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REVIEW ARTICLE

Role Of Exercise Intensity in Skeletal Muscle Hypertrophy

Peran Intensitas Latihan dalam Hipertrofi Otot Skeletal

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ABSTRACT

Endurance training, a form of physical activity that relies on continuous aerobic exercise and repetitive muscle contractions, is widely acknowledged for its positive effects on overall physical fitness. Aerobic exercise, an essential component of endurance training, has numerous benefits including improved cardiovascular and respiratory health, increased muscle endurance, and enhanced resistance against fatigue. It has also been found to contribute to skeletal muscles, potentially by stimulating the synthesis of proteins involved in muscle fiber formation. Although resistance exercise has been favored for promoting muscle growth, some suggests that aerobic exercise can also produce skeletal muscle hypertrophy comparable to that of resistance exercise if performed correctly. The duration, intensity, and specific type of aerobic exercise play important roles in determining skeletal muscle mass. The mammalian target of rapamycin (mTOR) known as a key regulator of muscle protein synthesis that associated with exercise activity. Several signaling pathways, such as Akt/mTOR and MAPK, are involved in controlling muscle protein synthesis during exercise. This review aimed to understand the impact of aerobic exercise intensity and other training parameters on skeletal muscle, to provide valuable insights for optimizing exercise programs and fostering muscle hypertrophy. In this review, we had systematically searched PubMed and Google Scholar from January 2013 to May 2023. Our result indicated that aerobic exercise can be expected to promote skeletal muscle hypertrophy and improve muscle mass and function. The regulation of skeletal muscle mass is complex, involving various signaling pathways such as mTOR, as well as the influence of hormones and growth factors.

Keywords: exercise; hypertrophy; intensity; muscle mass; skeletal muscle

ABSTRAK

Latihan ketahanan adalah suatu bentuk aktivitas fisik berupa latihan aerobik dan kontraksi otot berulang, yang telah diketahui memiliki efek positif terhadap kebugaran fisik secara keseluruhan. Latihan aerobik, yang merupakan komponen penting dari pelatihan ketahanan, memiliki banyak manfaat termasuk meningkatkan kesehatan kardiovaskular dan pernafasan, meningkatkan daya tahan otot, dan meningkatkan ketahanan terhadap kelelahan. Latihan aerobi juga ditemukan berkontribusi pada otot rangka, dan berpotensi merangsang sintesis protein yang terlibat dalam pembentukan serat otot. Meskipun latihan resistensi lebih disukai untuk meningkatkan pertumbuhan otot, terdapat studi yang berpendapat bahwa latihan aerobik juga dapat menghasilkan hipertrofi otot rangka yang sebanding dengan latihan resistensi jika dilakukan dengan benar. Durasi, intensitas, dan jenis latihan aerobik tertentu berperan penting dalam menentukan massa otot rangka. Mammalian target of rapamycin (mTOR) dikenal sebagai pengatur utama sintesis protein otot yang berhubungan dengan aktivitas olahraga. Beberapa jalur sinyal, seperti Akt/mTOR dan MAPK, terlibat dalam pengendalian sintesis protein otot selama latihan. Tinjauan ini bertujuan untuk memahami dampak intensitas latihan aerobik dan parameter latihan lainnya pada otot rangka, untuk memberikan informasi dalam mengoptimalkan program latihan dan mendorong hipertrofi otot. Metode yang digunakan adalah penelusuran melalui PubMed dan Google Cendekia secara sistematis untuk artikel dari Januari 2013 hingga Mei 2023. Hasil kami menunjukkan bahwa latihan aerobik diharapkan dapat meningkatkan hipertrofi otot rangka serta meningkatkan massa dan fungsi otot. Regulasi massa otot rangka sangatlah kompleks, melibatkan berbagai jalur sinyal seperti mTOR, serta pengaruh hormon dan faktor pertumbuhan.

Kata Kunci: intensitas; hipertrofi; massa otot; olahraga; otot skeletal.

INTRODUCTION

Endurance training involves engaging in continuous physical activity that relies on aerobic metabolism and repetitive isotonic contractions of major skeletal muscles.[1] It is a planned and systematic form of endurance exercise that is widely acknowledged for its beneficial effects on overall physical fitness. Acute aerobic exercise, which is a fundamental aspect of endurance training, is renowned for its capacity to enhance cardiovascular and respiratory health by optimizing cardiac output and meeting the metabolic demands of the musculoskeletal system.[2,3] Engaging in aerobic exercise results in an elevation of maximal oxygen uptake and a positive alteration in the size and quantity of mitochondrial proteins. These adaptations contribute to improved muscle oxidative capacity and increased endurance against fatigue.[4–6] Furthermore, aerobic exercise has the potential to induce skeletal muscle hypertrophy, potentially through the stimulation of myofibrillar protein synthesis.[7,8] Exercise is widely recognized as a highly effective approach for preventing and managing skeletal muscle aging. With the aging population, there has been a rise in the occurrence of age-related conditions and diseases, including sarcopenia which is characterized by reduced muscle mass and strength.[9,10] Engaging in suitable exercise can enhance the adaptability and functioning of older individuals, leading to improved skeletal muscle function and overall quality of life. It can effectively enhance overall health and longevity.[11,12]

Stimulating muscle protein synthesis is a key factor in promoting increases in skeletal muscle mass. The mammalian target of rapamycin (mTOR) is a highly acknowledged regulator in this process.[11,13,14] serine/threonine kinase plays a vital role in protein synthesis and is associated with exercise activity.[15] Multiple studies have provided evidence supporting the beneficial effects of exercise, specifically resistance exercise, on muscle protein synthesis and remodeling. In the past,

aerobic exercise training was believed to have a limited impact on skeletal muscle mass and received less scientific focus compared to resistance exercise. However, evidence and reviews suggest that aerobic exercise can indeed promote skeletal muscle hypertrophy in sedentary individuals from age 20 to 80 years.[5] When performed correctly, aerobic exercise can lead to skeletal muscle hypertrophy comparable to that achieved through resistance exercise training.[15,16] While numerous reviews have emphasized the advantageous effects of exercise on alterations in skeletal muscle mass, there is a limited discussion regarding the impact of aerobic exercise intensity on the regulation of skeletal muscle mass. This review aims to elucidate the significance of precise training parameters, including exercise intensity in the regulation of skeletal muscle mass.

METHODS

This study aims to outline the literature of the review narrative. Articles found in the databases such as Pubmed and Google Scholar. The following words were used in the searching procedure "skeletal muscle", "aerobic training", "endurance training" and "muscle hypertrophy". The following articles included in the review are in English and in a period from January 2012 to May 2023.

RESULTS

Skeletal Muscle Adaptation to Exercise

Skeletal muscle is a dynamic, highly adaptive tissue that continuously responds to environmental stimuli. Its adaptive responses include the well-studied hypertrophic capacity of skeletal muscle, which refers to an increase in size in response to specific physical activities, such as exercise, as well as hormonal influences, such as androgens, which account for the differences in muscle size.[17] Muscle hypertrophy occurs when there is an imbalance between protein synthesis and muscle protein degradation. Exercise can maintain or increase the synthesis of skeletal muscle protein and cause hypertrophy in the muscles.[18] Observation of skeletal muscle hypertrophy can be done by using various imaging modalities, such as ultrasound assessment, computed tomography (CT) scanning, and magnetic resonance imaging (MRI). Evaluation of muscle hypertrophy at a microscopic level can be assessed through the cross-sectional area (CSA) of the individual muscle fibers.[17]

Skeletal muscle hypertrophy refers to the increase in the cross-sectional area of muscle fibers (CSA) leading to an overall increase in muscle volume and mass.[19] When muscles undergo excessive stimulation, such as during exercise, it leads to the disruption of myofibers (also known as muscle fibers) and their associated extracellular matrix. This disruption states a series of myogenic events that resulted in the enlargement of the size and quantity of myofibrillar contractile proteins, that is actin and myosin, along with the increment of the overall number of sarcomeres. Consequently, this causes an enlargement in the diameter of the skeletal muscle fiber, leading to an expansion in the muscle's cross-sectional area.

In Table 1, studies demonstrate that aerobic exercise gave hypertrophy adaptation to skeletal muscle. However, some studies also found that resistance exercise can increase muscle protein synthesis and protein deposition.[20,21] Further investigations are necessary to elucidate the precise effects of varying intensities and durations of aerobic exercise training.[21] A study investigated the

association between individuals who are active aerobically and sedentary and found that young, middle, and older individuals who are highly active have greater knee extensor power and correlated leg lean mass.[22] Another study was conducted in a short-interval, low-intensity, slow-jogging (SJ) program consisting of sets of 1 min of SJ at walking speed and 1 min of walking in 81 older adults (age 70.8 ± 4.0 years). There were no significant changes in muscle CSA by the SJ program, while thigh intracellular water increased in the SJ group. However, the study found that slow jogging can improve aerobic capacity, muscle function, and muscle composition in older adults.[23]

Table 1. The effects of aerobic exercise on the skeletal muscle in human studies

No	Reference	Participants	Exercise Training	Exercise Intensity	Duration	Importance
1	Konopka et al., 2014[5]	13 men, young (n=7); old (n=6)	Aerobic exercise using cycle ergometer	60%–80% heart rate	20–45 min for 12 weeks	Exercise increased skeletal muscle size and markers in both young and old men
2	Ikenaga et al., 2017[23]	81 older adults	Jogging and walking	low-intensity	1 min jogging and 1 min of walking, total 180 min per week, in 12 weeks	No change in the NDMA (Normal-density muscle and LDMA (Low-density muscle are) found lower in SJ group ($p < 0.05$)
3	Estes et al., 2017[24]	12 active males and females; Males (n=2); Females (n=10)	Running	90-95% HRmax high-intensity	4 minutes for 10 weeks	Exercise significantly increased muscle cross sectional area in the high intensity group ($p<0.05$)
4	Crane et al., 2013[22]	74 adults; Men (n=42); Women (n=32), divided into two groups, active (ACT) and sedentary (SED)	Various aerobic exercise	moderate to vigorous exercise (ACT group)	4 hours or more for at least the last 10 years (ACT group)	Exercise lowered age-related reductions in muscle strength

Exercise-induced muscle hypertrophy is facilitated through various signaling pathways that promote a favorable balance between muscle protein synthesis and degradation.[25,26] Key anabolic signaling pathways involved include Akt/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and calcium-dependent (Ca2+) pathways. Hormones and growth factors play crucial roles in regulating muscle mass and promoting skeletal muscle hypertrophy. These include insulin-like growth factor 1 (IGF1), follistatin-myostatin-bmp, androgens, β2-agonists, and osteocalcin. IGF1 is a potent growth factor that contributes significantly to muscle growth during development. IGF acts as a paracrine/autocrine factor produced by skeletal muscle. Another member of the TGF superfamily, myostatin, and activin A, have a role as the negative regulators of skeletal muscle mass. They bind to the activin type II receptor (ActRII) and inhibit muscle growth. However, follistatin, an endogenous inhibitor, counteracts the effects of myostatin and activin A, acting as a pro-hypertrophic signal. Studies in adult mice have demonstrated that inactivation of myostatin or overexpression of follistatin in muscles induces muscle hypertrophy and leads to alterations in fiber-type composition.[17]

These hormones and growth factors, such as androgens like testosterone, play crucial roles in regulating muscle mass and can be targeted to promote skeletal muscle hypertrophy and enhance muscle growth. Testosterone acts by binding to the androgen receptor (AR) and translocating into

the nucleus to regulate target genes. It can also be converted into dihydrotestosterone, which is a highly potent androgen that exhibits a strong affinity for the AR. In skeletal muscle, the enzyme 5-alpha-reductase type 1 (Srd5a1) is responsible for converting testosterone into dihydrotestosterone. This enzyme is expressed in skeletal muscle and can be upregulated by physical exercise in rats. Androgens, such as dihydrotestosterone, exert their influence on muscle hypertrophy by stimulating the proliferation of satellite cells. This proliferation subsequently leads to fusion and an increase in the content of myonuclei within muscle fibers. It is important to note, however, that these processes are not indispensable for androgen-induced muscle hypertrophy. Even in satellite cell-depleted mice treated with testosterone, muscle fiber size can still increase. Collectively, androgens contribute significantly to the promotion of muscle hypertrophy through diverse mechanisms, including activation of androgen receptors (AR), regulation of gene expression, and involvement in satellite cell-related processes.[17]

mTOR Regulation on Skeletal Muscle Mass

The mTOR pathway plays a pivotal role in regulating the delicate equilibrium between anabolic (muscle-building) and catabolic (muscle-breaking) processes during exercise. Specifically, mTOR exerts its influence by inhibiting autophagy, a process associated with muscle atrophy, through the PI3K/Akt/mTOR pathway. In a study conducted on aged sarcopenic rats, a 12-week exercise protocol incorporating treadmill training, resistance training, and a combination of both was found to effectively counteract the loss of muscle mass. This beneficial effect was achieved by modulating autophagy through the Akt/mTOR and Akt/FoxO3a signaling pathways.[11] The regulation of skeletal muscle mass involves maintaining a balance between anabolic and catabolic processes. Within this context, mTOR, a type of serine/threonine kinase, plays a crucial role by sensing and responding to different environmental and intracellular factors such as nutrient availability and energy levels. By doing so, mTOR coordinates a range of cellular processes including cell growth, differentiation, autophagy, survival, and metabolism.[27]

Phosphorylation plays a crucial role in the activation or deactivation of proteins within the Akt-mTOR pathway, which is essential for the regulation of protein synthesis in response to muscle contractions. The MAPK pathway, along with the Akt-mTOR pathway, participates in the control of the translation process during muscle contractions. One specific protein affected by phosphorylation is p38 MAPK, which can influence the function of transcription factors such as peroxisome proliferator-activated receptor coactivator 1 (PGC-1). PGC-1 serves as a critical regulator of mitochondrial biogenesis and coordinates the transcriptional activity necessary for the synthesis of mitochondrial and nuclear DNA. This process is vital for the development of new mitochondria.[7]

While the contribution of mTOR signaling in muscle growth is well known, the exact underlying mechanisms of this process are still unknown. During early studies, mTOR signaling in the muscle revealed that rapamycin-sensitive mTOR complex 1 (mTORC1) activation is associated with muscle hypertrophy. IGF-1 and leucine also known to promote hypertrophy through the activation of mTORC1 signaling in rats and mice.[21,28]

mTORC1 plays a central role in the regulation of protein synthesis and also ribosome biogenesis. Protein synthesis is stimulated by mTORC1 by phosphorylating eukaryotic initiation factor 4E-binding protein (4E-BP) and ribosomal protein kinase 1 (S6K1). [17] Moreover, Akt can inhibit protein degradation through phosphorylation, and thus inhibit the forkhead box O (FoxO) family

of transcription factors. The activation of FoxO1 and 3 in skeletal muscle has been identified in conditions of muscle atrophy.[29]

Exercise Intensity and Muscle Mass

Hypertrophy refers to the physiological process characterized by an enlargement in muscle size. Maintaining adequate muscle mass is crucial for various activities involved in daily life, particularly locomotion, and insufficient muscle mass can heighten the susceptibility to various diseases. Achieving muscle hypertrophy adaptations can be accomplished through the implementation of diverse resistance training programs.[30] Current Physical Activity Guidelines for Americans recommend that adults exercise 150 minutes of moderate-intensity physical activity concurrently with muscle-strengthening exercise for at least two days per week. The American College of Sports Medicine (ACSM) provides specific recommendations for resistance training. For beginners, it is suggested to perform 1-3 sets of 8-12 repetitions at 70-85% of their one repetition maximum (1RM). Advanced individuals, on the other hand, are encouraged to aim for 3-6 sets of 1-12 repetitions at 70-100% 1RM. However, recent research has expanded the scope of training possibilities. Several studies have demonstrated that achieving muscle hypertrophy can be comparable with training using lower loads, typically ranging from 30% to 60% of 1RM, as long as participants reach the point of volitional fatigue. This challenges the traditional belief that moderate and high loads (>60% 1RM) are indispensable for promoting muscle hypertrophy.[18]

The resistance training model has traditionally been favored in aiming for the enhancement of muscle mass and is also believed to be the optimal training for muscle hypertrophy. This training method is characterized by moderately high intensity and high volume (8-12 repetitions maximum [RM] or more) with short resting intervals (1-2 minutes). This belief was partially based on scientific evidence showcasing higher post-exercise levels of anabolic hormones. It was thought that these elevated hormone levels would enhance the binding of hormones to their receptors, triggering a series of intracellular reactions that contribute to muscle growth.[31]

Aerobic exercise has demonstrated its potential to mitigate the age-related decline in muscle mass through various physiological mechanisms. These include reducing the expression of catabolic mRNA, promoting biogenesis and mitochondrial dynamics, and enhancing the synthesis of muscle proteins that support muscle fibers and facilitate hypertrophy across different age groups. To achieve these benefits through aerobic exercise, it is crucial to attain an adequate training intensity (70%-80% of Heart Rate Reserve), duration (30-45 minutes), and frequency (4-5 days per week) to optimize muscle contraction when compared to a resistance training program. Moreover, acute aerobic exercise has shown the ability to restore the sensitivity to the anabolic effects of insulin in older adults, leading to the stimulation of intracellular anabolic signaling pathways and the promotion of a positive protein balance that is not evident in sedentary individuals.[16].

Another systematic review investigated the effects of high-intensity interval training (HIIT) and aerobic-based exercise, on muscle protein synthesis (MPS). The review indicates that both HIIT and aerobic exercise can significantly increase MPS rates, specifically for mixed and myofibrillar proteins.[32] Another study found that a single session of high-intensity aerobic exercise performed while in a fasted state leads to a sustained increase in both mitochondrial protein synthesis

(MitoPS) and myofibrillar protein synthesis (MyoPS) during the 24-28 hour recovery period following exercise.[7]

Exercise plays a crucial role in improving overall health, and its effects depend on factors such as exercise frequency, intensity, duration, and type. Aerobic exercises like running, walking, swimming, and cycling are particularly effective in training the cardiovascular system and reducing the risk of diseases associated with reactive oxygen species (ROS). Aerobic exercise promotes the body's adaptation to oxidative stress by increasing antioxidant levels and expressing antioxidant enzymes. The intensity of exercise is a critical factor that determines the health benefits obtained. Light exercise may not elicit significant physiological changes, whereas high-intensity exercise can increase oxidative stress. Excessive or intense exercise can disrupt the balance between ROS production and elimination, resulting in oxidative stress. ROS generated during exercise can trigger an inflammatory response through phagocyte infiltration.

CONCLUSION

In summary, the growth of skeletal muscles, known as hypertrophy, is a complex process influenced by multiple factors, including resistance exercise, hormonal effects, and signaling pathways like mTOR. Resistance exercise stimulates muscle protein synthesis and promotes hypertrophy by activating the mTOR signaling pathway. Additionally, aerobic exercise can also induce muscle hypertrophy, particularly when performed at moderate to high intensities. Both resistance and aerobic exercises offer benefits in terms of muscle mass, composition, and function. The regulation of skeletal muscle mass involves a delicate balance between processes that build and break down muscle, with mTOR playing a crucial role in this balance. The intensity, duration, and frequency of exercise are key factors in determining the extent of muscle hypertrophy. Overall, exercise, whether resistance or aerobic, plays a vital role in promoting skeletal muscle hypertrophy and improving muscle mass. Incorporating appropriate exercise routines into daily life can lead to significant physiological changes, enhancing overall health and reducing the risk of various diseases.

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AUTHOR CONTRIBUTIONS

Study concept and design, data collection, preparation of manuscripts and corresponding author: NAV; data analysis, interpretation of results: NAV, NS, and LL. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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