Chronic Exercise Activity and the Fatigued Athlete Myopathic Syndrome (FAMS)

A St Clair Gibson, MI Lambert, M Collins, L Grobler, KA Sharwood, EW Derman, and TD Noakes

There is recent evidence to suggest that long-term endurance training of high mileage may result in cumulative, irreversible muscle damage. This muscle damage includes poor organization of muscle fascicles, abundant connective tissue, increased internal nuclei, changes in cytoskeletal muscle proteins and, in particular, mitochondrial pathology. The fatigued athlete myopathic syndrome (FAMS) describes athletes who present with chronic fatigue and evidence of these muscle abnormalities. The symptoms of FAMS vary, but the common features of athletes with this syndrome are (i) a history of high-volume training for many years, who present with decreased exercise performance and a clinical picture dominated by skeletal muscle symptoms, and (ii) a history of consulting many clinicians unsuccessfully. It is still not clear how the muscle pathology relates to the symptoms of fatigue in FAMS individuals. Theories include (1) chronically activated afferent nerve fibers from chemoreceptors, golgi tendons, or nociceptors in the damaged muscles; (2) changes in the hypothalamic-pituitary-adrenal axis impinging on cortical or midbrain structures; (3) changes in brain structures themselves either as a result of, or unrelated to, the muscle damage; and (4) the symptoms of fatigue may be part of a clinical depression in the FAMS individual due to the affect on his/her lifestyle or psychological makeup of the deterioration in their athletic performance. Further work is required to isolate which of these causes is responsible for the onset of FAMS in susceptible, exercising individuals.

Key Words: fatigue, mitochondria, muscle, myopathy, fatigued athlete myopathic syndrome, chronic fatigue

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• Long-term endurance training of high mileage may result in cumulative, irreversible muscle damage.

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Introduction

Regular exercise is widely regarded as being beneficial to an individual, by reducing cardio-vascular risk factors and increasing longevity (1, 2). Recently, however, there has been speculation that excessive exercise may be deleterious to various biological systems (3, 4). The finding that participation in unaccustomed exercise results in transient short-term muscle damage is well-documented (5, 6). Other studies have shown that acute high-intensity exercise causes damage to the mitochondrial cell membrane and DNA (7). One may speculate as to whether repetitive bouts of this acute muscle damage results in premature ageing and decreased longevity, but as yet there is no firm evidence that such a causal relationship exists (3, 8).

In this review, the existing evidence regarding the effect of chronic exposure to high-intensity or endurance exercise on skeletal muscle and other tissues is examined. Mechanisms explaining how this damage is related to the central nervous system symptoms of chronic fatigue are suggested. The combination of muscle damage and fatigue has recently been described as the fatigued athlete myopathic syndrome (FAMS) (9, 10).
Skeletal Muscle Pathology Associated With High Volume Training: A Case Description

St Clair Gibson et al. (8) described a 28-year-old male runner who experienced a sudden decline in running performance and an inability to tolerate high training loads. The subject began running at the age of 12 years and by the age of 19 years was the national junior running champion with a best 10-km time of 28:35 (min:s). Although this athlete was accustomed to high-volume, high-intensity training (about 6,000 km per year), he suffered repeated bouts of overtraining (11, 12), including physical exhaustion, fatigue, weakness in his lower limbs and recurrent upper respiratory tract infections. These symptoms became increasingly regular and eventually became chronic and continuous, resulting in the athlete never returning to the level of training and racing that he had previously achieved. His training distance and 10-km running times declined during the 4 years following the onset of his symptoms (Figure 1). After consultation with a physician who diagnosed him as clinically depressed, fluoxetine hydrochloride (Prozac) was prescribed for 3 months in an attempt to improve his physical and mental symptoms. This medication had no effect on his symptoms.

Medical examination revealed no obvious clinical pathology. A vastus lateralis muscle biopsy revealed a predominance of slow twitch fibers, with no signs of inflammation, necrosis or excessive muscle fiber regeneration. The mitochondria, however, were grossly abnormal, varying in size and containing a dense matrix with an increased number of coarse and broad cristae. The abnormal mitochondria were observed in large subsarcolemmal aggregates (Figure 2). A muscle biopsy, taken from the triceps muscle, was completely normal (Figure 3), with no visible damaged muscle fibers or mitochondria. The authors concluded that the mitochondrial myopathy in the vastus lateralis either: (i) existed previously but was undiagnosed, (ii) was acquired as a result of unknown agents, or (iii) was acquired after prolonged training. The fact that the myopathy was localized to the lower limbs suggests that this was not a classical mitochondrial myopathy and was caused rather by (ii) or (iii).

Another example of mitochondrial pathology associated with excessive exercise was that of the American cyclist Greg LeMond, who won the Tour de France three times, and the world championship twice. His performance decreased dramatically, and muscle biopsies of his lower limb showed similar mitochondrial pathology to that described above. His physician concluded that this pathology was caused either by his chronic exercise activity or from lead poisoning resulting from a shooting accident that left pellets in his body (13).

Derman et al. (9) described a clinical syndrome to explain this pathology—the fatigued athlete myopathic syndrome (FAMS). Similar symptoms of chronic fatigue and associated muscle pathology

Figure 1 — (a) Subject’s fastest average running speed for 10 km for each year from the age of 17 to 28 years compared to the U.S. record for each age. (b) Patient’s total training distance for each year.

Figure 2 — Electron micrograph from the subject’s vastus lateralis muscle showing large mitochondria with dense matrices and coarse, abnormal cristae. A normal mitochondria in the center of the figure (original magnification, x35,040).
Mechanisms of Muscle Damage in Chronic Exercise Activity

Research has shown that muscle may be acutely damaged by either high-intensity or endurance activity (7). Muscle glycogen concentrations, depleted immediately after a marathon, remain low 5 days after the event, indicating possible pathological alteration in the glycogen synthesis pathways (14, 15). It has been suggested that these changes are either due to mechanical damage to muscle cell membranes, resulting in damage to glucose transporters (16), or to alterations in the muscle cell response to glucocorticoid hormones (15).

Muscle biopsies performed on runners immediately after a marathon or high-intensity exercise, showed severe muscle damage, with signs of fiber necrosis and inflammation (17, 18, 19). In a similar study of runners after a marathon race, up to 25% of the muscle fibers showed areas of myofibrillar loss (20). Intra- and extracellular edema with endothelial injury, myofibrillar lysis, dilation and disruption of the t-tubule system, and focal mitochondrial degeneration without inflammatory infiltrate was also present. It is not clear whether these changes were the result of oxygen-derived free-radical damage (21, 22) or muscle cell membrane disruption leading to calcium-mediated cell damage to the individual muscle fibers (23).

Damage to the cytoskeletal muscle proteins (desmin, titin, and nebulin), that are responsible for structural integrity and muscle elasticity, have been implicated as a cause of the symptoms in FAMS athletes. Studies have shown that within the first few minutes of eccentric activity, desmin in particular is degraded in damaged muscle (7, 24). Similarly, it has been suggested that damage to the titin molecule may cause a common FAMS symptom, where athletes complain that they have lost their muscle “springiness,” resulting in a “shuffling” gait during training and endurance exercise (10, St Clair Gibson; unpublished observations). In addition to the soft tissue of the lower limb, the bones of the lower limbs also show signs of overuse stress (25).

Research has also shown that these pathological changes induced by exercise activity may have long-term implications on muscle structure and function. Sherman et al. (14) showed that isokinetic leg extensor strength was reduced immediately after a 42-km footrace and was not fully recovered 7 days after the event. Chambers et al. (26) showed that vertical jump height, a measure of leg extensor muscle power, was significantly decreased immediately after a 90-km race, and remained significantly lower than pre-race values for 18 days. Warhol et al. (20) showed that signs of muscle regeneration were present 12 weeks after a 42-km marathon. In addition, alterations in neural activation were demonstrated during both the braking and push-off phases of the running cycle after a 42-km footrace. These changes were maintained for a period of time after the marathon (27, 28).

Evidence from top-class marathon runners suggests that there is approximately a 10-year period during which they can expect to perform well in their age group (29, 30). Thereafter, a decline in marathon running performance seems to occur at a faster rate than is expected for their age. This anecdotal observation supports the hypothesis that there is
cumulative fatigue after many years of excessive training and racing, which results in skeletal muscle aging at a faster rate than is expected.

Scientific proof to support this anecdotal observation is emerging. Kuipers et al. (12) studied runners over a 7-month period while they trained for a marathon. They found a gradual increase in degenerative changes in both type I and type II fibers in the subjects’ vastus lateralis muscles over the 7-month period. These authors suggested that the pathological changes were minor and were related to the total distance covered in training rather the intensity of training. However, abnormal mitochondria and signs of muscle fiber regeneration and inflammation have been found in “resting” and post-exercise muscle biopsies of experienced marathon runners (17, 20, 31). Sjöström et al. (4) studied national class runners and found that the overall morphological picture of the marathon runners varied between individuals. Only one of the five runners in the study had normal muscle structure. The abnormalities in the muscle biopsies collected before the race included a poor organization of muscle fascicles, abundant connective tissue, and an excessive level of internal nuclei found in a majority of fibers. Other abnormalities included flat angular fibers and fiber type grouping, both pathognomonic of denervation atrophy (32, 33) and incomplete regeneration. Recently, Sharwood et al. (34) found that runners who had raced an accumulated distance of greater than 5,000 km showed a significant dissociation in neuromuscular efficiency after a downhill run compared to less experienced runners. They concluded that cumulative muscle damage might negatively affect central responses during fatigue caused by an exercise protocol with a large eccentric component.

There is much evidence to suggest that long-term endurance training of high intensity and mileage may result in cumulative irreversible muscle damage. This muscle damage may be related to the onset or existence of the fatigued athlete myopathic syndrome. Although speculative, evidence indicates that there may be a finite capacity for muscle regeneration which, when exceeded, initiates the onset of FAMS and the deterioration of athletic performance.

The Relationship Between Muscle Damage and Fatigue Symptoms in FAMS

While there may be a strong link between muscle damage and the symptoms of chronic fatigue present in the FAMS athletes, a causal relationship between the two has yet to be established. Indeed, fatigue as exhibited in the chronic fatigue syndrome and FAMS athletes, shows the complexity of the relationship between fatigue and physiological processes. Individuals with chronic fatigue syndrome describe symptoms of fatigue, even at rest. Any activity is performed with difficulty and is initiated with reluctance. Yet, when tested for maximal voluntary force output, these individuals are able to perform similar levels of maximal force compared to asymptomatic athletic individuals (35; St Clair Gibson, unpublished observations). Because of this finding, and because a single pathological entity causing fatigue has not been elicited, Enoka and Stuart (35) have suggested that the source of the fatigue signal lies “above the level of the motor cortex.”

Fatigue therefore may not only be a physiological process, but also a symptom or external signal of underlying central processes that occurs either during or in the absence of exercise performance. The finding that fatigue occurs at rest in cases of chronic fatigue syndrome indicates that as an entity or sensory process, fatigue is, at best, poorly correlated to the underlying physiological process or metabolic perturbation originally suggested as a cause of fatigue during exercise. Similarly, the symptoms of fatigue are felt after a long period of concentration without any physical activity, suggesting that fatigue, as a signal or thought process, originates in regions of the brain involved in higher mental functioning. These regions may be the limbic system, reticular formation, or other brain structures involved in setting arousal states in the normally functioning individual.

One can therefore postulate four possible mechanisms for the relationship between chronic muscle damage and the symptoms of fatigue in FAMS athletes. Firstly, afferent signals from the damaged muscle may be chronically activated and induce symptoms of fatigue as a protective mechanism to prevent further exercise activity and further resultant muscle damage. These afferent signals may be derived from nociceptors (pain receptors) in the damaged muscle, from muscle spindle or golgi tendon organs activated by mismatches in neuromuscular efficiency due to muscle damage (34), or from type iii or iv chemoreceptors responding to continuous regenerative processes in the damaged muscles.

Secondly, changes in the hypothalamic-pituitary-adrenal axis, caused by chronic overtraining, may result in changes in cortisol concentrations in the periphery, which contribute to muscle damage, and changes in neurotransmitter signals from the hypothalamic nuclei, impinging on cortical or midbrain structures involved in fatigue (36) resulting
in increased symptoms of fatigue. This would indicate an indirect link between the muscle damage and fatigue symptoms.

Thirdly, changes in the brain structures themselves, unrelated to the muscle damage, caused by the chronic exercise activity, may lead to chronic fatigue symptoms. This may be either “hardwiring” of the cortical impulses as a physiological protective mechanism, or pathological damage to either neurotransmitter release processes or cortical or midbrain cellular structures caused by the chronic excessive exercise activity.

Fourthly, the symptoms of fatigue may be part of a syndrome of clinical depression in the FAMS individual due to the affect on lifestyle or psychological makeup of the deterioration in performance. Indeed, a number of FAMS subjects who consulted medical doctors about their deteriorating athletic performance were diagnosed as being depressed and prescribed anti-depressant medication (8; St Clair Gibson, unpublished observations).

Finally, the symptoms of fatigue may be unrelated to the muscle pathology described in the FAMS subjects, but may be caused by infectious agents or disease processes not elucidated by the research methods described in this review. Evidence of previous episodes of Ebstein-Barr virus were found in most of the FAMS athletes, and perhaps the clinical symptoms of fatigue are related rather to a subclinical undiagnosed or recurring mild form of glandular fever or other medical entity.

**Summary**

In a number of athletes with symptoms of chronic fatigue and reduced performance capacity, evidence of muscle pathology, particularly in the mitochondria but also involving the myofibrillar cytoskeletal proteins, have been identified. This syndrome has been defined as the fatigued athlete myopathic syndrome. A direct relationship between the muscle pathology and symptoms of chronic fatigue has not been clearly proven, and further work is therefore required to isolate whether one or several of the causes of fatigue described above is responsible for the onset of FAMS in an exercising individual. Further research is also needed to assess why only a small percentage of athletes develop FAMS, and whether these athletes have a unique susceptibility or genetic predisposition to the development of muscle damage from chronic exercise. This work has implications for the prescription of exercise and training to athletes in the future.

**References**


