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CURRENT OPINION

Decoding Ultramarathon: Muscle Damage as the Main Impediment to Performance

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Abstract

The biological determinants of performance have been well described for running races up to and including the marathon (42.2 km). Ultramarathon is more complex. Events range from 50 to 5000 km in single or multiple stages, are contested in various environments and terrains, and force athletes to contend with diverse performance-limiting issues such as fueling, hydrating, gastrointestinal distress, muscle damage, and sleep deprivation. Ultramarathons are not simply "long marathons." Nevertheless, scientific developments over the past decade have inched us toward a more complete picture of the psychophysiological factors underpinning performance. In this Current Opinion, we argue that muscle damage and associated fatigue is the main impediment to performance in long ultramarathons; more performance-limiting than aerobic capacity, running economy, or gastrointestinal distress. To assess an athlete's tolerance to ultramarathon-specific muscle damage and fatigue, we propose a lab-based protocol comprising downhill running with pre- to post-exercise measures of muscle contractile function following electrical or magnetic stimulation of the quadriceps muscles or their central nerves, muscle damage biomarkers (e.g., creatine kinase, lactate dehydrogenase, and myoglobin), and muscle morphology via imaging techniques. We close by offering training and racing advice on mitigating the deleterious effects of muscle damage. The twofold aims of this paper are (i) to enable athletes and their teams to better prepare for races and (ii) to help medical personnel identify the physiological milieu most likely to afflict the ultrarunner.

Key Points

In this Current Opinion, we present an evidence-based argument that muscle damage and its associated fatigue is the main impediment to performance in long ultramarathons; more performance-limiting than aerobic capacity, running economy, or gastrointestinal distress.

We propose a lab-based protocol for assessing an athlete's tolerance to ultramarathon-specific muscle damage/fatigue and offer guidance on how runners can mitigate its effects.

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1 Introduction

The biological determinants of performance have been well described for running races up to and including the marathon (42.2 km) [1, 2]. For the most part, endurance performance can be predicted using lab-based metrics such as maximal oxygen uptake ($\dot{V}O_2$max), running economy, and lactate threshold (sometimes called the anaerobic threshold or gas exchange threshold). Of these, $\dot{V}O_2$max and velocity at the "anaerobic" threshold are most predictive, explaining 60–70% and 88–92% of marathon variance, respectively [3, 4].

Ultramarathon, however, is a more complex and complicated sport. Distances range from 50 to 5000 km in single or multiple stages, with variable terrain (i.e., road, trail), environmental extremes (e.g., heat, cold, altitude), and positive or negative elevation (see Fig. 1 for examples). The factors determining performance are equally diverse. Ultrarunners must pace themselves over many hours, days, or weeks, meet changing nutrition and hydration needs (compounded by taste fatigue whereby food becomes less

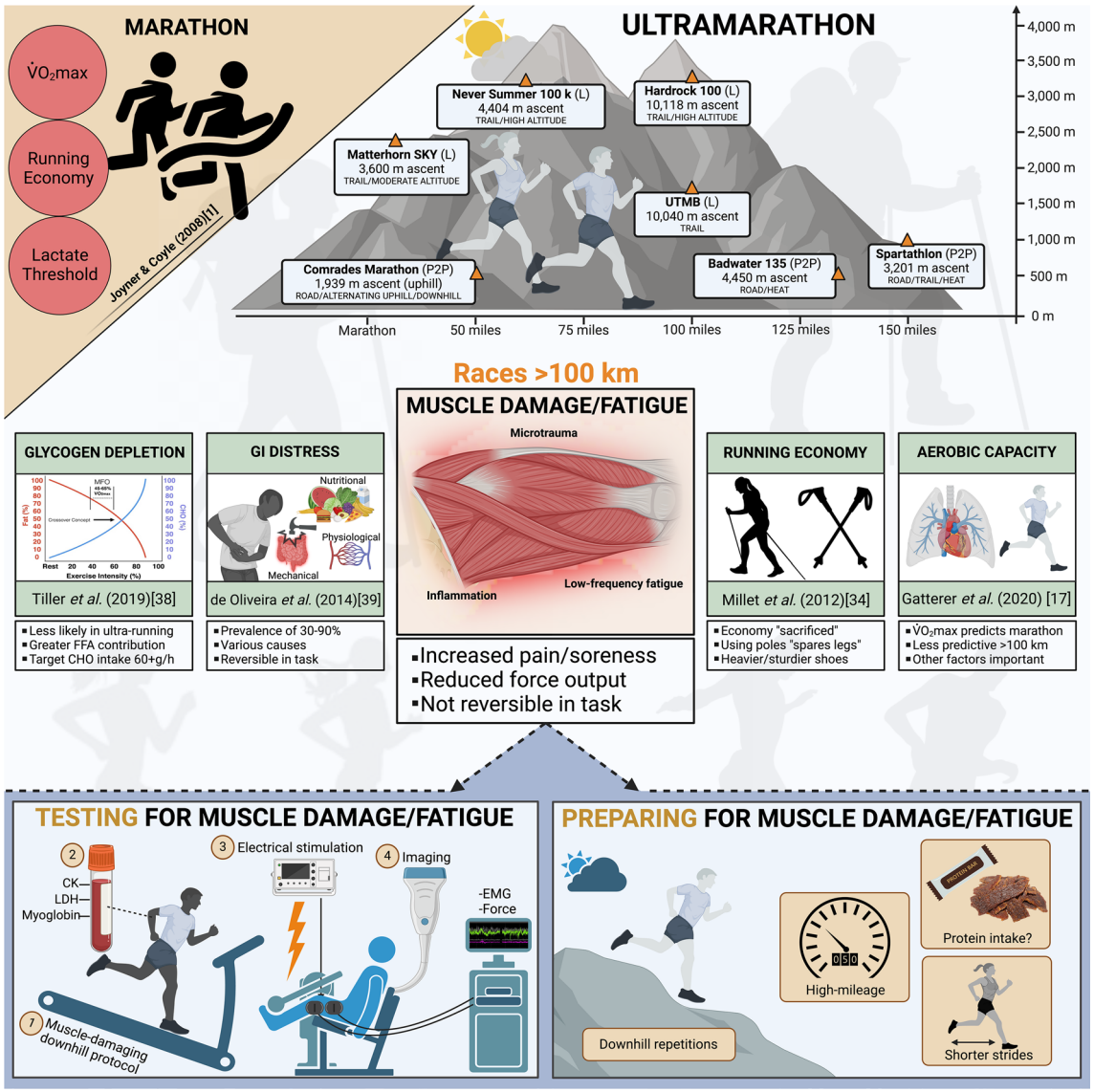

Fig. 1 A graphical overview of our discussion. The marathon is a standard distance (26.2 miles/42.2 km) and, from a physiological perspective, depends on $\dot{V}O_2$max, running economy, and lactate threshold. Ultramarathons are considerably more diverse, with each race exhibiting unique characteristics. For example, the Hardrock 100 is a mountainous loop (L) contested at an average of 3352 m, with a total ascent of > 10,000 m. By contrast, the Comrades Marathon is a 50-mile point-to-point (P2P) road race alternating uphill or downhill each year, with 1939 m of ascent when run uphill. *$\dot{V}O_2$max* maximal oxygen uptake, *CHO* carbohydrate, *FFA* free fatty acids, *CK* creatine kinase, *LDH* lactate dehydrogenase, *EMG* electromyogram, *UTMB* Ultra-Trail du Mont-Blanc, *MFO* maximal fat oxidation, *GI* gastrointestinal

enjoyable and palatable with prolonged consumption), and contend with gastrointestinal distress, muscle damage, injury, sleep deprivation, and even hallucinations, all while trying to mitigate considerable health risks [5, 6]. Ultramarathons are not simply "long marathons."

There was a relative paucity of ultramarathon research before 2010. Since then, nearly 800 studies have been deposited on PubMed, with more papers published in the past decade than in the preceding five. Despite variable quality, each new study adds a piece to a larger picture, inching us toward a more comprehensive understanding of the psychophysiological factors underpinning performance.

In this Current Opinion, we argue that a single factor most often limits ultramarathon performance for the most runners. Specifically, we suggest that the mechanical, metabolic, and oxidative stress of racing causes locomotor muscle damage and neuromuscular fatigue [7] that is more performance-limiting than any other issue, including aerobic capacity, running economy, or gastrointestinal distress. We then propose a lab-based protocol for assessing an athlete's tolerance

to ultramarathon-specific muscle damage and fatigue, and close by offering training and racing advice on how athletes can mitigate its deleterious effects. The twofold aims of this article are (i) to enable athletes and their teams to better prepare for races, thereby improving performance and longevity in the sport, and (ii) to assist medical personnel in identifying the physiological milieu most likely to afflict the runner, thus enhancing athlete safety at competitions.

2 Discussion

2.1 Aerobic Metabolism is Strongly Correlated with Performance in "Standard" Endurance Events Such as the Marathon, but Its Predictive Power Diminishes as a Function of Race Distance and Time

The longer the race, the slower the pace. In other words, individuals run their ultramarathons slower than they do standard endurance footraces. This obligatory shift in velocity allows for more even pacing, increasing the chances of a faster finish time [8]. Higher work rates in shorter events (e.g., marathons relative to ultramarathons) require faster ATP turnover and greater glycogen use (and, therefore, increased likelihood of glycogen depletion), cardiac output, and O_2 delivery. Aerobic metabolism thus plays a pivotal role in performance. Approximately 60% of the variance in marathon finish time can be predicted by $\dot{V}O_2$max alone [3, 9–13], whereas 88–92% of the variance can be explained by velocity at the "anaerobic" threshold [4]. Furthermore, in races up to half-marathon, a composite of velocity at $\dot{V}O_2$max ($v\dot{V}O_2$max) and velocity at the metabolic thresholds predicts up to 95% of performance variance [14, 15]. Notwithstanding the critical roles of motivation and psychosocial factors, the metrics above, easily assessed in an exercise physiology laboratory, comprise the major components of the marathon physiology model [1].

In 1979, Davies and Thompson speculated that aerobic capacity's contribution to performance diminished with increasing distance and decreasing speed [16]. Several studies have since supported their hypothesis.

At the Südtirol Ultra Skyrace event in Italy, Gatterer et al. showed that $\dot{V}O_2$max and O_2 uptake at the metabolic thresholds correlated with performance in a 69 km race but not in a ~ 121 km race [17]. Similarly, in three events at the Sulphur Springs Trail Race, Canada, Coates et al. reported that performance in the 50 km race correlated with $\dot{V}O_2$max and $v\dot{V}O_2$max, performance in the 80 km race correlated with $v\dot{V}O_2$max, but performance in the 160 km race had no correlates [18]. Furthermore, at the Ultra-Trail du Mont-Blanc (UTMB), Pastor et al. showed that performance in a short race (< 55 km) could be explained by $\dot{V}O_2$max and lipid metabolism and that performance in a 100 km race could be explained by $\dot{V}O_2$max, maximal isometric strength, and body fat percentage, but that performance in a race > 145 km could not be explained using any linear model [19].

In one of the strongest statistical correlations observed thus far, Sabater-Pastor et al. found that ~ 52% of performance variance at the UTMB (166 km) could be predicted using $\dot{V}O_2$max alone and that a model combining $\dot{V}O_2$max and the energy cost of running predicted 62% of the variance [20]. Thus, while it may be possible to predict performance in long ultramarathons using measures of aerobic metabolism, predictive power remains considerably below that observed in shorter races.

Lastly, Martinez-Navarro et al. assessed performance predictors of a 66 mile/107 km footrace, showing that $\dot{V}O_2$max predicted performance differently according to athlete caliber [21]. Specifically, $\dot{V}O_2$max predicted 75% of performance variance in "faster" runners (when split by mean finish time) but only 33% of performance variance in "slower" runners [21].

Collectively, the available data support the following two contentions: (i) measures of aerobic metabolism cannot consistently and robustly predict performance in long ultramarathons (> 100 km) with the same fidelity that they predict performance in shorter events, and (ii) with increasing distance and time, factors other than (maximal) aerobic metabolism have a predominating influence on race outcomes.

2.2 Ultramarathon Runners Appear to Sacrifice Running Economy to Mitigate Muscle Damage

All elite distance runners have an exceptionally high $\dot{V}O_2$max, with values up to 80 mL/kg/min and 90 mL/kg/min in females and males, respectively [22]. Therefore, in homogeneous groups of athletes, the distinguishing physiological feature is running economy—the energy and, thus, oxygen required to sustain a submaximal velocity [23, 24]. Indeed, $\dot{V}O_2$max and running economy are weakly related [25] and can be independently trained such that $\dot{V}O_2$max can decrease, but marathon performance increase via improved running economy [26].

In ultramarathon, running economy is secondary or tertiary to more urgent performance limiters. The muscle damage sustained during racing is extreme. Common biomarkers such as creatine kinase (CK) exhibit resting values of 34–171 U/L but increase up to 1000 U/L after a marathon and > 10,000 U/L after a long ultramarathon [27–32]. Functionally, muscle damage can reduce muscle strength and range of motion by disrupting force transmission, calcium homeostasis, excitation–contraction coupling, and metabolic function [33]. More importantly, the trauma of muscle damage evokes an inflammatory response that manifests as swelling, pain, and soreness. In a long ultramarathons, this

often occurs during the race, e.g., before the athlete completes the middle third. As such, even though decreases in maximal strength after an ultramarathon are most likely due to central fatigue (i.e., reduced motor output from the central nervous system), decreases in running velocity as a function of time are most likely due to peripheral factors, i.e., greater perceptions of pain and soreness caused by structural damage to sarcomeres, membranes, and cytoskeleton.

In the face of such profound peripheral stress, runners often make strategic decisions, such as using poles or wearing sturdy trail shoes, that likely sacrifice running economy to protect the muscles from damage [34]. Poles, in particular, obligate the runner to carry a little more weight and change their biomechanics but, in turn, reduce the average force exerted by the feet on the ground [35], transfer a portion of locomotor work to the upper body [36, 37], and attenuate muscle damage [36].

2.3 Ultramarathon Runners Report "Muscle Damage and/or Muscle Fatigue" as More Performance-Limiting than GI Distress

Gastrointestinal (GI) distress occurs in 30–80% of runners during ultramarathons [38]. It has three leading causes: (i) physiological, i.e., redistribution of blood to skeletal muscles and changes in gastrointestinal nervous control; (ii) mechanical, i.e., damage to the intestinal lining due to repetitive impact forces and gastric "jostling"; and (iii) nutritional, inappropriate energy or fluid intake, specifically anything that slows gastric emptying [39]. Despite its debilitating effects, GI distress, once it manifests during an event, can often be resolved through behavioral interventions. These may include resting or slowing down (assuming one has the luxury of time), adjusting energy or fluid intake, or using medication to mitigate stomach cramps or nausea. The prevalence and severity of GI distress can also be mitigated through progressive gut training [40]. As such, GI distress per se is rarely responsible for race withdrawal. Rather, the inability to continue racing usually results from the inappropriate management of GI distress and the subsequent failure to fuel and hydrate.

By contrast, once it occurs during a race, muscle damage cannot be reversed with changes in pace or energy/fluid intake, or by using medication. Muscle damage may take days or weeks to repair and fully resolve, and low-frequency fatigue recovers over hours or days of rest [41]. The degree of damage to peripheral tissues, and thus the recovery time, depends more on the intensity of muscle load (the eccentric load from total negative elevation) than the amount [42, 43], so performance declines in short and long footraces likely have a distinct etiology. We, therefore, hypothesize that muscle damage and low-frequency force depression, acting via activation of type III–IV afferent fibers, are the main (indirect) impediments to performance in ultramarathons longer than ~ 100 km, irrespective of the race terrain or environmental conditions.

We conducted a brief, informal survey of ultramarathon runners on social media to gauge their perspectives on the main impediments to performance. The following question and four possible answers were posed: "What is the single physiological factor that most often limits your ultramarathon performance? (i) lungs or breathing; (ii) gastrointestinal distress; (iii) muscle damage/fatigue; (iv) other (please state)." The poll received 824 responses, shown in Fig. 2.

Overall, 542 (66%) answered "muscle damage/fatigue," 186 (23%) answered "gastrointestinal distress," 62 (7%) answered "other" (citing injury or blisters), and the remaining 34 (4%) answered "lungs or breathing."

If muscle damage is indeed the single factor most often limiting ultramarathon performance in the most runners, two questions need to be explored. First, is the capacity to resist muscle damage/fatigue something that we can test for, and if so, what form would this test take? Secondly, how can we mitigate muscle damage during competition?

2.4 Assessing Ultramarathon-Specific Muscle Damage and Fatigue

Prolonged exercise, especially that to which the individual is unaccustomed, results in structural changes (e.g., muscle damage) and functional changes (e.g., muscle fatigue). Although these two phenomena can be discerned independently, they are interconnected, often overlap, and result in similar impairments in performance [44]. As such, the assessment needs to quantify both.

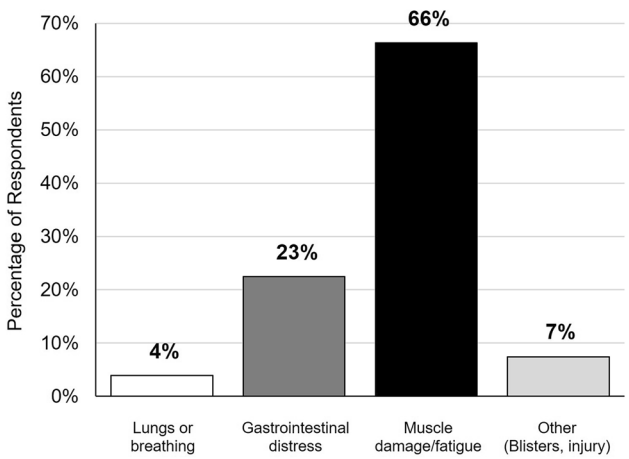

Fig. 2 Results from an online poll: "What is the single physiological factor that most often limits your ultramarathon performance? (i) Lungs or breathing; (ii) gastrointestinal distress; (iii) muscle damage/fatigue; (iv) other (please state)." The poll received 824 responses

We first need a damage-inducing protocol. Most of those used in the literature involve high-intensity aerobic or high-force resistance exercises, neither of which are ultramarathon specific. However, although replicating the conditions of long ultramarathons in a laboratory is technically possible (e.g., Ref. [45]), it is fraught with difficulties, not least because of the durations typical of competition (24–48 h). A reasonable compromise is a downhill running protocol that damages the muscles with eccentric contractions—when the muscles are lengthening under load. Downhill running is common in ultramarathons, and owing to long muscle lengths and braking forces, it induces muscle damage and fatigue distinct from that caused by heavy eccentric resistance exercise [46].

The downhill running protocol should mimic descents typical of major mountain races. We propose a 5 km downhill running protocol comprising 700–1000 m negative elevation, equating to a slope of approximately − 15%. This should be performed on the treadmill so that elevation and speed are reproducible in subsequent assessments that evaluate training-induced adaptations. Note that even ultramarathons that are considered relatively "flat" still have substantial ascent and descent owing to the extreme distances (e.g., the Javelina Jundred, a race run on hard-packed granite, rocks, and sand comprises 2410 m of total ascent; and Badwater 135, a race contested almost entirely on paved tarmac, involves ~ 4500 m of ascent and ~ 2000 m of descent). Accordingly, wherever possible, one should design an assessment protocol that resembles the demands of the target event.

In a downhill running protocol, treadmill speed is not as important as the decline. Speeds of 10–12 km/h [47, 48] and equating to 70% $\dot{V}O_2$max [49, 50] have been used, but we suggest a speed that is either bespoke to the runner's ability or kept consistent among athletes, depending on the research question. At each assessment, athletes should be instructed to run in the most comfortable style, with a natural gait, stride frequency, and length. However, stride frequency should be measured to determine if any physiological changes between sessions can be (at least partially) explained by biomechanical alterations.

To assess outcomes from the damage-inducing protocol, a two-step approach is required. First, pre- to post-exercise changes in muscle contractile function must be assessed. The gold-standard measurement requires nerve stimulation of the relevant muscles, e.g., the quadriceps muscles, either directly via electrical stimulation or indirectly via magnetic stimulation of the spinal nerves innervating the muscles. Muscle and nerve stimulation are well tolerated and allow for the objective measurement of changes in muscle contractile function that are independent of voluntary activation (i.e., athlete effort and motivation). Muscle force and electrical activity following stimulations can be measured using isometric dynamometry and surface electromyography (EMG), respectively. The muscles should be relaxed to eliminate the influence of central fatigue, and we suggest assessing low-frequency fatigue since this has been shown to systematically decline following downhill running [48, 51, 52]. Lastly, there should be a 30 min delay in post-race measures to determine if changes in force are due to muscle damage or metabolic fatigue.

The second phase of the assessment involves measures of muscle damage. To our knowledge, no studies have directly quantified muscle damage during ultramarathon or an athlete's ability to tolerate muscle damage. The relevant biomarkers, such as creatine kinase, lactate dehydrogenase, and myoglobin, should be measured before and 30 min after the damage-inducing protocol, following the assessment of low-frequency fatigue. Whole blood is usually sampled from the antecubital vein in the forearm, centrifuged to separate cells from serum/plasma, and analyzed using spectrophotometry or immunoassay. Point-of-care devices providing instantaneous results are also common. Irrespective, researchers should be consistent with the type of measurement and CK isoenzyme used between sessions.

Despite their utility in assessing muscle damage, blood biomarkers have been criticized because they are nonspecific. For example, CK has a delayed response to exercise and is sometimes released from other body tissues without strenuous exercise. Accordingly, it is worth considering other ways of quantifying muscle damage to complement the biomarker analysis.

Several imaging techniques show promise in assessing structural changes in the muscle following prolonged exercise. Shear-wave elastography (SWE) is an emerging method in which acoustic sheer waves are propagated throughout the tissues. Recorded using ultrasound or magnetic resonance imaging, SWE is used increasingly to assess muscle stiffness in clinical practice and research [53] and can provide information on the physical characteristics of the muscle. Changes in SWE seem to reflect changes in intramuscular calcium homeostasis—the same mechanism underpinning low-frequency fatigue. Recent studies suggest that diagnostic ultrasound could also be used to assess muscle damage [54], and contrast-enhanced micro-computed tomography (CT), despite presently being inappropriate for assessing the mechanisms underpinning superficial muscle soreness and/or delayed-onset muscle soreness, has been used to monitor recovery from skeletal muscle injury [55]. As such, while imaging techniques to evaluate exercise-induced muscle damage are preliminary, it may not be long before they can be incorporated into standard lab-based assessments.

Theoretically, an individual who exhibits a smaller decline in contractile function and lesser biomarker perturbations following the sports-specific damage-inducing protocol would be expected to perform better in a race evoking

such disturbances. We are a long way from being able to use the results from such an assessment to predict performance variance in long ultramarathons. Nevertheless, the data obtained will be valuable for assessing athlete trained status, monitoring training adaptation, and assessing race readiness and recovery. The above is a guide. Extensive pilot testing will be required, specifically to determine the downhill-running protocol that elicits the most appropriate muscle damage and neuromuscular fatigue.

2.5 Mitigating Running-Related Damage

The degree of muscle damage occurring during footraces can be profoundly performance limiting. Indeed, pacing studies show that individuals who slowed the most during a typical marathon tended to exhibit the greatest post-race concentrations of myoglobin, lactate dehydrogenase, and creatine kinase; moreover, pace was better preserved when markers of muscle damage were lower [56]. Accordingly, in this section, we briefly summarize the training and racing interventions that may attenuate the degree of muscle damage occurring during ultramarathon.

2.5.1 During Training

Weekly running mileage is significantly and positively associated with running performance, such that runners with a higher mileage run faster over 42.2 km, 100 km, and 24 h [57, 58]. It is plausible that a high running mileage could protect against running-related muscle damage. Indeed, running more miles at a relatively slower pace distinguishes marathon from ultramarathon runners [59]. It could also be that genetically gifted and less injury-prone runners can sustain a higher mileage. Thus, it is unclear if the relationship between mileage and performance is causal.

Downhill running is a strategy that directly affects running-related muscle damage. Studies showed that, with repeated exposures, trail runners had a muted response to downhill running-induced muscle damage, such that muscle soreness, the rise in CK, and the loss of maximum force were mitigated in subsequent trials [48] [47]. Accordingly, slow progression to a high weekly mileage, running at relatively slow velocities, and a relatively large volume of downhill running may be viable strategies to train the peripheral musculature and protect against race-induced mechanical damage.

2.5.2 During Racing

The most well-documented strategy for mitigating race-induced muscle damage is using poles since they redistribute some of the locomotor work to the upper body [36]. In mountain ultramarathons, poles can alleviate impact forces at the foot [35] and lower limb work when walking uphill [60], reduce plantar pressure when running downhill [61], and decrease net joint moments and power in the lower body when walking downhill with a backpack [62]. Thus, even though poles obligate runners to carry a little more weight, the compromise to economy may benefit performance by "saving the legs" [34, 35].

A strong body of evidence supports the idea that taking shorter strides, even reducing stride length by just 10%, may decrease vertical excursion, musculoskeletal loads, and energy absorbed at the hip, knee, and ankle [63, 64]. These biomechanical changes may mitigate muscle damage in prolonged running. Although cause and effect have not been decisively shown, taking shorter strides when running downhill has been observed to result in less muscle soreness [47].

Regarding nutritional interventions, Dohm et al. posited that supplemental protein might be beneficial in accounting for the increased protein degradation during racing [65]. However, few studies have tested the hypothesis, and those that have were poorly controlled. For instance, endurance athletes who co-ingested protein and carbohydrate during 6 h of exercise had a greater net protein balance than when they consumed carbohydrates alone; however, researchers did not control for the additional protein-derived calorie intake [66]. In another study, taking 52.5 g of amino acids before and during a 100 km race did not affect muscle damage or performance relative to placebo [67]; but the 10 h race time may be too short for effects to manifest. Finishers of the Western States Endurance Run had a significantly greater protein intake than nonfinishers, even when expressed as intake per hour of running (0.08 g/kg/h versus 0.04 g/kg/h) [68]; however, the lower protein intake in nonfinishers could be explained by other factors, such as greater GI distress and/or lack of appetite. As such, it is plausible that protein intake during long ultramarathons may mitigate muscle damage and improve performance, but empirical data are lacking, and the hypothesis needs a more thorough exploration.

Lastly, there is little robust evidence that other in-task strategies, such as dietary supplements, compression garments, or muscle taping, have any influence on mitigating muscle damage during races [38, 69–71]. Runners should look upon these commercial interventions with skepticism. Athletes often use nonsteroidal anti-inflammatory drugs (NSAIDs) to mitigate the unpleasant symptoms of muscle damage, with 50–70% of ultramarathon runners admitting to using NSAIDs or other analgesics during competition [72, 73], mostly for pain prevention (56%) and pain relief (31%) [72]. However, due to the potential for serious adverse effects on cardiovascular, musculoskeletal, gastrointestinal, and, perhaps most importantly, renal systems, use of NSAIDs during ultramarathons is actively discouraged [38].

3 Conclusion and Take-Home Messages

Performance variance in traditional endurance events can be predicted using lab-based measures of aerobic metabolism. But ultramarathon, with its diverse range of distances, terrains, environments, and psychophysiological challenges, is impossible to predict using a simple regression model of performance. Thus, we collated the literature on the various factors limiting ultramarathon performance and concluded the following:

(i) Muscle damage, its unpleasant symptoms, and the associated force decline most often limit performance in long ultramarathons (> 100 km) for most people.
(ii) Assessing athlete tolerability to ultramarathon-specific muscle damage may assist in monitoring training adaptation, provide a snapshot of training status, and indicate the degree of race readiness and recovery. We propose a muscle-damage-inducing downhill running protocol with pre- to post-exercise assessment of changes in muscle force using muscle or nerve stimulation and changes in biomarkers of muscle damage (e.g., CK and myoglobin). Imaging techniques to quantify muscle morphology could be used when validated protocols are developed.
(iii) Muscle damage and associated declines in force output can likely be mitigated. In training, athletes can progress slowly to a high weekly mileage and carefully integrate downhill running to accumulate negative elevation. When racing, athletes can use poles, make small adjustments to stride length and pace, and perhaps take additional protein.

Figure 1 illustrates the main points of our discussion. We encourage ongoing discourse to expand upon and develop the ideas presented.

Declarations

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Author contributions N.B.T. conceived the idea for the article. N.B.T. and G.Y.M. conducted the literature search and selected the articles for inclusion. N.B.T. wrote the first draft. N.B.T. and G.Y.M. edited the draft and approved the final version.

Data availability No data were included in this manuscript.

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