# Biosolids Term Paper – Final Project

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## Introduction

As the name implies, the human musculoskeletal system comprises of muscles and bones, while also comprising of "cartilage, tendons, ligaments, joints, and other connective tissues that support and bind tissues and organs together", providing the human body with mobility and stability [1]. Although each component makes its own unique contribution in providing the body with the aforementioned functions, the muscles and bones contribute the most to these functions. Therefore, encouraging their growth and health will promote better mobility and stability while reducing the development of potential diseases. There are various ways to approach maintaining muscle and bone health, such as consuming a balanced diet and intaking certain supplements; however, it seems as though the most favored method of achieving muscle and bone health, along with overall health in general, is via exercise. In fact, it seems universally accepted that regular exercise provides numerous benefits, primarily positive, to the body both physically and mentally, with nearly all medical professionals promoting their patients to incorporate some sort of exercise into their lifestyles. This paper serves to explore exactly what effect regular exercise and the lack thereof has on the musculoskeletal system and the human body at large. The intent is to take the universal idea of exercise being beneficial for the body and conducting an in-depth, unbiased analysis on the physiology of skeletal muscles, observing the mechanics of muscle movement and the consequences of no stimulation, adequate stimulation, and overstimulation of skeletal muscles.

Muscles are segmented into three different types: skeletal, smooth, and cardiac. Although exercise affects all three muscle types, it does so in varying degrees, affecting skeletal muscles directly and cardiac muscles indirectly (with a small effect on smooth muscles). This is because smooth and cardiac muscles are involuntary muscles, meaning that the body automatically regulates their contraction and dilation without any conscious contribution from the person, whereas skeletal muscles are voluntary and can be controlled consciously. Since exercise requires specific movements, voluntary muscles (i.e., skeletal muscles) will be under scrutiny when analyzing the impact muscle stimulation has on the body. Also, considering how there are over 600 named skeletal muscles in the human body, only the prominent muscles located in the legs, abdominals, arms, chest, back, and shoulders will be implied throughout the paper. To address the previous point made regarding exercise indirectly affecting cardiac muscles, the reason for this is because exercises require conscious movement, which would exclude cardiac muscles since they are involuntarily controlled. However, most exercises stimulate the cardiovascular system to pump more blood throughout the body, which over time results in cardiac muscle becoming thicker and more efficient at pumping blood, thus strengthening it.

Additionally, various types of diseases and conditions related to the musculoskeletal system will be addressed in this paper, specifically those that are either induced or prevented by exercise. These clinical studies serve to contribute to the overall assessment of exercise and what effects they may produce in the body. Other physiological changes such as muscle growth or decline will be addressed, also discussing how this may prove beneficial or detrimental to the overall health and well-being of the musculoskeletal system and the human body at large.

## Skeletal muscle mechanics

Prior to analyzing the impact of physical activity on the body, one needs to understand the mechanics of muscles and how they function physiologically. As mentioned above, muscles are divided into three types: skeletal, smooth, and cardiac. Skeletal muscles comprise of 40-45% of total body weight and are divided into three categories: slow oxidative, fast oxidative, and glycolytic. Each category can be found within any given muscle in varying degrees of composition, but each type is best suited for different activities. Slow oxidative muscles produce ATP via aerobic respiration and are best for endurance activities, fast oxidative also produce ATP aerobically but are best suited for shorter-term strength activities, and glycolytic muscles produce ATP anaerobically and are best for high intensity strength activities. Now, each of these muscles are comprised of long muscle fibers, which contain thousands of myofibrils that are comprised of sarcomeres (Fig. 1). At the sarcomere level is where one finds muscle contraction, which ultimately leads to the ability to perform physical activity [2].

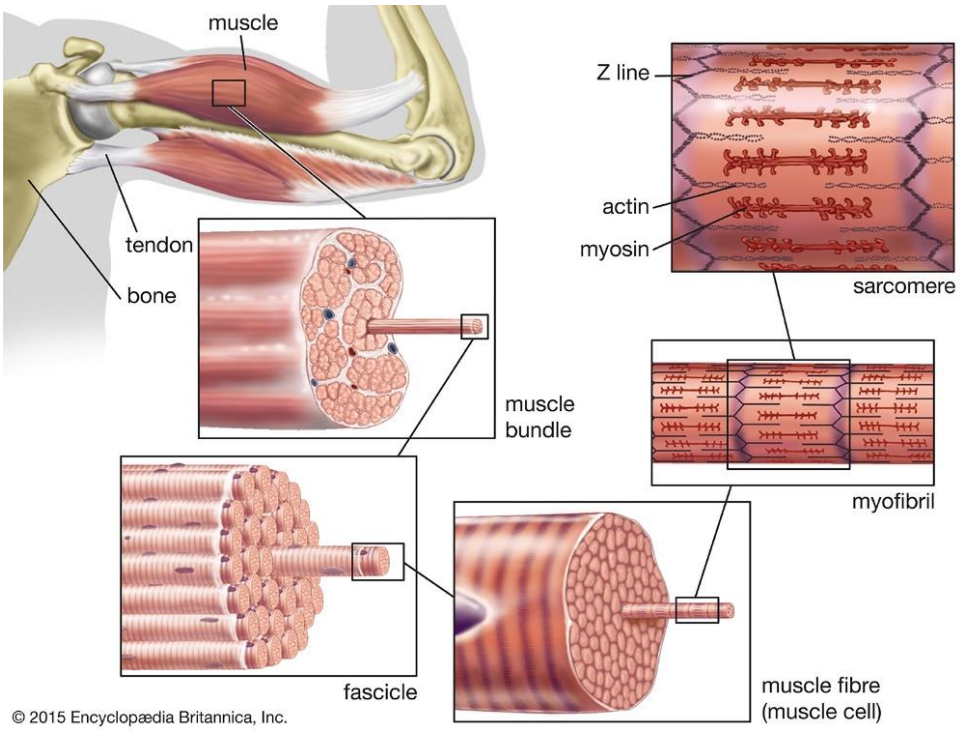


Fig. 1. Breakdown of skeletal muscle [3].

The sarcomere is the repeat, contractile unit within the myofibril; the myofibril itself is comprised myofilaments, namely two types: thick and thin filaments. The primary thick filament is myosin while the primary thin filaments are actin, tropomyosin, and troponin. Myosin and actin are motor proteins that work in tandem to generate tensile force in the muscles whereas tropomyosin and troponin work in tandem to oversee the reception of calcium ions to induce contraction. Also, proteins like titin and nebulin serve to keep myosin filaments centered (maintaining adequate tension to maintain muscle structure) and regulate the assembly of actin filaments, respectively. Each of these proteins, along with certain band locations (A, I, H, Z, and M bands) all come together to make up the sarcomere unit (Fig. 2) [2].

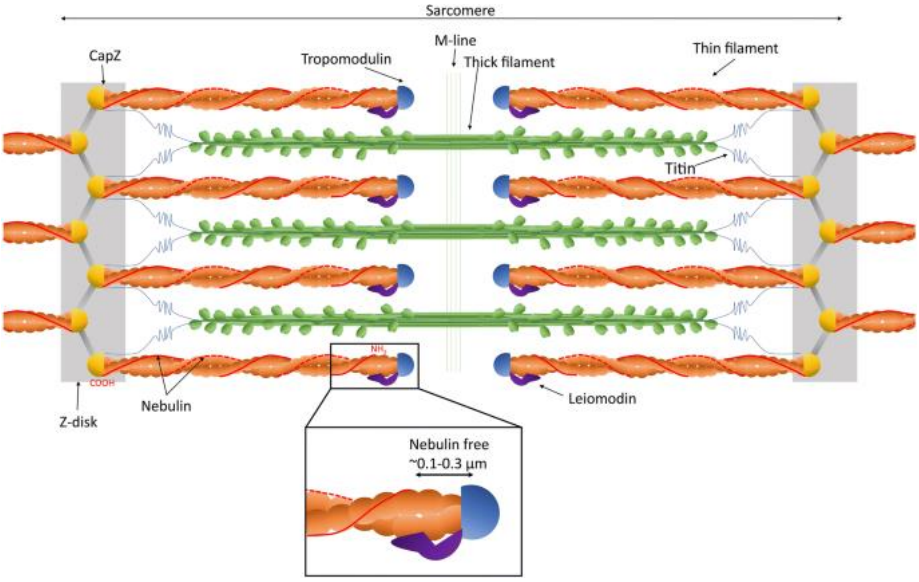


Fig. 2. Sarcomere diagram ("thin filament" is actin and "thick filament" is myosin) [4].

The sliding process that occurs within the sarcomeres, which results in muscle contractions, is known as the cross-bridge cycle. However, the process that precedes this, which initiates the cross-bridge cycle, entails neurotransmission and the use of motor end plates. Contraction begins with an action potential, which is sent out to the end of a motor neuron to a muscle fiber; this location is known as the neuromuscular junction, which comprises of the nerve terminal and the motor endplate (synapse between nerve and muscle cell). This action potential initiates the release of Acetylcholine into the synaptic space, which then bind to ion channels, opening the channels to allow sodium to enter the muscle cells. This depolarizes the cell membrane, producing an end plate potential, which must reach a certain threshold in order to activate another action potential in the muscle cell. This second action potential travels through T-tubules to reach the sarcoplasmic reticulum of muscle fibers. Then, voltage-gated calcium channels are activated, which releases calcium into the cytosol of the muscle cells (Fig. 3) [5].

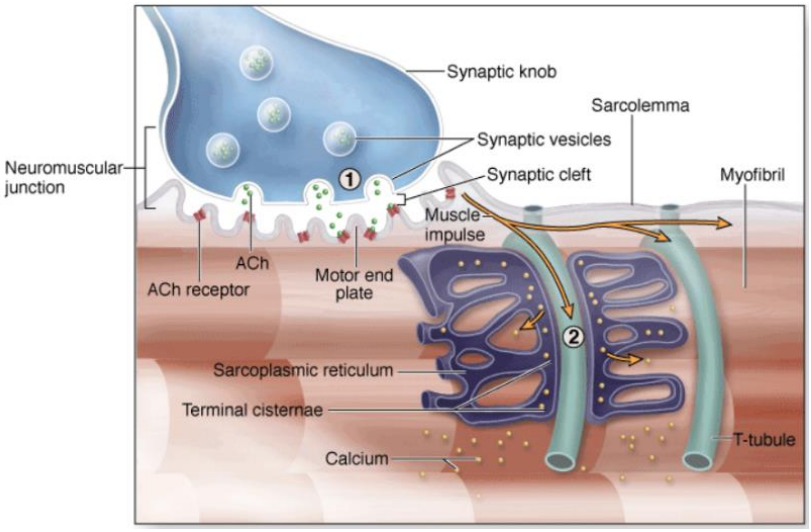


Fig. 3. Activity in the neuromuscular junction [6].

The cross-bridge cycle begins once the calcium ions bind onto the troponin units on the actin filament. This binding promotes tropomyosin movement, exposing the myosin binding sites. The myosin heads on the thick filament are bound to ADP and a phosphate molecule, which remain from the previous muscle contraction. The phosphate molecule is released, which causes the myosin heads to attach to the binding sites. The chemical energy stored in the myosin heads is released, which causes the myofilaments to slide past each other. This is known as the power stroke, and ADP is released in this process. The sliding of many myofilaments is ultimately what causes muscle contraction; the contraction ends when ATP molecules bind to the myosin heads, which detach the myosin heads from actin. Then, ATP decomposes into ADP and a phosphate molecule; the energy released in this process is then stored in the myosin heads for future muscle contractions. As calcium ions are reintroduced into the system, the cross-bridge cycle begins anew, resulting in additional muscle contractions (Fig. 4) [7].

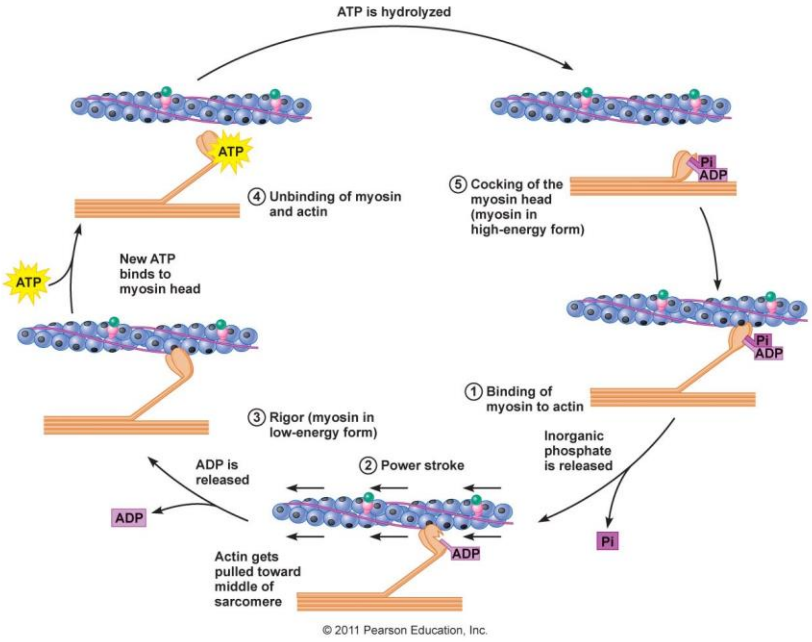


Fig. 4. Cross-bridge cycle [8].

These processes are how skeletal muscles are stimulated, allowing the body to move via muscle contraction. Now that the physiology and underlying mechanisms of skeletal muscles have been discussed, the effects of muscle stimulation via exercise and the lack thereof will now be addressed, analyzing and how different levels of stimulation affect the body.

## The effects of no skeletal muscle stimulation

A comparison was made between childhood and adolescent obesity in the United States between the following sets of years: 1965 to 1985 and 1985 to 2008. The results showed that between 1965 to 1985, obesity ranged between 4-6% of the population whereas from 1985 to 2008 obesity was approximately 20%, increasing almost five-fold. There are many potential factors that could have led to such a dramatic increase in obesity; however, the most likely reason is due to a lack of emphasis on exercise. When skeletal muscles are not stimulated regularly via some sort of

exercise, this inactivity puts people at a substantially higher risk for contracting chronic diseases in the future, which will be addressed shortly [9].

A vast amount of research was compiled into one document, which listed the various negative consequences associated with physical inactivity. As previously mentioned, obesity occurs when skeletal muscles are not stimulated enough. Particularly for the children and adolescents that demonstrated said obesity, they also demonstrated higher fasting glucose levels among, which put them at risk for developing prediabetes and diabetes as adults (3.4 and 2.1 times more likely, respectively). In fact, type II diabetes has become increasingly more common among adolescents, putting them at risk "for complications as adults from the disease, including retinopathy, neuropathy, and cardiovascular and renal disease that may require decades of treatment", which can be seen in Figure 5 (among other potential diseases from physical inactivity [9].

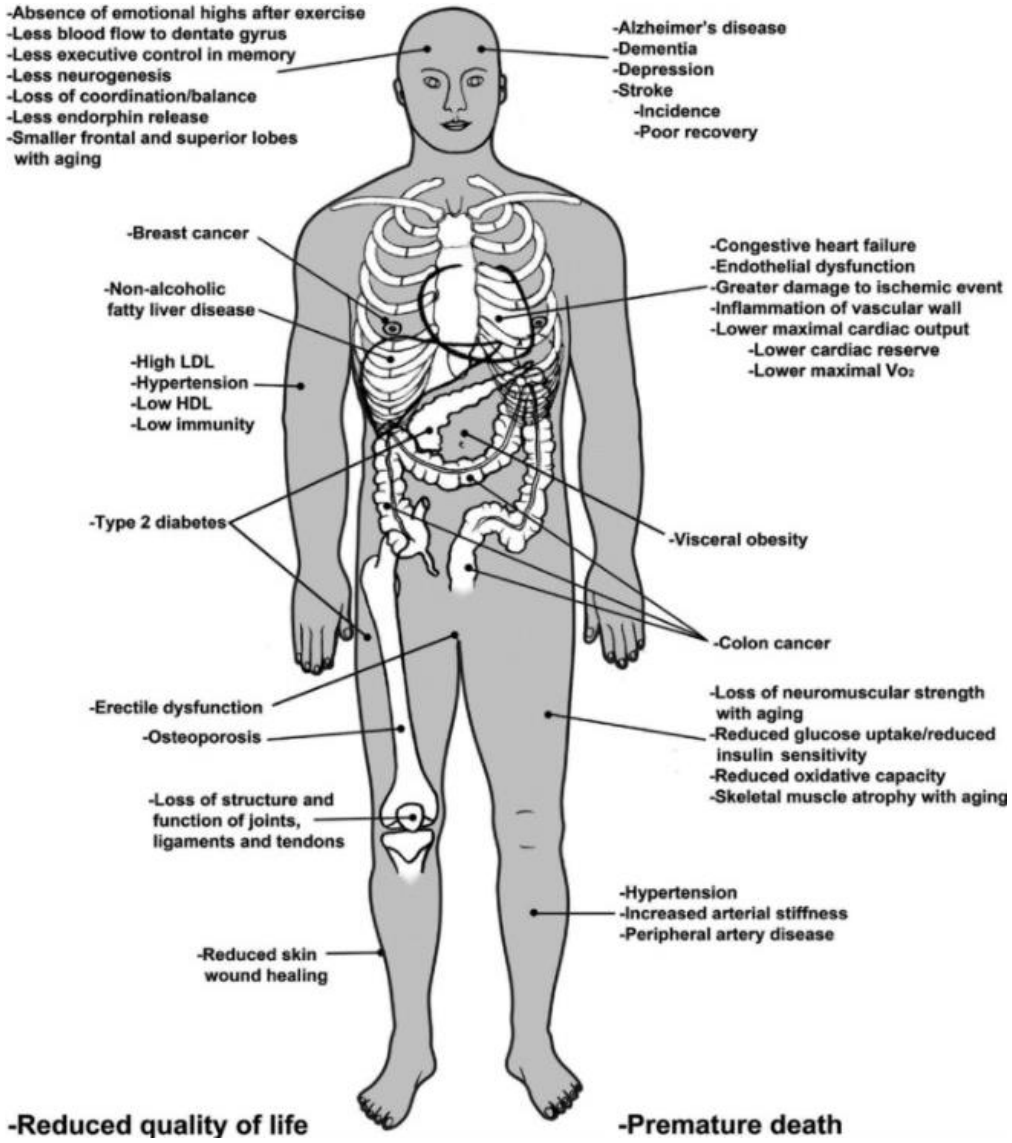


Fig. 5. Potential diseases and deficiencies accelerated by physical inactivity [9].

**The effects of adequately stimulating skeletal muscle**

When referring to "adequate" stimulation of skeletal muscles, this simply entails stimulation without producing chronic damage or injury. Some damage is necessary in order to promote muscle hypertrophy, which is the process by which muscle fibers grow in cross sectional area, resulting in an increase in muscle mass. However, damage that persists long-term and causes excessive pain begins to classify itself as overstimulation. Regarding adequate stimulation of skeletal muscles, research indicates that engaging in certain exercises and physical activities not only promotes musculoskeletal health (and overall health in general), but it can also prevent the contraction of various types of diseases.

One study concluded a correlation between energy expenditure in exercise and the risk of death in participants with various pre-existing risk factors for cardiovascular diseases. The study evaluated the risk of death for 6213 men ages 59 ± 11.2; 2534 of the men did not have cardiovascular disease whereas the remaining 3679 men did have cardiovascular disease, including "hypertension, chronic obstructive pulmonary disease [COPD], diabetes, smoking, elevated body mass index [BMI ≥ 30] and high total cholesterol level [TC ≥ 5.70 mmol/L]" [10]. The men were divided into three groups based on the amount of energy expended during their exercise routines: those that expended less than 5 metabolic equivalents (METs), those that expended 5-8 METs, and those that expended more than 8 METs. The study concluded that "people who are fit yet have other risk factors for cardiovascular disease may be at lower risk of premature death than people who are sedentary with no risk factors for cardiovascular disease", which can be seen in Figure 6 with those achieving higher levels of energy expenditure during exercise having the least risk of death, regardless of pre-existing health conditions [10], [11].

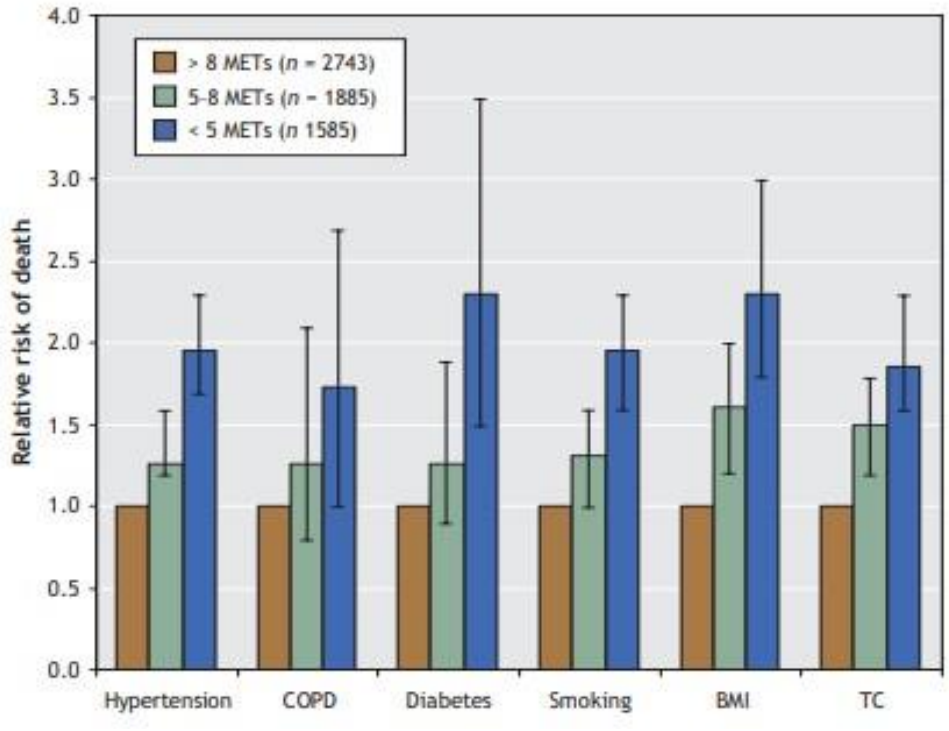


Fig. 6. Results from study with error bars representing 95% confidence intervals [10].

Additionally, resistance exercise (also known as weightlifting) has been shown to “increase muscular strength and endurance”, preventing the contraction of musculoskeletal disorders and altering the “muscle fiber type distribution” within a given muscle. This type of exercise was found to be beneficial for individuals who suffer from heart failure since this type of exercise can “alter contractile proteins and result in a redistribution of muscle fiber type from fast fatigue to fatigue-resistant” [12]. Another study also revealed that individuals who performed resistance exercises “had increased bone mineral density compared with those who did not do such training”, which resulted in lower risk of developing osteoporosis [10].

Stimulation of skeletal muscles via exercise has also been shown to improve mental health, resulting in lower levels of stress and anxiety. By improving mental health, this in turn can prevent the contraction of “chronic diseases such as diabetes, osteoporosis, hypertension, obesity, cancer and depression” [10].

## The effects of overstimulating skeletal muscles

A common occurrence among high-performing athletes is the diagnosis of overtraining syndrome (OTS), which results from overstimulation of skeletal muscles via excessive exercise. The muscle forces produced during exercise are “primarily muscle contractions carried out at the submaximal level”; these forces can be reduced for several weeks during exercise recovery when muscles have been overstimulated. This process is known as prolonged low-frequency force depression (PLFFD), which prevents peak performance during an exercise due to a smaller output force coming from the appropriate skeletal muscles. Continued stimulation prior to sufficient recovery time can exacerbate OTS, increasing fatigue and prolonging complete recovery. Unfortunately, “physiological assessments of OTS [and PLFFD] by coaches and athletes” has been limited since conducting practical tests on the skeletal muscles during performance proves difficult. However, researchers at York University have complied four hypotheses on the cause for OTS and PLFFD: “glycogen depletion, ultrastructural damage, inflammation, and oxidative stress” [13]

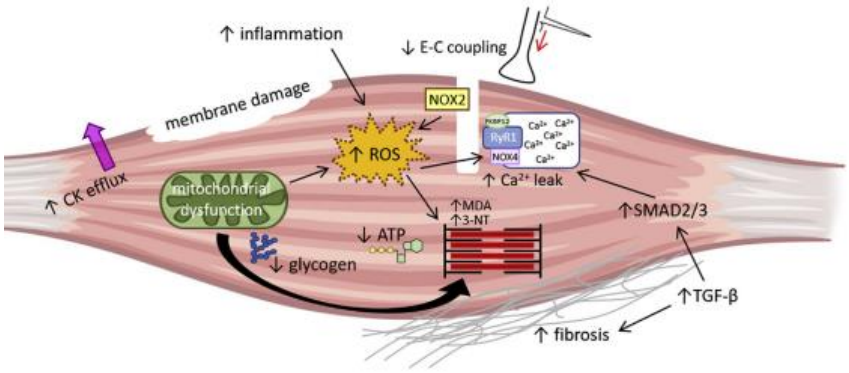


**Fig. 1.** Illustration picturing potential intramuscular mechanisms of OTS, including glycogen depletion, membrane damage, creatine kinase efflux, reduced excitation-contraction (E–C) coupling, inflammation and cytokine signaling with e.g. enhanced TGF-β1 signaling, mitochondrial dysfunction and increased ROS signaling. Current data implicates ROS and inflammatory pathways as the most likely mechanisms contributing to OTS in skeletal muscle.

Fig. 7. Hypotheses for OTS and PLFFD generation with a description provided by York University researchers [13].

The glycogen hypothesis suggests that glycogen has an essential role in the cross-bridge cycle since it provides muscle cells with ATP to induce contraction. Also, the fact that around "50-80% of the total energy" in skeletal muscle is a result of the cross-bridge cycle, along with the fact that glycogen is abundant in skeletal muscles, further supports the importance that glycogen plays during contraction. Due to its importance, the hypothesis claims that a depletion of glycogen due to muscle stimulation results in lower performance [13].

The second hypothesis entails ultrastructural damage, which results from repeated eccentric contractions of skeletal muscle. This would result in the loss of Z-disc integrity at the sarcomere level, preventing adequate contraction for muscles. The third hypothesis deals with inflammation, which proves beneficial in the short term for muscle recovery. However, chronic inflammation results in reduced muscle function and mitochondrial respiration, thus resulting in weaker muscles. It is mentioned that high-intensity exercises "induce a persistent intramuscular molecular cytokine signature, which shares commonalities with disease states of chronic inflammation" like rheumatoid arthritis [13].

The fourth hypothesis has to do with oxidative stress, which involves a bit of the third hypothesis. Cytokines, certain peptides that assist in cell signaling, have been found to increase the production of reactive oxygen species (ROS), which promote the release of pro-inflammatory cytokines. When ROS increases via exercise (skeletal muscle stimulation), this exposure of ROS to the muscle fiber causes the force capacity of the muscles to decrease due to the excessive oxidation, representing a state of severe OTS and fatigue. In fact, diseases such as "rheumatoid arthritis, Duchenne muscle dystrophy, malignant hyperthermia, and normal ageing" all show "chronic intramuscular increases in ROS and oxidative stress", which have all resulted in "skeletal muscle dysfunction and muscle weakness" [13].

Regardless of the hypotheses, the study makes clear that overstimulation of skeletal muscles results in decreased performance and can potentially put people at risk of contracting certain diseases. Another study addressing overstimulation of skeletal muscles claims that overstimulation can impair cognitive ability. In this study, the researchers claim that "physical training overload reduces the excitability of left MFG [middle frontal gyrus] and the capacity to resist temptation of immediate reward in inter-temporal choice", meaning that overtraining has been shown to prevent people from making better, long-term choices. The study claims that this may be why athletes who suffer from OTS fail to recover from fatigue signals and are at a higher risk of doping in order to increase short term performance rather than consider the long-term effects of their actions [14].

## The future of skeletal muscle mechanics and stimulation

Regarding continued research and challenges within the realm of muscle mechanics and skeletal muscle stimulation, researchers are currently trying to tackle the problem of recreating functional skeletal muscles in vitro, also known as engineered skeletal muscle tissues (SMTs). In vivo models of the muscle tissues are quite complex due to the various factors that play a role in the development and maintenance of the skeletal muscle tissue; however, previous attempts at recreating these tissues shed light on how to approach the process anew, providing an opportunity to build upon previous attempts. If these muscles can be recreated in vitro, then more detailed experiments on muscle stimulation could be conducted since humans would not have to be tested on. Human test subjects pose a limitation to current studies on the topic since special care needs

to be taken when overstimulation experiments are conducted in order to ensure the safety of the participants. However, if muscle tissue could be recreated, then more aggressive experiments could be done, which could lead to newer insights without the risk of harming people [15].

## Conclusion

Skeletal muscle stimulation via exercise plays a significant role in the overall health and well-being of the human body, particularly the musculoskeletal system. Abstaining from any sort of physical activity dramatically increases the chances of contracting chronic diseases in the future, especially if such habits are instilled at a very young age, and overstimulation can lead to significant levels of pain and discomfort, along with the potential of also contracting other kinds of chronic diseases. The contraction of any disease attributed to no stimulation or overstimulation results in a lower life expectancy and medical complications to deal with along the way. To maintain a healthy body and increase life expectancy, literature shows that engaging in activities that produce adequate skeletal muscle stimulation will do just that. With a simple change in lifestyle, numerous physical and psychological benefits can be attained. The repercussions of excluding physical activity are seen throughout the paper as dangerous and detrimental, proving that the universally accepted idea of regular exercise providing numerous benefits is founded upon extensive, legitimate research. As for the future of skeletal muscle stimulation, this may lie in the ability to reproduce them in vitro. If skeletal muscle can be reproduced, then they can either be left entirely idle to represent the effects of zero muscle stimulation over time, observing what happens physiologically, or aggressively stimulated to see how the tissues react to overstimulation. Research on muscle stimulation has only been done on human or animal subjects; therefore, zero stimulation is nearly impossible to observe since each subject uses their muscles to some degree throughout the day, and overstimulation would violate the health and well-being of the subjects. However, these limitations could be lifted if skeletal muscles could be ethically reproduced, which may lead to new physiological discoveries in the field.

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