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Plasma marker for systemic inflammation is increased in Mexican Tarahumara following ultra-distance running

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Abstract

Objectives: Previous studies have suggested that acute exercise-induced cardiac and kidney damage following ultra-distance running is low in Mexican Tarahumara even though C-reactive protein (CRP) remained elevated 24 hours post-race. We aimed to study if the plasma biomarker, soluble urokinase-type plasminogen activator receptor (suPAR), could replace or complement CRP as a systemic inflammation biomarker in Tarahumara men and women following ultra-distance running.

Methods: Plasma samples were collected pre-race and at three to six different time points post-race in Mexican Tarahumara competing in three independent ultramarathons; men running 78 km (*GroupI*, n = 9), women running 52 km (*GroupII*, n = 3), and men running 63 km (*GroupIII*, n = 10). Baseline anthropometry, blood pressure, glycated hemoglobin, and hemoglobin were measured, aerobic fitness was estimated by submaximal step test, absolute and relative running intensity assessed using combined heart rate and accelerometry. Plasma was collected pre- and post-race to analyze concentrations of suPAR, and—for women only—a panel of inflammatory, cardiac and kidney plasma biomarkers. Mixed-effect models were used to evaluate the effect of ultramarathon running on plasma suPAR concentrations.

Results: Compared to pre-race values, suPAR was significantly elevated in plasma <5 minutes after the three ultramarathon races (70%-109% increase of the mean for the three groups). Furthermore, plasma suPAR remained significantly elevated up to 6 hours post-race for all three groups of runners independent of running intensity.

Conclusions: The results suggest that suPAR can complement, but not replace CRP following ultra-distance running in Tarahumara men and women.

1 | INTRODUCTION

The Tarahumara of northern Mexico are best known for their ultramarathon running feats, in traditional races still performed by men and women, as well as in modern sports races (Rascón, 1994). Tarahumara men may run up to 150 km, and women between 25 and 45 km (Lieberman et al., 2020), but mean aerobic fitness for men is lower than in European recreational marathon runners (54.5 vs 57.8 ml O_2 min^{-1} kg^{-1}) (Christensen et al., 2017; Waskiewicz et al., 2012). Nevertheless, we have shown aerobic fitness as high as 70.1 mlO_2 min^{-1} kg^{-1} in Tarahumara runners (Christensen et al., 2017), indicating that aerobic fitness range is large in this population. Scientific literature on female Tarahumara runners and physical activity is scarce, and limited to habitual physical activity and aerobic fitness descriptions (Christensen, Alcala-Sanchez, Leal-Berumen, Conchas-Ramirez, & Brage, 2012), and cultural accounts (Lieberman et al., 2020). In the scientific community, there is a special interest in ultramarathon-induced impact on the cardiovascular system, kidney and muscle fiber damage that results from extreme exercise (Knechtle & Nikolaidis, 2018). Several studies have demonstrated ultra-endurance exercise resulting in an unspecific inflammatory response as seen by an increase in interleukin-6 and C-reactive protein (CRP) (Nieman et al., 2003; Waskiewicz et al., 2012).

A relatively new protein marker for unspecific assessment of systemic inflammation has emerged, named urokinase-type plasminogen activator receptor (suPAR) (Desmedt, Desmedt, Delanghe, Speeckaert, & Speeckaert, 2017), which is the soluble form of urokinase-type Plasminogen Activator Receptor (uPAR/CD87) (Saleem, 2018). Elevated plasma suPAR concentration is associated with a general activation of the immune system. Therefore, suPAR concentrations in plasma can change in response to various states of low-grade inflammation, such as viral infection, parasitical infections, autoimmune disease, cancer, and metabolic status (Desmedt et al., 2017). Consequently, suPAR is an unspecific biomarker of immune system activation.

Thus, we aimed to investigate whether cellular-released suPAR could be used as a biomarker to monitor an inflammatory response induced by ultra-distance running in male and female Tarahumara runners. We hypothesized that suPAR would be able to perform as a substitute biomarker for CRP.

2 | MATERIALS AND METHODS

Runners (n = 22) participating in three different races volunteered for this study. In the first race (*GroupI*), nine male runners from the village of Choguita, Chihuahua, participated in a 78 km running race organized for the purpose of the study (Christensen et al., 2014). In race two (*GroupII*), three female runners from Choguita participated in a 52 km race (results not previously reported) carried out as part of the 78 km race. In race three (*GroupIII*), ten runners also from Choguita participated in a 63 km race named *Ultramaratón de los Cañones* (Christensen et al., 2017). All three races started and ended in the town of Guachochi. All runners were recruited through local advertisement in the village of Choguita for the study, as Tarahumara from this residential area were regular participants in ultramarathon races. All interested runners were included if they agreed to participate the full research protocol including tests and measurements before, during and after the race events. We decided to exclude three potential participants from the *Ultramaratón de los Cañones* study group as they were participating in the 100 km event, which would have resulted in post-race tests during the night. Time-wise, we regarded such tests as impractical and borderline ethical.

All three races started in the town of Guachochi, Chihuahua at an altitude of ∼2400 m. The 78 km and 52 km running events took place in November 2011, and began at 5:55 AM The male participants had to cover a flat loop of 26 km three times, that is, 78 km on a dirt road. For the female 52 km race, participants did two loops of 26 km on the same route. All participants were encouraged to cover the race distances as fast as possible. In the 63 km race, the event took place in July 2012 and began at 6:00 AM; the route was an out-and-back course including a drop of ∼1800 m into the bottom of a canyon, the *Barranca de la Sinforosa* from where the runners had to return. Regular depots with snacks and water were available in all three races as was paramedical support en route.

For all three races, 10 ml blood was collected in lithium heparin-containing BD-Vacutainer tubes at each time point, that is, at pre-race (baseline), <5 minutes, 6 hours, and 24 hours post-race, using an intravenous catheter. For races one and two, further blood samples were collected at 1 hour, 3 hours, and 48 hours post-race. Blood was centrifuged, and the plasma was stored in cryogenic tubes and frozen in aliquots at −80°C until analysis.

For all three races, participants gave written or thumb print (in case of illiteracy) consent based on written and oral information including the opportunity for the participants to ask questions. Ethical approval was given by the Ethical Committee of Science in Chihuahua, Mexico (no. 00039259).

Concentrations of suPAR were measured in plasma using a commercial ELISA (suPARnostic AUTO Flex Kit,

Lot. No. 204LA1-1, Virogates). Plasma was analyzed in duplicate. Aerobic fitness was assessed using heart rate response to a submaximal step test (Brage et al., 2007). Physiological intensity of the race was assessed using combined heart rate and movement sensing (Brage, Brage, Franks, Ekelund, & Wareham, 2005). Intensity was averaged for the race and expressed as relative to maximal aerobic capacity.

3 | STATISTICS

For each individual runner the mean pre-race value (R_0) was subtracted from the post-race mean values (R). The change in suPAR values over time was analyzed by linear mixed-effect model, with separate models for each group. All estimates ($R - R_0$) are therefore interpreted as a change in relation to baseline values. The models included a random effect for runners and a fixed time effect. Missing suPAR values were assumed missing at random and are taken into account by the ignitability assumption in the maximum likelihood estimation method used in the mixed-effect models (R Core Team, 2015), and the nlme R-package (Pinheiro, Bates, DebRoy, Sarkar, & Team aRC, 2015). Multi-level modeling was used to account for multiple post-race measurements of the biomarker response per person, also when adjusted for physiological intensity (J min^{-1} kg^{-1}) on suPAR values. Furthermore, linear mixed-effects models were used to analyze differences between pre-race and post-race mean inflammation, cardiac, kidney, and hemolysis biomarker values for the female runners only. All biomarker values were log-transformed for *P*-value presentations, and presented as geometric mean (SD). *P*-values <.05 were considered statistically significant.

4 | RESULTS

Background characteristics of Tarahumara runners are shown in Table 1. Change estimates in the suPAR concentrations are shown in Table 2. In brief, all three groups of runners had changes from baseline values that were significant from <5 minutes post-race to 6 hours post-race (*P*-values<.001). Time-course measurements of suPAR concentrations in plasma of individual runners and the percentage increase in mean suPAR compared to pre-race mean values are shown in Table 3, and data from the three groups are shown graphically in Figure 1. A more comprehensive panel of biomarkers compared to baseline values for the *GroupII* female runners—previously presented for the *GroupI* and *GroupIII* runners (Christensen et al., 2014; Christensen et al., 2017) are shown in Table 4. All cardiac, kidney and hemolysis biomarkers were normalized within 48 hours. No statistically significant correlations were found between suPAR and physiological intensity (J min^{-1} kg^{-1}) or running duration in any of the three groups of runners (results not shown).

5 | DISCUSSION

We showed that ultra-distance running induced an increase in plasma suPAR concentration <5 minutes.

TABLE 1 Background characteristics of Tarahumara runners presented as mean (SD) (n = 22)

Variable	*GroupI* men 78 km race (n = 9)	*GroupII* women 52 km race (n = 3)	*GroupIII* men 63 km race (n = 10)
Age (years)	37.3 (12.7)	29.1 (11.2)	29.9 (6.6)
Height (m)	163.1 (3.7)	154.8 (1.8)	161.8 (6.7)
Weight (kg)	60.1 (6.2)	58.4 (4.4)	54.2 (5.7)
Body mass index (kg m^{-2})	22.5 (1.9)	24.4 (1.7)	21.2 (1.7)
Systolic blood pressure (mmHg)	123 (15)	121 (4)	105 (9)
Diastolic blood pressure (mmHg)	73 (11)	70 (12)	64 (7)
Glycated hemoglobin (%)	5.5 (0.2)	5.3 (0.1)	5.7 (0.2)
Hemoglobin (mmol/L)	9.2 (1.2)	8.6 (0.3)	9.7 (0.9)
Estimated Fitness (mLO_2 min^{-1} kg^{-1})	47.2 (10.0)	40.6 (2.8)	54.5 (8.8)
Race time (hours and minutes)	8.57 (1.42)	6.46 (0.30)	6.58 (0.43)
Absolute intensity (km h^{-1})	8.9 (1.7)	7.8 (0.6)	9.1 (0.9)
Physiological intensity (J min^{-1} kg^{-1})	558 (174)	618 (71)	746 (143)
Relative intensity (% est. fitness)	66 (10)	83 (5)	72 (1)

TABLE 2 Estimating mean difference $R - R_0$ (lower and upper CI) of plasma suPAR concentrations (μg/L) using mixed-effect models with build-in multiple imputation in Tarahumara runners ($n = 22$)

	Lower CI	$R - R_0$ estimate[a]	Upper CI	*P* value
GroupI[b]				
<5 minutes	2.1	2.5	3	<0.001
1 hour	1.5	2.0	2.4	<0.001
3 hours	1.1	1.6	2.1	<0.001
6 hours	0.7	1.2	1.6	<0.001
24 hours	0	0.4	0.9	0.086
48 hours	−0.5	0	0.4	0.918
GroupII[c]				
<5 minutes	2.3	3.1	3.9	<0.001
1 hour	1.5	2.2	3.0	<0.001
3 hours	0.8	1.5	2.3	0.005
6 hours	0.3	1.0	1.8	0.035
24 hours	−0.1	0.6	1.4	0.164
48 hours	−0.5	0.4	1.2	0.445
GroupIII[d]				
<5 minutes	1.5	1.8	2.0	<0.001
6 hours	0.4	0.7	1.0	<0.001
24 hours	−0.2	0.1	0.4	0.501

[a]$R - R_0$: R is mean suPAR concentration at given post-race time-point, and R_0 is mean pre-race suPAR concentration.
[b]*GroupI* refers to Tarahumara men (n = 9) running 78 km.
[c]*GroupII* refers to Tarahumara women (n = 3) running 52 km.
[d]*GroupIII* refers to Tarahumara men (n = 10) running 63 km.

Post-race (70%-107%), and that this effect was still significant up to 6 hours post-race following three different race conditions, and in both sexes. Interestingly, no statistically significant correlations were found between suPAR and physiological intensity (J min^{-1} kg^{-1}) or running duration in any of the three groups of runners. However, a previous study by (Niemela, Kangastupa, Niemela, Bloigu, & Juvonen, 2016) showed a significant 3 hours post-race increase in plasma levels of suPAR in half-marathon (n = 4) and marathon runners (n = 4), with increases being more pronounced in the latter group, and decreasing to baseline levels within 48 hours in both groups. In our study, elevated suPAR could be detected up to 6 hours post-exercise, a data-point that was missing in the study by (Niemela et al., 2016), and retuning to baseline by 24 hours.

Ultra-distance running has been shown to induce a state of transient acute kidney disease (Kao et al., 2015). Consequently, the elevated plasma suPAR concentration measured in this study could also stem from exercise-induced mild transient acute kidney injury.

In general, strenuous exercise introduces a state similar to that of the acute phase response seen in infections as well as elevation of the leucocyte count (Nieman & Wentz, 2019). The plasma samples in this study have previously been analyzed for other biomarkers for the male runners (Christensen et al., 2014, 2017), as well as in the present study for the female runners. For all the runners, we demonstrated that CRP, a marker of the acute phase response, was significantly elevated up to 24 hours, and for *GroupI* and *GroupII*, CRP had returned to baseline levels at 48 hours (Christensen et al., 2014, 2017). CRP as a reliable marker of inflammation is highly debated, due to conflicting data being released demonstrating that CRP exhibit intra-individual diurnal variation (Bogaty et al., 2013). At present, no evidence is available that suPAR exhibits diurnal variation and for this reason suPAR may be more suitable as inflammation marker where repeated sampling is performed within a relatively short time period.

We have previously established impaired renal function by up to a 10-fold increase in plasma copeptin, and an elevation in creatinine up to 24 hours post-race in male runners (Christensen et al., 2014, 2017), and largely confirmed these findings in the present study in the female runners. Similar results of ultramarathon-induced renal impairment have been shown in studies where runners covered distances ranging from 42 to 100 km (Kao

TABLE 3 Individual absolute and relative increase in suPAR plasma concentrations (μg/L) at different post-race time-points compared to pre-race baseline concentrations in Tarahumara runners (n = 22)

	Pre-race	<5 minutes	1 hour	3 hours	6 hours	24 hours	48 hours	Sex	Distance (km)
GroupI[a]									
Runner #2	2.1 ± 0.1	3.7 ± 0.1 (76%)	4.3 ± 0.1 (104%)	2.4 ± 0.3 (14%)	3.3 ± 0.4 (57%)	2.2 ± 0 (5%)	2.3 ± 0.1 (10%)	♂	78
Runner #3	3.2 ± 0.6	4.9 ± 0.4 (53%)	4.3 ± 0.1 (34%)	3.6 ± 0 (13%)	4.1 ± 0.1 (28%)	3.2 ± 0.3	3.6 ± 0.9 (13%)	♂	78
Runner #4	2.9 ± 0.1	7.3 ± 0.4 (151%)	5.2 ± 0.3 (79%)	5.4 ± 0.3 (86%)	4.7 ± 0.4 (62%)	3.5 ± 0.4 (21%)	2.7 ± 0.1 (−6%)	♂	78
Runner #7	3.1 ± 0.1	5.9 ± 0.5 (92%)	5.1 ± 0.3 (65%)	5.4 ± 0.2 (73%)	5 ± 0.3 (61%)	4.3 ± 0.1 (39%)	3.3 ± 0 (6%)	♂	78
Runner #8	3.1 ± 0.1	5.6 ± 0.3 (81%)	6 ± 0.3 (94%)	6.3 ± 0.1 (103%)	4.3 ± 0.1 (39%)	3.5 ± 0.1 (13%)	2.8 ± 0.3 (−10%)	♂	78
Runner #9	2.7 ± 0.1	5.5 ± 0.1 (104%)	5.4 ± 0 (100%)	4.8 ± 0.3 (78%)	4.1 ± 0.4 (52%)	2.9 ± 0.4 (7%)	2.5 ± 0.1 (−7%)	♂	78
Runner #10	3 ± 0	6 ± 0.3 (100%)	4.2 ± 0 (40%)	4 ± 0 (33%)	3.2 ± 0 (7%)	n.a.	2.7 ± 0.1 (−10%)	♂	78
Runner #11	3.9 ± 0.1	5.9 ± 0.4 (51%)	5.9 ± 0.1 (51%)	–	–	4.7 ± 0.1 (21%)	4.2 ± 0.3 (8%)	♂	78
Runner #12	3.6 ± 0	5.6 ± 0 (56%)	5 ± 0 (39%)	4.6 ± 0 (28%)	4.3 ± 0.1 (19%)	4 ± 0.3 (11%)	n.a.	♂	78
GroupII[b]									
Runner #5	2,8 ± 0	5,3 ± 0.1 (89%)	4.7 ± 0.1 (68%)	3.8 ± 0 (36%)	3.2 ± 0.3 (14%)	3.8 ± 0.3 (36%)	2.8 ± 0 (0%)	♀	52
Runner #6	2.3 ± 0.1	5.7 ± 0.1 (148%)	5 ± 0 (117%)	4.6 ± 0.3 (100%)	4.7 ± 0.1 (104%)	3.3 ± 0.1 (43%)	n.a.	♀	52
Runner #13	3.6 ± 0.3	7 ± 0.3 (94%)	5.7 ± 0.7 (58%)	4.9 ± 0.7 (36%)	3.9 ± 0.4 (8%)	3.5 ± 0.1 (−3%)	3.8 ± 0.3 (6%)	♀	52
GroupIII[c]									
Runner #14	2.1 ± 0.1	3.9 ± 0.1 (86%)	—	—	3.1 ± 0.1 (48%)	2.85 ± 0.1 (36%)	—	♂	63
Runner #15	3.8 ± 0.2	5.9 ± 0.1 (56%)	—	—	4.1 ± 0.1 (8%)	3.3 ± 0.1 (−12%)	—	♂	63
Runner #19	4.5 ± 0.7	5.8 ± 0.3 (29%)	—	—	5.3 ± 0.1 (18%)	4.2 ± 0.2 (−8%)	—	♂	63
Runner #20	2.2 ± 0	4.3 ± 0 (95%)	—	—	3.1 ± 0.2 (39%)	2.5 ± 0.1 (11%)	—	♂	63
Runner #21	2.2 ± 0.1	3.9 ± 0.1 (75%)	—	—	2.7 ± 0 (23%)	2.4 ± 0.1 (7%)	—	♂	63
Runner #22	2.8 ± 0.1	4.1 ± 0.2 (47%)	—	—	n.a.	n.a.	—	♂	63
Runner #23	1.9 ± 0.1	3.8 + −/ 0.1 (102%)	—	—	n.a.	n.a.	—	♂	63
Runner #24	1.9 ± 0	3 ± 0.1 (58%)	—	—	2.3 ± 0.2 (18%)	1.9 ± 0.1 (3%)	—	♂	63
Runner #25	2.3 ± 0.1	3.9 ± 0 (70%)	—	—	3.2 ± 0.1 (37%)	2.5 ± 0 (9%)	—	♂	63
Runner #26	2.3 ± 0.1	5.2 ± 0.2 (124%)	—	—	3.3 ± 0.1 (41%)	2.6 ± 0.1 (13%)	—	♂	63

Note: n.a. denotes too little plasma available for analysis.
[a]*GroupI* refers to Tarahumara men (n = 9) running 78 km.
[b]*GroupII* refers to Tarahumara women (n = 3) running 52 km.
[c]*GruopIII* refers to Tarahumara men (n = 10) running 63 km.

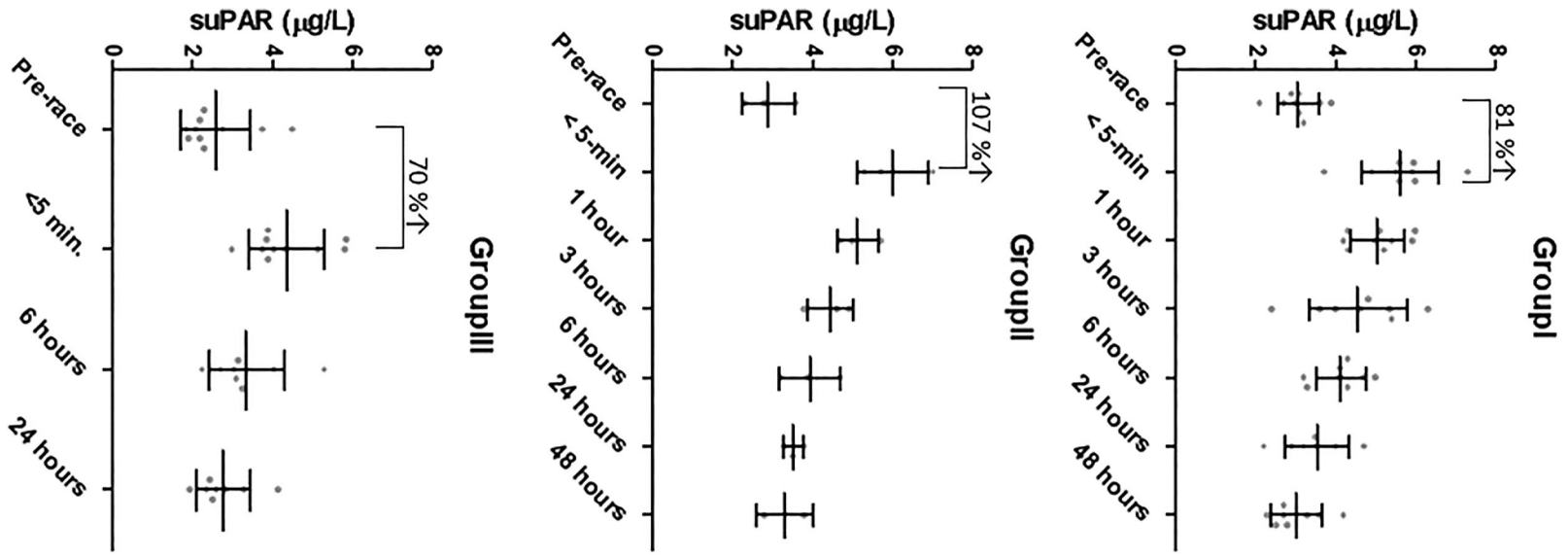

FIGURE 1 Graphical overview of mean (SD) plasma suPAR concentrations (µg/L) with percentage increase in mean suPAR concentrations from pre-race to <5 minutes. Post-race for *GroupI*, *II*, and *III*, respectively, of Tarahumara runners (n = 22)

TABLE 4 Alterations of plasma markers following 52 km of running at moderate altitude in female Tarahumara (n = 3)

	Post-race values (geometric mean (SD) with statistical differences from pre-race value)[a]								
Plasma biomarkers	**Pre-race**	**<5 minutes**	***P* value**	**6 hours**	***P* value**	**24 hours**	***P* value**	**48 hours**	***P* value**
hs-cTnT (ng/L)	22.7 (2.1;247.3)	207.1 (18.6;2313)	<0.001	84.3 (11.0;645.0)	<0.001	28.5 (3.5;233.5)	0.525	22.4 (2.6;190.6)	0.976
MR-proANP (pmol/L)	33.1 (18.4;59.8)	64.1 (39.3;104.8)	<0.001	26.5 (8.2;85.6)	<0.003	23.6 (14.7;37.9)	<0.004	33.8 (13.0;87.7)	0.179
Copeptin-us (pmol/L)	5.7 (2.3;14.2)	14.6 (3.2;67.6)	<0.001	4.3 (0.3; 64.3)	<0.038	5.7 (0.5;59.2)	0.138	5.3 (2.8;10.0)	0.578
Creatinine (µmol/L)	45.4 (31.3;65.7)	56.2 (38.1;83.0)	<0.010	62.9 (26.7;148.0)	<0.001	58.6 (23.4;147.1)	<0.032	48.6 (30.3;77.9)	0.945
hs-CRP (mg/L)	7.5 (2.7;20.6)	0.9 (0.2;4.8)	<0.001	9.1 (4.5;18.2)	0.212	22.3 (7.0;71.2)	<0.001	7.9 (2.5;24.9)	0.912
Iron (µmol/L)	13.8 (6.3;30.3)	19.4 (12.8;29.4)	0.777	9.9 (6.0;16.2)	0.053	19.0 (4.8;74.9)	0.256	9.3 (1.6;54.4)	0.070
Haptoglobin (g/L)	1.2 (0.6;2.3)	0.3 (0.03;2.7)	<0.001	0.4 (0.1;1.4)	<0.001	1.0 (0.4;2.7)	<0.035	1.3 (0.6;2.8)	0.868
LDH (U/L)	317 (51;1981)	286 (94;868)	0.280	381 (280;517)	0.477	277 (124;620)	0.817	148 (93;234)	0.195
Creatine kinase (U/L)	3486 (395;30 773)	8333 (1224;56 749)	<0.001	8482 (1843;39 036)	<0.001	8323 (1014;682 181)	<0.001	4065 (408;40 448)	0.369
Creatine kinase-MB (µg/L)	50.7 (2.7;951)	181.2 (12.4;2655)	<0.001	168.2 (24.6;1152)	<0.001	129.6 (9.4;1784)	<0.001	55.0 (2.5;1212)	0.507

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; MR-proANP, mid-regional proatrial natriuretic peptide; Copeptin-us, copeptin ultra-sensitive; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; creatine kinase-MB, creatine kinase isoform myocardial band.

[a]Analyses age-adjusted.

et al., 2015; McCullough et al., 2011; Trivax et al., 2010). Consequently, the present runner cohorts are typical in their inflammation response, and in the effect on the renal capacity, and could therefore be used for evaluation of suPAR as an exercise-induced inflammation biomarker.

In conclusion, the present study has demonstrated that ultra-distance running induce an increase in plasma suPAR concentration lasting up to at least 6 hours post-race in Tarahumara men and women. The finding suggests that the utility of suPAR as an inflammation biomarker could supplement the existing protein markers CRP and interleukin-6, but may not fully substitute CRP.

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AUTHOR CONTRIBUTIONS

Peter Skottrup: Conceptualization; formal analysis; methodology; writing-original draft. **Thomas Kallemose:** Formal analysis; writing-review and editing. **Diana Espino:** Investigation; writing-review and editing. **Rocio Infante-Ramirez:** Investigation; methodology; writing-review and editing. **Soren Brage:** Data curation; methodology; writing-review and editing. **Dijana Terzic:** Formal analysis; methodology; writing-review and editing. **Jens Goetze:** Formal analysis; methodology; writing-review and editing. **Jesper Kjaergaard:** Conceptualization; funding acquisition; methodology; writing-review and editing. **Dirk Christensen:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; writing-original draft.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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