Muscle hypertrophy in athletic training from a medical point of view - what do we know

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Abstract

Introduction

Hypertrophy is the process of increasing the mass of a tissue. In this article, we focused on the impact of the mechanisms of muscle hypertrophy, its effect on the human body,
correlation with the course of diseases and tolerance of treatment. We considered the benefits of having well-developed, and also touched on the problems of underdeveloped muscle mass.

**Results**

The main factors causing hypertrophy are resistance exercise training, mechanotransduction, metabolic pathways, ribosomal biogenesis, gene expression and the impact of hormones. The beneficial effect of high concentrations of testosterone and growth hormone, also IGF1, on skeletal muscle hypertrophy has been proven. On the other side, the studies have shown that high concentrations of glucocorticoids, such as cortisol are associated with reduced muscle mass.

There are many positive aspects of a well-developed muscle mass such as an impact on the prognosis in patients with cancers and sometimes reduces mortality among them. The problems of low muscle mass and sarcopenia are also mentioned. Low muscle mass can affect the poor prognosis of diseases such as cancer, hepatic cirrhosis and COVID-19. Postoperative complications are more common in patients with low muscle mass. One way to prevent this process may be to introduce resistance exercise training in patients struggling with problems of muscular atrophy.

**Conclusion**

Skeletal muscles have multiple functions in the human body. In addition to movement, they play a role in molecular processes like hormonal regulation. In addition, they can, when well developed, positively influence healing processes and the course of disease.

**Keywords:** skeletal muscle, hypertrophy, testosterone, growth hormone, cortisol, IGF1,
Introduction

Skeletal muscles play a crucial role in the human locomotor system. Interestingly, they also fulfill the role in the healing and recovery processes of patients. Low muscle mass is associated with higher mortality not only among patients, but also in healthy adults.

Muscular hypertrophy involves an increase of the size of skeletal muscles through the growth of the cells that build them. Two main groups can be mentioned as sources that induce muscle growth: external and internal stimuli. The strongest non-pharmacological external stimulus that develops muscle tissue is exercise resistance training[1]. This is a prominent element not only for muscle development, but often also for muscle maintenance. The main source of muscle growth is contraction during load on the muscles, which leads us to the conclusion that mechanical signaling plays a major role. However, the exact mechanisms with which that muscle hypertrophy is reached are still unexplored.

In addition, internal factors also have an effect on the development of muscle tissue. These include systemic and local processes within the muscles. A major influence on the development of muscle mass is hormonal management, in particular testosterone, but also growth hormone. Androgens are sex hormones occurring in higher concentrations in men than women that contribute, among other, to the development of lean muscle mass. The concentration of testosterone as one of the androgens correlates with muscle hypertrophy induced by resistance exercise training. Growth hormone is produced by the pituitary gland and stimulates growth in children and adolescents. It also helps regulate body composition, body fluids, and bone and muscle growth.

Hypertrophy is of great importance for people training at the professional level, but also at the amateur level. People who train often aim to expand their muscle mass as much as possible. This is especially often the case when training for sports such as, powerlifting or bodybuilding. So what are the best ways and what mechanisms affect the development of skeletal muscle hypertrophy in humans?

Materials and Methods

In our study, we relied on literature and articles published on Pubmed, based on current knowledge and ongoing scientific research. We searched them for hypertrophy, exercise resistance training, growth hormone and testosterone. As a result, we gathered 38 publications on the basis of which we are writing our paper.
Mechanism

Skeletal muscle hypertrophy is a complex process on many levels. As shown in Figure 1, we can divide the factors that cause skeletal muscle hypertrophy into several groups. The first is external factors, which include resistance exercise training. This is the strongest of the non-pharmacological stimuli[1]. It involves mechanical loading of skeletal muscles. Internal ones include systemic and local processes in the muscles. These are metabolic processes resulting from a multitude of variables, among others that can be induced by resistance exercise training. Whether and to what extent internal factors affect muscle development, as well as their relationship to external factors, remains a matter of consideration.

![Diagram showing the influence of external and internal variables for skeletal muscle hypertrophy.](image)

**FIGURE 1[2]**
*Showing the influence of external and internal variables for skeletal muscle hypertrophy. External variables like resistance exercise (RE) are necessary to activate internal variables and the response of internal variables is a key determinant of skeletal muscle hypertrophy. The size of the squares reflects the importance of the factor for muscle hypertrophy.*

Mechanotransduction

All mechanical stimuli, especially those associated with exercise, trigger a number of cellular processes. Mechanical signals generated by skeletal muscle contraction initiate responses that ultimately result in hypertrophy. During myofibrillar contraction, multiprotein complexes process and transmit muscle signals into biochemical information that ultimately regulates and controls muscle mass. Two protein complexes are identified as the main ones: the dystrophin glycoprotein complex (DGC) and the integrin adhesion complex[3]. They act as a
scaffold for signaling proteins, which allows us to conclude that they mediate the hypertrophic process under high stress.

Integrins are connected to actin via the protein talin[4]. This allows them to participate in various pathways to act as transmitters in the mechanotransduction process. Also associated with integrins is the protein melusin, considered a load receptor, as its levels decrease in unloaded muscles. However, overexpression of melusin causes muscle atrophy[5].

The dystrophin glycoprotein complex, on the other side is probably associated with transmitters that promote hypertrophy. Studies show that dystrophin deficiency in mice causes reduced hypertrophy despite applied functional overload[6]. Another correlation between DGCs and hypertrophy is insulin receptors binding to DGC-rich clusters in costamers which contributes to insulin transmission via the PI3K-Akt-mTOR pathway[7].

However, the extracellular matrix plays a key role in the mechanotransduction process. In order to transfer force from the sarcomere to the extracellular matrix, costamers located in the Z-line of the sarcomere are used. With the help of proteins localized around the costamers, effectors of the HIPPO pathway are activated, which affects the control of cell growth and the regulation of myoblast proliferation and differentiation[8], [9].

Another major protein structure is a protein comprising half of the sarcomere - titin. It is a major determinant of the force generated during eccentric contraction[10]. In fact, the exact role of titin has not been determined. It is treated as a regulator of anabolic processes due to its mechanosensoric properties. It may also be associated with protein metabolism and regulation of muscle mass.

There is another protein structure in the Z-lineage - filamin-C Bag3. It is responsible for regulating hypertrophic mechanisms as a result of the response to mechanical loading. Two mechanisms of its action have been recognized so far. The first is the inhibition of binding of HIPPO suppressor proteins. The second is the increase of the rate of muscle protein breakdown, leading to adaptation and skeletal muscle hypertrophy[9].
mTOR/ PI3K-Akt-mTOR signaling pathway

The rate of protein synthesis in muscle depends on growth factors (e.g. Insulin-like Growth Factor 1 (IGF1)) and the phosphoinositide 3-kinase (PI3K), Akt (protein kinase B (PKB)) and the mechanistic target of rapamycin (mTOR)[11].

In mammals, mTOR contains two protein complexes: mTORC1 and mTORC2. They include similar subunits, although they differ slightly. For example, thanks to the Raptor subunit, increases in nutrients (e.g. leucine), growth factors (e.g. IGF-1) or mechanical stimuli are detected by mTORC1[12]. Therefore, it can be concluded that mTORC1 plays an important role in muscle hypertrophy induced by exercise resistance training. Lysosome translocation just induced by resistance exercise is required for mTORC1 activation. In addition, mTORC1 controls the translation of terminal oligopyrimidine (TOP) mRNAs, which encode ribosomal proteins and initiation and elongation factors. Unfortunately, the exact pathways linking resistance exercise and mTOR activation are still unknown.

Instead, scientific studies confirm that Akt activation leads to significant hypertrophy of the muscle fibers undergoing testing. Activation of this pathway is essential for skeletal muscle hypertrophy induced by resistance exercise training[13].

Ribosomal Biogenesis

A ribosome is a complex of proteins and RNAs used to produce proteins during translation. It contains in its structure two subunits large (60S) and small (40S). Ribosomal biogenesis regulates hypertrophy induced by resistance exercises. Coordinated regulation of ribosomal RNA and muscle-specific genes is required for this. An increase in translation efficiency leads to an increase in the rate of mRNA translation at a constant number of ribosomes. Studies demonstrate that increased total RNA is associated with skeletal muscle hypertrophy[14].

Admittedly, one cycle of exercise does not induce an increase in RNA content in trainees, even though muscle protein synthesis rates have increased. Figure 2 shows an initial increase in muscle protein synthesis, but this is in response to the remodeling of damaged muscle proteins during training. For untrained athletes, the damage is much greater than for experienced athletes, so synthesis decreases as training progresses. After about 2 weeks, markers of ribosomal gene expression and transcription reach a plateau[15]. Thereafter, muscle damage decreases, resulting in a decline in muscle protein synthesis values. The next step is an increase in translational efficiency, which regulates protein synthesis. The end result is an increase in muscle size and mass, shown in Figure 2 as muscle fiber cross-sectional area (CSA)[16].

Despite individual differences in hypertrophic abilities, the mechanism remains the same, namely that the same training program is responded to by adequate changes in ribosomal biogenesis[17]. Also, the amount of training correlates with RNA accumulation and muscle mass growth[18].
As can be seen, the regulation of protein synthesis and transcription adapts relatively quickly to exercise resistance training, so there is no need to increase translational efficiency.

**Figure 2[16]**

*Illustration of changes in muscle protein synthesis (MPS), translational capacity, whole muscle and muscle fiber cross-sectional area (CSA) in response to resistance training over weeks.*

1. Early stage of MPS growth
2. Weakening of muscle damage and decrease in MPS,
3. Increase in translational capacity and upregulation of MPS
4. Increase in muscle size and mass

**Gene expression**

Thanks to advances in technology, we can say that exercise causes changes in the abundance of more than 2,000 gene transcripts[19]. These changes are also concerned with the amount and level of modification of post-translational proteins in skeletal muscle[19], [20]. It seems that resistance exercise training mostly increases the levels of mRNA genes responsible for extracellular matrix remodeling. However, whether and what role this plays in the hypertrophy process has not been proven. Instead, it has been proven that about 600 genes correlate with muscle and strength growth after 12 weeks of exercise resistance training[21]. Many of these genes have been linked to overall exercise adaptation.
Hormonal changes

Androgens
Sex hormones prevalent in men. They are stimulators of skeletal muscle hypertrophy through binding to the androgen receptor (AR), which is followed by nuclear translocation and regulation of target genes. Decreased androgen levels contribute to decreased muscle myofibrillar protein synthesis, likely due to decreased IGF1 expression.

The primary of the androgens, testosterone, can be converted to dihydrotestosterone obtaining the highest affinity for AR[22]. Its exogenous administration in supra-physiological doses to healthy men contributes to an increase in lean muscle mass[23]. Resistance exercise allows endogenous increases in this hormone. Immediately after resistance exercise, testosterone levels rise reaching a peak about 30 min after the start[24]. In addition, resistance exercise increases AR binding to DNA improving anabolic synthesis. While the testosterone response to resistance exercise declines relatively quickly, AR mRNA stimulation and protein content can persist for up to 1-2 days after exercise. This increases the uptake of testosterone into the muscle and its anabolic effects for a much longer period of time. Thus, there is a possibility that elevated testosterone levels and increased AR stimulation after training may cooperate to produce an additional mechanism for regulating hypertrophy[24].

The mechanism of action of testosterone can be divided into two groups: genomic and non-genomic signaling pathways. The non-genomic ones can include the Akt/mTOR/S6K1 pathway, which is an integrated step in the hypertrophic response[24]. These pathways likely increase protein turnover in muscle, which induces an increase in protein accumulation and hypertrophy.

It can be concluded that adequate levels of androgens, most notably testosterone, play a key role in the process of skeletal muscle hypertrophy, and that appropriate exercise may even increase its amounts[24].

Growth hormone
Human growth hormone (GH) is secreted from the somatotropic cells of the anterior lobe of the pituitary gland. Resistance training is the strongest physiological external stimulus releasing GH in both men and women[24]. As early as 10-20 min of training, its serum level rises and peaks at the end of training, and does not drop until 30 min after the end of training[25]. It does not return to baseline values until 60 minutes after the end of training. Whole-body training is most effective for this purpose. Biceps and triceps, for example, only allow the level to rise by half that of full-body training. Workouts of moderate intensity and short intervals between series result in higher circulating concentrations of growth hormone[24]. It is thought the increase in GH levels may be related to increased estrogen levels in women, although the exact mechanism is not yet understood[24]. The effects of estrogen may involve both the release and action of GH. A correlation has been found between increases in GH levels induced by resistance training and long-term skeletal muscle hypertrophy[24].
IGF1
Insulin-like growth factor is a compound produced in the liver, it is built similarly to insulin. It is secreted under the influence of growth hormone. Strongly influences muscle growth during development. It acts both systemically and locally as a paracrine/autocrine factor produced by muscles[26]. The local production of IGF1 is mainly controlled by GH, which means that its indirect effects may also be local. Nevertheless, the effect of IGF1 on the processes of hypertrophy induced by resistance training is evident. This can be seen on the basis of the increase in systemic IGF1 concentration during and immediately after resistance exercise. Importantly, during the period of active muscle mass building, IGF1 concentration in the blood decreases probably due to its redistribution to muscle. This suggests that autocrine secretion of IGF1 in muscle may be a trigger for anabolic metabolic pathways[24]. The response to resistance exercise may be an increase in IGF1 levels, which will translate into activation of the PI3K-Akt-mTOR signaling pathway and ultimately induce stimulation of muscle cells to hypertrophy.

Follistatin-Myostatin-BMP
Myostatin (GDF8) and activin A are responsible for the negative regulation of muscle mass. In contrast, their action is blocked by follistatin, which acts as a signal to stimulate hypertrophy[3]. Inactivation of myostatin or overexpression of follistatin causes muscle hypertrophy. Binding of myostatin to its receptor disrupts the Akt-mTOR pathway, and follistatin is responsible for its activation and promoting protein synthesis[3]. Some bone morphogenetic proteins (BMPs) may also be responsible for muscle hypertrophy. They have the opposite effect to myostatin in stimulating muscle hypertrophy[3].

Estrogen
These are female sex hormones. They may discover an important role in muscle hypertrophy by reducing exercise-induced muscle damage and regulating anabolic signaling pathways[24]. However, the direct effect on muscle hypertrophy induced by exercise stress training is uncertain.

β2- agonists
The most abundant receptor in muscle fibers is the G protein-coupled receptor. Binding of β2 agonists to it triggers activation of adenylate cyclase and activation of protein kinase A. Chronic treatment with β2 agonists leads to muscle hypertrophy. The mechanism is not well understood, but most likely involves the PI3K-Akt-mTOR pathway with IGF1[27].

Osteocalcin
A hormone derived from bones. Osteocalcin supports muscle protein synthesis. Its absence has been shown to contribute to skeletal muscle atrophy. However, treating adult mice with osteocalcin for 4 weeks helps increase their muscle mass[28]. The exact mechanisms are not known yet.
Cortisol
This is a steroid hormone produced in the adrenal cortex. Studies show that it is associated with reduced strength and muscle mass[26]. It plays a role in the pathogenesis of sarcopenia, and research on this topic is still ongoing. Interestingly, the negative effects of cortisol on muscle strength and mass may be partially dependent on hyperglycemia. Hyperglycemia itself may also contribute to muscle atrophy by inducing the expression of specific genes[26].

Muscle damage, inflammatory mediators
Muscle damage leads to this induced inflammatory response. This one triggers the activation of satellite cells and the release of inflammatory mediators and pro-inflammatory cytokines, which can contribute to skeletal muscle hypertrophy. It has been shown that satellite cell content increases during the first week of resistance exercise[29]. However, there is no proven correlation between these cells and the rate of muscle protein synthesis. Perhaps they are related to muscle recovery during the initial stages of exercise resistance training. The details of satellite cells still require further research.

Positive sides of hypertrophy
Studies show that the impact of muscle mass is now considered crucial not only as a mechanical organ, but also as a component of endocrine and paracrine metabolism[31]. Low muscle mass has been linked to a poor prognosis in diseases such as cancer or cirrhosis, and even COVID-19[32]. In COVID-19, patients with sarcopenia were more susceptible to a severe course of the disease, and as a result, there was a higher mortality rate in this group. They should therefore be prioritized for receiving vaccines[32].

Having a well-developed lean muscle mass, can positively affect the prognosis of cancer treatment, as well as take part in disease prevention. It can be said that the examination of body composition and the amount of lean muscle mass should be taken seriously and carried out during hospital admissions. This would allow assessment of the patient's capabilities and adjustment of appropriate treatment. Adequate early detection of abnormalities could allow preventive interventions to be carried out[33].

The exact mechanism for the effect of muscle mass on the course of disease has not yet been developed.

Less medically significant, but quite important to many, is the visual aspect and attractiveness to others. Studies show that a muscular upper body is a major factor in men's attractiveness[34]. Interestingly, women indicated the oblique muscles as the most attractive, followed by the glutes, abdominal muscles, biceps or triceps. Men, on the other hand, indicated the abdominal muscles first, followed by the obliques, biceps, glutes and pectoralis[34].
Problems of low muscle mass

Sarcopenia is a process in which there is a loss of muscle mass, strength, as well as physical performance. It is commonly observed among patients struggling with cancer. In addition, studies show that populations with sarcopenia have higher cancer-related mortality. Sarcopenia also likely causes increased toxicity of ongoing cancer therapy. Thus, the risk of complications during, as well as after, surgery increases, and full recovery is delayed. It turns out that pharmacological measures are not very effective in this regard. Resistance exercise training, on the other hand, shows effectiveness. It allows not only to maintain the muscle mass possessed so far, but also, under the right conditions, to develop it[35].

The incidence of low muscle mass, limited functionality and sarcopenia is related to the area of occurrence. Studies show that the prevalence of sarcopenia in the elderly was higher in rural areas than in urban areas[36]. The differences may be due to work mode and nutrition[36].

Another factor leading to loss or low muscle mass is elevated levels of glucocorticoids, such as cortisol. This occurs in certain diseases, e.g. cancer, sepsis, diabetes, kidney disease, COPD. It activates the process of protein breakdown and reduces the activity of the PI3K-Akt-mTOR pathway. This leads to a process of muscular atrophy[37]. Studies have also shown reduced capillaries in the muscles, leading to reduced muscle perfusion. This is probably the main reason for muscular atrophy[38]. Studies also show that high-intensity interval training can effectively improve muscle damage[38].

Conclusion

Skeletal muscles play many important roles in humans. Among the most obvious are mechanical functions that enable movement. In addition, muscles play an important role in molecular processes such as hormonal regulation. Furthermore, muscle mass can also determine the body's response to disease factors, condition immunity, or improve treatment outcomes. It can serve as a predictor of the incidence and course of cancer. Developed muscle mass also affects the attractiveness of men.

That's why it's so important to ensure proper development of muscle mass. The exact mechanisms are described above, but it is important to remember that the most important stimulus for anabolic processes in skeletal muscle is resistance exercise training. Studies show that moderate intensity and short intervals are the most effective way to hypertrophy muscles. In addition to external factors, internal ones play an important role, such as nutritional status, recovery time, hormone concentrations, concomitant diseases, or genetic predisposition. The most significant effects among hormones on skeletal muscle hypertrophy are testosterone, growth hormone and IGF-1.

Unfortunately, the state of current knowledge still does not allow to draw clear conclusions about the ways and exact mechanisms of skeletal muscle hypertrophy. We have several hypotheses, however, it is necessary to study how each element affects the overall growth of muscle mass. Studies show that resistance exercise training is the most important, as well as the influence of hormones such as testosterone or GH.
References


