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How exercise affects the musculoskeletal system in the biological sexes: A literature review

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HOW EXERCISE AFFECTS THE MUSCULOSKELETAL SYSTEM
IN THE BIOLOGICAL SEXES: A LITERATURE REVIEW

A Thesis Submitted
in Partial Fulfillment
of the Requirements for the Designation
University Honors

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Introduction

Exercise has countless benefits for the human body. Physical activity increases overall health and reduces the risk of developing many chronic diseases. While the entire body is impacted by exercise, the musculoskeletal system is perhaps targeted most directly. Muscle contraction is required to complete any form of exercise, which helps build muscle mass and consequently strengthens bones. The physiology of musculoskeletal growth after exercise is the same for all individuals. However, the magnitude of this growth is not the same for men and women. Men have a profound ability to gain muscle mass that most women are not capable of obtaining, even after years of training. As a competitive woman who loves weight training, I have had a growing curiosity as to why I couldn't lift weights as heavy as the men around me. To understand the biological differences that contribute to this disparity, I conducted a literature review to explore what anatomical factors are involved with musculoskeletal growth and determine how this process may vary among men and women. For the purposes of this study, I will be focusing on cisgender males and females, or those who identify with their birth sex. The process of transitioning or hormone therapy among transgendered individuals may present unique factors that go beyond the scope of this paper.

A Brief Overview of the Musculoskeletal System

The musculoskeletal system consists of the body's muscles, bones, and the tendons and ligaments that hold them together. Tendons attach muscle to bone, while ligaments attach two bones together. The muscular system has several functions involving movement, including movement of the body or movement of materials through the body. It's also important for support and protection. Three types of muscle tissue can be found within the human body. Cardiac muscles are involuntary muscles associated with the heart. Contraction of cardiac

muscle allows the heart to beat. Other organs and vessels utilize involuntary smooth muscle to complete their processes. Smooth muscle contraction accounts for digestion, voiding, and blood circulation, just to name a few. The muscles that are attached to bones are known as skeletal muscles. Skeletal muscle is the only type of muscle that is voluntary. The human body holds over 650 skeletal muscles. Each time we move a part of our body, we are using skeletal muscles to do so. Exercise focuses largely on growing and shaping skeletal muscles.

Bones work closely with muscles to support the human body. They give shape in the form of our skeleton and protect our organs from damage. It is generally known that the ribs protect the heart and lungs, while the skull protects the brain. All 206 bones in the human body are connected to each other, with the exception of the hyoid bone at the front of the neck. Calcium gives bones their toughness, while collagen allows for some flexibility. Bones can be categorized as spongy or compact, and further subdivided into long, short, flat, or irregular bones. Like the name suggests, spongy bone is porous. It is typically found under compact bone, which is much more dense than spongy bone. Long, short, flat, and irregular bones are named for their shape. Skeletal muscles are typically attached to the end of a bone, near a joint like the elbow or shoulder. Muscle contraction pulls on the bone that the contracting muscle is connected to, resulting in movement.

Physical activity can cause muscles and bones to grow larger; however, the extent of this growth is not the same for men and women. To understand why exercise affects men and women differently, we must start by reviewing the process of musculoskeletal development to determine where certain disparities may lie.

Literature Review

Skeletal Muscle Development

Muscle tissue develops during a process called myogenesis. Muscle cells, or myocytes, consist of bundles of elongated fibers. In skeletal muscles, cells are simply known as muscle fibers. Each muscle fiber contains its own bundle of smaller filaments called myofibrils. Primary myogenesis occurs during the 8 weeks following fertilization. In the fetus, muscle development begins in the trunk of the fetal body. First, the mesoderm that lines the thoracic cavity of the developing embryo becomes segmented. The mesoderm is the central germ layer that differentiates into connective tissues, including muscle and bone. A particular segment along the back of the fetus forms a compartment that becomes the vertebral column. The first skeletal muscles are formed in the same location. These muscles are known as the myotome, which is a general term for muscles that are connected to nerves in the spinal cord. In general, muscles grow in an outward direction from the myotome through the rest of the body (Hill, 2012). When the muscle is ready to form, available cells differentiate into myoblasts, which are the precursor to myocytes. Myoblasts then fuse together to form myotubes that will eventually give rise to multinucleated muscle fibers (Matsakas, 2010).

Secondary myogenesis takes place during fetal development, between 9 and 38 weeks of gestation. During this time, myoblasts continue to fuse along the developing myotubes. The continuous addition of myoblasts to myotubes gives rise to the first muscle fibers. Neurons become implemented among the developing muscle fibers, which allows the fibers to start contracting. The formation of neuromuscular junctions that stimulate muscle contraction results in the differentiation of the remaining myotubes into muscle fibers. The majority of the muscle fibers that are found in adults are formed during this stage (Hill, 2012).

The extent of muscle growth is largely influenced by one particular protein, myostatin. Myostatin is produced by myocytes to prevent excessive muscle hypertrophy. It is found in developing embryos and continues to function throughout one's life (Deng, 2017). Myostatin has roles in both muscle growth and decay. Under normal conditions, muscle growth occurs through the activation of the Akt/mTOR pathway. TOR is a protein that simultaneously activates protein synthesis and inhibits protein degradation (Alberts, 2018). When myostatin is available, however, it inhibits this pathway, thus reducing how much a muscle can grow (Kalinski, 2019). Another protein called Growth/differentiation factor 11, or Gdf11, has similar functions in regulating muscle growth. Gdf11 is secreted by many different cell types but is especially abundant in skeletal muscle tissue. The mechanism by which Gdf11 inhibits muscle growth has been highly disputed. Some studies indicate that this protein prevents myoblasts from differentiating into myocytes, while others believe it prohibits myotubes from developing into muscle fibers. Regardless of the exact cause, Gdf11 has demonstrated inhibitory effects on skeletal muscle development (Zhang, 2017).

Secondary myogenesis determines the number of muscle fibers that a person has throughout their lifetime. After birth, the body no longer produces new muscle fibers. This is evidenced by the fact that skeletal muscle cells enter a dormant state known as G0 in the cell cycle. This is a permanent "resting stage" where the cell no longer undergoes cell division and therefore cannot produce new cells (Alberts, 2018). However, muscle fibers can grow larger due to the activity of satellite cells. Satellite cells are stem cells that can differentiate into myoblasts. Satellite cells are able to fuse to existing muscle fibers, allowing them to grow in size. Muscle fibers are limited as to how much they can grow; as a result, the amount of muscle mass that can be added to existing muscle is limited from birth (Yang, 2014).

Muscle mass is also dependent on myofibril development. While the number of muscle fibers doesn't change, new myofibrils can be added to existing muscle fibers. Myofibril addition is one of the primary ways in which muscle mass increases. During maturation, myostatin regulates myofibril development. In adults, elevated myostatin levels inhibit the number of new myofibrils that are able to form, further limiting muscle hypertrophy (Kalinski, 2019).

Three types of muscle fibers can be found in skeletal muscle. Fiber types are categorized by how quickly they contract. Type I fibers are the slowest to contract and are consequently called slow-twitch muscle fibers. These fibers have a weaker contraction but are resistant to fatigue. Type I fibers are used for low-intensity activities that require endurance, such as going on a walk. Fast-twitch fibers constitute Type II fibers. These fibers contract more strongly than Type I fibers but are also quicker to fatigue. Type II muscle fibers are further subdivided into Type IIA and Type IIB fibers. Type IIB fibers are used for rapid movements that are not sustained, like the exercises seen in strength training. These fibers fatigue the quickest out of the three fiber types. Type IIA fibers are also known as intermediate fibers, as the contraction strength and fatigue rate are between Type I and Type IIB fibers (LaMarco, 2021).

Bone Development

There are two mechanisms in which bones develop. Bones that form from mesenchymal cells develop in a process called intramembranous ossification. Mesenchymal cells are stem cells that originate from the same germ layer as muscle cells, known as the mesoderm. These cells travel throughout the fetus to their final location and accumulate in a process called condensation. Gene expression then allows mesenchymal cells to differentiate into osteoblasts, or cells that build bone. Osteoblasts release an osteoid bone matrix that becomes calcified through the addition of hydroxyapatite, a compound made of mineralized calcium. These

osteoblasts then differentiate into bone cells, known as osteocytes. The bone continues to grow outward by the addition of osteoblasts onto existing bone, which in turn divide and differentiate into osteocytes.

Endochondral ossification is the second mechanism in which bones form. These bones develop from cartilage. The majority of bones are formed through this mechanism, with the exception of the skull, clavicle, and parts of the mandible that are formed through intramembranous ossification. Initially, a cartilaginous model creates a framework for the bone. Once mesenchymal cells condense and gene expression of osteoblasts is turned on, the osteoblasts create a ring of bone representing the middle of the bone shaft. Cartilage under this ring loses nutrients and breaks down. Osteoblasts continue to divide on either side of the ring toward both ends of the bone, replacing cartilage as they go. Once the bone has been set, osteoblasts differentiate into osteocytes (Hall, 2005).

After birth, cartilage continues to make up a portion of the bones that develop through endochondral ossification. Bones mature by adding osteoblasts onto existing bone, which divide and differentiate into osteocytes, as they do during fetal development (Hall, 2005). During adolescence, osteoblasts facilitate remodeling of bone. Remodeling allows the bone to grow in width and length as the individual grows. Osteoclasts break down existing bone cells, which allows osteoblasts to deposit new cells in the direction the bone is growing. This process exists in all bones regardless of their initial mechanism of development and continues throughout a person's lifetime. Old bone is broken down by osteoclasts and replaced by new osteoblasts. Remodeling is regulated and is essential to repair bone damage caused by natural stresses and strains on the body (Scheuer, 2000).

Effects of Exercise on Skeletal Muscle Growth

Now that we've discussed the process of development, we can look more closely at the effects of exercise on musculoskeletal growth. Muscle hypertrophy is stimulated by all types of physical activity. However, certain types of exercise have a stronger effect on muscle growth. Any activity that loads muscle, such as weightlifting or bodyweight training, directly activates the pathways that increase muscle mass. These exercises utilize Type IIB muscle fibers, which provide quick and powerful movement. As the body adapts to the stress put on muscles during exercise, the process of muscle growth slows down. In order to see continuous muscle growth, it's important to increase the weight being used and the number of reps being performed to avoid a plateau (LaMarco, 2021). This practice also improves the connection between neurons and muscle cells, allowing the body to respond to signals more efficiently. This is due to motor unit recruitment adaptation. A motor unit consists of a neuron and all of the muscle fibers connected to it. Consistent use of a motor unit decreases the force required to stimulate that unit. This decreased threshold reduces the amount of time it takes to activate the unit. As a result, the muscle can contract more easily (Del Vecchio, 2019).

Before muscle growth has taken place, muscles can appear larger after a workout from sarcoplasmic hypertrophy. The cytoplasm of a muscle cell is known as the sarcoplasm. Within the sarcoplasm are organelles called glycosomes, which store glycogen. When undergoing physical activity, the body experiences metabolic stress. This stress releases glycogen from glycosomes into the sarcoplasm, causing the entire cell to inflate. Consequently, the entire muscle seemingly increases in size as each cell expands (Leyva, 2020). This is similar to bloating that many people experience after eating. When a person is bloated, the circumference of their abdomen has increased, although the person hasn't really gained weight.

Muscles grow larger by increasing either the overall thickness of a muscle fiber or the number of myofibrils in a muscle fiber. The actual number of fibers remains constant, predetermined at birth. In fact, the definition of “hypertrophy” in regard to muscle hypertrophy refers to an increase in cell size, not cell number. Muscle hypertrophy occurs at rest following physical activity. The process of growth consists of two steps, the first of which is muscle degeneration. Muscles undergo mechanical stress during exercise. This causes the muscle to break down, which is clinically seen as muscle damage. Creatine kinases and other muscle proteins that are typically found in the sarcoplasm enter the bloodstream as the plasma membrane around the fiber becomes more permeable. These serum proteins stimulate an inflammatory response, which activates various white blood cells in the bloodstream. Neutrophils respond almost immediately, followed by macrophages within 2 days of injury. These cells facilitate further degradation of the muscle tissue. Macrophages are phagocytic cells that ingest pathogens, dead cells, or other cellular debris. In muscles, macrophages phagocytize the broken-down fibers, after which the next step of the repair process can begin.

Muscle mass increases during the second step of muscle repair, known as muscle regeneration. After the muscle has been degraded, growth takes place through the division of myogenic cells in the muscle tissue. After myogenic cells divide, they differentiate into myoblasts (Charge, 2004). Satellite cells are the primary myoblasts used in muscle repair. Recall that embryonic muscle fibers form from the fusion of myoblasts. Damaged fibers are repaired in the same way. During muscle regeneration, satellite cells fuse within the fiber, essentially filling in the spaces where the tears exist. The resulting fiber has a cross sectional area that is larger than it was before the damage occurred (Hryvniak, 2021). Satellite cells can also differentiate into myofibrils. A bundle of myofibrils makes up a muscle fiber. Adding new myofibrils allows

the overall fiber to grow in size. Satellite cells remain active during adolescence as muscle growth is relatively constant. As individuals age, satellite cell activity slows down and muscle mass stops increasing. After an individual reaches the end of puberty, satellite cells become dormant and are activated only in response to tissue injury. As exercise causes clinical tissue damage, satellite cells are stimulated (Yang, 2014).

Another proposed mechanism for how exercise causes skeletal muscle growth is known as titin mechanosensing. Titin is a protein found in specific locations along the myofibril. The placement allows titin to recognize when the body is undergoing certain movements, so it can send signals that activate skeletal muscle growth. During physical activity, the muscle is actively contracting. The contraction applies tension to the titin protein, which essentially acts as a switch. When the force is applied, the protein “opens”, which triggers intracellular signals that stimulate muscle growth. The strength of the signal is determined by the weight used during exercise. At high loads, the switch is opened rapidly, which sends a much stronger signal. The stronger signal stimulates greater muscle hypertrophy. Lower weights send a weak signal and result in minimal muscle growth (Ibata, 2021).

Exercise also influences muscle growth by inactivating myostatin. Myostatin is an inhibitory protein that reduces muscle hypertrophy. During cardiovascular and strength training exercises, myostatin levels are decreased in the muscle tissue. As a result, the muscle repair process can take place without being limited by myostatin. The mechanism that reduces myostatin expression during physical activity is still being researched. However, it may be related to an increase in follistatin levels, which has also been noted during physical activity (Legård, 2019). Follistatin is an inhibitor of myostatin. Follistatin binds to myostatin receptors, which prevents myostatin from binding and reducing muscle growth (Fife, 2018). The

combination of myostatin production being repressed and follistatin inhibition of myostatin allows exercise to induce muscle hypertrophy to its maximum extent.

Effects of Exercise on Bone Growth

Bone growth after exercise occurs through the process of bone remodeling. Certain protein biomarkers, such as carboxy-terminal cross-linked telopeptide of type I collagen, are seen in the blood when bone resorption occurs. Blood tests after resistance training have shown increased levels of this biomarker, which indicates that exercise induces bone resorption (Gombos, 2016). Physical activity increases the rate at which bone remodeling takes place (Khan, 2001). Like muscles, mechanical stress is applied to bones during exercise, which causes a physical strain on the bone. This strain is felt by mechanoreceptors on osteocytes. As the name suggests, mechanoreceptors respond to mechanical forces. When osteocytes feel this strain, they signal osteoclasts to resorb bone. Osteoblasts are then activated to rebuild the bone. A minimum force needs to be applied to stimulate bone remodeling. Think about pushing a door open; lightly tapping the handle will not move the door forward. Similarly, mechanoreceptors will not feel any force under a certain threshold. Using a heavier weight applies a larger force on the bone. Bone and muscle mass tend to correlate in either direction; a loss of one is paralleled by a loss of the other, while an increase of one is followed by an increase of the other (Khan, 2001).

One way that exercise strengthens bones is through tissue adaptation. The remodeled bone can support a heavier weight, which the body has done as a prophylactic measure to reduce any future strain. This occurs through a complex mechanism that has not been extensively researched at this time (Troy, 2018). In a similar way, bones become thicker through periosteal expansion. The periosteum is the outermost layer of bones, made of connective tissue. Periosteal expansion is stimulated by bone resorption (Kemp, 2013). As osteoclasts become activated to

break down a bone, the periosteum of that bone begins to grow. This demonstrates further tissue adaptation, as a thicker periosteum can protect against fractures and other forms of bone damage.

Frequent muscle contraction has been shown to stimulate bone growth in the bones attached to the contracting muscle. Athletes that focus on building certain muscles have the greatest bone density in that area (Khan, 2001). Bone development is greatest through physical activity that uses the earth's gravitational pull. Activities that use another mechanism to support body weight, such as water during swimming, do not stimulate bone growth as efficiently as exercises in which a person is standing on two feet. This is because the activity has to load a minimum force on the vertebral column to stimulate bone growth (Khan, 2001). These exercises also need to be of high intensity and should contain a combination of cardiovascular activity and resistance training (Benedetti, 2018). Cardiovascular exercises successfully activate osteoblasts, which build bone. On its own, however, the effect of cardiovascular activity on bone growth is minimal. Resistance training is necessary to stimulate the mechanoreceptors that induce bone remodeling. Lower intensity exercises, such as walking or yoga, do not increase bone mass; however, they do prevent bone loss in conditions such as osteoporosis. As with muscle growth, the weight being used during exercise needs to increase to continue strengthening bones. As the weight becomes familiar, osteocytes no longer respond to the applied force (Khan, 2001). Workouts that increase the integrity of bones and muscles can also be intensified by increasing the number of reps or sets, as well as decreasing rest time between sets.

Biological Differences Between Males and Females

After looking into the pathways that lead to musculoskeletal growth after exercise, we can look more closely at the variables that differ between men and women. As previously discussed, myostatin limits muscle hypertrophy by inhibiting a pathway that stimulates muscle

growth, the Akt/mTOR pathway. Like myostatin, Gdf11 is a protein that prevents muscle regeneration. Women were found to have higher plasma serum levels of both myostatin and Gdf11. Increased levels of these proteins cause muscle growth to be inhibited more in women than in men. As a female's muscles are broken down after exercise, it is harder for the body to rebuild them. On the contrary, men have higher plasma levels of follistatin, a myostatin inhibitor. Consequently, men see an increase in muscle hypertrophy for two reasons- one, myostatin is present in smaller quantities, and two, the myostatin that is available is more likely to be hindered by follistatin (Fife, 2018).

There is also a negative correlation between myostatin and muscle strength, meaning those with higher levels of myostatin have weaker muscles (Fife, 2018). This can be explained by looking at the muscle fibers that contract during strength training. Type II muscle fibers are the primary fibers used when lifting weights. These fibers contain more myofibrils, which allows for a stronger muscle contraction. Myostatin controls the number of myofibrils that develop prenatally (Kalinski, 2019). Because women have more myostatin, they develop fewer myofibrils, resulting in smaller muscle fibers. In fact, the average Type II muscle fiber is 60% larger in a male than a female (Haizlip, 2015). This also means fewer myofibrils are available to contract, resulting in a weaker contraction. Even if a man and a woman have the same muscle mass, the man will be able to lift heavier weights using that muscle. These larger fibers are also slower to fatigue than their female counterparts, so a man can lift longer before the muscle stops contracting.

Another determining factor of how much muscle mass a person can gain is the number of muscle fibers present in an individual muscle. Recall that muscle fibers can become larger, but new ones cannot develop after birth. Because myostatin regulates myofibril development, it

indirectly controls how many muscle fibers can develop in the fetus, as muscle fibers are made up of myofibrils. The increased myostatin levels found in females causes fewer muscle fibers to develop than males. Fibers are then limited as to how large they can grow (Yang, 2014).

Ultimately, women are genetically predisposed to have less muscle mass as adults.

Satellite cells are vital for muscle regeneration. Two distinct processes, maintenance of muscle tissue and muscle regeneration after exercise, require satellite cells. A study by the Dubowitz Neuromuscular Center (Neal, 2012) found that male mice had more satellite cells than female mice. This allows males to gain more muscle mass during an individual repair process than females, as more cells are available to repair the broken tissue. Interestingly, it has been suggested that myostatin is also an inhibitor of satellite cell development, corroborating the idea that the increased levels of myostatin in females restricts muscle growth (Charge, 2004).

Strength training is greatly impacted by grip strength, which can be described as an individual's ability to hold on to a particular object. While a muscle may be directly capable of loading a certain weight, the individual is limited to the weight they can carry in their hands. This component of weightlifting can be evaluated by measuring the force applied by an individual's hand. Through this measurement, Leyk (2007) determined that 95% of men had a stronger grip strength than 90% of women. Even the majority of trained female athletes were unable to apply a force as strong as untrained male participants. This study demonstrated that men are biologically capable of holding heavier weights before any training occurs. Recall that heavier weights send stronger signals to the pathways that activate muscle growth. Men are able to activate these pathways relatively easily, while women might need to work significantly longer to see the same results.

In addition to differences in the pathways that lead to muscle growth, other biological factors suggest why men can grow musculoskeletal tissue more successfully than women. Differences in the male and female immune system play a role in how muscle tissue is built. One of these differences includes the number of white blood cells available in the bloodstream. Men have more neutrophils (Newcomb, 2021) and macrophages (Chen, 2021) circulating through their body than women. Both of these white blood cells are activated by damaged muscle tissue to facilitate the first step in muscle repair. Elevated levels of both allows the male body to degrade muscle tissue more quickly and efficiently, which stimulates muscle regeneration in a shorter period of time. Macrophages are also more mobile in men, so they can more easily find and respond to the tissue damage that occurs through exercise (Chen, 2021).

The ability of muscle to perform depends on how well oxygen is delivered to muscle tissue. Oxygen is required for aerobic respiration in cells, which generates the ATP that muscle cells use as an energy source during muscle contraction. Oxygen is carried through the body by a protein called hemoglobin, found in red blood cells. Oxygen delivery is improved with increasing hemoglobin levels. If oxygen can be delivered to the active muscle tissue, aerobic respiration can occur, ATP can be generated, and the muscle has an energy source to maintain contraction (Cesari, 2004). Not surprisingly, males have more hemoglobin in their bloodstream than females. It is theorized that male hormones, which will be discussed in the next section, stimulate the production of hemoglobin. This disparity is even seen in children. From a young age, boys have a better oxygen delivery system than girls, once again demonstrating that musculoskeletal differences are defined at an early stage in development (Garvin, 2010).

A visual indication of peak physical fitness is the presence of bulging veins where large muscles have developed. Veins can become more prominent during exercise, when oxygen is

being delivered to muscle tissue at a faster rate. In general, men who exercise regularly seem to have always pronounced veins. Higher muscle mass and lower body fat lead to veins that stick out further in the skin (Kassel, 2019). Overall, males have lower body fat than females for a multitude of reasons. First, muscle tissue requires more energy to fuel. Because men naturally have greater muscle mass, their resting metabolic rate is higher than women. To maintain a higher metabolism, the body burns more fat cells as a source of energy. Men also tend to store fat in their abdomen, where it is easily accessible to serve as a fuel source. Women, on the other hand, have a thicker layer of fat just below the skin. These fat cells are not an efficient source of fuel as they are not easily attainable (Holland, 2018). Additionally, it has been suggested that myostatin contributes to the accumulation of fat. Feher (2012) found that mice which were genetically modified to develop without myostatin were leaner and had very little fat when compared to mice with normal levels of myostatin. As men have less myostatin in their body, fewer fat cells are produced in males than in females. For a multitude of reasons, a female's veins are typically not as prominent as a male who may follow a similar exercise routine. While veins might be desired for more aesthetic purposes, they are a clear attestation of an individual's progress when working to gain muscle.

Hormonal Differences

Let's switch gears and look into the role of sex hormones in tissue development. Testosterone is the major sex hormone in males, while estrogen and progesterone are primarily seen in females. All three hormones are found in every individual, but in varying amounts. This difference in hormone concentration contributes to differences in musculoskeletal growth. A study by Roberts (2007) demonstrated that adolescent boys had 30% more muscle mass than girls of the same age due to the presence of testosterone. As men aged, muscle and bone mass

decreased as testosterone levels decreased. Starting around puberty, men see a continuous secretion of testosterone, while estrogen and progesterone secretion fluctuates throughout a woman's menstrual cycle. Exercise, specifically strength training, stimulates an increase in testosterone secretion (Kraemer, 2005). Physical activity also increases testosterone receptor sensitivity (Leyva, 2020). This allows the available testosterone to be used more efficiently.

As many would guess, testosterone is one of the foremost reasons why men see more muscle growth than women. Although the exact mechanisms are still being studied, this hormone largely influences several factors that lead to musculoskeletal tissue growth (Dandona, 2021). Testosterone triggers the production of satellite cells, which subsequently stimulates muscle hypertrophy. Satellite cells are activated by proteins such as Fibroblast Growth Factor 2 and Insulin Growth Factor 1. These proteins are found in higher levels in individuals with more testosterone. IGF-1 also induces muscle growth by increasing amino acid uptake. In addition, testosterone is an inhibitor of myostatin (Leyva, 2020). While men already have lower levels of myostatin than women, the available myostatin is easily hindered by both follistatin and testosterone. Where muscle damage occurs, testosterone increases neurotransmitters that stimulate growth hormone, which in turn speeds up the rate of muscle regeneration. Testosterone also decreases fat cell accumulation, possibly utilizing the excess glucose for energy during muscle growth. As well as aiding musculoskeletal growth, testosterone also slows down muscle degeneration. As a result, less muscle tissue is broken down during the first step of the repair process before muscle regeneration begins (Leyva, 2020). Additionally, individuals with higher testosterone levels were likely to have greater bone density, indicating that muscle and bone growth coincide (Dandona, 2021).

While testosterone plays a large role in stimulating musculoskeletal growth, other hormones are able to control tissue growth through their own mechanisms. Insulin, adrenaline, and thyroid hormone are all able to induce muscle growth. Insulin helps to facilitate the production of muscle proteins by making amino acids more available for the cell to use (Fujita, 2006). Adrenaline, which tends to increase during exercise (Watt, 2001), induces glycogenolysis, the pathway that breaks down glycogen into glucose. This glucose is then used as energy to build muscle tissue. Adrenaline also decreases the amount of glucose that is removed from muscle cells, so more glucose is present during exercise and muscle regeneration. Thyroid hormone increases the number and diameter of muscle fibers in a developing embryo and activates satellite cells in adults (Lee, 2014). Men have higher levels of all three of these hormones than females, and therefore see more muscle growth through these pathways.

Cortisol causes the opposite effect as the above hormones in that it inhibits muscle growth. This catabolic hormone breaks down muscle tissue as a source of energy. Females tend to have higher levels of cortisol than males due to having increased levels of estrogen. Estrogen induces the production of cortisol-binding globulin (CBG), a protein that, as the name suggests, binds to cortisol. When more CBG is present, more cortisol can bind and enter the bloodstream. Consequently, more muscle tissue is broken down in females. In women, estrogen and cortisol levels are positively correlated. As estrogen levels rise and fall during a woman's menstrual cycle, the amount of cortisol found in the blood varies. This makes it difficult for women to see a steady increase in muscle mass (Edwards, 2008).

Another way in which estrogen influences musculoskeletal growth is by indirectly leaving women more susceptible to injury. Lifting heavy weights puts significant tension on a person's joints. Progressing to heavier loads requires tendons and ligaments to become stronger

alongside the growing muscles and bones. Collagen production is necessary to strengthen tendons and ligaments. Not surprisingly, male bodies are able to produce collagen at a much faster rate than women. Estrogen seems to slow down or cease collagen production altogether (Magnusson, 2007). As a result, women endure more frequent injuries during exercise than men. Injuries can cease or reduce musculoskeletal growth if they render an individual unable to exercise while recovering.

Behavioral Considerations

The extent of musculoskeletal growth is dependent on various proteins, hormones, and maximum weightlifting ability. The heavier an individual can lift, the more muscle and bone mass they will accumulate. Since men are biologically capable of lifting heavier before any training takes place, muscle and bone formation is stimulated more easily as many processes, such as titin mechanosensing or skeletal remodeling, require a minimum load to be lifted in order to be activated. Women have to work longer and harder to reach this minimum load. Meanwhile, men are gaining muscle mass at an exponentially faster rate. However, biological differences are not the only reason why males tend to have larger muscles and stronger bones than females. It's also necessary to consider behavioral differences between men and women that contribute to musculoskeletal growth.

One of the most influential factors on musculoskeletal growth is the type of exercise being performed. Strength training directly works the musculoskeletal system, while other activities will target different systems in the body. Running, walking, or other movements that raise a person's heart rate will be more beneficial for the cardiovascular or respiratory systems. Lower intensity exercises, such as yoga and Pilates, improve flexibility and mobility. Societal factors strongly influence how men and women spend their time while in the gym. Motivated by

appearing strong and buff, men tend to focus on weightlifting in order to build muscle. Women are more likely to work out to achieve the opposite effect. From a young age, girls are exposed to media that displays only thin body types as acceptable. Therefore, women typically focus on exercises that have a slimming effect or will allow for weight loss. This normally consists of performing different types of physical activity in a circulating pattern. Women may do some variation of strength training one day, cardio the next day, and yoga the day after that. While most fitness experts advocate for this balance of physical activity, it does not lead to musculoskeletal growth at the same rate as a program that is exclusively designed for weightlifting. Physical therapist Vincent Perez believes “women take instruction better” when it comes to following a well-rounded exercise regimen (Sorgen, 2004).

Even when men and women are both lifting weights, the specific exercises being performed can vary. As discussed earlier, stimulation of bone remodeling occurs when the vertebral column is loaded. Women were found to use more seated machines while strength training, which alone does not load the spine (Feito, 2018). Body proportions also play a role in how effective an exercise is. Females tend to have longer torsos than males relative to their heights, which obstructs a perfect squatting form. Males also have a larger chest cavity, which benefits movements like a bench press (Haff, 2021). Whether doing the same type of physical activity or even the exact same movement, the impact is greater in men than in women. Men are also likely to workout longer than women during each training session (Feito, 2018). An interesting evolutionary theory describes men gaining muscle as a way to attract sexual partners. The larger a man appeared, the more he was considered to be a successful provider and protector. (Roberts, 2007).

Conclusion

Prior to completing this review, I believed testosterone to be the sole variable which allowed men to grow larger muscles and lift heavier weights than women. This idea has been a consensus among the public for as long as I can remember. The findings from my research have demonstrated that the ability of men to grow muscle is actually a culmination of several factors. Men can more easily stimulate the pathways that lead to musculoskeletal growth, in part from having fewer inhibitory proteins, but also because of a natural ability to lift heavier and reach the threshold that activates growth. On the contrary, women not only have a harder time stimulating these pathways, but musculoskeletal growth is also more limited when it occurs. Additionally, men can contract their muscles for a longer duration of time and do not fatigue as quickly as women. Biological differences that start before birth render women unable to grow muscle or bone as large as men.

It's important to recognize all of these factors to understand that musculoskeletal development does not simply occur through the action of testosterone. Women who find themselves frustrated by limited muscle growth might be quick to assume that they will never build muscle due to a lack of testosterone. However, knowing all of the physiological differences between men and women can help individuals formulate workout plans that are beneficial to themselves. For example, because women tend to store fat right under the skin, they may need to work on losing fat before they can expect to see an increase in muscle mass. Additionally, because protein synthesis is more easily stimulated in men, women might be able to overcome this disparity by increasing protein consumption. While these biological differences seem to favor males, knowing the factors that contribute to musculoskeletal growth provides insight on

how females can work to reduce these differences. As a result, women can start to build muscles and bones that rival men.

This study is limited by the extent of current scientific research. Many factors contributing to the differences in musculoskeletal growth have been found, but the reason why they occur is not known. Further research could provide more insight on why these variables impact the body as they do. Through my literature review, I came across many studies that took place in mice, which are model organisms with many genes and molecules with direct counterparts in humans. However, a human version of these studies has not been accomplished. Additionally, some studies may be outdated but have not been repeated at this time. It's also possible that the influence of physical activity on other systems in the body contributes to musculoskeletal development. For example, increased lung capacity from cardiovascular activity improves overall endurance and may correspond with how quickly a person fatigues. Nevertheless, these factors were not considered for research as they go beyond the scope of this paper.

I suggest more research looks into how women can reduce the disparities seen with musculoskeletal growth after exercise. How can women more actively grow muscle and bone? Can women take supplements such as follistatin to inhibit the effects of myostatin on muscle growth? Would hormone replacement therapy for adrenaline or thyroid hormone induce musculoskeletal growth in women? How can women stimulate musculoskeletal growth if they are unable to reach the threshold that activates various pathways? Answering these questions would provide further insight into how women might one day gain muscle and bone mass in a way that's comparable to men.

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