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Muscle damage is linked to cytokine changes following a 160-km race

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Abstract

Muscle damage and perceived soreness following the 160-km Western States Endurance Run were related to changes in plasma cytokines and use of nonsteroidal anti-inflammatory drugs (NSAIDS). Subjects included 60 ultramarathoners (mean ± SE, age 45.3 ± 1.1 years) who finished the race in under 30 h (26.3 ± 0.4 h). Blood samples were collected the morning prior to and immediately following the race, and subjects recorded muscle soreness during the week following the race using a 10-point Likert scale (DOMS). Seven plasma cytokines were measured including IL-6, IL-10, IL-8, IL-1ra, granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 1β (MIP-1β). Cytokine changes were compared between NSAID users and nonusers, and correlated with creatine phosphokinase (CPK) and DOMS. Significant increases were measured for all seven cytokines, with the greatest fold increases seen for IL-6 (125×), IL-10 (24×), and G-CSF (12×). CPK was correlated with changes in IL-6, G-CSF, IL-10, IL-1ra, and MCP-1 ($r = .49$–$.68$), ($P < .001$), but not IL-8 or MIP-1β. DOMS averaged 7.1 ± 0.3 the day after the race, and 5.0 ± 0.3, 2.5 ± 0.2, and 1.6 ± 0.1 3 days, 5 days, and 7 days post-race, respectively, and each was correlated with CPK ($r = .40$–$.63$, $P < .001$) and changes in IL-6, G-CSF, IL-10, and MCP-1 ($r = .28$–$.77$, $P < .05$). A comparison of NSAID users (72% of athletes) and nonusers showed no differences in CPK or DOMS, but did reveal greater increases in five of seven cytokines in the NSAID users ($P < .05$). In conclusion, muscle damage in athletes competing in a 160-km race was significantly correlated with post-race DOMS and increases in five of seven cytokines. NSAID users did not experience a reduction in muscle damage or DOMS, but did have higher post-race plasma levels in five of seven cytokines.

Keywords: IL-6; IL-10; IL-1ra; IL-8; Muscle soreness; NSAIDs

1. Introduction

Cytokines are potent intercellular signaling molecules that regulate inflammation and immune responses. We and others have shown that sustained, intense exertion (e.g., marathon or ultramarathon races) causes large increases in specific types of cytokines (e.g., IL-6, IL-10, IL-1ra, IL-8, granulocyte colony-stimulating factor or G-CSF, monocyte chemotactic protein 1 or MCP-1, and macrophage inflammatory protein 1β or MIP-1β) (Nieman et al., 2001, 2002, 2003; Ostrowski et al., 2000; Suzuki et al., 2000, 2002).

Runners competing in marathons and ultramarathons experience large increases in these cytokines, but there is substantial variation between runners (Nieman et al., 2001, 2003). Potential triggers of cytokine release during exercise include leakage of endotoxins (lipopolysaccharide or LPS) from the intestines during exercise, elevation in catecholamines and cortisol, high core body temperature, glycogen deficiency, and other metabolic demands, oxidative stress, and muscle damage (Bruunsgaard et al., 1997; Camus et al., 1998; Jeukendrup et al., 2000; Nieman et al., 2001; Steensberg, 2003; Steinacker et al., 2004; Suzuki et al., 2002).

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Contraction-induced muscle injury produces an inflammatory response, with evidence that first neutrophils and then macrophages invade muscle tissues in large numbers (Tidball, 2005). The inflammatory cells promote both injury and repair through the combined actions of free radicals, growth factors, and chemokines.

The link between exercise-induced muscle damage and elevations in plasma cytokines has been difficult to establish. Part of the problem has been the mismatch in timing of peak plasma levels for markers of muscle damage (most common, creatine phosphokinase or CPK that peaks 1–3 days following exercise) and cytokines that can reach a zenith within 2–3 h of high intensity, endurance exercise, and then remain at this level until exercise is completed (Nieman et al., 2003). Another confounding factor is that during short term eccentric exercise, increases in plasma CPK are delayed and large, while changes in cytokines are transient, and of small magnitude. These factors may explain why most researchers have failed to find a positive relationship between plasma CPK and cytokines following exercise. Hirose et al. (2004), for example, failed to demonstrate a relationship between muscle damage using CPK and plasma cytokines following elbow flexor eccentric exercise (6 sets of 5 repetitions). Brenner et al. (1999) reported no relationship between plasma CPK and cytokines after 5 min of high intensity cycle ergometer exercise, a standard circuit-training routine, or 2 h of moderate intensity cycle ergometer exercise.

Ultramarathon race events allow the relationship between muscle damage, perceptions of muscle soreness, and cytokines to be tested in an extreme exercise environment of long lasting duration. We chose the arduous 160-km Western States Endurance Run race event to test these relationships, reasoning that elevations in plasma cytokines and significant muscle damage would occur within the first few hours of this high altitude race in the Sierra Nevada Mountains, and then be maintained for 20–30 h when correlations with CPK could be tested at the end of the race. We hypothesized that plasma CPK, delayed onset of muscle soreness (DOMS), and each of the seven cytokines measured in this study would be positively correlated in ultramarathon athletes completing this 160-km race.

2. Methods

2.1. Subjects and race description

Seventy-one experienced ultramarathoners were recruited and provided pre-race blood samples. Of these, 60 completed the race and provided post-race blood samples, and included both males ($N = 45$) and females ($N = 15$) without age restriction. Informed consent was obtained from each subject, and the experimental procedures were in accordance with the policy statements of the Institutional Review Board of Appalachian State University. To enter the study, subjects must have completed a 160-km race, and qualified for the 2004 160-km Western States Endurance Run. To qualify for the Western States Endurance Run, runners must have completed a 160-km race in under 24 h, or a 100-km race in 12-13 h, depending on age.

The 160-km Western States Endurance Run is a point-to-point trail run in the Sierra Nevada Mountains of northern California, and is regarded as one of the most arduous organized running events in the United States. The race starts at Squaw Valley, California (1890 m altitude), and finishes at Auburn, California (366 m). The trail race course ascends 777 m to Emigrant Pass (2668 m, the highest point) within the first 7-km and then passes through remote and rugged territory to Auburn. The total altitude gain and loss during the race is 5500 and 6700 m, respectively. The race starts at 5:00AM, and runners must reach the finish line within 30 h to be eligible for an award. Up to half of the trail may be traveled by some runners at night.

2.2. Research design

Subjects provided blood during registration, held the morning before the race. Pre-race body mass and percent body fat (via 3-site skinfolds) were measured, and subjects filled in a questionnaire on basic demographics, training history, and use of supplements during training. On race day, body mass was measured at the 90-km aid station (Michigan Bluff, 1220 m) and within 5–10 min post-race at Auburn. Subjects completed a post-race questionnaire indicating self-selected use of medications and supplements during the race. Athletes were categorized as NSAID users if they reported use during the race, and nonusers if they reported complete avoidance of NSAIDs during the race. Subjects consumed food and beverages ad libitum during the race.

2.3. Blood cell counts and creatine phosphokinase

Blood samples were drawn from an antecubital vein with subjects in the seated position. Complete blood counts and differentials were measured using a Coulter STKS instrument (Coulter Electronics, Hialeah, FL). Plasma creatine phosphokinase (CPK) was measured using an LX-20 clinical analyzer (Beckman, Brea, CA, USA). Plasma volume changes were estimated using the method of Dill and Costill (1974).

2.4. Cytokine measurements

Total plasma concentrations of interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein 1

(MCP-1), and macrophage inflammatory protein 1β (MIP-1β) were determined using quantitative sandwich ELISA kits provided by R&D Systems, (Minneapolis, MN). All samples and provided standards were analyzed in duplicate. A high sensitivity kit was used to analyze IL-6 in the pre-race plasma samples.

2.5. Delayed onset of muscle soreness (DOMS)

Subjects recorded muscle soreness following the race, and during the week following the race using a 10-point Likert scale (Smith et al., 1993). Runners were asked to supply a number that best described any general feeling of painful, sore, aching leg muscles using this scale: 1 (no soreness), 2.5 (dull, vague ache), 4 (slight soreness), 5.5 (more than slight soreness), 7 (sore), 8.5 (very sore), and 10 (unbearably sore).

2.6. Statistical analysis

Data are expressed as means ± SE. Changes from pre-race to post-race values were assessed for the entire group using paired *t* tests. Comparisons between genders and NSAID users and nonusers were conducted using Student's *t* tests. Pearson product–moment correlations were used to test the relationship between changes in measured outcomes, with an emphasis on CPK, DOMS, and cytokines.

3. Results

Sixty of 71 subjects completed the 160-km race event (race time, 27.0 ± 0.4 h). Subject characteristics in Table 1 indicate that this group of ultramarathoners was highly experienced, having trained for long distance races for an average of 13.9 years and competed in 34 ultramarathon events. Male and female runners did not differ significantly in race time (26.1 ± 0.5 versus 26.9 ± 0.6 h, respectively) or any of the other variables measured in this study except for body mass (72.7 ± 1.2 versus 55.2 ± 1.1 kg), height (1.78 ± 0.01 versus 1.64 ± 0.01 m), and percent body fat (14.3 ± 0.7 versus 19.4 ± 1.0%, respectively). Thus, male and female runners were combined for this data analysis.

Plasma volume did not change appreciably (−1.5 ± 0.3%), and body mass was maintained near pre-race levels (Table 1). Subjects experienced a strong neutrophilia (305% increase) and monocytosis (213%) (Table 2). The blood eosinophil count decreased 83% from pre-race levels.

Significant increases were measured for all seven cytokines, with the greatest fold increase seen for IL-6 (125×), and then IL-10 (24×), G-CSF (12×), IL-1ra (7×), IL-8 (5×), MCP-1 (3×), and MIP-1β (1.2×) (Table 3). CPK increased from 159 ± 21 to 17,833 ± 2883 U/L (Fig. 1), and change in CPK was significantly correlated with changes in the blood neutrophil count ($r = .33$, $P = .010$), plasma IL-6 ($r = .68$, $P < .001$), G-CSF ($r = .67$, $P < .001$), IL-10 ($r = .53$, $P < .001$), IL-1ra ($r = .50$, $P < .001$), and MCP-1 ($r = .49$, $P < .001$), but not the blood monocyte count, plasma IL-8 or MIP-1β. DOMS averaged 7.1 ± 0.3 the day after the race, and 5.0 ± 0.3, 2.5 ± 0.2, and 1.6 ± 0.1 3 days, 5 days, and 7 days post-race, respectively (Fig. 2), and each was significantly correlated with CPK ($r = .40$–$.63$, $P < .001$), and changes in IL-6, G-CSF, IL-10, and MCP-1 ($r = .28$–$.77$, $P < .05$). Race time was negatively correlated with pre- to post-race changes in MIP-1β ($r = -.51$, $P < .001$), IL-10 ($r = -.46$, $P = .001$), IL-6 ($r = -.31$, $P = .021$), IL1-ra ($r = -.030$, $P = .027$), and IL-8 ($r = -.41$, $P = .002$), but not MCP-1, G-CSF, or CPK (−0.26, $P < .054$).

Use of NSAIDS during the race was reported by 72% of the athletes. In the NSAID group, ibuprofen was used by all athletes except aspirin by two runners, naproxen

Table 1
Subject characteristics ($N = 60$, with 45 males and 15 females) (mean ± SE; range)

Variable	Mean ± SE	Range
Age (year)	45.3 ± 1.1	28–67
Height (m)	1.75 ± 0.01	1.55–1.96
Pre-race body mass (kg)	68.5 ± 1.4	44.6–96.4
90-km (kg)	69.7 ± 1.3	46.7–97.5
160-km (kg)	69.1 ± 1.3	46.7–97.5
Body fat (%)	15.6 ± 0.6	5.0–26.0
Running history (year)	13.9 ± 1.3	1–42
Ultramarathons raced (number)	34 ± 69	1–378
Running distance (km/week)	80.5 ± 3.4	22.4–144
Race time, 160-km (h)	26.3 ± 0.4	19.1–29.9

Table 2
Pre- and post-race leukocyte subset blood counts ($N = 60$) (mean ± SE)

Variable ($10^9/L^{-1}$)	Pre-race	160-km
Total leukocytes	5.66 ± 0.20	15.6 ± 0.5**
Neutrophils	3.16 ± 0.18	12.8 ± 0.5**
Lymphocytes	1.53 ± 0.10	1.62 ± 0.08
Monocytes	0.38 ± 0.02	1.19 ± 0.05**
Eosinophils	0.12 ± 0.01	0.02 ± 0.01**
Basophils	0.03 ± 0.003	0.04 ± 0.004

** $P < .001$, change from pre-race.

Table 3
Plasma cytokines ($N = 60$) (mean ± SE)

Variable (pg/ml)	Pre-race	160-km
IL-6	0.85 ± 0.11	107 ± 18.1**
IL-10	1.54 ± 0.13	38.5 ± 4.3**
G-CSF	17.8 ± 1.3	222 ± 47.6**
IL-1ra	363 ± 19	2915 ± 363**
IL-8	6.06 ± 0.42	38.2 ± 4.4**
MCP-1	316 ± 14	1221 ± 128**
MIP-1β	58.3 ± 5.1	125 ± 19.1**

** $P < .001$, change from pre-race.

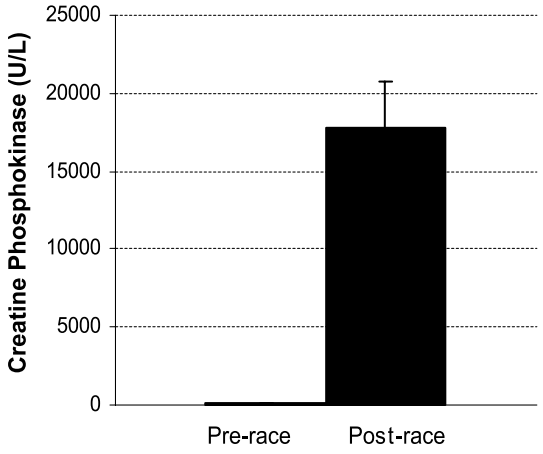

Fig. 1. Creatine phosphokinase increased significantly ($P < .001$) from 159 ± 21 to $17{,}833 \pm 2883$ U/L in 60 athletes competing in the 160-km Western United States Endurance Run.

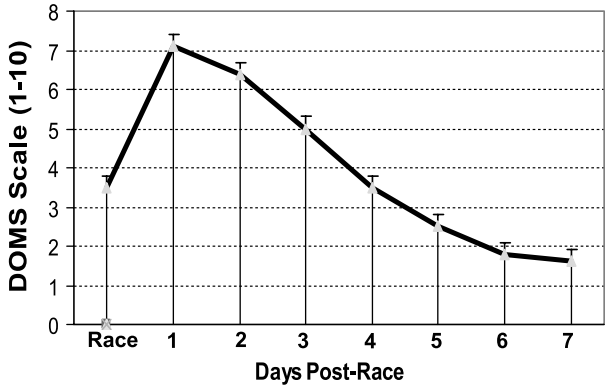

Fig. 2. DOMS averaged 7.1 ± 0.3 the day after the 160-km race ("sore"), and 5.0 ± 0.3 (close to "more than slight soreness,") 2.5 ± 0.2 ("dull, vague ache"), and 1.6 ± 0.1 (close to "no soreness"), 3 days, 5 days, and 7 days post-race, respectively. The *Y*-axis represents the DOMS scale (Likert scale of 1–10). See the text for a description of this scale.

by one, and cox-2 inhibitors in three runners. A comparison of NSAID users ($N = 43$) and nonusers ($N = 17$) showed no differences in race time, pre-race plasma cytokine levels, CPK or DOMS, but did reveal significantly greater increases in IL-6, IL-8, G-CSF, MCP-1, and MIP-1β in the NSAID users ($P < .05$) (Table 4). Blood neutrophil counts tended to increase more in the NSAID users compared to nonusers (Table 4). Self-selected use of antioxidant supplements either in the months before (70%) or during the race (18%) had no effect on CPK, DOMS, or changes in cytokines.

4. Discussion

In agreement with our hypothesis, perceptions of muscle soreness, muscle damage as assessed by CPK, and plasma levels of several cytokines were positively correlated in ultramarathon athletes following a 160-km race event. Unexpectedly, pre-to-post-race changes in most of the cytokines we measured were two to three times greater in NSAID users compared to nonusers.

Plasma CPK concentrations rose to high levels post-race and correlated with perceptions of muscle soreness throughout the week following the race. This is an indication that within the context of this study, plasma CPK concentration was a marker of muscle damage, but may not have necessarily reflected the amount of structural damage (Kuipers, 1994). Change in CPK was significantly correlated with changes in five of seven cytokines with the strongest relationship seen with IL-6 and G-CSF. Steensberg (2003) and Suzuki et al. (2002) have proposed that during exercise, IL-6 inhibits the release of the pro-inflammatory cytokines IL-1β and TNF-α, stimulates other anti-inflammatory cytokines such as IL-1ra and IL-10, mobilizes and augments neutrophil function, and helps regulate the release of glucose and fatty acids for use by the working muscle. G-CSF may support the anti-inflammatory actions of IL-6 by inducing its release and inhibiting the release of IL-1β and TNF-α (Suzuki et al., 2002).

No significant correlation was measured between changes in CPK and IL-8 or MIP-1β. A moderate relationship was found between changes in CPK and blood neutrophil counts. IL-8 is a potent neutrophil

Table 4
Comparison of change in blood neutrophil and monocyte counts, plasma cytokines, CPK, and DOMS between NSAID users ($N = 43$) and nonusers ($N = 17$) in the 160-km race

Variable (post-race minus pre-race)	NSAID users	NSAID nonusers	*P* value
Neutrophil count ($10^9/L^{-1}$)	10.19 ± 0.51	8.20 ± 0.93	.051
Monocyte count ($10^9/L^{-1}$)	0.80 ± 0.06	0.83 ± 0.06	.786
IL-6 (pg/ml)	129 ± 24	48.4 ± 8.4	.003
IL-10 (pg/ml)	40.8 ± 5.3	27.0 ± 6.9	.154
G-CSF (pg/ml)	251 ± 65	87.1 ± 19.8	.019
IL-1ra (pg/ml)	2805 ± 453	1912 ± 573	.273
IL-8 (pg/ml)	37.2 ± 5.8	19.5 ± 3.3	.010
MCP-1 (pg/ml)	1029 ± 171	593 ± 72	.022
MIP-1β (pg/ml)	82.3 ± 26.2	25.5 ± 7.8	.044
CPK (U/L)	$18{,}649 \pm 3787$	$15{,}211 \pm 3523$	.509
DOMS (1-day post-race)	7.4 ± 0.3	6.5 ± 0.6	.177

chemotactic and activation chemokine referred to as neutrophil activating peptide. IL-8 may aid in transfer of neutrophils to metabolically active muscle tissue after exercise to aid in repair (Suzuki et al., 2002). MIP-1β is a macrophage inflammatory protein that chemoattracts monocytes and T-lymphocytes, and may be involved in a variety of inflammatory diseases (Suzuki et al., 2002). Thus, athletes exhibiting the greatest muscle damage and post-race DOMS also experienced the strongest anti-inflammatory actions of IL-6 and G-CSF. At the same time, plasma IL-8 and MIP-1β needed to chemoattract neutrophils and monocytes, differed little from other athletes with lower muscle damage. This cytokine balance following a 160-km race event may enhance the process of muscle cell repair in athletes with the greatest damage. As reviewed by Tidball (2005), neutrophils promote muscle damage soon after muscle injury and no evidence exists that these immune cells play a beneficial role in muscle repair. Macrophages invade the injured muscle tissue after neutrophils, and appear to both promote muscle damage and repair.

We are unaware of other published studies attempting to link muscle damage with plasma cytokines following ultramarathons. Ostrowski et al. (2000) reported no association between peak concentrations of IL-6 immediately after a 42.2-km marathon and creatine kinase one day after the race.

Use of NSAIDS (primarily ibuprofen) during the 160-km race was reported by 72% of the athletes in our study. NSAID use did not attenuate plasma CPK levels or post-race DOMS, but was associated with two to three times greater increases in IL-6, IL-8, G-CSF, MCP-1, and MIP-1β. A majority of other investigators have also reported no beneficial effect of NSAIDS in alleviating muscle soreness and damage after contraction-induced muscle injury (Donnelly et al., 1990; Peterson et al., 2003; Trappe et al., 2002).

We are unaware of other published studies indicating elevated cytokines in NSAID users compared to nonusers following ultramarathons. Scheett et al. (2001) showed that ibuprofen compared to placebo use had no influence on cytokine responses following eccentric exercise-induced muscle damage. Increased gastrointestinal permeability and endotoxemia have been reported in athletes following prolonged endurance events (Bosenberg et al., 1988; Jeukendrup et al., 2000). Gastrointestinal permeability is increased in marathoners using NSAIDs compared to nonusers (Smetanka et al., 1999). Camus et al. (1998) demonstrated a relationship between exercise-induced endotoxemia and TNF-α. Thus NSAID use during ultramarathons may augment cytokine increases by inducing endotoxemia, but these relationships have not yet been verified using appropriate research designs.

In summary, we demonstrated associations between plasma CPK, perceptions of muscle soreness, and plasma cytokines in a group of 60 athletes completing the 2004 160-km Western States Endurance Run. Changes in plasma cytokines were significantly greater in athletes using NSAIDS despite no differences in CPK and DOMS compared to nonusers. Further, research is warranted to determine whether NSAID use increases cytokine responses following ultramarathons through an endotoxemia pathway.

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References

Bosenberg, A.T., Brock-Utne, J.G., Gaffin, S.L., Wells, M.T., Blake, G.T., 1988. Strenuous exercise causes systemic endotoxemia. Journal of Applied Physiology 65, 106–108.

Brenner, I.K., Natale, V.M., Vasiliou, P., Moldoveanu, A.I., Shek, P.N., Shephard, R.J., 1999. Impact of three different types of exercise on components of the inflammatory response. European Journal of Applied Physiology and Occupational Physiology 80, 360–452.

Bruunsgaard, H., Galbo, H., Halkjaer-Kristensen, J., Johansen, T.L., MacLean, D.A., Pedersen, B.K., 1997. Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage. Journal of Physiology 499 (Pt 3), 833–841.

Camus, G., Nys, M., Poortmans, J.R., Venneman, I., Monfils, T., Deby-Dupont, G., Juchmes-Ferir, A., Deby, C., Lamy, M., Duchateau, J., 1998. Endotoxemia, production of tumor necrosis factor alpha and polymorphonuclear neutrophil activation following strenuous exercise in humans. European Journal of Applied Physiology and Occupational Physiology 79, 62–68.

Dill, D.B., Costill, D.L., 1974. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. Journal of Applied Physiology 37, 247–248.

Donnelly, A.E., Maughan, R.J., Whiting, P.H., 1990. Effects of ibuprofen on exercise-induced muscle soreness and indices of muscle damage. British Journal of Sports Medicine 24, 191–195.

Hirose, L., Nosaka, K., Newton, M., Laveder, A., Kano, M., Peake, J., Suzuki, K., 2004. Changes in inflammatory mediators following eccentric exercise of the elbow flexors. Exercise Immunology Reviews 10, 75–90.

Jeukendrup, A.E., Vet-Joop, K., Sturk, A., Stegen, J.H.J.C., Senden, J., Saris, W.H.M., Wagenmakers, A.J.M., 2000. Relationship between gastro-intestinal complaints and endotoxemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Clinical Science 98, 47–55.

Kuipers, H., 1994. Exercise-induced muscle damage. International Journal of Sports Medicine 15, 132–135.

Nieman, D.C., Dumke, C.L., Henson, D.A., McAnulty, S.R., McAnulty, L.S., Lind, R.H., Morrow, J.D., 2003. Immune and oxidative changes during and following the Western States Endurance Run. International Journal of Sports Medicine 24, 541–547.

Nieman, D.C., Henson, D.A., McAnulty, S.R., McAnulty, L., Swick, N.S., Utter, A.C., Vinci, D.M., Opiela, S.J., Morrow, J.D., 2002. Influence of vitamin C supplementation on oxidative and immune changes following an ultramarathon. Journal of Applied Physiology 92, 1970–1977.

Nieman, D.C., Henson, D.A., Smith, L.L., Utter, A.C., Vinci, D.M., Davis, J.M., Kaminsky, D.E., Shute, M., 2001. Cytokine changes after a marathon race. Journal of Applied Physiology 91, 109–114.

Ostrowski, K., Schjerling, P., Pedersen, B.K., 2000. Physical activity and plasma interleukin-6 in humans—effect of intensity of exercise. European Journal of Applied Physiology 83, 512–515.

Peterson, J.M., Trappe, T.A., Mylona, E., White, F., Lambert, C.P., Evans, W.J., Pizza, F.X., 2003. Ibuprofen and acetaminophen: effect on muscle inflammation after eccentric exercise. Medicine and Science in Sports and Exercise 35, 892–896.

Scheett, T.P., Stoppani, J., VanHeest, J.L., Collins, V.A., Hatch, H.L., Sutherland, J.W., D'Alfonso, M.R., Armstrong, L.E., Hoffman, J.R., Kraemer, W.J., Maresh, C.M., 2001. Administration of ibuprofen or hydrocodone bitartrate with ibuprofen on the pro- and anti-inflammatory cytokines following eccentric exercise-induced muscle damage. Medicine and Science in Sports and Exercise 33 (suppl. 1), S303.

Smetanka, R.D., Lambert, G.P., Murray, R., Eddy, D., Horn, M., Gisolfi, C.V., 1999. Intestinal permeability in runners in the 1996 Chicago marathon. International Journal of Sports Nutrition 9, 426–433.

Smith, L.L., Brunetz, M.H., Chenier, T.C., McCammon, M.R., Houmard, J.A., Franklin, M.E., Israel, R.G., 1993. The effects of static and ballistic stretching on delayed onset muscle soreness and creatine kinase. Research Quarterly in Exercise and Sports 64, 103–107.

Steensberg, A., 2003. The role of IL-6 in exercise-induced immune changes and metabolism. Exercise Immunology Review 9, 40–47.

Steinacker, J.M., Lormes, W., Reissnecker, S., Liu, Y., 2004. New aspects of the hormone and cytokine response to training. European Journal of Applied Physiology 91, 382–391.

Suzuki, K., Nakaji, S., Yamada, M., Totsuka, M., Sato, K., Sugawara, K., 2002. Systemic inflammatory response to exhaustive exercise. Exercise Immunology Reviews 8, 6–48.

Suzuki, K., Yamada, M., Kurakake, S., Okamura, N., Yamaya, K., Liu, Q., Kudoh, S., Kowatari, K., Nakaji, S., Sugawara, K., 2000. Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. European Journal of Applied Physiology 81, 281–287.

Tidball, J.G., 2005. Inflammatory processes in muscle injury and repair. American Journal of Physiology Regulatory, Integrative and Comparative Physiology 288, R345–R353.

Trappe, T.A., White, F., Lambert, C.P., Cesar, D., Hellerstein, M., Evans, W.J., 2002. Effect of ibuprofen and acetaminophen on post-exercise muscle protein synthesis. American Journal of Endocrinology and Metabolism 282, E551–E556.