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 (ability to keeo moving for longer time) 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 hypertrophyduring 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(ability to be active for longer period of time)[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(traing lasting for longer time with low or moderate intensity) 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 (oxygen difusion distance in muscle tissue, mitochondrial density, myoglobin concetration, oxidative enzime activity...) 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 fibresin 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 fibreshave 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 regeneration capacity of this muscle tissue [26]. Satellite cells are functionally differentand recruited for different tasks[32, 33]. After serious damage old rodents skeletal muscle did not regenerate as fast as muscles in younger animals [34]. Slower regeneration capacity of skeletal muscles is a result of extrinsic causes, but it is likely a combination of both extrinsic and intrinsic factors are responsible to slow muscle regeneration[35, 36]. In weight-bearing skeletal muscles of old rodents a contraction-induced muscle injury causes decrease in muscle mass and force [37]. At the same time in the aging muscle the degradation rate of contractile proteins increased about twice and muscle strength and motor activity decreased [30]. Sarcopenia is a result of decreased synthesis rate and increased degradation rate of contractile proteins.As a result the muscle proteins turnover is slower, particularly contractile proteins which in turn, causes the decrease in muscle strength (Fig. 2). It has shown that protein intake in combination with anabolic agents attenuates the muscle loss [38].

Etiology of disability in elderly is wide and risk factors for loss in physical activity have significant importance [39]. The decrise of strength is a result of a combination of neurologic and muscular factors. The impairment of neural activation may due to a reduction in descending excitatory drive from supraspinal centers, suboptimal motor unit recruitment and neuromuscular transmission failure [40, 41]. Muscle atrophy, changes in contractile quality as the result of changes in the contractile proteins, and infiltration of adipocytes into structure of muscle fibres are indicators of the decrease of muscle strength and motor activity [10, 22].

Rearrangements in contractile apparatus

Changes in strength and endurance capacity in elderly are related with slow synthesis rate and fast degradation rate of contractile proteins, which causes structural and functional damages in myofibrillar apparatus [42]. It has been shown that an integral indicator of muscle 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 striated muscle tissue proteins [49].

INTERACTION BETWEEN MITOCHONDRIA AND SARCOMERES

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

Prolonged endurance type of exercise cause the depletion of the muscle energy system,neuromuscular fatigue and muscle damage [58]. Children and elderly people have less muscle mass than adults and generate lower absolute power during high intensity exercise. Childres's muscle are better equipped for oxidative than glycolytic pathwaysof ATP resynthesis during exercise (during increased physical activity) and this is the reason why they have lower ability to activate their fast-twitch muscle fibres [59]. Decrease of skeletal muscle oxidative capacity in elderly is accompanied with the decrease of anaerobic capacity[19]. Endurance training increased oxidative capacity of skeletal muscle and an age associated decline in oxidative capacity is increasing. Increase in oxidative capacity is accompanied with increase in fitness [60]. Aerobic kind of endurance training increases capillary density, decreases oxygen diffusion distance and increase oxygen supply in muscle

146 fibres with higher oxidative capacity(type I and IIA fibres) [3, 42, 61]. As oxidative capacity
147 of muscle fibres with higher oxidative capacity decreases in the elderly,endurance training is
148 effective measure in its restoration.Endurance exercise training stimulates mitochondrial
149 biogeneses and improves functional parameters of mitochondria[15, 20]. Skeletal muscle
150 fibres with low oxidative capacity (type IIX and IIB fibres) exhibit increased adenosine
151 diphosphate (ADP)concentrations in response to endurance exercise training. It shows that
152 the respiratory control is different in skeletal muscle fibretypes I, IIA and IIX, IIB.

153 ## EFFECT OF ENDURANCE EXERCISE

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

169 **Effectof endurance exercise 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(heart muscle) 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. Enduranceexercise 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 exercise 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(type I) with lower ATPase activity [71, 72]. This change increases the economy of ATP consumption [73]. Enduranceexercise training increasingNa^{+}-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 (Fig 4) 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(type I and IIA fibres) [77, 80]. Increased energy metabolism during endurance training is related with transition from carbohydrate utilization to fat utilization and this is the basement of increase of the endurance capacity [81].

195 Responses of mitochondria to endurance training in muscle cells with high oxidative capacity
196 is ambiguous. Endurance exercise training increased mitochondrial enzymes activity in
197 muscle tissue, and enhanced oxidative capacity in heart muscle [82, 83].Endurance exercise
198 training do not cause changes in mitochondrial enzymes and their yield in muscle tissue with
199 high oxidative capacity [84]. Endurance exercise training decreased the oxidation rate of
200 palmitoylcarnitine/malate without changes in pyruvate, 2-oxoglutarate and succinate
201 oxidation [85], increased or no changes in mitochondria-to-myofibril ratio [86,87].
202 Endurance training caused hypertrophy and increased oxidative capacity of heart muscle, but
203 did not increase the volume density of mitochondria [88], mitochondrial volume, but
204 increased weight and size of the heart [89]. The reason of conflicting data on mitochondrial
205 biogenesis anclear. The reasons like training intensity,training volume, time for
206 recovery,gender and age differences may lead to contraversial results [90]. Changes in
207 oxidative capacity and CSA of striated muscle fibres during endurance training exclude each
208 other via the balance between the biosynthesis of myofibrillar proteins and mitochondria [5].
209 The mechanisms of muscle fibre hypertrophy and mitochondrial biogenesis are different.

210 **Regulation of oxidative metabolism**

211 Peroxisome proliferator-activated receptor gamma coacivator-1alpha (PGC-1α) is a
212 regulator of oxidative metabolism and mitochondrial content in muscle fibres. PGC-1α binds
213 to DNA-binding transcription factors(nuclear respiratory factors NRF-1 and NFR-2), and
214 trans-activates genes which control the electron transport chain, mitochondrial protein import,
215 and transcription factors Tfam, TFB1M, and TFB2M [91].Endurance training increases the
216 activity and expression of PGC-1α in muscle cells through multiple mechanisms.
217 Glucocorticoids activate PGC-1α through genomic and non-genomic effects [92]. Endurance
218 training activates the p38 MAPK [93] which phosphorylates the PGC-1α repressor protein
219 $p160^{MBP}$ 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 different 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 ofcardiocytes but not of muscle fibres with lower(type I and IIA) and low oxidative capacity (type IIB/X). Skeletal muscles respond to endurance training by increasing the fiber composition towards increase of fibres with higher oxidative capacity (type I and IIA) at the expense of proportion of fibers with low oxidative capacity(type IIB/X).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 inyoung and elderly is also open for debate.

REFERENCES

[1] Saks VA, Kuznetsov AV, Vendelin M, Guerrero K, Kay L, Seppet EK. Functional coupling as a basic mechansim of feedback regulation of cardiac energy metabolism. Mol Cell Biochem. 2004;256/257:185–99.

[2] Seene T, Alev K, Kaasik P, Pehme A. Changes in fast-twitch muscle oxidative capacity and myosin isoforms modulation during endurance training. J Sports Med Phys Fitness.2007; 47:124–32.

[3] Seene T, Kaasik P, Umnova M. Structural rearrangements in contractile apparatus and resulting skeletal muscle remodelling: effect of exercise training.J Sports Med Phys Fitness. 2009;49*:*410-23

[4] Seppet EK, Eimre M, Anmann T, Seppet E, Peet N, Käämbre T, *et al.* Intracellular energetic units in healthy and diseased hearts. Exp Clin Cardiol. 2005;10:173–83.

[5] van Wessel T, de Haan A, van der Laarse WJ, Jaspers RT. The muscle fiber type-fiber size paradox: hypertrophy or oxidative metabolism*?* Eur J Appl Physiol.2010;110:665–94.

[6]Hickson RC, Rosenkoetter MA. Separate turnover of cytochrome c and myoglobin in the red types of skeletal muscle. Am J Physiol. 1981;241:C140–4.

[7] Haus JM, Carrithers JA, Trappe SV, Trappe TA. Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. J Appl Physiol(1985).2007;103:2068–76.

[8] de Souza Santos CA, Dantas EEM, Rodrigues Moreira MH. Correlation of physical aptitude; functional capacity, corporal balance and quality of life (QoL) among elderly women submitted to a post-menopausal physical activities program. Arch Gerontol Geriatr.2011;53:344–9.

[9] Trappe T. Influence of aging and long-term unloading on the structure and function of human skeletal muscle. Appl Physiol Nutr Metab. 2009;34:459–64.

[10] Barazzoni R, Short KR, Nair KS. Effects of aging on mitochondrial DNA copy number and cytochrome c oxidase gene expression in rat skeletal muscle, liver, and heart.J Biol Chem. 2000;275:3343–7.

[11] Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, *et al.* Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy. Ageing Res Rev.2010;9:369–83.

[12] Kim JH, Kwak HB, Leeuwenburgh C, Lawler JM. Lifelong exercise and mild (8%) caloric restriction attenuate age-induced alterations in plantaris muscle morphology, oxidative stress and IGF-1 in the Fischer-344 rat. Exp Gerontol.2008;43:317–29.

[13] Goldspink G, Harridge SD R. Growth factors and muscle ageing. ExpGerontol. 2004;39:1433–38.

[14] Roubenoff R. Catabolism of aging: is it an inflammatory process? CurrOpinClinNutrMetab Care. 2003;6:295–99.

[15] Hood DA. Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle. Appl Physiol Nutr Metab. 2009;34:465–72.

[16] Ljubicic V, Joseph AM, Saleem A, Uquccioni G, Collu-Marchese M, Lai RY, *et al.* Transcriptional and post-transcriptional regulation of mitochondrial biogenesis in skeletal muscle: effects of exercise and aging. Biochim Biophys Acta.2010; 1800:223–34.

[17] Reznick RM, Zong H, Li J, Morino K, Moore KJ, Yu HJ, *et al*. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. Cell Metab.2007;5:151–6.

[18] Winder WW, Hardie DG. Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise. Am J Physiol.1996;270: E299–304.

[19] Seene T, Kaasik P. Muscle weakness in the elderly: role of sarcopenia, dynapenia, and possibilities for rehabilitation. European Reviews of Aging & Physical Activity.2012a;9:109-17.

[20] Seene T, Kaasik P. Role of exercise therapy in prevention of decline in aging muscle function: glucocorticoid myopathy and unloading. Journal of Aging Research. 2012b;Doi: 10.1155/2012/172492.

[21] Moritani T, deVries HA. Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med. 1979;58:115–30.

[22] Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB.; Valasquez-Mieyer P, *et al.* Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr.2009;90:1579–85.

[23] Frontera WR, Suh D, Krivickas LS, Huges VA, Goldstein R, Rubenoff R. Skeletal muscle fiber quality in older men and women. Am J Physiol Cell Physiol. 2000;279:C611–8.

[24] Clark BC, Manini TM, Bolanowski SJ, Ploutz-Snyder LL. Adaptations in human neuromuscular function following prolonged unweighting: IINeurological properties and motor imagery efficacy. J Appl Physiol.2006;101:264–72.

[25] Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev. 2001;81:1725–89.

[26] Kadi F, Ponsot E. The biology of satellite cells and telomeres in human skeletal muscle: effects of aging and physical activity. Scand J Med Sci Sports.2010;20: 39–48.

[27] Roberts MD, Kerksick CM, Dalbo VJ, Hassell SE, Tucker PS, Brown R. Molecular attributes of human skeletal muscle at rest and after unaccustomed exercise: an age comparison. J Strength Cond Res.2010;24:1161–8.

[28] Bassaglia Y, Gautron J. Fast and slow rat muscles degenerate and regenerate differently after cruch injury. J Muscle Res Cell Motil. 1995;16:420–9.

342 [29] Shultz E, Darr K. The role of satellite cells in adaptive or induced fiber transformations.
343 In: Pette D, editor The dynamic state of muscle fibers. Berlin: W de Gruyter; 1990. p. 667–
344 81.
345 [30] Kaasik P, Umnova M, Pehme A, Alev K, Aru M, Selart A, Seene T. Ageing and
346 dexamethasone associated sarcopenia: Peculiarities of regeneration. J. Steroid Biochem Mol
347 Biol. 2007;105:85–90.
348 [31] Verney J, Kadi F, Charifi N, Feasson L, Saafi MA, Castells J, Piehl-Aulin K, Denis C.
349 Effects of combined lower body endurance and upper body resistance training on the satellite
350 cell pool in elderly subjects. Muscle & Nerve2008;38: 1147–54.
351 [32] Ono Y, Boldrin L, Knopp P, Morgan JE, Zammit PS. Muscle satellite cells are a
352 functionally heterogeneouspopulation in both somite-derived and branchiomeric muscles.
353 Dev Biol. 2010;337:29–41.
354 [33] Tatsumi R. Mechano-biology of skeletal muscle hypertrophy and regeneration: possible
355 mechanism of stretch-induced activation of resident myogenic stem cells. Anim Sci J.
356 2010;81:11–20.
357 [34] Kaasik P, Umnova M, Alev K, Selart A, Seene T. Fine architectonics and protein
358 turnover rate in myofibrils of glucocorticoid caused myopathic rats. Journal of Interdiscipl
359 Histopathology 2012;1:5-10.
360 [35] Carlson BM, Dedkov EI, Borisov AB, Faulkner JA. Skeletal muscle regeneration in very
361 old rats. J Gerontol A Biol Sci Med Sci. 2001;56:B224–33.
362 [36] Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA.
363 Rejuvenation of aged progenitor cells by exposure to a young systemic environment.
364 Nature.2005;433:760–4.
365 [37] Rader EP, Faulkner JA. Recovery from contraction-induced injury is impaired in weight-
366 bearing muscles of old male mice. J Appl Physiol (1985). 2006;100:656–61.

[38] Evans WE. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr. 2010;91:1123S–7S.

[39] Clark BC, Manini TM. Functional concequences of sacropenia and dynapenia in the elderly. Curr Opin Clin Nutr Metab Care. 2010;13:271–6.

[40] Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA. Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. Phys Ther. 2001;81:1102–9.

[41] Weisleder N, Brotto M, Komazaki S, Pan Z, Zhao X, Nosek T, *et al.* Muscle aging is associated with compramised Ca^{2+} spark signaling and segregated intracellular Ca^{2+} release. Cell Biol. 2006;174:639–45.

[42] Seene T, Kaasik P. Muscle damage and regeneration: response to exercise training. Health. 2013;5:136-45.

[43] Seene T, Kaasik P, Pehme A, Alev K, Riso EM. The effect of glucocorticoids on the myosin heavy chain isoforms' turnover in skeletal muscle. J Steroid BiochemMol Biol. 2003;86:201–6.

[44] PehmeA, Alev K, Kaasik P, Seene T. Age-related changes in skeletal muscle myosin heavy-chain composition: effect of mechanical loading.J Aging Phys Act 2004;12:29–44.

[45] Abate N, Chandalia M. The impact of ethnicity on type 2 diabetes. J Diabetes Complications. 2003;17:39–58.

[46] Rooyackers OE, Adey DB, Ades PA, Nair KS. Effect of age in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proc Natl Acad Sci USA. 1996;93:15364–9.

[47] Barazzoni R, Short KR, Nair KS. Effects of aging on mitochondrial DNA copy number and cytochrome c oxidase gene expression in rat skeletal muscle, liver, and heart. J Biol Chem. 2000;275:3343–7.

392 [48] Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM, *et al.*
393 Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle
394 oxidative capacity. Diabetes. 2003;52:1888–96.
395 [49] Nair KS. Aging muscle. AmJ Clin Nutr. 2005;81:953–63.
396 [50] Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS. Age and aerobic exercise
397 training effects on whole body and muscle protein metabolism. Am J Physiol Endocrinol
398 Metab. 2004;286:E92–101.
399 [51] Yarasheski KE, Welle SL, Nair KS. Muscle protein synthesis in younger and older men.
400 JAMA. 2002;287:317–8.
401 [52] Seppet EK, Käämbre TP, Sikk P, Tiivel T, Vija TH, Tonkonogi M, *et al.* Functional
402 complexes of mitochondria with Ca, MgATPases of myofibrils and sarcoplasmic reticulum in
403 muscle cells. Biochim Biophys Acta. 2001;1504:379–95.
404 [53] Vendelin M, Béraud N, Guerrero K, Andrienko T, Kuznetsov AV, Olivares J, *et al.*
405 Mitochondrial regular arrangement in muscle cells: a "crystal-like" pattern. *Am.*J Physiol Cell
406 Physiol. 2005;288:C757–77.
407 [54] Dirks AJ, Leeuwenburgh C. The role of apoptosis in age-related skeletal muscle atrophy.
408 Sports Med. 2005;35:473–83.
409 [55] Saks V, Kaambre T, Sikk P, Eimre M, Orlova E, Paju K, *et al.* Intracellular energetics
410 units in red muscle cells. Biochem J. 2001;356:643–57.
411 [56] Aschenbach WG, Sakamoto K, Goodyear LJ. 5'adenosine monophosphate-activated
412 protein kinase, metabolism and exercise. Sports Med. 2004;34:91–103.
413 [57] Nader GA. Concurrent strength and endurance training: from molecules to man. Med Sci
414 Sports Exerc. 2006;38:1965–70.
415 [58] Abbiss CR, Laursen PB. Models to explain fatigue during prolonged endurance cycling.
416 Sports Med. 2005;35:865–98.

[59] Ratel S, Duché P, Williams CA. Muscle fatigue during high-intensity exercise in children. Sports Med. 2006;36:1031-65.

[60] Russ DW, Kent-Braun JA. Is skeletal muscle oxidative capacity decreased in old age? Sports Med. 2004;34:221–9.

[61] Harris BA. The influence of endurance and resistance exercise on muscle capillarization in the elderly: a review. Acta Physiol Scand. 2005;185:89–97.

[62] Green HJ, Reichmann H, Pette D. Fibre type specific transformations in the enzyme activity pattern of rat vastus lateralis muscle by prolonged endurance training. Pflügers Arch. 1983;399:216–22.

[63] van der Vusse GJ, Glatz JFk, Stam HC, Reneman R S. Fatty acid homeostasis in the normoxic and ischemic heart. Physiol Rev. 1992;72:881–940.

[64] Matsakas A, Macharia R, Otto A, Elashry M, Mouisel E, Romanello V, *et al.* Exercise training attenuates the hypermuscular phenotype and restores skeletal muscle function in the myostatin null mouse. Exp Physiol. 2012;97:125-40.

[65] Pierce GN, Sekhon PS, Meng HP, Maddaford TG. Effects of chronic swimming training on cardiac sarcolemmal function and composition. J Appl Physiol (1985). 1989;66:1715–21.

[66] Jin H, Yang R, Li W, Lu H, Ryan AM, Ogasawara AK, *et al.* Effects of exercise on cardiac function, gene expression and apoptosis in rats. Am J Physiol Heart Circ Physiol. 2000;279:2994–3002.

[67] Rupp H. The adaptive changes in the isoenzyme pattern of myosin from hypertrophied rat myocardium as a result of pressure overload and physical training. Basic Res Cardio. 1981;76:79–88.

[68] Wisloff U, Loennechen JP, Falck G, Beisvag V, Currie S, Smith G, *et al.* Increased conractility and calcium sensitivity in cardiac myocytes isolated from endurance trained rats. Cardiovasc Res. 2001;50:495–508.

442 [69] Diffee GM, Seversen EA, Stein TD, Johnson JA. Microarray expression analysis of
443 effects of exercise training: increase in atrial MLC-1 in rat ventricles. Am J Physiol Heart
444 Circ Physiol. 2003;284:830–7.
445 [70] Diffee GM, Seversen EA, Titus MM. Exercise training increases the Ca2+ sensitivity of
446 tension in rat cardiac myocytes. J Appl Physiol. 2001;91:309-15.
447 [71] Bottinelli R. Functional heterogeneity of mammalian single muscle fibres: do myosin
448 isoforms tell the whole story? Pflügers Arch. 2001;443:6–17.
449 [72] Rupp H. The adaptive changes in the isoenzyme pattern of myosin from hypertrophied
450 rat myocardium as a result of pressure overload and physical training.Basic Res Cardiol.
451 1981;76:79–88.
452 [73] Baldwin KM, Haddad F. Effects of different activity and inactivity paradigms on myosin
453 heavy chain gene expression in striated muscle. J Appl Physiol (1985). 2001;90:345–57.
454 [74] Mohr M, Krustrup P, Nielsen JJ, Nybo L, Rasmussen MK, Juel C, et al. Effect of two
455 different intense training regimes on skeletal muscle ion transport proteins and fatigue
456 development. Am J Physiol Regul Integr Comp Physiol. 2007;292:1594–602.
457 [75] Hood DA. Invited review: contractile activity-induced mitochondrial biogenesis in
458 skeletal muscle. J Appl Physiol (1985). 2001;90:1137–57.
459 [76] Menshikova EV, Ritov VB, Fairfull L, Ferrell RE, David E, Kelley D, et al. Effects of
460 exercise on mitochondrial content and function in aging human skeletal muscle. J Gerontol A
461 Biol Sci Med Sci. 2006;61:534–40.
462 [77] Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial
463 oxygen uptake and respiratory enzyme activity in skeletal muscle. J Biol Chem.
464 1967;242:2278–82.
465 [78] Tyler CM, Golland LC, Evans DL, Hodgson DR, Rose RJ. Skeletal muscle adaptations
466 to prolonged training, overtraining and detraining in horses. Pflugers Arch. 1998;436:391–7.

467 [79] Silva LA, Pinho CA, Scarabelot KS, Fraga DB, Volpato AM.; Boeck CR, *et al*. Physical
468 exercise increases mitochondrial function and reduces oxidative damage in skeletal muscle.
469 Eur J Appl Physiol. 2009;105:861–7.
470 [80] Baldwin KM, Klinkerfuss GH, Terjung RL, Mole PA, Holloszy JO. Respiratory capacity
471 of white, red, and intermediate muscle: adaptative response to exercise. Am J Physiol.
472 1972;222:373–8.
473 [81] Spina RJ, Chi MM, Hopkins MG, Nemeth PM, Lowry OH, HolloszyJO. Mitochondrial
474 enzymes increase in muscle in response to 7-10 days of cycle exercise. J Appl Physiol 1985.
475 1996;80:2250–4.
476 [82] Stuewe SR, Gwirtz PA, Agarwal N, Mallet RT. Exercise training enhances glycolytic
477 and oxidative enzymes in canine ventricular myocardium.J Mol Cel Cardiol. 2000;32:903–
478 13.
479 [83] Sun B, Wang JH, Lv YY, Zhu SS, Yang J, Ma JZ. Proteomic adaptation to chronic high
480 intensity swimming training in the rat heart. Comp Biochem Physiol Part D Genomics
481 Proteomics. 2008;3:108–17.
482 [84] Kemi OJ, Hoydal MA, Haram PM, Garnier A, Fortin D, Ventura-Clapier R, *et al*.
483 Exercise training restores aerobic capacity and energy transfer systems in heart failure treated
484 with losartan. Cardiovasc Res. 2007;76:91-9.
485 [85] Terblanche SE, Gohil K, Packer L, Henderson S, Brooks GA. The effects of endurance
486 training and exhaustive exercise on mitochondrial enzymes in tissues of the rat (Rattus
487 norvegicus). Comp Biochem Physiol A Mol Integr Physiol. 2001;128:889–96.
488 [86] Bozner A, Meessen H. The ultrastructure of the myocardium of the rat after single and
489 repeated swim exercises. Virchows Arch B Cell Pathol. 1969;3:248–69.
490 [87] Anversa P, Beghi C, Levicky V, McDonald SL, Kikkawa Y. Morphometry of right
491 ventricular hypertrophy induced by strenuous exercise in rat.Am J Physiol. 1982;243:856–61.

[88] Kayar SR, Conley KE, Claassen H, Hoppeler H. Capillarity and mitochondrial distribution in rat myocardium following exercise training. J Exp Biol. 1986;120: 189-99.

[89] Paniagua R, Vázques JJ, López-Moratalla N. Effects of physical training on rat myocardium. An enzymatic and ultrastructural morphometric study. Rev Esp Fisiol. 1977;33:273–81.

[90] Noble EG, Moraska A, Mazzeo RS, Roth DA, Olsson MC, Moore RL, *et al.* Differential expression of stress proteins in rat myocardium after free wheel or treadmill run training. J Appl Physiol (1985). 1999;86:1696–701.

[91] Gleyzer N, Vercauteren K, Scarpulla RC. Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NFR-2) and PGC-1 family coactivators. Mol Cell Biol. 2005;25:1354–66.

[92] Scheller K, Sekeris CE. The effects of steroid hormones on the transcription of genes encoding enzymes of oxidative phosphorylation. Exp Physiol. 2003;88:129–40.

[93] Akimoto T, Pohnert SC, Li P, Zhang M, Gumbs C, Rosenberg P B, *et al.* Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway.J Biol Chem. 2005;280:19587–93.

[94] Fan M, Rhee J, St-Pierre J, Handschin C, Puigserver P, Lin J, *et al.* Suppression of mitochondrial respiration through recruitment of p160 myb binding protein to PGC-1alpha: modulation by p38 MAPK. Genes Dev. 2004;18:278–89.

[95] Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, *et al.* Cytokine stimulation of enenrgy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Mol Cell. 2001;8:971–82.

[96] Lee WJ, Kim M, Park HS, Kim HS, Jeon MJ, Oh KS, *et al.* AMPK activation increases fatty acid oxidation in skeletal muscle by activating PPARalpha and PGC-1. Biochem Biophys Res Commun. 2006;340:291–5.

[97] Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, et al. AMPK and PPARdelta agonists are exercise mimetics. Cell. 2008;134:405−15.

[98] Menzies KJ, Hood DA. The role of SirT1 in muscle mitochondrial turnover. Mitochondrion. 2012;12:5−13.

[99] Amat R, Planavila A, Chen SL, Iglesias R, Giralt M, Villarroya F. SIRT1 controls the transcription of the peroxisome proliferator-activated receptor-gamma Co-activator-1alpha (PGC-1alpha) gene in skeletal muscle through the PGC-1alpha autoregulatory loop and interaction with MyoD. J Biol Chem. 2009;284:21872−80.

[100] Dumke CL, Davis JM, Murphy EA, Nieman DC, Carmichael MD, Quindry J, et al. Successive bouts of cycling stimulates genes associated with mitocondrial biogenesis. Eur J Appl Physiol. 2009;107:419−27.

[101] Pillai VB, Sundaresan NR, Jeevanandam V, Gupta MP. Mitochondrial SIRT3 and heart diseases. Cardiovasc Research. 2010;88:250−6.

[102] Gurd BJ, Holloway GP, Yoshida Y, Bonen A. In mammalian muscle, SIRT3 is present in mitochondria and not in the nucleus; and SIRT3 is upregulated by chronic muscle contraction in an adenosine monophosphate-activated protein kinase-independent manner. Metabolism. 2012;61:733−41.

[103] Palacios OM, Carmona JJ, Michan S, Chen KY, Manabe Y, Ward JL, *et al.* Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1alpha in skeletal muscle. Aging (Albany NY). 2009;1:771−83.

[104] Hokary F, Kawasaki E, Sakai A, Koshinaka K, Sakuma K, Kawanaka K. Muscle contractile activity regulates Sirt3 protein expression in rat skeletal muscles. J Appl Physiol (1985). 2010;109:332−40.

[105] Wu Z, Huang X, Feng Y, Handschin C, Feng Y, Gullicksen PS, *et al.* Transducer of regulated CREB-binding proteins (TORCs) induce PGC-1α transcription and mitochondrial biogenesis in muscle cells. Proc Natl Acad Sci USA. 2006;103:14379–84.

[106] Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, *et al.* P53 regulates mitochondrial respiration. Science. 2006;312:1650–3.

[107] Achanta G, Sasaki R, Feng L, Carew JS, Lu W, Pelicano H, *et al.* Novel role of p53 in maintaining mitochondrial genetic stability through interaction with DNA Pol gamma.EMBO J. 2005;24:3482–92.

[108] Park JY, Wang PY, Matsumoto T, Sung HJ, Ma W, Choi JW, *et al.* P53 improves aerobic exercise capacity and augments skeletal muscle mitochondrial DNA content. Circ Res. 2009;105:705–12.

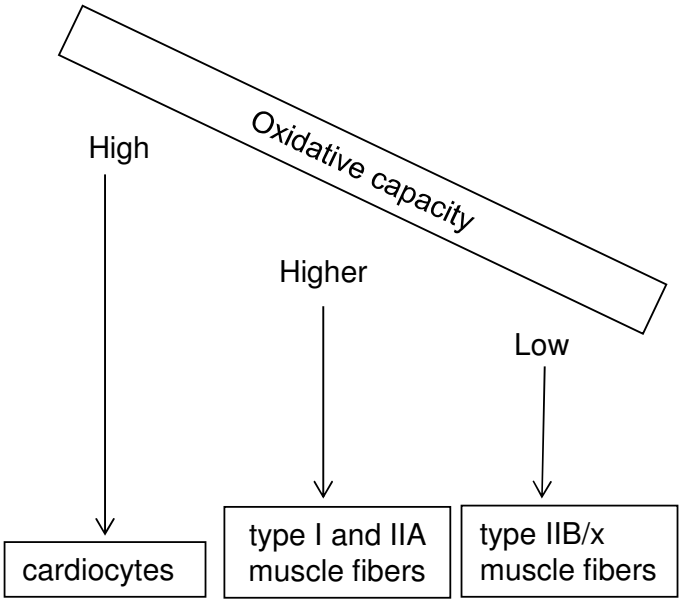
[109] Saleem A, Adhihetty PJ, Hood DA. Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. Physiol Genomics. 2009;37:58–66.

[110] Seene T, Kaasik P. Role of myofibrillar protein catabolism in development of glucocorticoid myopathy: aging and funcional activity aspects. Metabolites. 2016;6:15. doi:10.3390/metabo6020015

565 Table 1. List of the key references

van Wessel T, et al., 2010 [5]
Trappe T, 2009 [9]
Buford TW, et al., 2010 [11]
Hood DA, 2009 [15]
Ljubicic V, et al., 2009 [16]
Reznick R, et al., 2007 [17]
Seene T., Kaasik P, 2012 [19]
Fontera WR, et al., 2000 [23]
Clark BC, et al., 2006 [24]
Roberts MD, et al., 2010 [27]
Kaasik P, et al., 2007 [30]
Verney J, et al., 2008 [31]
Tatsumi R, 2010 [33]
Kaasik P, et al., 2012 [34]
Carlson BM, et al., 2001 [35]
Conboy M, et al., 2005 [36]
Evans WE, 2010 [38]
Clark BC, Manini TM, 2010 [39]
Stackhouse SK, et al., 2001 [40]
Weisleder N, et al., 2006 [41]
Seene T, Kaasik P, 2013 [42]
Pehme A, et al., 2004 [44]
Seppet E, et al., 2001 [52]
Dirks AJ, Leeuwenburgh C, 2015 [54]
Saks V, et al., 2001 [55]
Russ DW, Kent-Barun JA, 2004 [60]
Matsakas A, et al., 2012 [64]
Diffee GM, et al., 2003 [69]
Bottinelli R, 2001 [70]
Mohr M, et al., 2007 [74]
Holloszy JO, 1967 [77]
Silva LA, et al., 2009 [79]
Gleyzer N, et al., 2005 [91]
Akimoto T, et al., 2005 [93]
Puigserver P, et al., 2001 [95]
Lee WJ, et al., 2006 [96]
Narkar VA, et al., 2008 [97]
Menzies KJ, Hood DA, 2012 [98]
Amat R, et al., 2009 [99]
Dumke CL, et al., 2009 [100]
Pillai VB, et al., 2010 [101]
Gurd BJ, et al., 2012 [102]
Wu Z, et al., 2006 [105]
Matoba S, et al., 2006 [106]
Saleem A, et al., 2009 [109]
Seene T, Kaasik P, 2015 [110]

566



567

568

Figure 1:	Oxidative capacity of striated muscle cells

569

570

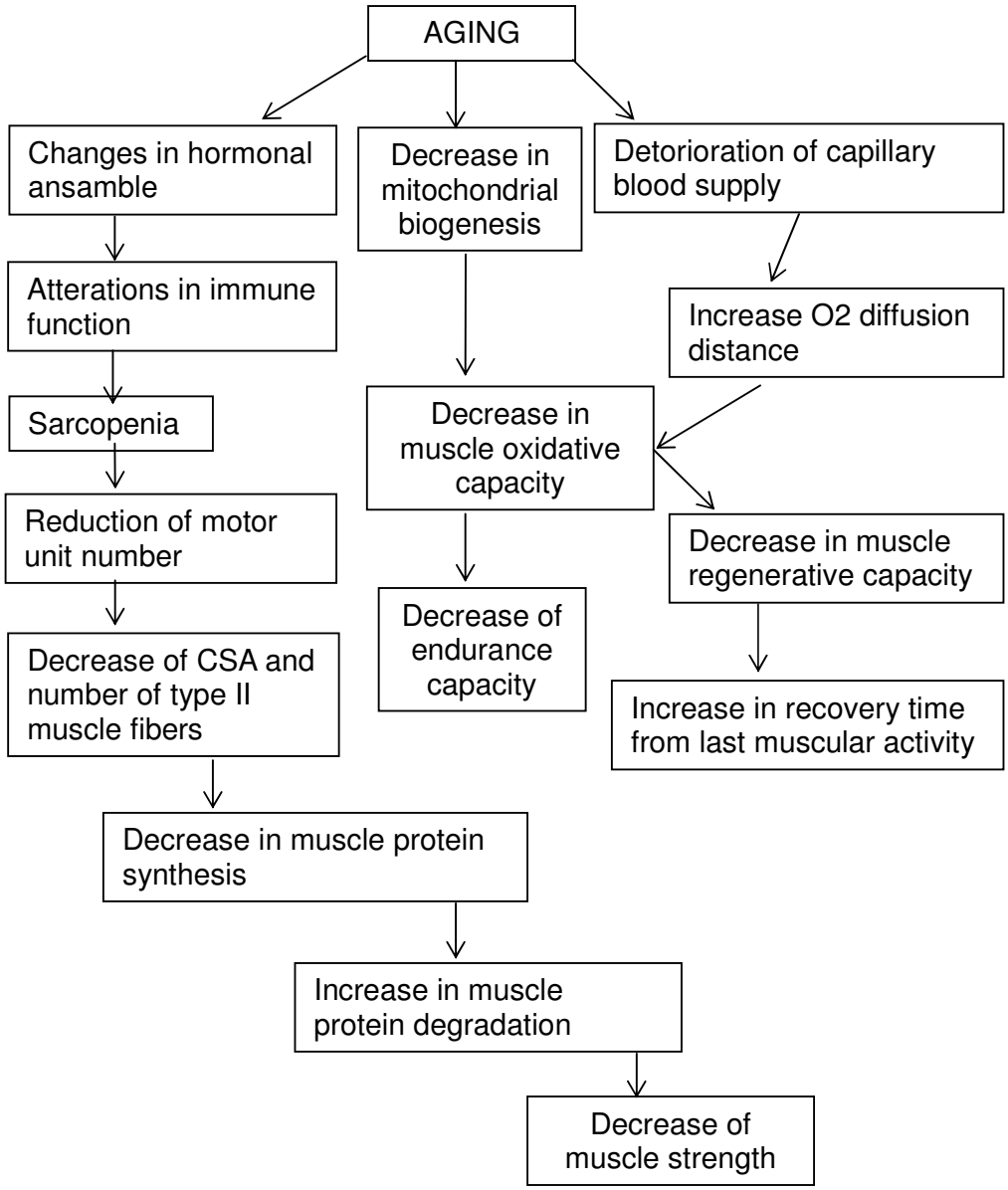


Figure 2:	Effect of aging on skeletal muscle

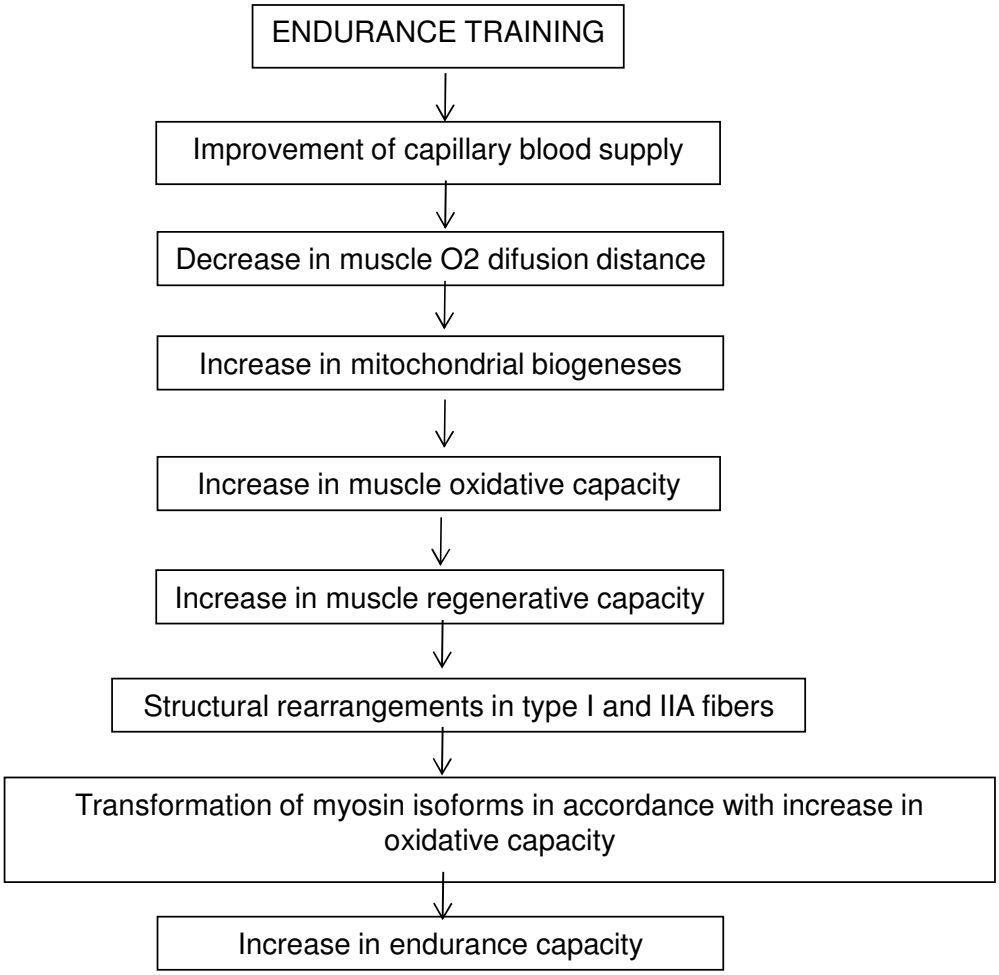


Figure 3:	Effect of endurance training on aging skeletal muscle

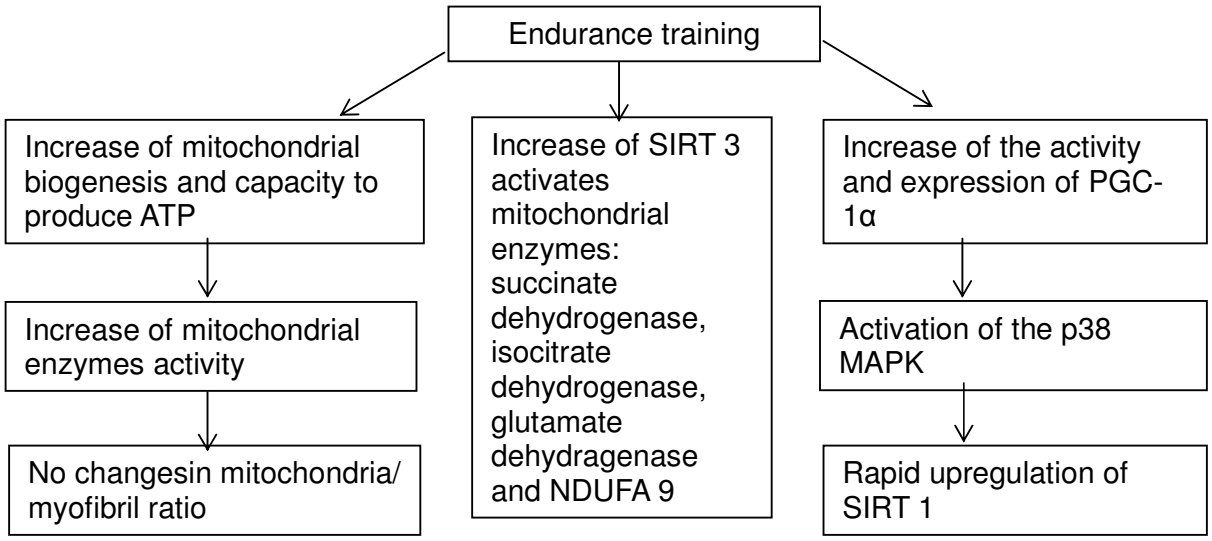


Figure 4:	Effect of endurance training on aging muscle mitochondrial biogenesis