they remain significantly elevated until 144 hours (6 days) after the race. This pattern is similar to that presented by Arakawa et al., and by Lijnen et al., who also described a maximum peak at 24 hours after the race, decreasing from this point onward, although on the sixth day after the race, the levels continued to be higher than the baseline values (1,23). Niemelä et al. (29), in a comparative study between marathons and half-marathons, defined the maximum peak of CK at 3 hours after marathon, noting a decrease after 48 hours after marathon, but they did not calculate the normalization point with respect to the baseline. Baird et al. (3) described the normalization of CK between 7 and 9 days after intense physical effort.
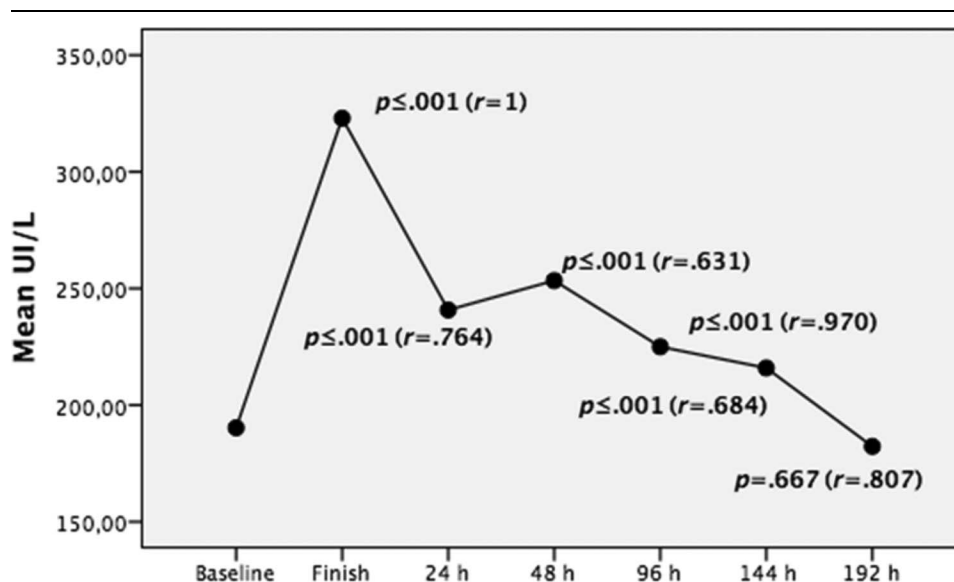
Figure 1. Results of the Wilcoxon test. Evolution of LDH. $p \leq 0.005$. Magnitude of effect sizes (r: 0.10 small effect, 0.030 medium effect, and 0.50 great effect). LDH = lactate dehydrogenase.

Regarding the peak of CK, this study coincides with most authors, except with the results presented by Roca et al. (35), who obtained a maximum peak at 48 hours after marathon. As for the normalization point, in this study, it is slightly earlier. It should be noted that the peak value of CK does not exceed 11,287 IU (except in 1 case), reaching the lower limit for the diagnosis of rhabdomyolysis (17). In view of these results, coaches should avoid programming training sessions eliciting greater muscle damage (i.e., running and strength training) during the immediate 96 hours after a road Marathon, especially among their faster coaches.

The levels of troponin (hs-TNT) increase considerably, reaching their maximum peak after the marathon and normalizing after 4 days, as other studies have reported (16,34,44). We have observed that these values continue to fall, and at 7 days after marathon, they are significantly lower than the prerace baseline values. This could be explained by the usual absence of high-intensity efforts during the week after a road Marathon. It has been described that levels of troponin are significantly risen after short but high-intensity physical activities such as a 1-hour kettlebell or a spinning, so last preparatory trainings before the Marathon could be responsible for the higher measured prerace hs-TNT values (9,36).

Niemelä et al. (29) found the maximum peak of troponin at 3 hours after marathon and appreciated a decrease at the 48-hour evaluation, in congruence with this study. However, these
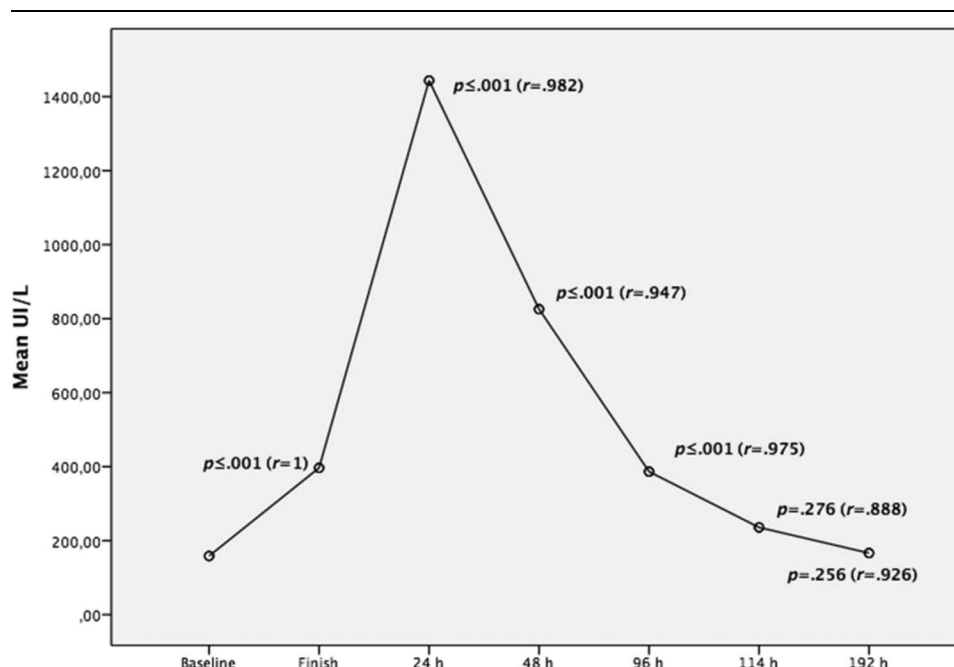

Figure 2. Results of the Wilcoxon test. Evolution of CK. $p \leq 0.005$. Magnitude of effect sizes (r: 0.10 small effect, 0.030 medium effect, and 0.50 great effect). CK = creatine kinase.
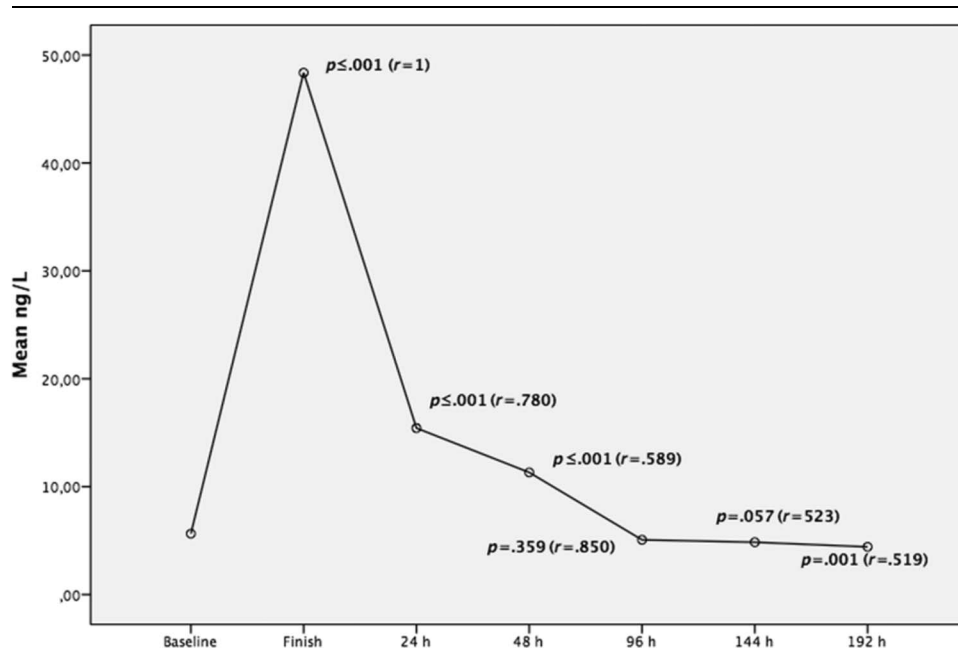
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Figure 3. Results of the Wilcoxon test. Evolution of hs-TNT. $p \leq 0.005$. Magnitude of effect sizes (r: 0.10 small effect, 0.030 medium effect, and 0.50 great effect). hs-TNT = high-sensitivity troponin T.

authors did not indicate the temporal moment of normalization. Several studies indicate that, after intense physical effort, troponins are released, increasing their blood concentration; yet, despite this and the morphological (right atrial and ventricular dilation) and functional (reduced right ventricular ejection fraction) changes, no ischemic damage was observed for any cardiac chamber (43). The recent study by Arisi et al. (2), performed with rodents, indicates a clear relationship between aerobic exercise (similar to that performed by marathon runners) and myocardial dysfunction and cardiomyocyte damage, but this is attributed to an increase in plasma catecholamines rather than to the increase of troponins.

The CRP marker related to the acute inflammatory reaction reached its peak at 24 hours and began to decrease, although after
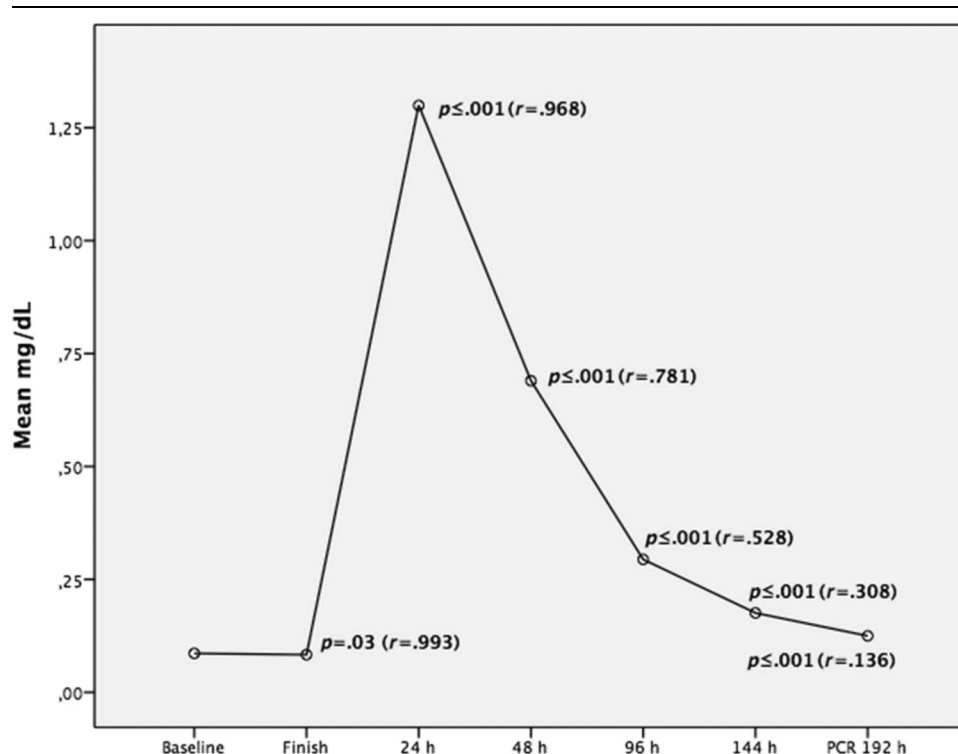

Figure 4. Results of the Wilcoxon test. Evolution of the CRP. $p \leq 0.005$. Magnitude of effect sizes (r: 0.10 small effect, 0.030 medium effect and 0.50 great effect). CRP = C-reactive protein.

Table 2

Results of the correlation between biomarkers (LDH, CK, hs-TnT, and CRP) with race time and total energy expenditures.*

	Race time		Energy expenditure Kcal	
	r_s	p	r_s	p
LDH (UI·L^{-1}) finish line	−0.18	0.083	0.22	0.041†
LDH (UI·L^{-1}) 24 h	−0.22	0.038†	0.26	0.016†
LDH (UI·L^{-1}) 48 h	−0.33	0.002‡	0.19	0.070
LDH (UI·L^{-1}) 96 h	−0.27	0.012†	0.22	0.038†
LDH (UI·L^{-1}) 144 h	−30	0.004‡	0.20	0.054
LDH (UI·L^{-1}) 192 h	−0.31	0.003‡	0.21	0.049†
CK (UI·L^{-1}) finish line	−0.05	0.634	0.35	≤0.001§
CK (UI·L^{-1}) 24 h	−0.15	0.151	0.34	≤0.001§
CK (UI·L^{-1}) 48 h	−0.10	0.353	0.39	≤0.001§
CK (UI·L^{-1}) 96 h	−0.17	0.111	0.40	≤0.001§
CK (UI·L^{-1}) 144 h	−0.17	0.116	0.26	0.015†
CK (UI·L^{-1}) 192 h	−0.20	0.056	0.24	0.025†
hs-TnT (ng·L^{-1}) finish line	−0.31	0.003‡	−0.07	0.487
hs-TnT (ng·L^{-1}) 24 h	−0.34	≤0.001§	−0.02	0.813
hs-TnT (ng·L^{-1}) 48 h	−0.44	≤0.001§	0.03	0.739
hs-TnT 96 h	−0.31	0.003‡	0.21	0.043†
hs-TnT 144 h	−0.26	0.013†	0.33	≤0.001§
hs-TnT 192 h	−0.30	0.004‡	0.30	0.004‡
CRP (mg·dl^{-1}) finish line	0.31	0.003‡	0.14	0.193
CRP (mg·dl^{-1}) 24 h	0.41	≤0.001§	0.09	0.378
CRP (mg·dl^{-1}) 48 h	0.39	≤0.001§	−0.16	0.131
CRP (mg·dl^{-1}) 96 h	0.19	0.068	−0.14	0.177
CRP (mg·dl^{-1}) 144 h	0.09	0.373	−0.02	0.845
CRP (mg·dl^{-1}) 192 h	0.19	0.078	−0.03	0.746

*LDH = lactate dehydrogenase; CK = creatine kinase; hs-TNT = high-sensitivity troponin T; CRP = C-reactive protein.
†Value of r_s (Spearman rho −1 to +1) (p value ≤0.05).
‡Value of r_s (Spearman rho −1 to +1) (p value ≤0.01).
§Value of r_s (Spearman rho −1 to +1) (p value ≤0.001).

192 hours (8 days), it still presented high values, which were significantly different from the prerace baseline value. Arakawa et al. (1) found similar results: Their last evaluation was 6 days after race, and their CRP still showed high values. Niemelä et al. (29) described the maximum peak at 48 hours, but they did not present its normalization point.

This study has not found a correlation between age and these biomarker values for any of the times analyzed, which is consistent with the results obtained with smaller samples, although with similar characteristics to those of this study (13,18,41). Regarding age, Presslel et al. (33) concluded that, in a cohort of marathon runners free from cardiovascular disease, only subclinical markers of vascular damage were found, but these were related only to a greater age of the runners, and not to the fact of that they perform endurance sports. Knebel et al. (20) evaluated the difference in troponin values between 2 groups of women (premenopausal and postmenopausal) and did not find any significant differences related to age.

As with other studies, this study has not found a relationship between the levels of biomarkers and the sex of the subjects (6,12). However, there is no consensus, as other studies such as that of Kong et al. (22), with a sample of young athletes, found differences in postrace troponin plasma concentrations, being significantly higher in men (median [range]: 210 [20–1,360] ng·L^{-1}) with respect to women (median [range]: 80 [10–550] ng·L^{-1}). Danielson et al. (5), with a sample of amateur triathletes, also showed that sex was a significant predictor of myoglobin and CK values in both, the postrace evaluation and at the week evaluation, with both times showing significantly lower values for

women. These authors also indicated that women tolerated postrace musculoskeletal adverse events better. Women are becoming increasingly involved in endurance sports, and it is necessary to continue with studies that analyze the possible differences and provide evidence that may improve their performance in sport and detect undesirable events.

Regarding the influence of race time on the release of biomarkers and their recovery, there is a negative and significant correlation between race time and the release of LDH and hs-TNT, and a positive correlation that relates a longer race time with a higher level of CRP up to 48 hours after a marathon. No relationship was found with the release and recovery of CK. These results, in the case of troponins, coincide with those published by Scott et al. (40), who indicate that this negative relationship associated with a longer race time coincides with a lower intensity of exercise or lower stress of the cardiovascular system (38). In this study, when correlating energy expenditure with biomarker values, we observed that higher energy expenditure was related to higher plasma levels of CK in all the analyzed times and higher values of hs-TNT for the recovery period between the third and sixth day.

The physical characteristics of the analyzed sample were quite similar, which may have influenced the fact that no differences were found in relation to the age and sex of the runners, who were healthy individuals who practiced sports regularly.

Practical Applications

Our results provide a comprehensive view of how muscle, cardiac, and inflammatory damage evolves the week after running a road Marathon and originally show that the normalization of the biomarkers associated with these 3 processes occurs at different time points. This is particularly important for both medical and coaching communities.

On one hand, the establishment of those expected normalization points could ease doctors with the interpretation of analytical values of amateur runners attending hospital emergency departments (because of any nonrelated illness) the week after competing in a road Marathon. On the other hand, the knowledge of these different time recovery for muscle, cardiac, and inflammatory damage should be taken into consideration by coaches when planning their athletes' training sessions after the race.

Moreover, according to the relationships found between race time and biomarkers release, it seems advisable that faster runners should avoid for a longer time training sessions associated with greater muscle damage (i.e., running and strength training), whereas in slower runners, a higher inflammatory response could be expected after a road Marathon.

Acknowledgments

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