

# The Effects of Aging on Skeletal Muscle ATP Production

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## Abstract

*The study of the aging process and its prevention is an incredibly popular field; the natural course of the human body is to age and theories abound on how to avoid it. Age affects every system and pathway of the body and alters many of the bodily functions. This paper, using articles from Touro's library database examines the different areas in which aging negatively affects ATP production. The multifaceted process associated with the production of ATP in the human body was analyzed. Several features such as the mitochondria, physical activity, and hormones are linked to ATP production and the relationship was further explored. The findings reveal that a dysfunction or lack of these factors, a feature of aging, is the initiator of the decrease in ATP production that is attributed to the natural aging process. Together, a lack of mitochondrial function, physical inactivity, reduced growth hormone levels, and increased insulin sensitivity levels contribute to the decline in ATP production that is concomitant with the progression of age. The diminishing presence of ATP then stimulates further dysfunction or lack of these elements, which in turn drives the aging process even further.*

## Introduction

Aging is a phenomenon that all creatures go through. It is believed to be a degenerative process caused by accumulated damage that leads to cellular dysfunction, tissue failure and death. The physiological changes which lead to senescence in humans may involve spine curving (kyphosis), reduced fertility, loss of hearing and eyesight, frailty, cognitive decline and many other symptoms (Trifunovic et. al., 2004). All these changes in the body are triggered by a variety of molecular and biochemical modifications. One of the major pathways that is altered as people age is the cellular respiration pathway which produces ATP, the body's main source of energy.

## Methods

The research discussed in this paper was collected from various different databases. The majority of the articles were compiled from databases such as PubMed and ProQuest, with access to restricted articles gained by using Touro's library system. Some articles were also found through google scholar.

## An Overview of Cellular Respiration

Cellular respiration is a set of metabolic reactions to convert biochemical energy from nutrients into adenosine triphosphate (ATP). ATP is the primary energy carrier in living organisms. When the cell requires energy, it breaks down ATP through hydrolysis; a high energy bond is broken where a phosphoryl group is removed and energy is released. In humans, aerobic cell respiration has three parts. Glycolysis is the breakdown of glucose into two pyruvate molecules where two molecules of ATP and two molecules of NADH are produced without necessitating oxygen. The next step is known as the Krebs cycle, the citric acid cycle or the tricarboxylic acid cycle. The carbons in the pyruvate molecules are pulled apart and the energy stored in those covalent bonds is released. This step produces two molecules of ATP, six NADH molecules and two FADH<sub>2</sub> molecules. The third and final step is the electron transport chain and oxidative phosphorylation. Here, oxygen is required and about thirty-four molecules of ATP are produced. The second two steps of cellular respiration, which are the main

energy-producing steps, occur in the mitochondria, unlike glycolysis which takes place in the cytoplasm (Fernie et. al., 2004).

Oxidative phosphorylation is the metabolic pathway in which cells use enzymes to oxidize nutrients. Electrons are fed from reduced substrates such as NADH, FADH<sub>2</sub>, fatty acids or glycerol phosphates into the electron transport chain located in the inner membrane of the mitochondria. Big membrane-bound enzymes such as the dehydrogenases of  $\beta$ -oxidation, glycerol phosphate dehydrogenase, NADH-Q oxidoreductase (Complex I) or succinate-Q oxidoreductase (Complex II) pass electrons down the gradient of redox potential to ubiquinone (Q) which is a mobile lipid-soluble carrier. The electrons then get passed down from ubiquinone to the final acceptor, oxygen, through Q-cytochrome c oxidoreductase (Complex III), cytochrome c (a second, water-soluble, mobile carrier) and cytochrome c oxidase (Complex IV). As the electrons move from less electronegative to more electronegative molecules, they lose energy, and with that energy, Complex I, Complex III and Complex IV pump protons against their electrochemical gradient from the matrix to the intermembrane space. A protonmotive force, consisting mostly an electrical gradient (membrane potential) and a small chemical gradient, (pH difference) is set up due to the pumping of protons. This protonmotive force then pushes the protons back into the matrix through the ion channel ATP synthase which harvests the energy and creates ATP (Saraste, 1999).

Being that the main organelle involved in cellular respiration is the mitochondrion, dysfunction of this organelle must be the driving force behind the lack of energy in cells, resulting in cell death. This implies that dysfunctional mitochondria must be of central focus in aging. The decline of mitochondrial function with age has been recognized for some time and has been linked to a decreased number of mtDNA and mitochondrial protein levels in human heart, brain and skeletal muscle cells. Additionally, aged muscle suffers from functionally impaired respiratory chain units, inhibiting respiration associated with ATP production (Zapico et. al., 2016). The mitochondria in elderly tissue has often been found to be larger, fewer in number and contain abnormal cristae, vacuoles and paracrystalline inclusions (Hutter et. al., 2007). When the quadriceps of thirty participants whose

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ages ranged from  $78.5 \pm 5$  years were examined, an inverse relationship between the fatigability level and the level of oxidative phosphorylation (ATPmax) was reported. Higher fatigue levels, a condition which is extremely common with advancing age, is caused by a decrease in mitochondrion capacity for oxidative phosphorylation (Santanasto et. al., 2014). In another study, permeabilized muscle fibers from the vastus lateralis were studied from twenty-four young (approximately thirty years) and thirty-one older (approximately sixty-five years) subjects. This study was to determine if there was a change in mitochondrial respiratory capacity and coupled respiration (respiration linked to ATP production) with age and the results showed a decline in both (Porter et. al., 2015). There are many possible reasons for this decline in mitochondrial function but the most accepted theory seems to be the Free Radical Theory of Aging.

### Mitochondrial Free Radical Theory of Aging

Oxidative damage is a main cause of cell degeneration. Since the mitochondria are involved in many redox reactions, they are extremely prone to oxidative stress. The source of oxidative damage is the free radicals known as oxidants or reactive oxygen species (ROS) which are a byproduct of redox-reaction and therefore produced during aerobic respiration (Harman, 1956). Normally, a small fraction of the oxygen consumed by the mitochondria is converted into reactive oxygen species, but defects in the respiratory chain lead to greater production of these free radicals (Lee et. al., 2000). Superoxide Dismutase (SOD), an enzyme whose activity is present in subcellular compartments where there is  $O-2\cdot$  formation, was used as a tool to reveal that the mitochondria are a principle source of endogenous oxidants. Some of the SOD activity was recognized in the matrix space and the other half in the inner and outer membranes of the mitochondria (Imray, Fridovich, 1991).

Ground state diatomic oxygen is not too reactive itself because its two unpaired electrons are located in different molecular orbitals and possess parallel spins. As a result, in order for  $O_2$  to simultaneously accept two electrons, they must both possess antiparallel spins relative to the unpaired electrons. Consequentially,  $O_2$  preferentially accepts electrons one at a time from other radicals (such as transition metals in certain valences). In living organisms, therefore, oxygen must participate in coordinated, serial, enzyme-catalyzed one-electron reductions in order to be reduced by two or four electrons. The enzymes that carry out these reactions generally possess active-site radical species such as iron. This method of  $O_2$  reduction generates  $O-2\cdot$  and hydrogen peroxide ( $H_2O_2$ ). When in the company of free transition metals (specifically iron and copper),  $O-2\cdot$  and  $H_2O_2$  together produce the hydroxyl radical ( $\cdot OH$ ) (Wood, 1988). This extremely reactive radical is presumed to be the species responsible for initiating the oxidative destruction of biomolecules (Harman, 1956). When mitochondrial DNA of cells which can no longer

reproduce undergoes oxidative damage it results in mutations and blocks in replication, leading to mitochondrial dysfunction and ultimately a decline in ATP production.

One study demonstrated that older people have significantly higher oxidative damage to DNA and that mtDNA abundance decreases with age. The decrease in mtDNA is attributed to the lessened content of mRNA transcripts that encode mitochondrial protein. The skeletal muscle of the elderly population was found to contain a reduced amount of mitochondrial proteins and oxidative enzymes (enzymes that catalyze redox reactions and increase the rate at which ATP is produced aerobically). Accumulated oxidative damage can be the reason for lessened mtDNA content in aging muscle. DNA oxidation, the process of oxidative damage on Deoxyribonucleic Acid, was observed to increase with age. Also, there is a higher activity of antioxidant enzymes in older rat muscles, indicating that the ROS production rate increases with age; the ROS production rate surpasses the activity of the antioxidants defense enzymes (Short et. al., 2005). The decline in mtDNA content is a contributing factor to dysfunctional mitochondria because it means that there is a lack of template availability for transcription and translation of crucial mitochondrial proteins. The reduction of mitochondrial protein synthesis and oxidative enzyme activity helps explain the reduced ability of mitochondria to perform oxidative phosphorylation in older muscle. This study concluded that there is a decline in mitochondrial ATP production rate (MAPR), and its point of validity comes from the fact that the subjects were well suited for the study. They had a large group of one hundred and forty-six healthy men and women ranging in age from nineteen to eighty-nine. Their physical activity was taken into account and they were subjects who were not regularly doing exercise (less than thirty minutes less than two days a week). In response to the studies which show that physical activity improves muscle mitochondrial biogenesis, the physical activity of the subjects was taken into account. Only men and women who were not regularly exercising, with activity totaling less than thirty minutes for less than two days a week, were chosen. Also, the participants were kept on a standard diet for three days before muscle biopsies from their vastus lateralis were taken for study. A key finding of this study was the decline in the MAPR of skeletal muscle with age due to a combination of reduced mitochondrial content and a functional alteration in the existing mitochondrial population (Short et. al., 2005).

In response to the production of ROS, uncoupling agents such as dinitrophenol (DNP) are produced. These agents are lipid-soluble weak acids that can cross the mitochondrial membrane. Once inside the mitochondria, these proteins eliminate the link between oxidation and phosphorylation. They accomplish this by setting up a catalytic cycle that dissipates the proton-motive force, allowing the continuation of substrate oxidation all the while lacking the driving force for coupled ATP synthesis.

This is a thermogenic process and occurs in many living cells including skeletal muscle cells (Brand, 2000). The first known UCP, UCPI is the one that controls brown fat which is one of the body's ways of regulating thermogenesis. In the brown adipose tissue, the proton leak through UCPI is a mechanism that exploits energy generally used to create ATP to generate heat. This method of thermogenesis regulated by brown fat UCPI is important in numerous physiological conditions such as arousal from hibernation and cold exposure in newborns. The question of the reason for this process arises. What reason is enough to validate a reduction in ATP level and such a high energetic price? To strengthen this question, it is known that thermogenesis is not enough of motivation because this uncoupling process is done by both endotherms and ectotherms. The reasoning behind this seemingly troubling process is the diminution of ROS production, a protection against cellular degeneration (Brand, 2000). When calculated, the respiratory capacity used for phosphorylation and respiratory function linked to ATP production in older adults was lower than in the young (Porter et al., 2015). Not only do the presence of free radicals (which are a result of aging) lower the skeletal muscle ATP production, but the cell's natural response and method to protect itself against oxidative damage, which involves uncoupling proteins, is also a major contributing factor to the reduction of ATP production.

A more indirect but lethal effect oxidants have on the mitochondria is that they disrupt the activity of the lysosomes. Oxidative damage is responsible for depositing lipofuscin in the lysosomes. Lipofuscin is the yellow pigment granules made up of lipid residues of lysosomal digestion, and accumulation of lipofuscin alters the lysosomal autophagic ability. Because the lysosomes take care of recycling unnecessary material and organelles (such as viruses or damaged particles), their failure results in a buildup of unwanted particles in the cell (Konig et al., 2017). Decreased macroautophagic activity from lysosomal leakage was observed in rat cells, and is a central reason for the accumulation of damaged mitochondria in aged cells. This buildup is associated with a decrease in mitochondrial efficiency and an increase in oxidant generation (Roberg, Ollinger, 1998). The decline in autophagic activity as a common characteristic of aging makes for clogged lysosomes due to lipofuscin and mitochondrial deterioration. This process in which mitochondrial ROS encourage lipofuscin generation while the accumulation of lipofuscin disturbs the mitochondrial autophagy is known as the "garbage catastrophe theory of aging" (Hutter et al., 2007).

Therefore, oxidative destruction of molecules involved in aerobic respiration (such as oxidative enzymes, mitochondrial proteins or mtDNA) leads to defective mitochondria. The mitochondria themselves are primary targets of oxidative damage and increase their production of ROS once destroyed. Putting these two processes together results in a disastrous vicious

cycle in which the synthesis of malfunctioning electron transport chain subunits results in oxidative phosphorylation impairment, decreased ATP production and further ROS generation.

### Physical Activity

There are many studies which say that the primary contributing factor to reduced mitochondrial function is the lack of physical activity. In one study, thirty-nine volunteers were to complete graded exercise tests to determine their daily physical activity, fitness, and exercise efficiency. The group of volunteers included ten young active people about thirty years old, ten older active people about sixty-seven years old and nineteen older sedentary people. Mitochondrial energetics from biopsies of the vastus lateralis were measured via magnetic resonance spectroscopy and respirometry. The results of this study showed a higher fitness level in the young active compared to the older active and older sedentary. The mitochondrial respiration, maximum mitochondrial capacity, Maximal ATP production/Oxygen consumption (P/O) ratio, and exercise efficiency were similar in the young active and older active and were significantly lower in older sedentary. This study concluded that constant physical activity makes for better mitochondrial capacity (Distefano et al., 2018).

Besides for physical activity having an effect on the mitochondrial efficiency (ATPmax/max O<sub>2</sub> consumption), the reverse is also true. Lessened mitochondrial efficiency seems to have a negative effect on older peoples' physical activity. A study was done to analyze whether or not slower walking speed in older adults is related to reduced mitochondrial capacity and efficiency. A group of thirty-seven older people (ages ranging from seventy to eighty-nine) who were of normal weight (under 286 lb for the men and under 251 lb. for the women) were chosen. They were able to walk unassisted and had no symptoms of cardiovascular or pulmonary disease. They had no pain or stiffness in the legs, hips, knees, feet, or ankles when walking and no difficulty bending or straightening the knees. The participants were told to complete a 400-meter walk within 15 minutes at their normal walking speed. Afterward, muscle fibers biopsies from the vastus lateralis were taken to be observed. A key finding was that muscle mitochondrial efficiency correlated with the participants walking speed. This study concluded that the loss of mitochondrial capacity and efficiency with age may be important contributors to the reduction in mobility and increase in disability. This is due to the relationship between mitochondrial capacity and walking speed (Coen et al., 2012).

The link between physical activity and mitochondrial energetics is that aerobic exercise enhances muscle mitochondrial biogenesis. Resistance training in older people can increase the protein synthesis rate. The content and function of certain proteins in the muscle which are vital to its functioning, depend on the protein synthesis rate (Short et al., 2005). Exercise counteracts decay which happens in aging muscle by heightening

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muscle protein turnover. Because muscle mitochondrial content and function is reduced with age, the resting and maximal oxygen consumption also decline with advancing age (Short et. al., 2004). The VO<sub>2</sub>max of an individual is closely associated with mitochondrial ATP production and so a decline in the VO<sub>2</sub>max with age means that it is correlated with a decline in ATP production. In muscle samples taken from healthy individuals ranging from eighteen to eighty-seven years, the VO<sub>2</sub>max while cycling declined approximately eight percent per decade (Short et. al., 2005). If constant physical activity throughout one's life is what can keep the VO<sub>2</sub>max at a decent level, it must be that physical decline, a common occurrence in aging, is in part a contribution to the reduction of ATP production.

### Sarcopenia and Physical Decline

Sarcopenia, a natural part of the aging process, is the progressive decline of muscle mass, strength and physical function. The loss rate is believed to accelerate after the age of sixty-five. The deterioration of muscle quantity and quality leads to a decline in strength and power and a slowing of movement, all features of sarcopenia (Baumgartner et. al., 1999). A deterioration in muscle mass is followed by a decline in physical activity which has been negatively linked to mitochondrial function.

Age-related hormonal changes seem to be a possible mechanism for the onset of sarcopenia. Insulin-like growth factor I (IGF-1) is a protein that is encoded by the IGF-1 gene. This hormone plays a fundamental role in childhood growth and continues to have anabolic effects in adulthood. The production of IGF-1 is stimulated by growth hormone. Growth hormone (GH) is made in the anterior pituitary gland, released into the blood stream, and then stimulates the liver to produce IGF-1. IGF-1 is the stimulation for systemic body growth, and has proliferating effects on many cells in the body, especially skeletal muscle (Laron, 2001). After twenty years of age, the secretion of growth hormone decreases by approximately fourteen percent per decade. This decline is followed by a reduction in IGF-1, which is responsible for cell production, energy metabolism, and inhibition of apoptosis (Giannoulis et. al., 2008).

Testosterone, an anabolic steroid which increases muscle protein synthesis, begins to drop in male serum levels in the late thirties and continues to decline throughout adulthood. A group of older men were treated with testosterone in order to increase their testosterone level to that of younger men. The treatment attenuated one symptom of sarcopenia, the loss of muscle mass (Storer et. al., 2016). In females, the positive correlation between plasma estrogen levels and muscle mass suggests that reduced estrogen following menopause may result in reduced muscle mass as well (Van Geel et. al., 2009).

Although there was no change in muscle mass or strength when healthy males were treated with GH alone, the addition

of testosterone to the treatment resulted in a 6.8% increase in muscle strength. There was also an increase in lean body mass (LBM=total body weight minus the fat) which indicates the correlation between lean body mass and strength; a change in LBM results in a change in strength. Along with increase in LBM came an increase in VO<sub>2</sub>max. (Blackman et. al., 2002). An effective mechanism to increase the endogenous levels of somatotrophic hormones (such as GH and IGF-1) in the blood is training and exercise. A thirteen-week combined sprint and resistance training in middle-aged men improved the body composition and increased circulating GH. There was also an increase in IGF-1 level following the exercise which shows that training can counteract the natural decline in somatotrophic hormones during aging (Sellami et. al., 2017). A decrease in GH and testosterone, vital anabolic hormones, plays a big role in the loss of muscle mass which is a key element in the development of sarcopenia.

Another possible cause of sarcopenia is the acceleration of apoptotic pathways. Apoptosis is the highly regulated and controlled process of cell death in multicellular organisms. This process can happen via the intrinsic pathway in which the cell kills itself because it senses cell stress, or the extrinsic pathway, where the cell kills itself because of signals from the other cells. Both pathways initiate the activity of caspases, enzymes that destroy proteins. Apoptosis is a homeostatic process which keeps our body balanced between all the new cells arising from stem cells and the billions of cells dying each day. This very beneficial process becomes a problem when it accelerates with age and results in the loss of muscle mass and strength. Although the mechanism for the acceleration of these pathways is unknown, what is known is that there are many contributing factors such as oxidative stress and impaired insulin sensitivity (Marzetti et. al., 2012).

### Insulin Resistance

A major finding in old age is insulin resistance. Insulin is a hormone produced by the pancreas and regulates the amount of glucose in the blood. Resistance to this hormone can result in type 2 diabetes. Age associated decline in mitochondrial function seems to be related to insulin resistance. The MAPR was found to be approximately thirty percent less in patients who were insulin resistant compared to those who were not, and that was consistent with the finding of altered mitochondria (Petersen et. al., 2004). The altered mitochondria and reduced MAPR is known to be a contributing factor to insulin resistance. In addition to that, insulin stimulates transcription and translation of mitochondrial proteins and genes thereby increasing MAPR and this effect is lacking in those with type 2 diabetes. So, whether insulin resistance causes a decrease in mitochondrial function or the reverse, both possibilities are plausible for they seem to each have an effect on the other (Short et. al., 2005).

In a study done to determine if insulin enhances the capacity of

mitochondrial ATP production in skeletal muscle, both subjects with and without type 2 diabetes were recruited and muscle biopsies of the vastus lateralis were examined. The muscles were infused with a low dosage of insulin and a high dosage of insulin and were studied after eight hours. Mitochondrial protein complexes, whose syntheses are dependent on coordinated transcriptional regulation of mitochondrial and nuclear genes, must be available for mitochondrial ATP production to occur. In the subjects without diabetes, the high dose insulin infusion resulted in a higher mitochondrial fractional synthesis rate. Additionally, there was an increase in the activities of the oxidative enzymes citrate synthase and cytochrome-c-oxidase subunit IV (a part of complex IV). (Citrate synthase is the pace-making enzymes of the first step in the citric acid cycle and increased activity of the citric acid cycle may increase the rate of ATP production.) There was also an increase in the mRNA level from both mitochondrial (NADH dehydrogenase subunit IV) and nuclear (cytochrome c oxidase subunit IV) genes encoding mitochondrial proteins. After eight hours of high dose insulin infusion, the mitochondrial ATP production rate of the individuals with type 2 diabetes did not change. Clearly, insulin infusion increases mitochondrial protein synthesis and the mitochondrial capacity for oxidative phosphorylation in skeletal muscle (Stump et al., 2003). Insulin is not only important for regulating the blood sugar level but it is also heavily involved in ATP production. Resistance to this hormone, resulting from dysfunctional mitochondria, causes a decrease in mitochondrial protein content thus reducing mitochondrial respiration and ATP production.

### Conclusion

The free radical theory of aging which gives reason for the malfunctioning mitochondria is itself a result of dysfunctional mitochondria. Increased ROS production, a byproduct of mitochondrial decay disrupts lysosomal activity creating the additional accumulation of damaged mitochondria followed by an increase in oxidants. An additional result of oxidative damage is the decrease in muscle mass, muscle strength and movement. The opposite is also true, physical activity has been shown to increase muscle mass and counteract the production of free radicals (ROS) while physical inactivity has shown to increase ROS levels, increase sarcopenia and decrease insulin sensitivity. Insulin resistance is another result of oxidant accumulation and physical inactivity and causes additional ROS content by disturbing mitochondrial protein synthesis. Essentially, all of these factors are negative feedback loops that influence each other. Studies which failed to see the correlation between these features and decreased ATP production with age, may be because they failed to look at all of these factors as a whole and recognize that when they all come together, create a vicious cycle. Although it is unclear how and where this natural process starts, once it does, there is no way to end it. The decrease in ATP production

in skeletal muscle is an ordinary part of the aging process which results in driving the aging process even further.

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