Review Paper

Crosstalk Between Mitochondria and Myofibrils in Adult and Aging Striated Muscle Tissue: Effect of Increased Functional Activity

Abstract: There has been much debate about changes of oxidative capacity in aging skeletal and heart muscle, and endurance capacity. Physiological changes during aging are associated with a decline in muscle mass, strength and endurance capacity. These changes in muscle structure and function are leading to disability in the aging population. The purpose of the present review is to discuss about decrease of oxidative capacity in adult and aging striated muscle tissue, changes in interaction between mitochondria and myofibrils and loss in life quality;describe the effect of increased functional activity (endurance exercise) on the oxidative metabolism.Decrease of endurance capacity during aging is related with reduced oxidative capacity of skeletal muscle due to decrease of mitochondrial biogenesis.Striated muscle cells with high oxidative capacity during endurance exercise.hypertrophy. Muscle fibres with lower and low oxidative capacity do not hypertrophy during endurance type of exercise. Skeletal muscle respond to endurance exercise training by increasing the fibre composition towards increase of fibres with higher oxidative capacity at the expense of proportion of fibres with low oxidative capacity. Decease of oxidative capacity in muscle tissue lead to the decrease of muscle quality, cause disability and loss in life quality of aging population.Endurance exercise training is the effective way to increase the oxidative and endurance capacity.

Keywords: Striated muscle tissue; aging, endurance capacity, oxidative metabolism, effect of endurance exercise

INTRODUCTION

In striated muscle tissue only cardiocytes have high oxidative capacity, type I and IIA fibres have higher oxidative capacity and type IIB/IIX low capacity [1 - 4] (Fig. 1). Type I muscle fibres with higher oxidative capacity are small in comparision fibres with low oxidative capacity, showing that there are relationship between fibrecross-sectional area (CSA)and VO_2max [5]. Turnover rate of cytochrome C, muscle contractile proteins and regeneration capacity of skeletal muscle is faster in these muscles where morefibres with higher oxidative capacity [2, 6]. Functional changes during aging are related with a decrise in skeletal muscle mass, strength andendurance [7 - 9]. These changes in muscle structure and function are leading to disability in the aging population [10]. The decrease of skeletal muscle mass is the result of type II fibre atrophy and loss in the number of these muscle fibers. Large variability in the muscle fibre size, accumulation of nongrouping, scattered and angulated fibres, and expansion of extracellular space are typical changes during striated muscle atrophy [11, 12]. Decrease of the number of skeletal muscle fibres and decreased level of anabolic hormones testosterone and growth hormone, insulin-like growth factor 1 (IGF-1), and an increased catabolism are the reasons of development of sarcopenia [13, 14]. Decrease of endurance capacity during aging is related with reduced oxidative capacity of skeletal muscle due to decrease of mitochondrial biogenesis [15, 16]. Reduction in AMP-actvated protein kinase (AMPK) activity may be the main factor in reduced mitochondrial function [17]. Endurance training is activated AMPK [18] and related with the adaptatinn of skeletal muscle to endurance exercise training. It is well known that the oxidative capacity of skeletal muscle decreases in the elderly, endurance training is the effective measure in its restoration via stimulation mitochondrial biogeneses and improves functional parameters of mitochondria [2, 15, 19, 20].In the present review, we will discuss about decrease of oxidative capacity in adult and aging striated muscle tissue and related decrease of muscle quality which cause a

disability and loss in life quality of aging population;describe the effect of endurance training on the interaction between mitochondria and contractile apparatus on dependence of increase in oxidative capacity, and focuses on the adenosine triphosphate consumption, mitochondrial biosynthesis in the light of increase in oxidative metabolism in aging muscle tissue.

AGING MUSCLE

There exists a relationship between skeletal muscle mass and strength, decrease of mass is leading to the decrease of strength. Therefore changes in muscle strength does not solely depend on changes in muscle mass [21]. It has been shown that in elderly the decrease in strength is more rapid than the loss of muscle mass [22, 23]and this loss of mass during muscle disuse is related with loss of strength only about 10% [24]. Therefore increase in muscle mass is not followed with increase in strength [22]. These experiments demonstrates that the loss of muscle strength is more deeply related with impairments of the neural activation of striated muscle tissue [25]. Aging accompanied decrease in several physical capacities is responsible for the progressive decline in physiological processes in the elderly [26]. It has been shown that in elderly skeletal muscle tissue protein synthesis rate is decreased in the translational level,but not in the transcriptional level [27]. Skeletal muscle fibres in elderly people have saved ability to regenerate [28] and regeneration capacity depends on the satellite cells.Muscle fibres with higher oxidative capacity have more satellite cells under the basal lamina and these fibres have also higher regeneration capacity [29].

Decrease of regeneration capacity

Regeneration capacityin old rats is relatively low in comparison with young animals [30], and this is related with a decrease in the number of satellite cells under the basal lamina of fast-twitch (FT) muscle fibres [31]. Decrease in the satellite cell pool and the length of telomeres in sarcopenic skeletal muscle explain the higher prevalence of muscle injuries andslow

74 regeneration capacity of this muscle tissue [26]. Satellite cells are functionally differentand
75 recruited for different tasks[32, 33]. After serious damage old rodents skeletal muscle did not
76 regenerate as fast as muscles in younger animals [34]. Slower regeneration capacity of
77 skeletal muscles is a result of extrinsic causes, but it is likely a combination of both extrinsic
78 and intrinsic factors are responsible to slow muscle regeneration[35, 36]. In weight-bearing
79 skeletal muscles of old rodents a contraction-induced muscle injury causes decrease in
80 muscle mass and force [37]. At the same time in the aging muscle the degradation rate of
81 contractile proteins increased about twice and muscle strength and motor activity decreased
82 [30]. Sarcopenia is a result of decreased synthesis rate and increased degradation rate of
83 contractile proteins.As a result the muscle proteins turnover is slower, particularly contractile
84 proteins which in turn, causes the decrease in muscle strength (Fig. 2). It has shown that
85 protein intake in combination with anabolic agents attenuates the muscle loss [38].
86 Etiology of disability in elderly is wide and risk factors for loss in physical activity have
87 significant importance [39]. The decrise of strength is a result of a combination of neurologic
88 and muscular factors. The impairment of neural activation may due to a reduction in
89 descending excitatory drive from supraspinal centers, suboptimal motor unit recruitment and
90 neuromuscular transmission failure [40, 41]. Muscle atrophy, changes in contractile quality as
91 the result of changes in the contractile proteins, and infiltration of adipocytes into structure of
92 muscle fibres are indicators of the decrease of muscle strength and motor activity [10, 22].

93 **Rearrangements in contractile apparatus**

94 Changes in strength and endurance capacity in elderly are related with slow synthesis rate and
95 fast degradation rate of contractile proteins, which causes structural and functional damages
96 in myofibrillar apparatus [42]. It has been shown that an integral indicator of muscle
97 proteins metabolism , turnover rate, shows that in old rodents, myosin heavy chain (MyHC)

renewal is about 35% and actin about 10% slower than in young animals[30, 43]. Rearrangements in the myofibrillar compartment of old rats include a decrease in MyHCIIb isoform (fastest isoform) relative content in skeletal muscle [44]. Changes in MyHC isoforms' composition in muscle tissue are related with changes in adenosine triphosphate (ATP)consumption in old rats because of muscle mitochondrial dysfunction and decrease in mitochondrial ATP synthesis [45,46]. There are many reason like decrease in mitochondrial DNA copy numbers, decrease of mRNA in genes encoding muscle mitochondrial proteins [47], changes in oxidative enzymes activity and mitochondrial protein synthesis rate [48]. Chemical mediators play an essential role in signaling hypothalamus from the periphery .It is important to stimulate the center of sympathetic nerves which signaling the paraventricular nucleus of the hypothalamic center [49]. In striated muscle tissue protein synthesis decreases with age [50, 51]. Particularly MyHC and mitochondrial proteins, at the same time sarcoplasmic proteins saved a relatively high synthesis rate [49]. It has been demonstrated that age-related decrease in muscle protein synthesis is not a global effect concerning all proteins, but selective for certain proteins [49]. It may be surprising but proteins that have a faster renewal contribute more to the striated muscle tissue protein synthesis rate despite their small amount. Proteins like myosin and actin which constitute a major part of muscle proteins, but have a slow renewal, have a smaller role in the synthesis rate of striatedl muscle tissue proteins [49].

INTERACTION BETWEEN MITOCHONDRIA AND SARCOMERES

In striated muscle tissue with high oxidative capacity intracellular phosphotransfer system constitute a major mechanism linking the mitochondria and ATPases within specific structures – intracellular energetic units [1, 52]. Mitochondria are located between the myofilaments through the whole muscle due to the fixed juxta position of the mitochondria

122 with sarcomeres [53]. The effectiveness of metabolic signalling depends on morpho-
123 functional relationships of the interaction between mitochondria and sarcomeres [4]. Under
124 conditions of hypoxia the connection between mitochondria and sarcomeres are disturbed as
125 sarcomeric components disintegrate the muscle cell structure and cause cell injury and death
126 [4]. Due to apoptosis protein degradation rate is increasing as well as loss of muscle nuclei
127 and this is leading to the local atrophy of muscle [54]. So, the disruption of desmin destrois
128 links between mitochondria and Z-disc andin muscle tissue the mechanism of oxidative
129 phosphorylation impired[55]. The AMPK is activated in skeletal muscle during exercise
130 training [56]. AMPK's role is to monitor the energy status of muscle fibres and maintain
131 muscle energy homeostasis [57].

132 Prolonged endurance type of exercise cause the depletion of the muscle energy
133 system,neuromuscular fatigue and muscle damage [58]. Children and elderly people have less
134 muscle mass than adults and generate lower absolute power during high intensity exercise.
135 Childres's muscle are better equipped for oxidative than glycolytic pathways during exercise
136 and this is the reason why they have lower ability to activate their fast-twitch muscle fibres
137 [59]. Decrease of skeletal muscle oxidative capacity in elderly is accompanied with the
138 decrease of anaerobic capacity[19]. Endurance training increased oxidative capacity of
139 skeletal muscle and an age associated decline in oxidative capacity is increasing. Increase in
140 oxidative capacity is accompanied with increase in fitness [60]. Aerobic kind of endurance
141 training increases capillary density, decreases oxygen diffusion distance and increase oxygen
142 supply in muscle fibres with higher oxidative capacity [3, 42, 61]. As oxidative capacity of
143 muscle fibres with higher oxidative capacity decreases in the elderly,endurance training is
144 effective measure in its restoration.Endurance exercise training stimulates mitochondrial
145 biogeneses and improves functional parameters of mitochondria[15, 20]. Skeletal muscle
146 fibres with low oxidative capacity exhibit increased adenosine diphosphate

(ADP)concentrations in response to endurance exercise training. It shows that the respiratory control is different in skeletal muscle fibres.

EFFECT OF ENDURANCE EXERCISE

In contrast to striated muscle cells with high oxidative capacity (cardiocytes), hypertrophy of skeletal muscle fibres with lower (type I and IIA) and low oxidative capacity (type IIB/X) is not happened during endurance exercise training. Skeletal muscles reaction to endurance exercise is increasing the fibres with higher oxidative capacity at the expense of fibres with low oxidative capacity [3, 42, 62]. This change do not increase muscle size, as CSA of fibers with higher oxitative capacity is less than fibres with low oxidative capacity [5]. The proteasome-, lysosome- and Ca^{2+}-mediated protein degradation occurs mainly in fibres with higher oxidative capacity [63].These two mechanisms stimulating either oxidative capacity of fibres or hypertrophy obviously exclude each other [5]. Stimulation of mitochondrial biogenesis via AMPK accompanied by suppression of the myofibrillar protein synthesis through pathways mediated by mitogen activated protein kinase (MAPK) and nuclear factor kappa B [5]. Endurance type of exercise, though increasing oxidative metabolism, decrease muscle fibre growth in myostatin knock-out mice [64]. It seems that muscle fibres followed certain mechanisms of regulation of the balance between oxidative potential and hypertrophy in response to endurance training (Fig. 3).

Effect on the ATP consumption

Adaptation of different fibre types to endurance exercise reflect differences on the level of ATP consumption. In muscles with high oxidative capacity endurance exercise increased myosin ATPase activity and muscle fibre contractility [65]. This change based on the myosin isoenzyme shift towards increased fast V1 (α) isoform [66, 67]and alterations in regulation of myosin ATPase. Endurance training results in increased myofilament sensitivity to Ca^{2+}[68],

and increase of atrial myosin light chain-1 isoform expression [69]that increases ATP consumption by myofibrils. Endurance exercise training also stimulatesthe expression of sarcoplasmatic reticulum (SR)Ca^{2+}ATPase (SERCA2) and increased Ca^{2+} transport into SR [70]. Ca^{2+} removal through transsarcolemmal route is due to activation of Ca^{2+}-ATPase in sarcolemma [65]. Endurance training increases the capacity of ATP consumption in muscle cells with high oxidative capacity, but not in muscles with higher and low oxidative capacity. Fibres with low oxidative capacity respond to endurance exercise training by increase the fibre profile towards oxidative fibres with lower ATPase activity [71, 72]. This change increases the economy of ATP consumption [73]. Endurance exercise training increasing Na^{+}-K^{+}-ATPase activity in musclefibres with low oxidative capacity [74] but not in high capacity [65].

Effect on the mitochondrial biosynthesis

Endurance exercise training stimulates mitochondrial biogenesis and increases the mitochondrial capacity to produce ATP in muscles with higher and low oxidative capacity [16, 75, 76].Increase in mitochondrial biogenesis reflects in mitochondrial content per gram of tissue [77], mitochondrial volume relative to muscle fibre area [78], and muscle tissue mitochondrial enzyme activity [79].Abowe described changes occur in muscle fibres with low and higher oxidative capacity [77, 80]. Increased energy metabolism during endurance training is related with transition from carbohydrate utilization to fat utilization and rhis is the basement of increase of the endurance capacity [81].

Responses of mitochondria to endurance training in muscle cells with high oxidative capacity is ambiguous. Endurance training increased mitochondrial enzymes activity in muscle tissue, and enhanced oxidative capacity in heart muscle [82, 83].Endurance training do not cause changes in mitochondrial enzymes and their yield in muscle tissue with high oxidative capacity [84]. Endurance exercise training decreased the oxidation rate of

palmitoylcarnitine/malate without changes in pyruvate, 2-oxoglutarate and succinate oxidation [85], increased or no changes in mitochondria-to-myofibril ratio [86,87]. Endurance training caused hypertrophy and increased oxidative capacity of heart muscle, but did not increase the volume density of mitochondria [88], mitochondrial volume, but increased weight and size of the heart [89]. The reason of conflicting data on mitochondrial biogenesis anclear. The reasons like training intensity,training volume, time for recovery,gender and age differences may lead to contraversial results [90]. Changes in oxidative capacity and CSA of striated muscle fibres during endurance training exclude each other via the balance between the biosynthesis of myofibrillar proteins and mitochondria [5]. The mechanisms of muscle fibre hypertrophy and mitochondrial biogenesis are different.

Regulation of oxidative metabolism

Peroxisome proliferator-activated receptor gamma coacivator-1alpha (PGC-1α) is a regulator of oxidative metabolism and mitochondrial content in muscle cells. PGC-1α binds to DNA-binding transcription factors(nuclear respiratory factors NRF-1 and NFR-2), and trans-activates genes which control the electron transport chain, mitochondrial protein import, and transcription factors Tfam, TFB1M, and TFB2M [91].Endurance training increases the activity and expression of PGC-1α in muscle cells through multiple mechanisms. Glucocorticoids activate PGC-1α through genomic and non-genomic effects [92]. Endurance training activates the p38 MAPK [93] which phosphorylates the PGC-1α repressor protein $p160^{MBP}$ that relieves the inhibitory effect of repressor on PGC-1α, thereby permitting PGC-1α to interact with target proteins [94].p38 MAPK also increases the transcriptional activity of PGC-1α through phosphorylation [95].AMP produced in exercising muscle cells stimulates AMPK that in turn upregulates the expression of PGC-1α [96, 97]. PGC-1α activated by reversible deacetylation carried out by class III histone deacylasesirtuin-1 (SIRT1) [98].SIRT1upregulate the expression of PGC-1α through formation of the SIRT1-

MyoD-PGC-1α complex on PGC-1α promoter [99].Endurance training upregulation of SIRT1 occurs rapidly, as its mRNA level increases together with mRNAs for PGC-1α, cytochrome C, and citrate synthase in muscle tissue after intensive cycling [100]. AMPK stimulate SIRT2 which activates the liver kinase B1, a serine-threonine kinase that impels AMPK [101]. In heart and skeletal muscle SIRT3 is localizedwithin mitochondria and the muscle SIRT3 protein content increases with elevations of citrate synthase activity and PGC-1α content in differentt muscle fibre types [102, 103]. Electrical stimulation increases SIRT3 protein and PGC-1α proteins in AMPK-independent manner [102].Endurance exercise increases SIRT3 and mitochondrial content in skeletal muscle [104]. SIRT3 activates mitochondrial enzymes succinate dehydrogenase, isocitrate dehydrogenase, glutamate dehydrogenase, NADH dehydrogenase (ubiquinome) 1 alpha subcomplex subunit 9 (NDUFA9) subunit of complex I of the respiratory chain, and acetyl-coenzyme A synthase, the targeted activation of SIRT3 may provide a means for shifting metabolism towards use of fatty acids thereby protecting failing heart [101].

Endurance exercise training activate via cyclic-nucleotide regulatory binding protein (CREB) and also PGC-1α with upregulation of mitochondrial proteins in striated muscle tissue [105]. The CREB related mechanism is targeted by catecholamines. The tumour suppressor protein p53, is participate in mitochondrial biogenesis. p53 is increasing synthesis rate of cytochrome C oxidase 2 (SCO2), an protein for assembling the cytochrome C oxidase complex and controlling the rate of mitochondrial respiration [106].p53 translocate into mitochondria and activates the mitochondrial DNA polymerase γ [107].p53 interacts with Tfam [108]and participate in regulation of mitochondrial biogenesis [109]. In skeletal muscle endurance training improves capillary blood supply, stimulates mitochondrial biogenesis, increases oxidative capacity in muscle fibres, faster renewal of sarcoplasmic proteins and qualitative remodelling in fibers with higher oxidative capacity [110].

CONCLUSION

In striated muscle tissue cardiocytes have high oxidative capacity, type I and IIA skeletal muscle fibres have higher oxidative capacity and type IIB/X low capacity. Skeletal muscle fibres which have higher oxidative capacity have smaller CSA compared to fibres with low oxidative capacity. Physiological changes during aging are associated with a decrease in muscle mass, strength and endurance.These changes in muscle structure and function leading to disability. Decrease of endurance capacity during aging is related with reduced oxidative capacity of skeletal muscle due to decrease of mitochondrial biogenesis. Endurance training causes hypertrophy of cardiocytes but not of muscle fibres with lower and low oxidative capacity. Skeletal muscles respond to endurance training by increasing the fiber composition towards increase of fibres with higher oxidative capacity at the expense of proportion of fibers with low oxidative capacity.Research suggests that in elderly striated muscle tissue oxidative capacity decrease. Decease of oxidative capacity in muscle tissue lead to the decrease of muscle quality, cause disability and loss in life quality of aging population.Endurance exercise training is the effective way to increase this capacity. Future studies should focus on regulation of ageing muscle oxidative metabolism, effect of exercise duration and intensity on the oxidative capacity in aging muscle tissue. The question of whether or not the mechanisms of regulation of muscle oxidative metabolism are the same im yong and elderly is also open for debate.

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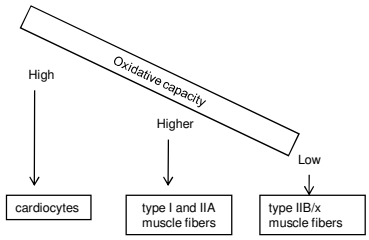

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Figure 1:	Oxidative capacity of striated muscle cells

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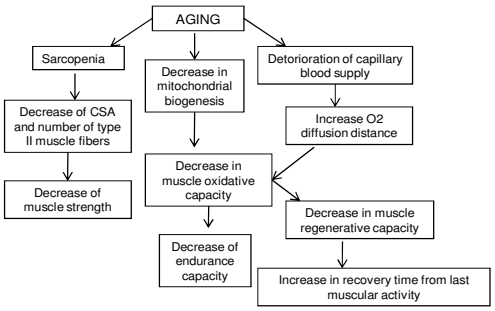

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Figure 2:	Effect of aging on skeletal muscle

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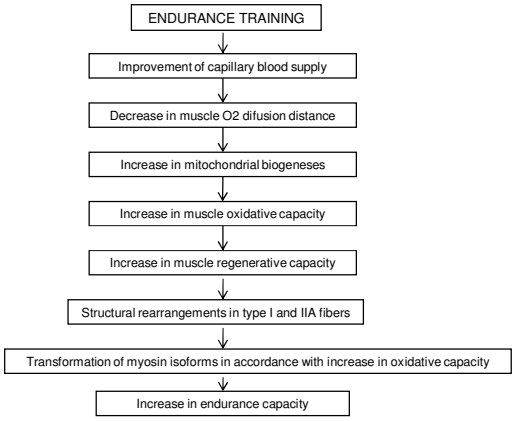

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Figure 3:	Effect of endurance training on aging skeletal muscle

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