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Fatigue associated with prolonged graded running

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Abstract Scientific experiments on running mainly consider level running. However, the magnitude and etiology of fatigue depend on the exercise under consideration, particularly the predominant type of contraction, which differs between level, uphill, and downhill running. The purpose of this review is to comprehensively summarize the neurophysiological and biomechanical changes due to fatigue in graded running. When comparing prolonged hilly running (i.e., a combination of uphill and downhill running) to level running, it is found that (1) the general shape of the neuromuscular fatigue-exercise duration curve as well as the etiology of fatigue in knee extensor and plantar flexor muscles are similar and (2) the biomechanical consequences are also relatively comparable, suggesting that duration rather than elevation changes affects neuromuscular function and running patterns. However, ‘pure’ uphill or downhill running has several fatigue-related intrinsic features compared with the level running. Downhill running induces

severe lower limb tissue damage, indirectly evidenced by massive increases in plasma creatine kinase/myoglobin concentration or inflammatory markers. In addition, low-frequency fatigue (i.e., excitation–contraction coupling failure) is systematically observed after downhill running, although it has also been found in high-intensity uphill running for different reasons. Indeed, low-frequency fatigue in downhill running is attributed to mechanical stress at the interface sarcoplasmic reticulum/T-tubule, while the inorganic phosphate accumulation probably plays a central role in intense uphill running. Other fatigue-related specificities of graded running such as strategies to minimize the deleterious effects of downhill running on muscle function, the difference of energy cost versus heat storage or muscle activity changes in downhill, level, and uphill running are also discussed.

Keywords Level · Uphill · Downhill · Running · Fatigue · Neuromuscular function · Tissue damage · Energy cost · Biomechanics

Abbreviation

$\dot{V}O_2$ Oxygen uptake

Introduction

The vast majority of biomechanical and physiological studies investigating running have considered only level running, likely due to the fact that most major running events are run on flat courses (e.g., most marathons). However, some popular road races are performed on hilly courses (e.g., Comrades Marathon in South Africa or Marvejols-Mende in France), and more importantly, (ultra)-trail running has seen an exponential increase in worldwide

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popularity over recent years (Hoffman et al. 2010). In Europe, the Ultra-Trail du Mont Blanc® is probably the best example of this increasing popularity. While it is not as popular as the most famous marathons in the world (>40,000 runners), the total number of participants is now close to 10,000 over 5 different distances, and the applications of 6500 runners were rejected in 2015.

Trail and ultra-trail races typically involve running over long or extreme distances on irregular terrain with large positive and negative elevation changes throughout (Millet et al. 2011b; Saugy et al. 2013; Vernillo et al. 2014a, b). Therefore, events such as these are likely to be at the extremes of human tolerance (Millet and Millet 2012) and induce extreme levels of neuromuscular fatigue. Neuromuscular fatigue is an exercise-related decrease in the maximal voluntary torque of a muscle or muscle group, regardless of whether or not the task can be sustained (Gandevia 2001). This may involve processes at all levels of the motor pathway (i.e., from the brain to the skeletal muscle). It is well known that the magnitude and etiology of fatigue depend on the exercise under consideration, the so-called task-dependency of fatigue. Critical task variables include the intensity and duration of exercise, the muscle activation pattern, the type of muscle group involved, and the type of muscle contraction. Regarding the latter factor, as previously reviewed, level running is characterized by continuous stretch–shortening cycles for lower limb extensor muscles (e.g., Nicol et al. 2006), while uphill and downhill running are mainly characterized by concentric and eccentric modes of contraction, respectively (Abe et al. 2011). As a result, the fatigue-related neurophysiological and biomechanical changes associated with prolonged graded running are likely different from those observed in level running. Yet, compared with other concentric (with the exception of cycling) or eccentric exercises traditionally studied (i.e., single-joint exercises), uphill and downhill running exercises are typically much longer in duration.

The purpose of this review is to provide a comprehensive overview of the literature related to fatigue induced by hilly and graded running, and to highlight the specific etiology of fatigue induced by different graded running bouts. In section “[Neuromuscular fatigue in hilly running and its consequences on running biomechanics: \(ultra\)-trail running](#),” we focus on the neuromuscular and biomechanical alterations observed after trail and ultra-trail races, and propose some underlying mechanisms to the observed changes in running kinematics and mechanics. In section “[Specificity of fatigue associated with downhill running](#),” we describe the neuromuscular dysfunctions associated with downhill running, review the strategies that aim to reduce the adverse effects of downhill running, and emphasize the fact that thermal stress is still elevated in downhill running despite a reduced energy cost of running. Finally, we

discuss in section “[Specificity of fatigue associated with uphill running](#)” the metabolic specificities of uphill running as well as the differences between uphill and downhill running in terms of induced neuromuscular dysfunctions.

Neuromuscular fatigue in hilly running and its consequences on running biomechanics: (ultra)-trail running

Fatigue can originate at several potential sites that are usually classified as being proximal (central fatigue) or distal (peripheral fatigue) to the neuromuscular junction (Millet et al. 2011a). Central fatigue reflects a reduction in voluntary activation. Indeed, it leads to an inability to recruit all motor units and/or discharge them at the rates necessary to maximize force or power. Although central fatigue might be of great importance, especially in prolonged exercises (Martin et al. 2010), this does mean that the contribution of peripheral fatigue is negligible. Current knowledge on the origins of peripheral fatigue suggests that endurance exercise could impair three main components: (1) action potential transmission along the sarcolemma, (2) excitation–contraction coupling, and (3) actin–myosin interaction. Although central and peripheral fatigues are sometimes independent, they often interact and central drive can also be reduced through a combination of supraspinal and spinal influences (Gandevia 2001). Several studies [e.g., (Fourchet et al. 2012; Millet et al. 2002, 2003, 2011b; Saugy et al. 2013; Temesi et al. 2014, 2015)] have measured fatigue during (ultra)-trail running with a large positive and negative elevation change and reported decrements in central and peripheral fatigue-related parameters. Changes in neuromuscular functions following (ultra)-trail running have been measured following a 30-km trail running race (duration/distance: ~3 h 50 min; positive and negative elevation change: ± 800 m) (Millet et al. 2003); a 5-h hilly run (37.5 km; ± 1730 m) (Fourchet et al. 2012); Le Grand Trail des Templiers (~8 h 30 min/65 km; ± 2500 m) (Millet et al. 2002); a shortened edition of the Ultra-Trail du Mont Blanc® (~20 h 15 min/110 km; ± 5860 m) (Temesi et al. 2014, 2015); Ultra-Trail du Mont Blanc® (~37 h 40 min; ± 9500 m) (Millet et al. 2011b) and the Tor des Geants® (~122 h 25; $\pm 24,000$ m) (Saugy et al. 2013). A non-linear relation between the force loss and running duration (Millet 2011) seems to be confirmed. Surprisingly, muscular strength loss seems to decrease as the running exercise increases above a duration corresponding to ~100 miles (Fig. 1). This result may be due to a more conservative pacing strategy in extreme duration races, allowing runners to preserve lower limb tissues during the initial part of the race, so as to avoid premature exercise termination (Saugy et al. 2013). Indeed, while the Ultra-Trail du Mont

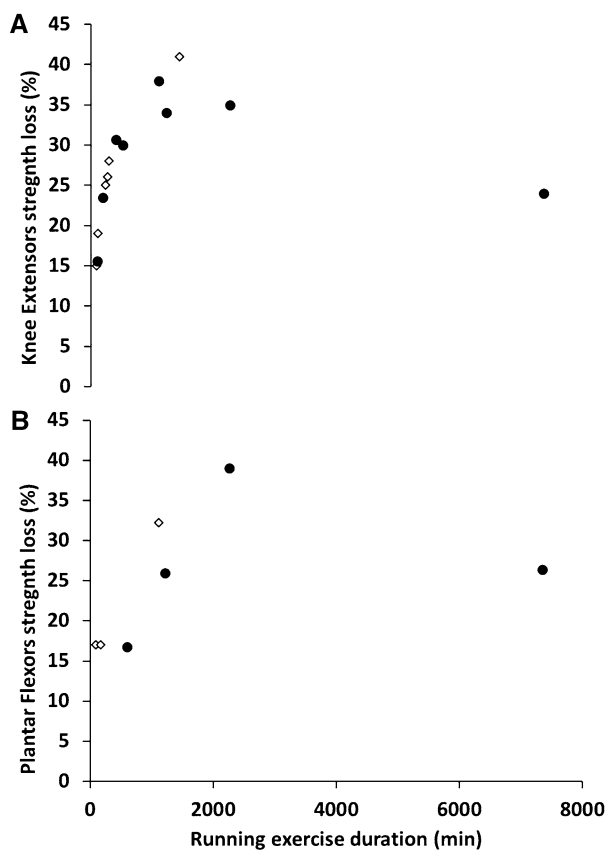


Fig. 1 Strength losses on **a** knee extensors and **b** plantar flexors muscles from pre- to post-exercise, as a function of exercise duration. *White diamonds* refer to level running exercises and *black circles* refer to trail or ultra-trails Adapted from Millet (2011)

Blanc® and the first half of the Tor des Geants® are comparable in terms of distance and positive and negative elevation change, average speed and all neuromuscular fatigue indices were much lower for the first half of the Tor des Geants® than for the Ultra-Trail du Mont Blanc® (Saugy et al. 2013).

Interestingly, whether these studies were conducted in (ultra)-trail running with a high positive and negative elevation change (Fourchet et al. 2012; Millet et al. 2002, 2011b; Saugy et al. 2013; Temesi et al. 2014, 2015) or on level ground (Davies and Thompson 1986; Lepers et al. 2000; Martin et al. 2010; Nicol et al. 1991; Place et al. 2004; Ross et al. 2010), and the general shape of the duration–fatigue curve is similar, suggesting that exercise duration rather than the positive and negative elevation change influences global neuromuscular fatigue. For instance, knee extensor muscles force loss, assessed by a decrease in isometric maximal voluntary contraction, was ~40 % after a 24-h simulated race on a level treadmill with an effective running time of 18 h 39 min (Martin et al. 2010) versus –34 % after a 110-km mountain ultra-marathon lasting

20 h 17 min (Temesi et al. 2014). Similarly, when comparing neuromuscular fatigue induced by a level running marathon (mean time: 2 h 35 min) (Petersen et al. 2007) versus 30-km trail running (duration: ~3 h 10 min; positive and negative elevation change: ± 800 m) (Millet et al. 2003), strength losses were found to be 22 and 23 %, respectively.

Some studies have considered fatigue-induced changes of plantar flexor muscles (Fourchet et al. 2012; Martin et al. 2010; Millet et al. 2011b; Saugy et al. 2013; Temesi et al. 2015; Petersen et al. 2007; Saldanha et al. 2008). The relationship between maximal voluntary force decline for plantar flexors and running exercise duration is shown in Fig. 1b. As for knee extensor muscles, strength loss was lower for extreme durations [−26 % in (Saugy et al. 2013)], again most likely due to conservative pacing strategies.

A few studies have assessed both plantar flexor and knee extensor muscles fatigue after a single running bout (Martin et al. 2010; Petersen et al. 2007), and to the best of our knowledge, only our research group has examined these parameters after ultra-trail running (Millet et al. 2011b; Saugy et al. 2013; Temesi et al. 2015). In these studies, changes in maximal voluntary contraction were similar between plantar flexor and knee extensor muscles; however, peripheral fatigue assessed by evoked twitches on relaxed muscle and central fatigue assessed by a decrease in maximal voluntary activation varied among studies. In other words, fatigue amplitude was similar for both muscle groups, but the etiology of fatigue differed between muscle groups as well as among studies.

The central component of fatigue has been demonstrated to be the main explanation for knee extensor muscles fatigue after ultra-marathon running whether the event consisted of substantial positive and negative elevation change (Millet et al. 2002, 2011b; Saugy et al. 2013; Temesi et al. 2014, 2015) or simply level running (Martin et al. 2010; Place et al. 2004). For both ultra-trails and level ultra-marathons, the changes in maximal voluntary activation were consistently lower for plantar flexor and knee extensor muscles. For instance, the reduction in the central activation level for both knee extensors and plantar flexor muscles was 19 and 6 %, respectively, after the Ultra-Trail du Mont Blanc® (Millet et al. 2011b); whereas it was 33 and 14.8 %, respectively, after a 24-h treadmill run (Martin et al. 2010). The opposite was found for peripheral fatigue (i.e., the evoked forces decreased more for plantar flexor than for knee extensor muscles). Again, this was true whether the ultra-marathon was run on flat ground or contained long portions of uphill/downhill running. For instance, a larger peripheral fatigue (e.g., M-wave peak-to-peak amplitude) was observed for plantar flexor compared to knee extensor muscles during the Ultra-Trail du Mont Blanc® (Millet et al. 2011b) as well as a 24-h treadmill run (Martin et al. 2010).

The changes in the physiological status of the lower limb neuromuscular system may affect running mechanics, as described by changes in the spring-mass behavior after (ultra)-trail running (Degache et al. 2013, 2015; Morin et al. 2011b), and the magnitude of the fatigue-induced kinematic changes, such as an increase in step frequency, loss of ankle flexion excursion, and a decrease in ankle dorsiflexion at foot strike (Giandolini et al. 2016a). Despite differences in the magnitude of changes, higher oscillating frequency and vertical stiffness have been reported, along with lower ground reaction forces and a reduced overall eccentric loading during the support phase of running. The aforementioned results were similar to that observed for a 24-h level running (Morin et al. 2011a). Giandolini et al. (2016a) observed correlations between percent changes in kinematic variables (i.e., ankle flexion excursion, ankle dorsiflexion, and step frequency) and percent changes in evoked forces at the plantar flexor muscles (i.e., peripheral fatigue). After a 110-km ultra-trail, the greater the peripheral fatigue at the plantar flexor muscles, the greater the increase in step frequency, the larger the loss in ankle flexion excursion, and the more pronounced the decrease in ankle dorsiflexion at foot strike. These biomechanical changes are associated with an overall stiffer lower limb, since step frequency, vertical oscillations, contact time, and ankle dorsiflexion at foot strike have been shown to be interrelated (Farley and Gonzalez 1996; Giandolini et al. 2013; Morin et al. 2007). As previously proposed, they may occur as compensatory and protective strategies during (ultra)-trail running races (e.g., Degache et al. 2013, 2015; Giandolini et al. 2016a; Morin et al. 2011b). First, it can be hypothesized that they occur to compensate for the deficit in propulsive function of plantar flexor muscles. Indeed, plantar flexor muscles fatigue may impair the contribution of these muscles during the propulsive phase of running, since they play a primary role in vertical acceleration, thereby permitting the flight phase (Ellis et al. 2014; Sasaki and Neptune 2010). Therefore, increasing leg stiffness (and so reducing contact time, increasing step frequency, and adopting a flatter foot strike) would be less costly for plantar flexor muscles by limiting vertical oscillations. Second, the kinematic reorganization may occur to accommodate to exercise-induced muscle damage and mechanical strains applied on the musculoskeletal system. Decreasing vertical oscillations may indeed reduce the negative work applied at knee extension during the braking phase and, as such, induce less pain. More precisely, this protective kinematic reorganization could be induced by the inhibition of damaged muscles' motoneurons via the increased discharge rate of metabosensitive and mechanosensitive afferent fibers (groups III and IV) (Gandevia

2001). Alternatively, it could be induced by a decline in muscle-spindle stretch sensitivity induced by muscle damage which has previously been observed after prolonged stretch-shortening exercises (e.g., marathon) (Avela et al. 1999b; Nicol et al. 1991). This muscle function impairment (called 'intrafusal fatigue') likely decreases tolerance to imposed stretch loads and impairs stiffness regulation during the leg compression, especially during braking phases (Gollhofer et al. 1987; Nicol et al. 1991).

In a recent study, Lussiana et al. (2016) measured the effects of 50 min of running alternating between level, uphill (+5 %), and downhill running (−5 %) on selected biomechanical variables. Similar biomechanical changes as a function of exercise time were observed on the uphill and downhill inclines, suggesting that slope does not modify the interpretation of fatigue outcomes. Yet, both the fatiguing exercise and the slopes were relatively moderate in this study. In a much harder fatiguing exercise (i.e., ultra-trail running), differences between level, uphill, and downhill running were noted. For instance, energy cost of running increased by 13.1 % in downhill but not in uphill and level running after a 65-km ultra-trail (Vernillo et al. 2015). Regarding the associated kinematics parameters, some changed for all slopes (e.g., duty factor, obtained by dividing contact time by step time, and stride frequency), while others (e.g., contact time) changed in uphill and downhill running but not in level running. The same authors performed a similar experiment (although downhill running was not tested) on a much more challenging ultra-trail (330 km) and found quite different outcomes. Surprisingly, they observed that energy cost of running was 13.8 % improved in fatigue conditions in uphill running only, and this was associated with an increased contact time and duty factor as well as a decreased swing time. However, further work is required to analyze the effects of fatigue on energy cost and biomechanics as a function of slope.

In summary, research has shown that lower limb muscle strength is severely depressed after (ultra)-trail running (−30 to −40 %), and the amplitude of fatigue is similar between plantar flexor and knee extensor muscles, but the etiology of fatigue is different between these two muscle groups. On the other hand, despite the fact that slope changes the respective activity of knee extensor and plantar flexor muscles, no systematic influence of graded running was found in relation to the fatigue of specific muscle groups. Furthermore, ultra-marathon running leads to alterations in running kinematics and spring-mass behavior, regardless of running grade. These changes presumably occur to minimize pain in the lower limbs associated with eccentric loading, allowing for a 'safer' and 'smoother' running technique (Millet et al. 2012).

Specificity of fatigue associated with downhill running

Physiological consequences of lower limbs tissue damage

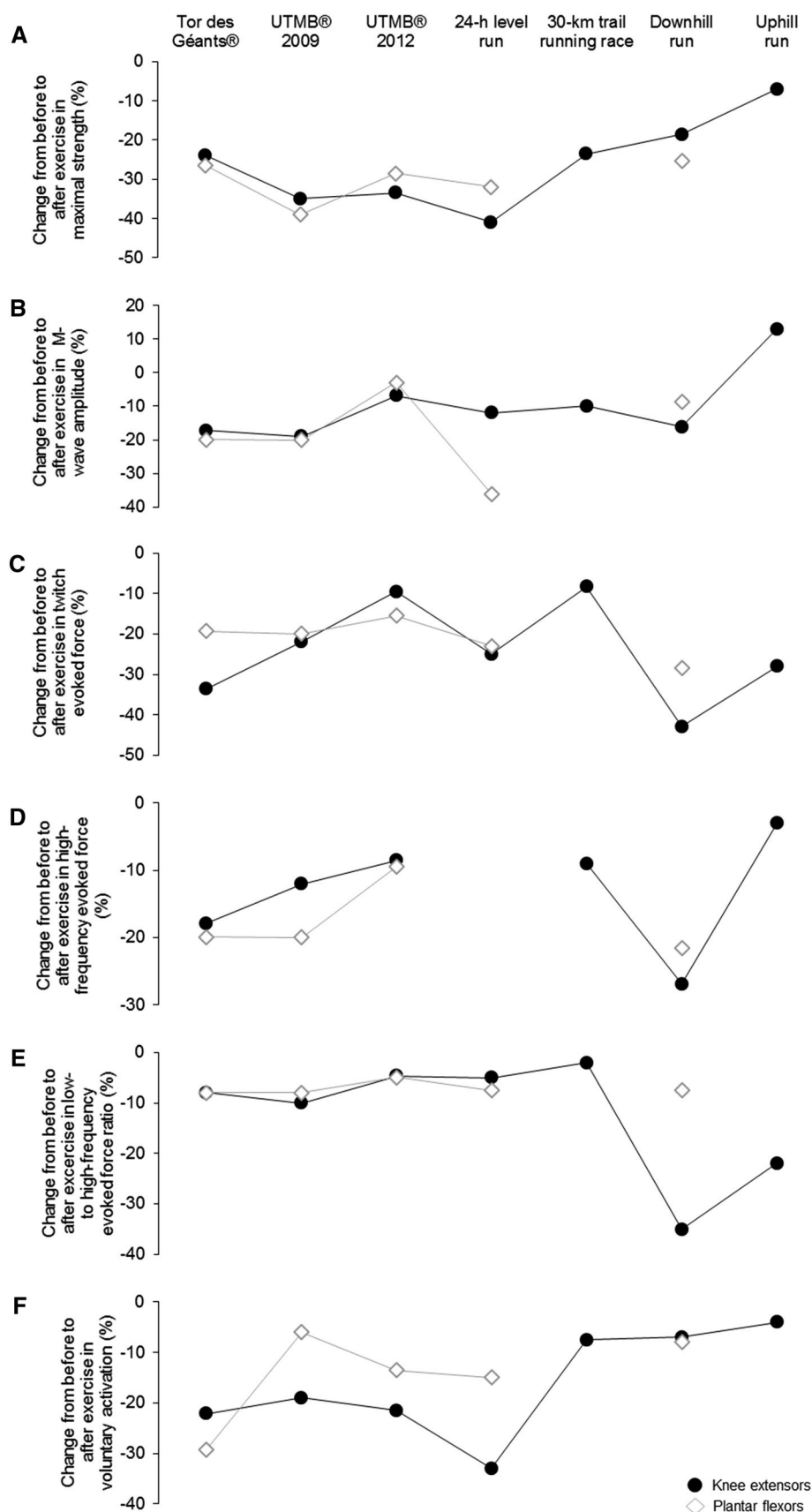
Downhill running is known to induce severe lower limb tissue damage and a specific type of fatigue called low-frequency fatigue that is typically associated with eccentric exercise. Low-frequency fatigue is usually assessed by muscle or nerve electrical stimulation and is defined as a reduction in the ratio between force evoked by low-frequency stimulation (e.g., 10–20 Hz) and force evoked by high-frequency stimulation (e.g., 50–100 Hz) (Jones 1996). This type of fatigue has been associated with excitation–contraction coupling failure (Hill et al. 2001). During eccentric exercise, it could involve decoupling at the T-tubule–sarcoplasmic reticulum interface, leading to a reduction in calcium release by the sarcoplasmic reticulum (Ingalls et al. 1998; Martin et al. 2005). Martin et al. (2004b) reported that 30-min bout of downhill running on a motorized treadmill (10 km h⁻¹ at –20 % grade) induced a (1) ~2.5 % decline in the maximal central drive assessed by maximal voluntary activation and (2) ~12.5 % decrease in the ratio between force evoked at 20 Hz and force evoked at 80 Hz. Both central and peripheral factors contributed to a ~15 % decrease in maximal voluntary contraction. Thus, these authors demonstrated that a 30-min bout of downhill running was a strong enough stimulus to induce both central (i.e., decline of maximal voluntary activation) and peripheral (i.e., low-frequency fatigue) fatigue. In real practice, field conditions, we have also recently demonstrated that runners performing a 6.5-km downhill running on trails (1264-m altitude drop) as fast as possible (mean time of 34 ± 6 min) experienced large knee extensor (–19 %) and plantar flexor (–25 %) muscles strength loss as well as knee extensors low-frequency fatigue. Interestingly, that intense, though short, bout also depreciated maximal voluntary activation during knee extensors (–7 %) and plantar flexors (–8 %) maximal voluntary contraction, indicating the presence of a moderate central fatigue. Decreases in evoked torques (knee extensors: from –27 to –43 %, plantar flexors: from –22 to –29 %), M-waves amplitudes (*vastus lateralis*: –16 %, *soleus*: –9 %), and in low-frequency fatigue (knee extensors: –35 %, plantar flexors: –9 %) also indicated the presence of substantial peripheral fatigue, which appears to be further marked at knee extensors (Fig. 2). Notably, force was still reduced 2 days after the downhill running bout (–9 % for knee extensors and –10 % for plantar flexors) (Giandolini et al. 2015).

Although Mizrahi et al. (2001) observed no difference in *rectus femoris* electromyographic activity within the first

15 min of downhill running compared with level running, it was greater during the last 15 min of downhill running when compared with level running. This may be attributed to the greater role of the knee extensor muscles in energy dissipation in downhill running than in level running (Buczek and Cavanagh 1990), likely resulting in a higher eccentric work load for the knee extensor muscles. It may, in turn, lead to an early onset of knee extensor muscles fatigue (e.g., low-frequency fatigue) and/or damage requiring an immediate increase in the central drive to motor units as a compensatory neural adjustment to perform the task. It is known that the role of the eccentric work in the lower limb muscles is accentuated during downhill running, and this eccentric phase seems to be one of the major contributors to a reduction in the motoneuron pool excitability (Bulbulian and Bowles 1992) and increased perceived exertion (Kolkhorst et al. 1996) during exercise as well as hours/days after. This has been observed after downhill running both in laboratory (Bulbulian and Bowles 1992; Malm et al. 2004) and field (Giandolini et al. 2015) settings, and seems to be characterized by morphological alterations within the muscle, including streaming, disruption, and dissolution of the Z-disk (Feasson et al. 2002). Eccentric exercise is also known to reduce maximal voluntary activation (Giandolini et al. 2015; Martin et al. 2004a, b, 2005), at least when measured with nerve stimulation as opposed to transcranial magnetic stimulation (Prasartwuth et al. 2005). The reasons behind this central fatigue after eccentric exercise are unclear. One could be tempted to propose that types III and IV afferent fibers are responsible for the maximal voluntary activation decrease due to an inflammatory response associated with eccentric exercise. However, we have shown (Millet et al. 2011b) that although inflammation (C-reactive protein response) was still present 2 days after an ultra-trail race, maximal voluntary activation was already back to pre-race values (Fig. 3). In addition, an inflammatory response cannot play a role after short duration exercise, since the eccentric-related inflammatory response begins 3–4 h after exercise (Peake et al. 2005). Another possible explanation for central fatigue after eccentric exercise is the disfacilitation from a reduction in the activity of the large-diameter afferents, resulting from the reduced sensitivity of muscle spindles to repeated stretch (Avela et al. 1999a).

As explained above, the muscle structural damage could explain low-frequency fatigue and is accompanied by major leakage of proteins and enzymes, such as creatine kinase, from the cell into circulation (Table 1). Dick and Cavanagh (1987) further argued that the skeletal muscle damage occurring during downhill running leads to an upward drift in oxygen uptake ($\dot{V}O_2$). Specifically, they reported a 10 and 23 % increase in $\dot{V}O_2$ and lower limb muscle activity, respectively, after 40 min of downhill running at 13.8 km h⁻¹ and –10 % grade. They concluded that with

Fig. 2 Pre- to post-exercise changes in neuromuscular indicators of central or peripheral fatigue for knee extensors (*black circles*) and plantar flexors (*white diamonds*). The presented variables are: **a** maximal strength, **b** M-wave amplitude (i.e., the electromyographic response to a single electrical stimulation delivered on the relaxed muscle), **c** force evoked by a single electrical stimulation, **d** force evoked by a high-frequency paired-pulses electrical stimulation, **e** ratio between the force evoked by a low-frequency paired-pulses electrical stimulation and the force evoked by a high-frequency paired-pulses electrical stimulation (a decrease in this ratio indicating the presence of low-frequency fatigue), and **f** maximal voluntary activation. The compared exercises include ultra-trail races [Tor des Géants® (330 km, \pm : 24,000 m), Ultra-Trail du Mont Blanc® (UTMB®) 2009 (distance: 166 km; positive and negative elevation change: \pm 9500 m), Ultra-Trail du Mont Blanc® 2012 (110 km; \pm 5860 m)], a 24-h level run (149 ± 15 km), a trail race (30 km; \pm 800 m), a single downhill run (6.5 km; -1264 m), and a single uphill run (10×1 min at 120 % maximal aerobic power, 2-min rest between repetition, slope: +18 %) Based on data from Saugy et al. (2013), Millet et al. (2011a, b), Temesi et al. (2015), Martin et al. (2010), Millet et al. (2003), Giandolini et al. (2015), and Lattier et al. (2004), respectively



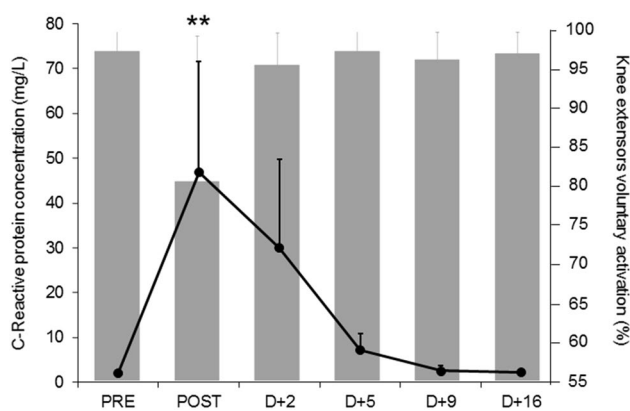


Fig. 3 Means and standard deviations of C-reactive protein concentration (black circles) and knee extensors maximal voluntary activation (gray bars) before (PRE), after (POST), and 2, 5, 9, and 16 days after (D + 2, D + 5, D + 9, and D + 16, respectively) a 166-km ultra-trail race with ± 9500 m of positive and negative elevation. Double asterisks indicates a significant difference with PRE values ($P < 0.01$) Adapted from Millet et al. (2011a, b)

downhill running-induced muscle damage, skeletal muscle fibers are no longer able to generate sufficient force, and that additional motor units must be recruited to maintain a given workload, resulting in an increase in $\dot{V}O_2$ (Dick and Cavanagh 1987). Importantly, deteriorated energy cost can still be observed up to 3 days after a single bout of downhill running, probably in relation to the biomechanical changes described above (e.g., reduced stride length) (Braun and Dutto 2003; Chen et al. 2007). However, no clear relationships were found between biomechanical variables and the energy cost of running (e.g., Kyrolainen et al. 2001; Williams and Cavanagh 1987). Nevertheless, Snyder and Farley (2011) observed in a non-fatigued state that drifts from the preferred stride frequency (from -15 to $+15$ %) induced increases in energy cost during downhill, level, and uphill running. Based on these findings, it seems that deviations from preferred stride frequency (or stride length) play a role in the deterioration of running economy, either in a fatigued or non-fatigued state. Otherwise, based on the fact that the magnitude of $\dot{V}O_2$ drift was similar in two downhill running bouts inducing various levels of muscle damage, a direct relationship between deteriorated energy cost and muscle damage has been challenged (Westerlind et al. 1992; Westerlind et al. 1994).

Damage to muscle tissues may also influence running gait (e.g., joint kinematics), resulting in a deterioration of running performance (Dutto and Braun 2004). These authors examined ankle and knee joint kinematics and stiffness before and after 30 min of downhill running at 75 % of maximal $\dot{V}O_2$ at -10 % grade and observed a 9.1 and 22.9 % increase in knee stiffness and vertical leg stiffness, respectively. Increased stride frequency and reductions

in ranges of motion of the ankle and knee have also been observed after a single bout of downhill running (Braun and Dutto 2003; Chen et al. 2007). These specific changes in joint mechanics may provide a protective mechanism to prevent further damage or pain, as already observed for ultra-marathon (Morin et al. 2011a) and (ultra)-trail running (Degache et al. 2013, 2015; Morin et al. 2011b) (see above).

Strategies to attenuate the deleterious effects of downhill running

Different strategies have been explored to attenuate the negative effects of downhill running, with mixed results. For instance, Hardin and Hamill (2002) investigated the influence of wearing different types of footwear (soft-, mid-, and hard-midsole) during 30 min of downhill running at 12.2 km h^{-1} and -12 % grade. They reported no differences in leg shock, haemolysis, and muscle damage between the three midsole conditions. Conversely, Rowlands et al. (2001) showed that 45 min of intermittent downhill running (9×5 min) at 10.5 km h^{-1} and -14.9 % grade was less harmful when increasing stride frequency (i.e., 108 % of the preferred stride frequency), despite the greater muscle activity found during downhill running with a greater frequency (Sheehan and Gottschall 2013). The reasons for this phenomenon may be that eccentrically based exercises performed at shorter muscle lengths (as observed in downhill running at a higher stride frequency) induce lower muscle damage than that performed at longer muscle lengths (as observed in downhill running at a lower stride frequency) (Child et al. 1998; Jones et al. 1989; Butterfield and Herzog 2006).

The foot strike pattern also influences the severity of peripheral fatigue on knee extensor and plantar flexor muscles after downhill trail running. Indeed, after a downhill trail run of 1264 m of altitude drop, Giandolini et al. (2016b) observed that runners demonstrating a forefoot strike profile (i.e., less than 33 % of heel strikes over the run) exhibited a greater knee extensors peripheral fatigue than those demonstrating a heel strike profile (i.e., more than 66 % of heel strikes over the run). This may be explained by a greater knee flexion at initial contact when using a forefoot strike profile that is typical of this type of running technique (Shih et al. 2013; Yong et al. 2014). This may then induce a longer lever arm between the rotation axis (i.e., the knee joint) and the ground reaction force vector as well as longer muscle fiber lengths prior to eccentric contraction which has been shown to increase the active strain applied at cross-bridges (e.g., Butterfield and Herzog 2006). Otherwise, it was also observed from this study that the severity of knee extensors peripheral fatigue and plantar flexors torque loss is negatively related to the foot strike

Table 1 Summary of studies examining the effect of downhill running on strength loss (i.e., maximal voluntary contraction) and peak creatine phosphokinase

Study	Sample size ^a	Running duration (min)	Running speed	Slope (%)	Δ Maximal voluntary contraction (%)	Δ Peak creatine phosphokinase at 24-h (%)	Δ Peak creatine phosphokinase (%)/time for peak (h)
Jamurtas et al. (2013)	12	45	60 % $\dot{V}O_{2\max}$	-15			1500/72
McKune et al. (2006)	11	60	75 % $\dot{V}O_{2\text{peak}}$ (bout 1)	-13.5		451	1150/9
van de Vyver and Myburgh (2014)	10	60 (12 \times 5 min)	75 % $\dot{V}O_{2\text{peak}}$ (bout 2 ^b)	-13.5		113	400/12
Pizza et al. (1995)	10		15 km h ⁻¹	-10		852	
Simpson et al. (2006)	8	Iso-time compared to level running	70 % $\dot{V}O_{2\max}$	-10		710	750/12
Sorichter et al. (2001)	9 female	20	80 % $\dot{V}O_{2\max}$	-10			
	9 male		70 % $\dot{V}O_{2\text{peak}}$	-16			504/6
Malm et al. (2004)	19	45	Subjective speed to complete the task	-16			507/6
				-14		461	
Buford et al. (2009)	29	45	60 % $\dot{V}O_{2\max}$	-17.5		455	
Peake et al. (2005)	10	45	60 % $\dot{V}O_{2\max}$	-10		420	
Hubinger et al. (1997)	6	40	75–80 % HR_{\max}	-13.4		388	
van de Vyver et al. (2015)	12	60 (12 \times 5 min)	15 km h ⁻¹	-10			362/4
Schwane et al. (1983)	7	45 (9 \times 5 min)	57 % $\dot{V}O_{2\max}$	-10		351	
Pokora et al. (2014)	20	60	60 % $\dot{V}O_{2\max}$	-10		307	
Park and Lee (2015)	13	40	70 % $\dot{V}O_{2\max}$ (bout 1)	-10		300	
			70 % $\dot{V}O_{2\max}$ (bout 2 ^c)	-10		80	
Close et al. (2004)	8	30	65 % $\dot{V}O_{2\max}$	-15		295	
Hickner et al. (2001)	24	30	60 % $\dot{V}O_{2\max}$ (subjects low % body fat)	-11		277	
			60 % $\dot{V}O_{2\max}$ (subjects normal % body fat)	-11		436	
Maughan et al. (1989)	16	45	75 % HR_{\max}	-21.2		275	
Westerlind et al. (1994)	6	45	50 % $\dot{V}O_{2\max}$ (bout 1)	-10		239	
			50 % $\dot{V}O_{2\max}$ (bout 2 ^b)	-10		65	
Koskinen et al. (2001)	7	45	60 % maximal aerobic speed	-17.6		222	

Table 1 continued

Study	Sample size ^a	Running duration (min)	Running speed	Slope (%)	Δ Maximal voluntary contraction (%)	Δ Peak creatine phosphokinase at 24-h (%)	Δ Peak creatine phosphokinase (%)/time for peak (h)
Byrnes et al. (1985)	22	30	Speed at 170 beats min^{-1} Bout 1	-17.6			140/6
			Bout 2 ^c	-17.6			53/6
			Bout 1	-17.6			243/6
			Bout 2 ^e	-17.6			40/6
			Bout 1	-17.6			258/20
			Bout 2 ^f	-17.6			247/20
Hardin and Hamill (2002)	24	30	12 km h^{-1}	-12		114	
Eston et al. (2000)	18	40 (5 \times 8 min)	11.2 km h^{-1} preferred stride frequency, bout 1	-12	-22	26	
			Preferred stride frequency, bout 2 ^d	-12	-18	16	
			92 % stride frequency, bout 1	-12	-26	31	
			92 % stride frequency, bout 2 ^d	-12	-20	15	
			108 % stride frequency, bout 1	-12	-26.5	25	
			108 % stride frequency, bout 2 ^d	-12	-42	13	
Malm et al. (2004)	19	45	50 % $\dot{V}\text{O}_{2\text{max}}$	-6.9		70	
Westerlind et al. (1992)	7	30	40 % $\dot{V}\text{O}_{2\text{peak}}$ (bout 1)	-10		61	
			40 % $\dot{V}\text{O}_{2\text{peak}}$ (bout 2 ^b)	-10		11	
Martin et al. (2004a, b)	11 male 9 female	30	10 km h^{-1}	-20	-13.6		
				-20	-16.4		
Rowlands et al. (2001)	18	45 (9 \times 5 min)	10.5 km h^{-1} preferred stride frequency	-14.9	-27		
			92 % preferred stride frequency	-14.9	-24.4		
			108 % preferred stride frequency	-14.9	-20.5		
Sharwood et al. (2000)	20	40	70 % peak aerobic speed	-10	-13.3		

Data are % change between pre- and post-interventions

 $\dot{V}\text{O}_2$ oxygen uptake, HR heart rate^a Males subjects unless specified; number of weeks of recovery: ^b 2; ^c 3; ^d 5; ^e 6; ^f 9

pattern variability during the downhill trail run. That is, switching between different running techniques reduces the magnitude of lower limb muscle fatigue induced by downhill running likely by changing muscle activation patterns (Giandolini et al. 2013; Shih et al. 2013; Warne and Warrington 2014) that may avoid overloading of certain muscle groups.

Interestingly, reducing body mass before exercise also seems to be a good strategy to minimize fatigue and damage in downhill running. Indeed, higher body fat mass (relative to lean mass) results in more severe muscle damage and greater decrements in leg strength after downhill running. Hickner et al. (2001) observed that the fat mass-to-fat free mass ratio accounted for a 44 % loss in muscle strength after 30 min of downhill running at 60 % of maximal $\dot{V}O_2$ and -11 % grade. Among all strategies to attenuate the negative effects of downhill running, training remains the best option. Several studies demonstrated that a previous bout of eccentric exercise produces a protective adaptation, such that, after a subsequent bout of similar exercise (the so-called ‘repeated bout effect’, e.g., Nosaka and Clarkson 1995), symptoms of muscle damage and strength loss are alleviated up to 10 weeks after exercise (Byrnes et al. 1985; Eston et al. 2000) (Table 1). This is likely due to the regeneration of previously disrupted muscle fibers leading to a ‘strengthening’ of the muscle fibers and connective tissue (Ebbeling and Clarkson 1989) after the first downhill running bout. This highlights the importance of incorporating bouts of downhill running into training programs to decrease the symptoms associated with this eccentrically based exercise. On the contrary, intermittent heat exposure before downhill running does not appear to provide protection against muscle damage (Rattray et al. 2011), confirming the results previously obtained with an acute heat exposure (Brock Symons et al. 2004).

Together, these studies suggest that downhill running induces central drive reduction and severe muscle damage resulting in delayed-onset muscle soreness and prolonged loss in muscle strength in unaccustomed subjects after downhill running. However, these symptoms can be mitigated by the adoption of proper strategies (e.g., increasing stride frequency) and incorporation of downhill running sessions in training programs.

Energy cost versus heat storage

Large inter-individual thermoregulatory responses to exercise exist (Cramer and Jay 2015). Traditionally, it was thought that the increase in body temperature was proportional to the percentage of maximal $\dot{V}O_2$, and not to absolute metabolic rate; however, this idea has been challenged. For instance, mass and body surface area-matched participants with heterogeneous maximal $\dot{V}O_2$ exercising at the

same level of heat production have demonstrated similar changes in core temperature, despite very different percentages of maximal $\dot{V}O_2$ (Jay and Cramer 2011). Core temperature increases with exercise intensity but does not seem to depend on contraction mode. Indeed, core temperature was similar at the same metabolic rate in downhill, level, and uphill work (Nielsen 1966).

$\dot{V}O_2$ is usually lower in downhill running compared with uphill running when running speed can be self-selected (Townshend et al. 2010). One could conclude that the increase in core temperature tends to be slightly lower in downhill running. However, in downhill running (i.e., negative work), the potential energy is converted into heat in the muscles, and the total heat liberation becomes greater than the metabolic rate (Nielsen et al. 1972). Thus, contrary to cycling, and despite higher running velocity compared with level and uphill running (i.e., higher heat dissipation due to convection), thermal stress will still be elevated in downhill running, which induces potential consequences in terms of central fatigue (Nielsen and Nybo 2003) and dehydration. Regarding the latter point, cardiac output and muscle blood flow at equal $\dot{V}O_2$ are the same for both types of contractions, despite more work being done in eccentric versus concentric exercise; however, skin blood flow may be higher during negative work (Nielsen et al. 1972). Local muscle temperature is the net result of the regional heat balance (i.e., the balance between the amount of heat liberated in the muscle and the heat transported by blood flow). As such, the extra heat produced during negative work demands a certain blood flow to be removed and carried to the skin from where it is dissipated. Finally, recent evidence suggests the important roles of body size and body fat, not only for heat transfer but also for cutaneous vascular and sudomotor responses (Cramer and Jay 2015; Notley et al. 2016). In this context, while this is not supported by scientific literature, it is generally accepted that anthropometric characteristics are different between road runners (mostly level running) and trail runners (graded running) (Millet et al. 2012).

Specificity of fatigue associated with uphill running

Uphill versus level running: increased metabolic response

Uphill running training is regularly used in the training programs of athletes running mostly or only on level ground. Despite the scarcity of research (Ferley et al. 2014), uphill running training is believed to improve power and neuromuscular function in ways similar to ‘classic’ resistance training, such as heavy load strength training, explosive

strength training, and plyometric training. As for traditional strength training (Balsalobre-Fernandez et al. 2015), uphill running training may also improve energy cost (Barnes et al. 2013), although opposite results have also been reported (Ferley et al. 2014). Studies comparing the chronic effects of level versus uphill running are rare, as are studies investigating acute effects. One study revealed that uphill running on a 10 % slope at a velocity equal to 68 % of the velocity associated with maximal $\dot{V}O_2$ in level running resulted in the same time to exhaustion as level running at 100 % of the velocity associated with maximal $\dot{V}O_2$ (Ferley and Vukovich 2015).

During a low-intensity exercise, $\dot{V}O_2$ plateaus following the rapid increase in oxygen consumption encompassed in the primary phase. At higher intensity, $\dot{V}O_2$ continues to gradually increase beyond what would have been estimated based on extrapolation of sub-threshold values. This rise is termed $\dot{V}O_2$ slow component and is defined as the rate of additional oxygen consumed following the completion of the primary component, where a steady state would have occurred at lower intensities. An increased contribution of concentric muscle activation due to peripheral fatigue induced by uphill running may lead to a greater $\dot{V}O_2$ slow component. Unfortunately, the only two studies that have examined this question are contradictory. Pringle et al. (2002) showed a 40 % higher $\dot{V}O_2$ slow component during uphill running at 10 % grade, whereas Reis et al. (2007) reported no difference in $\dot{V}O_2$ slow component between level and uphill running at 10.5 %. Reasons for this difference may include both the subjects' training status and habituation to uphill running training as well as differences in study design (e.g., assessment of the intensity domains). Pulled running (i.e., being pulled adding therefore braking horizontal forces) can be used as a surrogate of uphill running (Gimenez et al. 2014). The effects of high-intensity pulled running on changes in $\dot{V}O_2$, ground reaction forces, and muscle activity have been investigated (Avogadro et al. 2004). It was concluded that the $\dot{V}O_2$ slow component was not due to an increased mechanical work/muscle activity, so that the hypothesis of progressive recruitment of type II fibers was proposed but never demonstrated. No direct comparison with level running was done in that study, but the main findings (i.e., amplitude of the slow component, no increase in mechanical work) were similar to the results published in a level running study from the same group in level running (Avogadro et al. 2003).

Uphill versus downhill running: similarities and differences of fatigue

As described above, downhill running represents a good model to study the effects of fatigue associated with eccentrically based exercise. A few studies have analyzed fatigue

following uphill running, probably because concentric-based exercise is easier to investigate using cycling. Lattier et al. (2004) investigated $\times 1$ -min uphill running bouts at 120 % of maximal aerobic velocity at +18 % grade and reported that muscle fatigue (i.e., $a \sim 7$ % decrease in maximal voluntary contraction) was mainly due to significant alterations in peripheral fatigue as suggested by the large modifications of twitch contractile properties. Interestingly, low-frequency fatigue was also detected (Fig. 2); however, the cause of excitation–contraction coupling failure is likely very different than the low-frequency fatigue induced by downhill running/eccentric exercise. In high-intensity running, the role of inorganic phosphate may play a major role in low-frequency fatigue. Pi might enter the sarcoplasmic reticulum during fatigue and precipitate with Ca^{2+} –Pi, thus reducing the free Ca^{2+} available for release from the sarcoplasmic reticulum (Allen and Westerblad 2001). Yet, the presence of muscle damage cannot be completely ruled out. Surprisingly, Malm et al. (2004) observed that after 45 min of uphill running at +6.9 %, the creatine kinase concentration was ~ 290 UI L⁻¹, which is 200 % higher than downhill running at –6.9 % grade (~ 96 UI L⁻¹). However, because of the different running speeds examined (75 versus 50 % of maximal $\dot{V}O_2$ for uphill running and downhill running, respectively), these results may be biased by relative differences in exercise intensity. Indeed, Pokora et al. (2014) showed that after 1 h of uphill running at 60 % of maximal $\dot{V}O_2$ and +10 % grade, the creatine kinase activity illustrated no significant change, whereas a 307 % increase was observed after downhill running at the same relative intensity.

Lazzer et al. (2015) observed that after an extreme uphill marathon (“Supermaratona dell’Etna,” mean race duration: ~ 5 h 30 min/distance: 43 km; positive elevation change of ~ 3000 m), energy cost increased by 8.7 % paralleled by changes in running biomechanics (including increases in contact time and in vertical oscillations, and decreases in flight time, step frequency, and vertical and leg stiffness). The biomechanical changes in gait pattern were very different compared to those described above after ultra-trail running with both uphill and downhill bouts, especially regarding decreased step frequency and lower limb stiffness. However, due to the much lower eccentric load involved in this uphill marathon, the runners may not have needed to adopt a ‘safer’ and ‘smoother’ running motion. In the same experiment performed on the “Supermaratona dell’Etna,” these authors (Giovannelli et al. 2015) recently reported that the maximal mechanical power of lower limbs, assessed by a counter movement jump, was inversely correlated with changes in running biomechanics induced by fatigue. They concluded that lower limb power training could improve performance in prolonged uphill running. However, we are not aware of any study

investigating the effects of a prolonged low-intensity downhill running bout.

Conclusions and future directions

In conclusion, specific effects of eccentric versus concentric mode of contractions, traditionally studied during single-joint exercises, are observed when considering lower limb extensor fatigue in downhill versus uphill running. The observed decrease in maximal voluntary force is mainly related to mechanical damage and metabolic fatigue in downhill and uphill running, respectively. It potentially induces an increased energy cost of running as well as failure in excitation–contraction coupling in both grades, yet the reasons behind these changes are different between uphill and downhill running. In view of the neuromuscular, mechanical, and metabolic disturbances induced by uphill and downhill running, one could wonder which section(s) is/are the most strenuous and determinant for the overall performance during trail running. From a strategic point of view, it also raises the question of optimal pacing strategies to limit fatigue and tissue damage and improve performance, especially during ultra-trail running. This strategy may also depend on the metabolic and neuromuscular qualities of the runner. For instance, the uphill/downhill pacing strategy of a runner with a good resistance to muscle damage, but a relatively low maximal $\dot{V}O_2$ will be different compared to that of a road runner with a high maximal $\dot{V}O_2$, but less experience and/or less resistance to eccentric contraction in downhill. While this review provides useful information to improve performance during hilly running events, future studies should first confirm the role of pain versus fatigue on running biomechanics modification and the associated energy cost deterioration by using experimental muscle pain such as intramuscular injection of hypertonic saline. Second, there is the need to assess the effectiveness of other strategies (e.g., running technique, footwear) both to minimize fatigue and damage as well as to limit the deterioration of the energy cost and, thus, improve the performance during downhill running. Finally, future studies should compare the benefits of different pacing strategies on the overall performance during trail and ultra-trail events.

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