REVIEW PAPER

THE ROLE OF MUSCLE DAMAGE IN THE ETIOLOGY OF OVERTRAINING SYNDROME

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Abstract

A complex of conditions leads to the development of overtraining syndrome. Overtraining syndrome is associated with peripheral-cellular and central-cerebral processes, hormonal-neural regulation and transmission mechanisms. The decrease in physical work capacity is substantially related to the muscle damage and a decrease in muscle oxidative potential. The review describe mainly the balance between training stimulus and recovery, skeletal muscle damage and defense systems, regeneration as well as the role of reactive oxygen species, heat shock proteins and insulin-like growth factors in overtrained skeletal muscles.

Key words*: overtraining syndrome, skeletal muscle damage, regeneration*

Introduction

High volume or intensity exercise disrupts body homeostasis and the body has to recover. Inappropriate volume or intensity of exercise may cause a maladaptive cellular or tissue response due to an imbalance between load and recovery (Foster, Synder and Welsh, 1999). Disruptions in cellular homeostasis appear to be key factors in the development of overtraining syndrome (Steinacker et al., 2004; Hohl et al., 2009). Tissue effects arise from these cellular disruptions. Overtraining has been defined as stress-recovery imbalance, i.e. too much stress combined with too little time for regeneration (Halson and Jeukendrup, 2004; Meeusen et al., 2007; Lehmann et al., 1999). Short-term overload, also called overreaching or supercompensation training, is a usual part of athletic training, which leads to a state of overreaching in affected athletes (Halson and Jeukendrup, 2004; Lehmann et al., 1999). Overreaching is characterized by a transient

performance incompetence, which is reversible within a short-term recovery period and can be rewarded by a state of supercompensation (Meeusen et al., 2007; Lehmann et al., 1999; Foster, Daniels and Seiler, 1999). The aim of the present review is to describe the role of skeletal muscle damages in the development of overtraining syndrome

The role of recovery

A significant decrease in physical work capacity during overtraining as compared to the enhanced training protocol suggests, that lack of recovery in the training protocol leads to overtraining. If the training stimulus lasts too long and training sessions are so frequent that they interrupt the recovery phase, the necessary adaptation does not occur (Seene et al., 2008; Foster, Synder and Welsh, 1999; Lehmann et al., 1999). The importance of recovery is evident from the fact that after symptoms of overtraining appear, a much longer recovery time is needed than before (Seene et al., 2004). The day after the volume was decreased by 60%, the participants were able to tolerate 150% of the prior exercise volume. After the appearance of overtraining symptoms on the day after the training volume was decreased by 60%, the participants could tolerate only 110% of the prior exercise volume (Kaasik and Seene, 2010). A further decrease in the volume did not have any effect since the contractile apparatus had been exhausted, damaged and physical work capacity (PWC) did not recover sufficiently (Seene et al., 2008).

The role of muscle fiber damage

Reactive oxygen species (ROS) are involved in tissue damage (Pansarasa et al., 2002; Kang et al., 2009). The reactive species include superoxide anion, hydrogen peroxide and hydroxyl radical. ROS may cause cell injuries, such as lipid peroxidation, enzyme inactivation, changes in intracellular redox state and DNA damage (Halliwell and Gutteridge, 2007; Urso and Clarkson, 2003). Cells possess enzymatic defense systems to reduce the risk of oxidative injury, i.e. superoxide dismutase, glutathione peroxidase and catalase with superoxide radicals and organic hydrogen peroxides, respectively (Duntas, 2005; Yaegaki et al., 2008). Increase in ROS production occurs during physical exercise and the resulting oxidative damage arises in muscle, liver, blood and other tissues (Venditti and Di Meo, 1997; Itoh et al., 1998; Magonis et al., 2007). Exhaustive training has been associated with enhancement of oxygen consumption in skeletal muscles (Packer, 1986; El-Sayed, Ali and El-Sayed Ali, 2005; Santalla, Naranjo and Terrados, 2009; Malek and Olfert, 2009), an increase in lipid peroxidation, and inhibition of key mitochondrial enzymes, such as citrate synthase and malate dehydrogenase (Urso and Clarkson, 2003; Margonis et

al., 2007; Ji, Stratman and Lardy, 1988). Enhanced endurance training does not lead to functional damage and promotes muscular adaptation (Seene et al., 2007; Carcia-Pallares et al., 2009).

Regeneration in damaged skeletal muscle

Muscle fibers regenerate via activation of quiescent precursor cells (satellite cells) and proceed with the formation of proliferating progenitors that fuse to generate differentiated myofibers (Wagers and Conboy, 2005). These cells activated by muscle injury give rise to intermediate progenitor cells expressing the myogenic transcription factor Pax-3, which divide asymmetrically and differentiate into Pax-3^{-}, Myf-5^{hi}, $desmin^{hi}$ myoblasts (Conboy and Rando, 2002). Regeneration in overtrained skeletal muscle is slow as lack of Insulin-like growth factor-I (IGF-I) and mechano growth factor (MGF) prevents the activation of satellite cells under the basal lamina of muscle fibers (Fig.1).

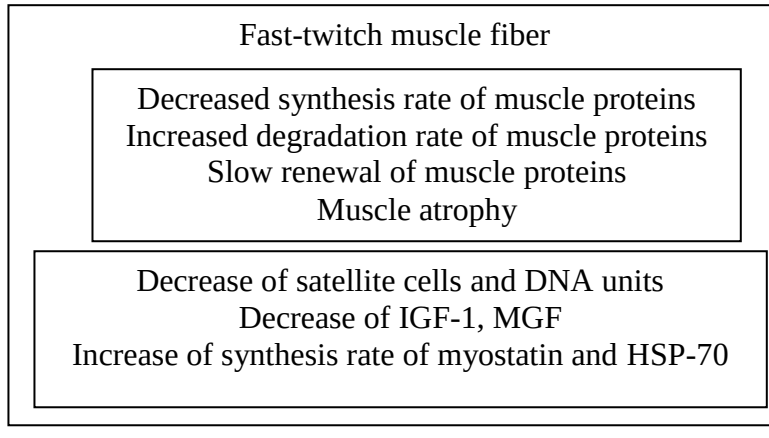

Figure 1. Reasons of slow regeneration in overtrained skeletal muscle
IGF-1 – insulin-like growth factor-1
MGF – mechano growth factor
HSP-70 – heat shock protein-70

If the number of satellite cells in skeletal muscle increased during endurance training (Seene and Umnova, 1992), overtraining led to a decrease in satellite cell number (Seene, Kaasik and Umnova, 1999). A decrease in the number of satellite cells is the reason why new fibers do not form and damaged fibers do not regenerate appropriately since satellite cells do not fuse with damaged fibers. Lack of satellite cells also leads to a decrease in the differentiation of fibers that form since levels of transcription factors, except for myostatin, decrease. Lack of MGF leads to

apoptosis. If muscle fibers do not regenerate, muscle atrophy develops. Only myostatin and heat shock protein (HSP-70) synthesis increases in atrophied muscle (Fig.1). A decrease of synthesis rates of muscle proteins, particularly myofibrillar proteins and increased protein degradation lead to the "wastage" of muscle. A decrease in myonucleus numbers and DNA damage lead to a decrease in DNA units in overtrained muscle (Fig.1). Lack of myonuclei, decreased synthesis and an increased degradation rate of muscle proteins, particularly myofibrillar proteins (Seene et al., 2004), lead to the development of overtraining caused myopathy (Seene, Kaasik and Umnova, 1999).

The activation of Sc is important for maintaining a muscle size, i.e. myonuclear domain size or DNA unit. The reason for decrease of muscle mass in overtrained skeletal muscle is the lack of addition of new nuclei (Seene et al., 2004). IGF-I is a factor that affect many steps in the control of gene expression, including cell proliferation, differentiation and degradation processes (Adams, 1998). It is widely accepted that many of the anabolic effects of the growth hormone may result from a growth hormone-stimulated increase in IGF-I production (Elloumi et al., 2005; de Graaf-Roelfsema et al., 2007; de Graaf-Roelfsema et al., 2009. IGF-I simulate amino acid transportation, which is essential to tissue growth. Autocrine/paracrine processes involving muscle-derived IGF-I may play a pivotal role in linking the mechanical stimulus to the muscle's morphological and biomechanical adaptations (Goldspink, 2000). It has been shown that in response to stretch or increased mechanical activity, the muscle locally produces a special isoform of IGF-I (autocrine) that is directly linked to the activation of gene expression necessary for muscle repair, maintenance and remodeling. The product of this isoform is called the MGF and differentiate it from the liver IGFs that have more systemic action (Goldspink, 1999). It has been shown that IGF-1 is associated with an impairment of blood fluidity, possibly due to a direct effect on red cell deformability and aggregability (Monnier et al., 2000).

Muscle atrophy develops further as myostatin expression in these muscles increases. Overtraining also leads to the decreased differentiation of muscle fibers since transcription factors are not expressed in overtrained muscle.

The role of immune reactions

Heat shock protein (HSP) play an important role as intracellular chaperones in the immune system and may protect cells from the harmful effects of environmental stress factors (Locke and Noble, 1995; Ferenbach and Niess,

1999). HSPs may also function as extracellular signals to activate the immune response (Moseley, 2000; Binder, Blachere and Srivastava, 2001).

Endurance exercise is a powerful stimulus of intracellular HSP expression in immune cells, in muscle and other tissues, such as myocardium, liver, spleen and brain (Locke and Noble, 1990; Liu et al., 1999; Ferenbach et al., 2000). An increased expression of heme oxygenase-1 in leucocytes, which appears only after long, intensive competitive endurance exercise, indicates that the duration of endurance exercise plays an important role in the activation of the anti-stress system. The release from intact muscle cells may be excluded because the increase of HSP-72 in the peripheral blood preceded any HSP-72 increase in exercising muscle (Walsh et al., 2001), and non-damaged muscle did not release HSP-72 into the circulation (Fabbraio et al., 2002). On the other hand, HSP-72 increased in muscle and early damage of skeletal muscle cells has been described after intense endurance exercise followed by secondary immunological changes (Tidball, 1995). Necrotic cells released HSP-72, delivered a maturation signal to dendritic cells and activated the NF-kappaB-pathway (Basu et al., 2000). Prolonged, competitive endurance exercise induces a more pronounced response of extracellular HSP-72 in the peripheral blood of endurance athletes compared with more intensive but shorter exercise (Ferenbach et al., 2002).

Cytokines have also role in the exercise-induced immune reaction and exercise-related metabolic and cellular signal transduction, and are capable of increasing HSPs synthesis (Liu and Steinacker, 2001). HSPs may act as a cytokine in reaction to exhaustive exercise, stimulate tumor necrosis factor-alpha (TNF-α), interleukin (IL)-β, and IL-8 in monocytes, and activate CD 14-dependent and Ca^{2+}-dependent pathways (Steinacker and Liu, 2002).
Exhaustive exercise increases athletes' energy and protein needs (Lowery and Forsythe, 2006). It has been shown that basal metabolic rate increases significantly after skeletal muscle trauma (Long et al., 1979). It is necessary to understand that the acquisition of new muscle mass of overtrained athletes in an energy-costly process as 2300-3500 kcal surplus is required to build each pound of new muscle tissue (Williams, 2005). Intensive fractional synthesis rate of myosin heavy chain (MyHC) in the muscle tissue protein intakes about two times (Brodsky et al., 2004).

Contracting muscle release cytokines, which in turn create many effects in other organs, including the brain. All these different mechanisms create sensations of fatigue and exhaustion in the mind of the exercising subject (Ament and Verkere, 2009). Exhaustive exercise induces an anti-inflammatory effect in skeletal muscle, especially in fast-twitch (FT) muscle

fibers and a pro-inflammatory effect in adipose tissue (Neto et al., 2009). This effect contributes to increased lipolysis to provide energy for the exercising muscle.

The DNA content in muscle, protein and DNA ratio in FT muscles decreases during overtraining showing signs of myopathy as a result of muscular overload (Seene et al., 2004). Overtraining caused myopathy is characterized by slow turnover of MyHC in FT muscle fibers, depressed neuromuscular and depressed alpha-motoneuron excitability (Seene et al., 2008).

The decreased synthesis and increased degradation rate of contractile proteins that was observed in overtrained muscles is in good agreement with the increased occurrence of destructive processes in FT fibers excitability (Fig.2).

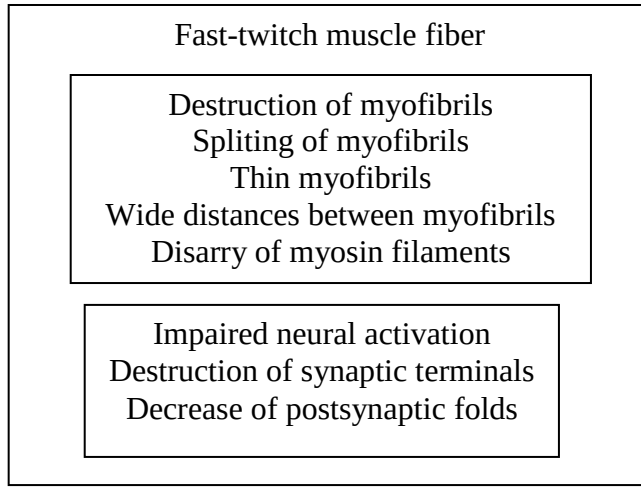

Figure 2. Destructive processes in nerve-muscle structures leading to the muscle weakness during overtraining

Contrary to the decreased turnover rate of contractile proteins, overtrained athletes show a persistent high synthesis rate or concentration of HSPs during exercise training, which might show the increased stress tolerance of affected cells and conduct cellular repair process (Salo, Donovan and Davies, 1991). Damaged muscle tissue releases cytokines, which act in the hypothalamus to re-set the regulatory mechanisms that, among other things, shut down functions that might promote further damage.

The molecular chaperones play a universal role in maintaining homeostasis of muscle fibers. HSPs in skeletal muscle are fiber-type specific (Liu and Steinacker, 2001) and may occur during overtraining in an effort to counteract the disruption of muscle function.

Muscle fiber phenotype maintenance and transition depends on motoneuron-specific impulse patterns, neuromuscular activity and mechanical load. Depending on the type, intensity, and duration of changes in any of these factors, muscle fibers adjust their phenotype to meet the altered functional demands (Pette, 2001).

Role of oxidative capacity of muscle

Skeletal muscle size is determined by a balance between protein accumulation and degradation. These two processes are tightly regulated and interrelated (Seene, Kaasik and Alev, 2011). Protein synthesis and protein degradation systems need ATP and muscle energy level is one of the cellular check points that decide either to promote growth or activate protein breakdown and atrophy (Sandri, 2008).

Overtraining is accompanied by a decreased synthesis rate of muscle proteins and an increased protein degradation rate in skeletal muscle (Seene et al., 2004; 2005; 2008).

The destruction of myofibrils is shown in volume-induced overtrained skeletal muscles, mainly in FT oxidative-glycolytic muscle fibers and in slow-twitch (ST) oxidative muscle fibers (Seene et al., 2008).

Changes in MyHC isoforms show that contractile properties of ST and FT muscles change in different ways in accordance with muscle oxidative capacity (Seene et al., 2007; 2008). Changes in myosin light chain (MyLC) isoforms during overtraining are much smaller in comparison with subsequent changes in MyHC isoforms (Kaasik and Seene, 2010). The most significant changes in MyLC isoforms during overtraining appeared in FT muscles (Seene et al., 2008). Regeneration of MyHC IIb and MyLC 3f isoforms, which have high affinity to each other in FT muscle fibers after tissue damage, proceeds at different speeds (Alev, 2009). MyLC 3f isoform regenerates about two times faster than that of MyHC IIb isoform in FT muscle fibers with low oxidative capacity (Alev et al., 2009). MyLC 1 isoform can negatively affect myoblast proliferation by facilitating myoblast withdrawal from cell cycle and differentiation (Zhang et al., 2009).

The changes in contractile protein isoforms pattern in overtrained skeletal muscle show the significance of changes in cellular and molecular level for diagnostics of overtraining syndrome. Molecular changes of contractile proteins may be the way how to prevent the development of overtraining syndrome among competitive endurance athletes.

Conclusions

Overtraining in the skeletal muscle is substantionally associated with muscle damage. Muscle damage is associated with calcium overload, free radical formation, a decrease in energy supply and a reduction in muscle defense system. Exhaustive exercise is associated with enhanced oxygen consumption in skeletal muscles, an increase in lipid peroxidation and inhibition of key mitochondrial enzymes. Cytokines play a role in the exercise-induced immune reaction, metabolic and cellular signal transduction as well as in increasing HSP synthesis. A decrease of IGF-1 and MGF results in the slow regeneration in overtrained muscles. Increased muscle protein degradation and a decreased synthesis rate in overtrained skeletal muscle as well as changes in MyHC isoform pattern are fiber type specific. Molecular changes of contractile proteins isoforms play the important role in changes in functional properties of overtrained skeletal muscle.

Acknowledgements

This study was supported by funding from the Ministry of Education and Research of Estonia, research project number TKKSB1787.

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Submitted: May 12, 2013
Accepted: June 7, 2013