

## ORIGINAL ARTICLE

## Skeletal muscle pathology in endurance athletes with acquired training intolerance

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**Background:** It is well established that prolonged, exhaustive endurance exercise is capable of inducing skeletal muscle damage and temporary impairment of muscle function. Although skeletal muscle has a remarkable capacity for repair and adaptation, this may be limited, ultimately resulting in an accumulation of chronic skeletal muscle pathology. Case studies have alluded to an association between long term, high volume endurance training and racing, acquired training intolerance, and chronic skeletal muscle pathology.

**Objective:** To systematically compare the skeletal muscle structural and ultrastructural status of endurance athletes with acquired training intolerance (ATI group) with asymptomatic endurance athletes matched for age and years of endurance training (CON group).

**Methods:** Histological and electron microscopic analyses were carried out on a biopsy sample of the vastus lateralis from 18 ATI and 17 CON endurance athletes. The presence of structural and ultrastructural disruptions was compared between the two groups of athletes.

**Results:** Significantly more athletes in the ATI group than in the CON group presented with fibre size variation (15 v 6;  $p = 0.006$ ), internal nuclei (9 v 2;  $p = 0.03$ ), and z disc streaming (6 v 0;  $p = 0.02$ ).

**Conclusions:** There is an association between increased skeletal muscle disruptions and acquired training intolerance in endurance athletes. Further studies are required to determine the nature of this association and the possible mechanisms involved.

It is well established that prolonged, exhaustive endurance exercise can induce skeletal muscle damage and temporary impairment of muscle function.<sup>1–10</sup> Although skeletal muscle has a remarkable capacity for repair and adaptation,<sup>5 6 11–13</sup> research on exercise induced muscle damage,<sup>1 3 4 8 14–16</sup> aging,<sup>17–20</sup> and the overtraining syndrome<sup>21 22</sup> suggest that this capacity may be limited.

Under experimental conditions in which the skeletal muscle is damaged in a controlled manner and the research subject is forced to rest, allowing the muscle adequate time to repair and adapt, the regeneration process is complete, and normal muscle function and morphology are fully regained.<sup>11 23–27</sup> In reality, however, most endurance athletes train six or seven days a week and often begin training again within 24–48 hours after a race. This despite evidence that the repair process after a 42.2 km road race takes 1–10 weeks to be completed.<sup>8 10</sup> Many endurance athletes train and race in this manner for several years, incurring repeated muscle damage which requires repair and regeneration. This raises the question: what are the long term, cumulative effects of repeated bouts of muscle damaging endurance training and racing, and potentially incomplete repair, on skeletal muscle function and morphology?

Case studies suggest an association between long term, high volume endurance training and racing and chronic skeletal muscle damage. For example, St Clair Gibson *et al*<sup>16</sup> described a 28 year old international male runner who experienced a sudden decline in running performance and an inability to tolerate high training loads. Analysis of a vastus lateralis biopsy sample revealed a predominance of type I fibres with no signs of inflammation, necrosis, or excessive regeneration. The mitochondria, however, were grossly abnormal. In contrast, a biopsy sample from the triceps muscle of the same subject showed no signs of abnormality.

Sjöström *et al*<sup>3</sup> studied a previously well trained (10000 km/year) 46 year old man, who ran a distance of 3529 km in

seven weeks. After the race, signs of neuromuscular pathology and skeletal muscle ultrastructural abnormalities were revealed by light microscopic analysis, and the subject's running speed continuously decreased. Although no causality between the ultrastructural abnormalities and running speed was established, it is tempting to speculate that the decreased performance resulted from the chronic skeletal muscle damage and the inability of the muscles to recover fully from this state of damage/degeneration.

Rowbottom *et al*<sup>28</sup> reported a decrement in performance capacity of a previously elite ultraendurance male cyclist who developed chronic fatigue syndrome. Although no skeletal muscle ultrastructural abnormalities were noted, the case further supports a possible association between ultraendurance activity, chronic fatigue, and decreased performance capacity. Similarly, Derman *et al*<sup>29</sup> described a group of endurance athletes with exercise associated chronic fatigue. The clinical condition of these athletes was called "fatigued athlete myopathic syndrome". The common characteristics among these athletes were a history of high volume endurance training and racing, a precipitous decline in running performance that was not related to ordinary aging, and an inability to tolerate and adapt to previously accustomed exercise training loads. The clinical profile of these athletes was dominated by skeletal muscle symptoms, including excessive delayed onset muscle soreness and muscle stiffness, tenderness, and weakness. On investigation, structural and ultrastructural abnormalities of the skeletal muscle typical of exercise induced muscle degeneration/regeneration were noted. The physical symptoms were not consistent with the acute consequences of overtraining, as, in most cases, the training loads of the athletes were significantly reduced, and extensive rest periods did not alleviate the symptoms, as would occur with overtraining.<sup>29 30</sup>

No study has systematically examined the impact of repeated bouts of muscle damage and repair over a number

**Table 1** Descriptive and physiological characteristics of acquired training intolerance (ATI) and control (CON) athletes

	ATI (n = 18)	CON (n = 17)
Males	14	10
Females	4	7
Age (years)	42 (8) (27–57)	39 (11) (24–56)
Height (cm)	174.0 (9.5) (153–187)	172.0 (8.7) (160–180)
Weight (kg)	76 (17) (51–110)	70 (11) (49–91)
% Body fat	22 (6) (13–31)	19 (6) (9–27)
VO <sub>2</sub> MAX		
(ml/kg/min)	50 (9) (31–68)	56 (10) (42–73)
MVC (N)	571 (166) (270–843)	568 (136) (372–825)

Values are expressed as mean (SD) (range).  
MVC, Maximal voluntary contraction.

of years on the structure and function of skeletal muscle. Accordingly, the aim of this study was to compare the presence of chronic skeletal muscle structural and ultrastructural pathology in endurance athletes who presented with a similar clinical and physiological profile to the subjects previously defined by Derman *et al*<sup>29</sup>—that is, decreased performance, training intolerance, and exercise associated chronic fatigue—with asymptomatic endurance athletes matched for age and years of endurance training.

## METHODS

### Subjects

The research ethics committee of the Faculty of Health Sciences at the University of Cape Town approved the study. Eighteen endurance trained athletes (12 runners, two cyclists, one rower, one canoeist, one squash player, one triathlete) with an extensive history of high volume endurance training and racing, clinical symptoms of skeletal muscle stiffness, tenderness, and weakness, acquired training intolerance, exercise associated chronic fatigue, and a precipitous decline in racing performance were recruited from the Sports Medicine Clinic at the Sports Science Institute of South Africa. These athletes had typically consulted a number of other clinicians without obtaining a successful diagnosis. Their physical symptoms were not consistent with classical overtraining, as in most cases they had radically reduced their training loads, and extensive rest periods did not alleviate the symptoms, as would occur with overtraining.<sup>29–30</sup> A sports doctor examined them before their participation in the trial in order to exclude chronic fatigue syndrome<sup>31</sup> or a related diseased state as possible diagnoses for their symptoms. Clinical characteristics and recognised skeletal muscle pathological features, including those associated with the muscular dystrophies and mitochondrial myopathies, were also excluded during the medical workup. The most commonly reported “symptom” that led these athletes to seek medical advice was acquired training intolerance (ATI)—that is, they were unable to tolerate endurance training loads to which they were previously accustomed.

Seventeen control athletes, without symptoms or signs of chronic fatigue or exercise training intolerance, were recruited from local running clubs (CON group). They were matched with the athletes with ATI for age and years of endurance training before the onset of ATI. A sports doctor also examined these athletes before their participation in the trial.

Informed consent was received from all the athletes before testing. On the day of testing, all subjects completed a retrospective training and racing questionnaire. The endurance runners and triathletes recalled their endurance training history from the age at which they started running more than

40 km a week. The endurance cyclists recalled their endurance training history from the age at which they cycled more than 150 km a week. The squash player and rower recalled their endurance training history from the age at which they participated in sport specific training for more than four hours a week. All subjects recalled the age at which they started high volume endurance training, the number of years of high volume endurance training, and their training volume (days/week, hours/week, and km/week) during this period. Athletes with ATI recalled their training volume both before and after the onset of symptoms of ATI.

### Anthropometry, exercise tolerance, and muscle function

All subjects were instructed to refrain from any strenuous or unaccustomed exercise for at least 72 hours before the test day. Body fat was assessed as the sum of seven skinfolds (biceps, triceps, subscapular, suprailiac, abdomen, thigh, and calf),<sup>32</sup> and stature and body mass were measured. Maximal oxygen uptake (VO<sub>2</sub>MAX) was determined after an incremental treadmill test to exhaustion as previously described.<sup>33</sup> The maximal voluntary isometric force output of the right knee extensor muscles of each subject was measured using a Kin-Com isokinetic dynamometer (Chattanooga Group Inc, Hixson, Texas, USA) as described previously.<sup>34</sup>

### Skeletal muscle biopsy and morphological analyses

A biopsy specimen of the vastus lateralis was obtained from each subject using the percutaneous needle biopsy technique of Bergstrom,<sup>35</sup> as modified by Evans *et al*.<sup>36</sup> Muscle was sampled from the same site on each subject: about 15 cm from the proximal border of the patella, at the midline of the vastus lateralis. A portion of the muscle sample was mounted on a piece of cork with embedding medium (Tissue-Tek; Miles Laboratories Inc, Naperville, Illinois, USA), frozen in liquid nitrogen-cooled isopentane, and stored at  $-20^{\circ}\text{C}$  for histological analysis.

Various histological stains (haematoxylin and eosin, gomori trichrome, succinate dehydrogenase, and NADH-tetrazolium reductase) were used to assess the presence of internal nuclei, variation in muscle fibre size, necrosis/inflammation, and subsarcolemmal aggregations of mitochondria. All are typical markers of skeletal muscle structural pathology. Proportions of muscle fibre types were determined using the myofibrillar myosin ATPase method.<sup>37</sup> On the basis of myosin ATPase activity, the fibres were classified as type I, IIA, IIB, and IIC, according to the nomenclature of Brooke *et al*.<sup>37</sup> Images of the stained sections were captured using an interactive graphic digitiser (Carl Zeiss “Axioplan” 2 MOT). Between 10 and 15 images were captured, and 400 fibres were counted per subject. Each fibre type was expressed as a percentage of the total number of fibres counted.

The remaining portion of the muscle sample was placed in chilled ( $4^{\circ}\text{C}$ ) fixative (3% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.2). After the initial fixation, the tissue samples were rinsed in cacodylate buffer, postfixed, stained with osmium tetroxide and uranyl acetate, dehydrated in graded ethyl alcohol, and then infiltrated and embedded in Spurr’s epoxy resin. Ultrathin sections of the tissue blocks were cut and stained with uranyl acetate and lead citrate. The sections were mounted on copper grids and viewed through a Phillips 201 electron microscope. The presence of z disc streaming, focal deletions of myofibrils, atrophic muscle fibres, enlarged mitochondria (mitochondria extend over the length of two sarcomeres), subsarcolemmal mitochondria, and lipid and glycogen accumulations, all of which are markers of skeletal muscle ultrastructural pathology,<sup>38</sup> were then determined. Sections containing hypercontracted muscle fibres were not

**Table 2** High volume endurance training history of the control (CON) and acquired training intolerance (ATI) athletes before and after the onset of symptoms

Training history	CON (n = 17)	ATI (n = 18)	
		Before	After
Age started high volume endurance training (years)	27 (10) (12–47)	27 (9) (13–44)	
Years of high volume endurance training	13 (5) (4–22)	12 (6) (3–25)	
Training (days/week)	5 (1) (3–7)	6 (1)* (4–7)	4 (3)† (0–7)
Training (km/week)‡	50 (25) (15–130)	87 (29)** (45–160)	32 (34)†† (0–100)
Training (hours/week)	5 (2) (2–13)	9 (5)*** (3–24)	3 (3)††† (0–9)

Values are mean (SD) (range).

‡The training distances of the squash player, the rower, and the two cyclists were excluded from this analysis.

\*p = 0.002, \*\*p = 0.0003, \*\*\*p = 0.02 compared with the control group.

†p = 0.0003, ††p = 0.0002, †††p = 0.001 compared with before the onset of symptoms.

analysed. Owing to technical problems, no electron microscopy data were obtained for one ATI and one CON athlete.

A pathologist, blinded to the identity and physical condition of the subject, screened and scored the muscle samples. A score of 0 represented an apparently normal muscle sample from a physically active, healthy person, with no visible signs of pathology. Scores of 1+ to 3+ indicated the increasing presence of various markers of skeletal muscle pathology. To ensure repeatability and true and accurate diagnosis, the same pathologist analysed and scored the samples three times until good agreement, defined by kappa statistics, was obtained between successive analyses.<sup>39–41</sup>

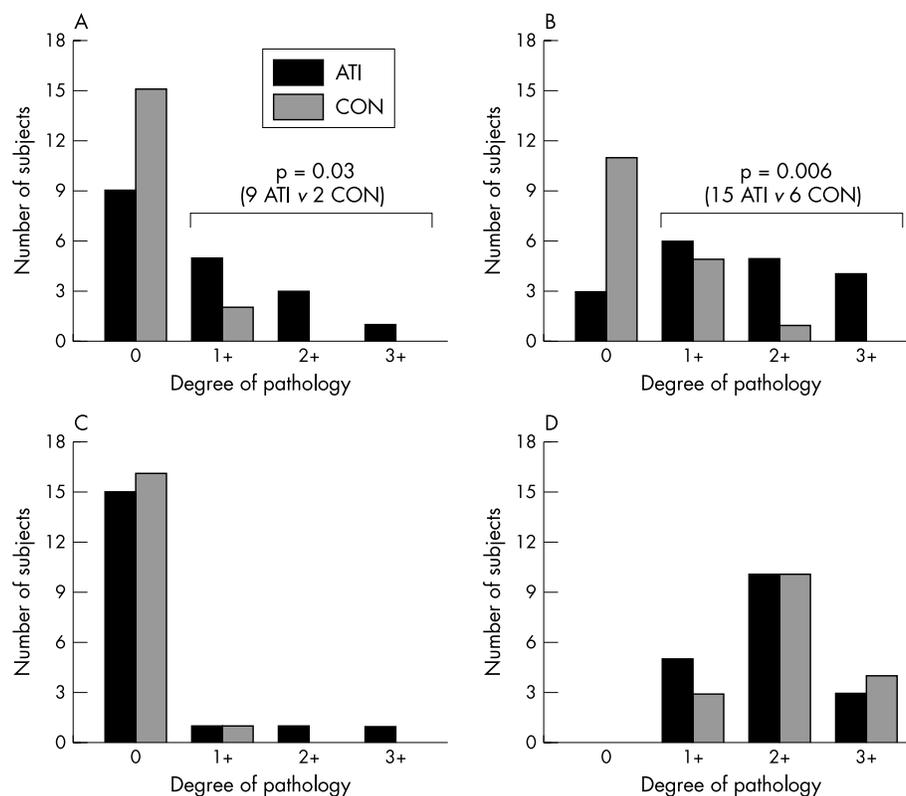
### Statistical analysis

Descriptive statistics are expressed as mean (SD). An independent *t* test was used to determine if there were any significant differences in the fibre type composition and

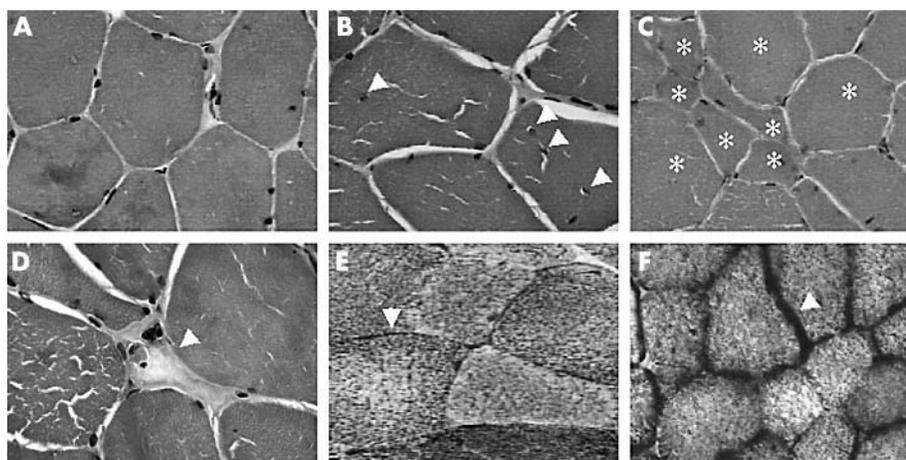
descriptive, physiological, and endurance training characteristics of the ATI and CON athletes.

A kappa statistic ( $\kappa$ )<sup>39–41</sup> was calculated to ascertain the level of agreement between the successive scores of the pathologist. An acceptable kappa score ( $\kappa = 0.8$ ) was obtained between the second and third observation for all the categories, except the category that rated the degree of accumulation of subsarcolemmal mitochondria. For this category,  $\kappa = 0.22$  was obtained, indicating only a fair agreement between repeated observations.

The pathology scores, determined on the third occasion by the pathologist for both the ATI and CON group, were divided into two groups, with a score of 0 indicating no pathology and scores of 1+, 2+, or 3+ indicating the presence of pathology. A Fisher's exact two tailed  $\chi^2$  test was used to determine if there was a significant difference ( $p < 0.05$ ) in the sex ratio between the two groups and in the proportion of



**Figure 1** Proportion of acquired training intolerance (ATI; n = 18) and control (CON; n = 17) athletes presenting with various markers of skeletal muscle structural pathology. (A) Internal nuclei; (B) fibre size variation; (C) necrosis/inflammation; (D) subsarcolemmal aggregation of mitochondria.



**Figure 2** Light micrographs showing typical markers of skeletal muscle structural pathology. (A) Control sample (haematoxylin and eosin stain,  $\times 40$ ); (B) 3+ internal nuclei, indicated by arrowheads (haematoxylin and eosin stain,  $\times 40$ ); (C) 3+ muscle fibre size variation, indicated by asterisks (haematoxylin and eosin stain,  $\times 40$ ); (D) necrotic cell indicated by an arrowhead (haematoxylin and eosin stain,  $\times 40$ ); (E) control sample with subsarcolemmal mitochondria, indicated by the arrowhead (NADH-tetrazolium reductase stain,  $\times 40$ ); (F) 3+ aggregations of subsarcolemmal mitochondria, indicated by the arrowhead (NADH-tetrazolium reductase stain,  $\times 40$ ).

athletes from the ATI and CON groups who presented with skeletal muscle pathology. The odds ratio (OR) within a 95% confidence interval (CI) was also calculated to determine if either group was more likely to present with skeletal muscle pathology.

## RESULTS

### Subject characteristics and training history

Table 1 shows the descriptive and physiological characteristics of the two groups of athletes. There was no difference in the sex ratio between the two groups. Both groups were well matched for age, height, weight, and % body fat. There was no significant difference in  $\text{VO}_{2\text{MAX}}$  and maximal force output between the two groups.

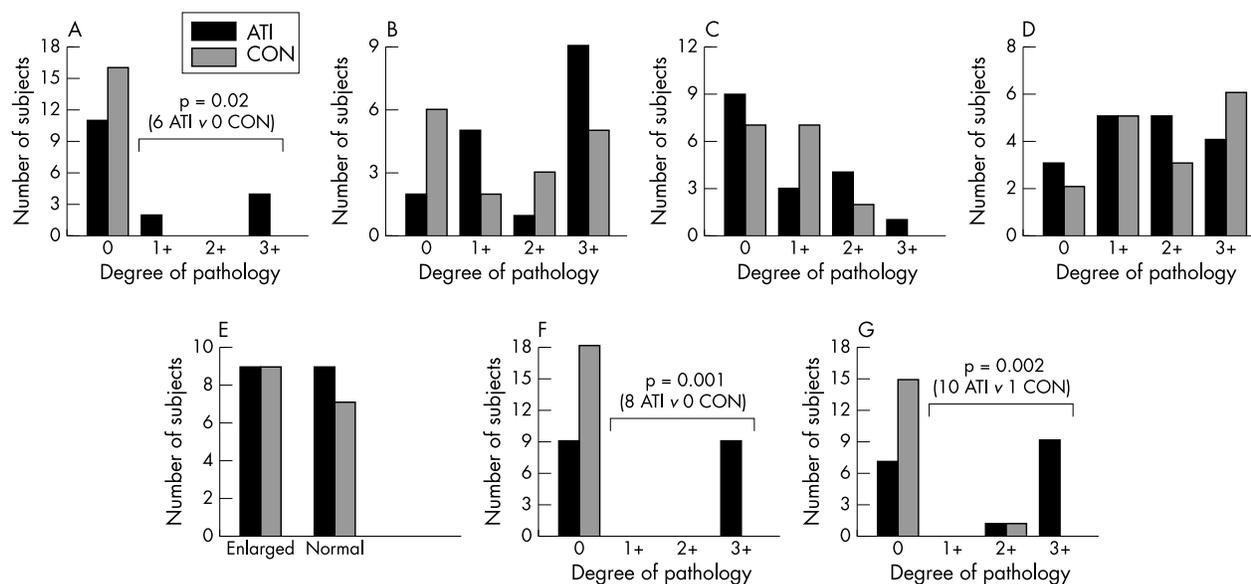
Athletes in both groups started high volume endurance training at a similar age and had a similar number of years of experience (table 2). However, before the onset of symptoms,

the ATI athletes trained significantly more than the CON athletes (6 (1)  $\nu$  5 (1) days/week,  $p = 0.002$ ; 9 (5)  $\nu$  5 (2) hours/week,  $p = 0.02$ ; 87 (29)  $\nu$  50 (25) km/week,  $p = 0.0003$ ). After the onset of symptoms, they significantly reduced their training (table 2).

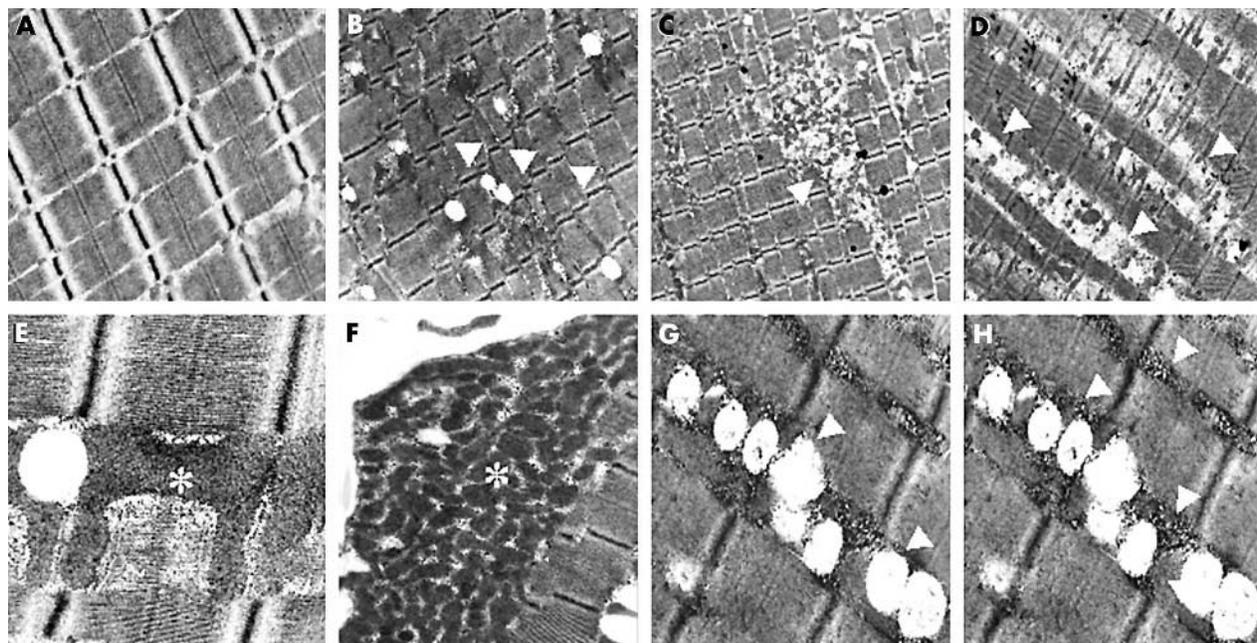
### Muscle pathology

There was no significant difference in the percentage of type I fibres between the ATI and CON groups (56.1 (17.5)  $\nu$  53.2 (10.6);  $p = 0.56$ ). Figure 1 shows the proportion of athletes from both groups who presented with varying degrees of internal nuclei, muscle fibre size variation, necrosis/inflammation, and aggregation of subsarcolemmal mitochondria. Figure 2 shows histological evidence of the markers of skeletal muscle pathology.

According to Fishers exact two tailed  $\chi^2$  test, significantly more ATI athletes presented with internal nuclei (9  $\nu$  2;  $p =$



**Figure 3** Proportion of acquired training intolerance (ATI;  $n = 18$ ) and control (CON;  $n = 17$ ) athletes presenting with various markers of skeletal muscle ultrastructural pathology. (A) z disc streaming; (B) focal deletions of myofibrils; (C) atrophic fibres; (D) subsarcolemmal aggregations of mitochondria; (E) enlarged mitochondria; (F) accumulation of lipid droplets; (G) accumulation of glycogen droplets.



**Figure 4** Electron micrographs showing typical markers of skeletal muscle ultrastructural pathology. (A) Control sample ( $\times 10\,000$ ); (B) 3+ z disc streaming indicated by arrowheads ( $\times 7000$ ); (C) 3+ focal deletions of myofibrils indicated by arrowheads ( $\times 7000$ ); (D) 3+ atrophic fibres indicated by arrowheads ( $\times 7000$ ); (E) enlarged mitochondria indicated by asterisk ( $\times 10\,000$ ); (F) 3+ subsarcolemmal aggregations of mitochondria indicated by asterisk ( $\times 7000$ ); (G) 3+ accumulation of lipid droplets indicated by arrowheads ( $\times 10\,000$ ); (H) 3+ accumulation of glycogen droplets indicated by arrowheads ( $\times 7000$ ).

0.03; fig 1A) and fibre size variation ( $15 \nu 6$ ;  $p = 0.006$ ; fig 1B) than CON athletes. Furthermore, the ATI athletes were significantly more likely to present with internal nuclei (OR = 7.5; 95% CI 1.3 to 42.8) and fibre size variation (OR = 9.2; 95% CI 1.9 to 44.9) than the CON athletes. There was, however, no significant difference in the proportion of ATI and CON athletes who presented with necrosis/inflammation ( $p = 0.6$ ; OR = 3.2; 95% CI 0.3 to 34.3; fig 1C) or subsarcolemmal aggregations of mitochondria ( $p = 0.7$ ; OR = 0.6; 95% CI 0.1 to 2.8; fig 1D).

Figure 3 depicts the proportion of ATI and CON athletes who presented with z disc streaming, focal deletions of myofibrils, atrophic fibres, subsarcolemmal aggregations of mitochondria, enlarged mitochondria, and lipid and glycogen deposits. Figure 4 presents electron micrographs of the various markers of ultrastructural muscle damage.

Significantly more ATI athletes had z disc streaming than the CON group ( $6 \nu 0$ ;  $p = 0.02$ ; OR = 17.2; 95% CI 0.9 to 334.3). There was, however, no significant difference in the proportion of athletes with focal deletions of myofibrils ( $16 \nu 6$ ;  $p = 0.11$ ; OR = 4.8; 95% CI 0.8 to 28.6), atrophic muscle fibres ( $8 \nu 9$ ;  $p = 0.7$ ; OR = 0.6; 95% CI 0.2 to 2.4), enlarged mitochondria ( $p = 0.74$ ; OR = 1.3; 95% CI: 0.3 to 5.0), or subsarcolemmal aggregations of mitochondria ( $p = 1.0$ ; OR = 0.8; 95% CI: 0.2 to 4.3).

Significantly more ATI athletes presented with lipid ( $8 \nu 0$ ;  $p = 0.001$ ; OR = 35.0; 95% CI 1.8 to 670.2) and glycogen ( $10 \nu 1$ ;  $p = 0.002$ ; OR = 20.0; 95% CI 2.2 to 185.0) deposits in the skeletal muscle than the CON group.

## DISCUSSION

This study set out to compare skeletal muscle pathology in athletes with ATI and asymptomatic controls matched for age and years of endurance training. The first important finding is that significantly more athletes with ATI presented with structural (internal nuclei and muscle fibre size variation) and ultrastructural (Z disc streaming) skeletal muscle pathology than asymptomatic control athletes.

Muscle fibres in a physically active, healthy person should all be a similar size and shape, and the myonuclei should be situated at the periphery of the muscle cell.<sup>38</sup> Although it is normal for some variation in the size of the muscle fibres, increased muscle fibre atrophy is usually associated with muscle degeneration.<sup>38</sup> Similarly, the presence of internal nuclei in more than 3% of the muscle fibres is considered abnormal and is usually associated with muscle degeneration and regeneration.<sup>38 42 43</sup>

Although a certain degree of z disc streaming may be present in normal muscle, extensive z disc streaming may indicate exercise induced muscle damage or a non-specific myopathy.<sup>38</sup> Prolonged, exhaustive endurance exercise has been reported to result in both acute<sup>4 8 10 44</sup> and chronic<sup>9</sup> alterations to the z discs, such as z disc streaming, smearing, broadening, disruption, and dissolution. The z disc appears to be the structure that is most susceptible to exercise induced muscle damage.<sup>5 15 24 45-50</sup>

Glycogen and lipid droplets accumulate in normal muscle in varying amounts depending on fibre type<sup>51-53</sup> and dietary<sup>54-56</sup> and training status.<sup>57-59</sup> Excessive accumulations of glycogen and lipid may indicate a diseased state or muscle pathology, as glycogen and lipid typically accumulate in the subsarcolemmal space and in the region of degenerated myofibrils.<sup>38</sup> Although accumulation of glycogen and lipid droplets in the muscle of athletes with ATI may indicate mitochondrial deficiency or non-specific muscle pathology, it may also reflect the decreased activity levels, and therefore decreased utilisation of endogenous fuel stores, in these endurance trained athletes.

The second important finding of this study is that the athletes with ATI had a significantly greater endurance training volume than the control athletes, even though groups were matched for the number of years of high volume endurance training.

Kuipers *et al*<sup>9</sup> investigated changes in skeletal muscle ultrastructure of previously untrained subjects who undertook an 18 month endurance training programme with the

### What is already known on this topic

Prolonged, strenuous endurance exercise induces muscle damage and impairs muscle function. Skeletal muscle is able to repair itself and adapt. There may, however, be a limit to its regenerative capacity and adaptability, resulting in an accumulation of chronic skeletal muscle pathology. Numerous case studies allude to a link between chronic skeletal muscle damage and impaired training and racing performance in endurance athletes with a history of high volume endurance training and racing.

end goal of completing a standard marathon (42.2 km). No signs of pathology were noted in biopsy samples from the untrained subjects before the trial. However, indicators of skeletal muscle degeneration gradually increased as the training distance increased. The increase in training distance had a more disruptive effect on skeletal muscle ultrastructure than the races in which the subjects participated during the 18 month training period.<sup>9</sup> Similarly, a greater incidence of skeletal muscle ultrastructural damage was observed in the muscle of endurance athletes after a marathon (42.2 km) than after a 25 km race, even though the shorter distance was run at a higher intensity and running speed.<sup>60</sup> From these studies, it is tempting to speculate that the greater presence of skeletal muscle pathology in the athletes with ATI may be associated with their higher training volume.

Even though the athletes with ATI were unable to tolerate endurance training loads to which they were previously accustomed and to maintain their expected levels of endurance racing performance, their  $\text{VO}_{2\text{MAX}}$  and maximal force output were not reduced compared with that of the asymptomatic controls. We are unable to draw any conclusions about the effect of the present state of health and fitness of these athletes on their short term, maximal performance capacity, as we do not have any data for these particular performance parameters before the onset of symptoms.

Previous case studies on the physiological characteristics of individual athletes with similar symptoms to those described by our ATI athletes have shown that, although their  $\text{VO}_{2\text{MAX}}$  is significantly reduced compared with before the onset of symptoms, the value is within the normal range expected for similarly aged and activity matched endurance athletes.<sup>16-28</sup> In addition, objective physiological data from people with chronic fatigue syndrome show very little reduction in muscle strength and peak aerobic power.<sup>61</sup>

It is also possible that the  $\text{VO}_{2\text{MAX}}$  test and the maximal voluntary isometric contraction test, although valid measures of  $\text{VO}_{2\text{MAX}}$  and strength in a healthy population, are not valid measures of competitive racing performance in athletes with ATI. A submaximal intensity exercise test that challenges the ability of athletes with ATI to resist fatigue over a longer period of time may be more appropriate. An alternative conclusion is that the skeletal muscle of the athletes with ATI is capable of performing short term, maximal contractions and that the impairment in muscle function only occurs after sustained contractions.

It is also interesting to note that, although a greater proportion of athletes with ATI presented with skeletal muscle pathology, there were signs of pathology in the muscle samples of the control athletes. A specific criterion for the selection of the control athletes was that they should have a similar number of years of endurance training and racing experience. Therefore the presence of skeletal muscle pathology is perhaps to be expected if the hypothesis that a history of high volume endurance training and racing is associated with an accumulation of chronic skeletal muscle

### What this study adds

An association between increased skeletal muscle pathology and training intolerance in endurance athletes is established.

pathology is accepted. It is interesting to speculate that the control athletes may be at risk of developing ATI; further research is required to establish this. Although we are confident that the increased incidence of pathology in muscle sampled from the athletes with ATI is a real finding, we are mindful of the limitations associated with extrapolating findings in a small biopsy sample to that of the entire muscle or limb.

In conclusion, the significantly increased proportion of ATI athletes who presented with structural and ultrastructural skeletal muscle pathology establishes an association between increased skeletal muscle pathology and ATI in endurance athletes with a history of high volume training and racing. Further studies are required to determine the nature of this association and the possible mechanisms involved.

We suggest that, although minor exercise induced muscle damage is a precursor to muscle adaptation, and skeletal muscle has a remarkable ability to repair this damage and to adapt,<sup>5-7 11 25 62 63</sup> there may be a limit to the regenerative capacity and adaptability of muscle.<sup>1 4 8 14 19-21 64</sup> Further muscle damage beyond this limit may be irreversible and irreparable.<sup>2</sup> This chronic muscle damage may underlie both the ATI and the decreased running performance in affected athletes. However, the extent of any causal relations between these variables requires further investigation.

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Conflict of interest: none declared

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