



## EXERCISE THERAPY AS THERAPEUTIC OPTION FOR MUSCLE ATROPHY: STUDY ON SIGNALING IGF-1 IN SKELETAL MUSCLE

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### Abstract

**Background** - Muscle wasting is caused by metabolic system disorders involving disorders of the musculoskeletal system, one of the risks is insulin growth factor (IGF1) damage. Exercise therapy is one of the physiotherapy interventions that can increase muscle mass and strength, reduce oxidative stress related to aging, chronic inflammation, increase autophagy, and improve mitochondrial function. **Methods** - The method used in this paper is a literature review using a search database of Google Scholar, Pubmed, and Researchgate with the topic search keywords "muscle wasting", "Biomarker and Molecular IGF1", and "exercise" which are used to expand or specify the search so that it can make it easier in determining the research articles or journals used. literature review selection using inclusion and exclusion categories and taking into account the interrelationships between keywords. **Results** - Exercise therapy is able to increase muscle mass and act as an alternative therapy in cases of metabolic disorders that cause muscle wasting. Exercise therapy that can be used to increase muscle mass is resistance training and controlled exercise programs. **Conclusion** - Exercise therapy is able to increase signaling activation of insulin growth factor (IGF1) which causes an increase in insulin sensitivity to improve the downregulation process of muscle wasting in patients with metabolic system disorders.

Keyword : exercise therapy, IGF1, muscle wasting, metabolic system disorder



## 1. Introduction

Non-communicable diseases (NCDs) have become a major health problem in today's modern world. Although many cases of this disease started in western countries, now the spread of lifestyle and health patterns is a global problem throughout the world. One of them is the metabolic syndrome (MetS) also known as syndrome X, insulin resistance, and is defined by WHO as a pathological condition characterized by abdominal obesity, hypertension and hyperlipidemia. Some of the elements that cause metabolic syndrome are due to a sedentary lifestyle, decreased physical activity, and a tendency to consume unhealthy and instant foods (Saklayen, M.G., 2018). cc

The prevalence of MetS is in the range of 11.9 to 37.1% in the Asia-Pacific region consisting of the Philippines, China, Sri Lanka, Taiwan, Singapore, South Korea, Mongolia and Malaysia with a prevalence of 11.9, 21.3, 24, 3, 25.5, 26.9, 31.3, 32.8 and 37.1%, respectively, based on different definitions of MetS syndrome. Among Southeast Asian countries, Indonesia based on data from Badan Pusat Statistik (2018-2022) is the most populous country in the region, reaching 275.77 million people. It was reported that the prevalence of metabolic syndrome in Jakarta was 28.4%, consisting of 25.4% in men and 30.4% in women. The highest component of metabolic syndrome in men was hypertension (84.7%) followed by hypertriglyceridemia (83.4%), central obesity (75.5%), hyperglycemia (50.9%) and low HDL levels (43.6%). Meanwhile, in women, the highest component of the metabolic syndrome was central obesity (91.3%), followed by hypertension (84.1%), hypertriglyceridemia (66.1%), low HDL levels (57.8%) and hyperglycemia (50.2%). Another study in Jakarta found the prevalence of metabolic syndrome in the executive group was 21.6%, 24.8% in men and 11.8% in women. while in South Kalimantan Province, especially based on data from



Idaman Banjarbaru Hospital, it is known that in 2021-2022 the number of medical rehabilitation poly patients with MetS disorders, such as diabetes mellitus, obesity, muscle atrophy, and cardiovascular disorders reach to 331 people.

Research also explains the loss of skeletal muscle mass, strength and/or physical performance in general due to a contribution to the development of metabolic diseases (Kim and Kim, 2020). Loss of muscle wasting as a recognized pathomechanism causes skeletal muscle weakness. Muscle wasting is the result of impaired muscle protein homeostasis, with protein degradation that is not balanced by protein synthesis in muscle. Systemic inflammation is one of the risk factors that provokes disruption of muscle protein homeostasis due to the occurrence of metabolic system disorders in patients. Model studies in cell culture, animals and humans have evaluated cytokines and growth factors that can regulate muscle growth. Insulin-like growth factor-1 (IGF-1) is a growth factor that has been shown to modulate the size of skeletal muscle cells and has an important effect on the regulation of muscle function. IGF-1 levels are mostly mediated through physical activity while lower in pathological conditions such as chronic disease, inflammation and malnutrition. IGF-1 also regulates protein synthesis and degradation pathways in muscle so that the balance affects the size of skeletal muscle cells (Yoshida and Delafontaine, 2020)

Nowadays, therapeutic measures and preventive apart from general treatment are exercise as an effort to prevent muscle wasting or muscle atrophy. Exercise therapy can counteract muscle atrophy through several metabolic adaptations and transcription factors. Exercise reduces age-related oxidative damage and chronic inflammation, enhances autophagy, and improves mitochondrial function, myokine profile, IGF-1-like signaling pathways, and insulin sensitivity. The exercise intervention targets resistance



(strength and power), aerobics, balance, and work flexibility (Angulo *et al.*, 2020). Exercise acts on signaling pathways involved in the maintenance of muscle mass, one of which is IGF-1. Exercise therapy can inhibit the occurrence of muscle atrophy by modulating muscle catabolic pathways as shown in resistance training for 12 weeks programmed to young women capable of modulating to the level of expression (Scicchitano *et al.*, 2018).

So that the physiological mechanism that underlies the therapeutic effect of exercise involves various methods and appropriate exercise programs in influencing changes in IGF-1 to prevent muscle wasting. Furthermore, studies on exercise as a therapeutic option in dealing with cases with MetS disorders that cause muscle wasting are still very limited. Therefore, in this study, we will discuss the effectiveness of exercise therapy as a modality to reduce the incidence of muscle wasting in patients with MetS through a study of the activation pathway of IGF-1 mRNA expression.

## 2. Methods

The method used in this paper is a literature review that uses a search database of Google Scholar, Pubmed, and Research Gate with the topics "muscle wasting", "Biomarker and Molecular", and "exercise". expand or specify the search so that it can make it easier to determine the article or research journal used. literature review selection using inclusion and exclusion categories and taking into account the interrelationships between keywords.

## 3. Results

### 3.1. Summary of Research



year	title	conclusion
2013	Physical activity for the prevention and treatment of metabolic disorders (Montesi <i>et al.</i> , 2013)	<ul style="list-style-type: none"> <li>Research related to exercise and patient counseling and intervention planning, recommends 30 minutes of moderate-intensity physical activity most days of the week, or vigorous-intensity physical activity &gt;3 times per week for &gt;20 minutes by looking at the NAFLD benchmark in patients with physical activity and no physical activity.</li> </ul>
2014	A metabolic link to skeletal muscle wasting and regeneration (Koopman <i>et al.</i> , 2014)	<ul style="list-style-type: none"> <li>Involvement of the complex mTOR pathway that plays a role in controlling the initiation and elongation of mRNA translation, integrating various extra and intracellular signals, one of which is IGF-1 as a strategy in regulating the events of protein synthesis, autophagy, cell growth and metabolism.</li> </ul>
2018	Molecular Insights into Muscle Homeostasis, Atrophy and Wasting (Scicchitano <i>et al.</i> , 2018)	<ul style="list-style-type: none"> <li>Resistant exercise for 12 weeks in young women moderately modulated the basal expression levels of two molecular markers of proteasome-dependent proteolysis in which genes such as MuRF-1 and FOXO3 were decreased. Exercise also increases cellular autophagic flux</li> </ul>
2018	The Role of IGF-1 Signaling in Skeletal Muscle Atrophy (Timmer <i>et al.</i> , 2018)	<ul style="list-style-type: none"> <li>During denervation and aging, overexpression of IGF-1 or injection against aging-associated denervation and muscle atrophy, although increasedabolic resistance with respect to</li> </ul>



		IGF-1 signaling with aging.
2019	Muscle atrophy in critically ill patients: a review of its cause, evaluation, and prevention (Nakanishi <i>et al.</i> , 2020)	<ul style="list-style-type: none"> <li>• Patients with critical conditions show a clear appearance of muscle atrophy, the cause of atrophy from various risk factors such as inflammation, immobilization, nutrition, hyperglycemia, drugs and mechanical factors. (monitoring atrophy using ultrasound)</li> <li>• Physiotherapy (early mobilization) is proven to be effective in preventing early disability and Electrical muscular stimulation (EMS) is effective for patients with limited physical movement</li> </ul>
2019	Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial (Wollersheim <i>et al.</i> , 2019)	<ul style="list-style-type: none"> <li>• Early mobilization of critically ill patients is generally recommended in international guidelines, whereas additional muscle activation measures are not recommended due to lack of evidence.</li> <li>• The data extend to findings showing that even if muscle atrophy is prevented, it does not necessarily increase muscle strength and functional independence in patients with MOD. so that preventive intervention against atrophy is not an effort to handle the incidence of muscle wasting - then exercise is needed</li> </ul>
2019	The Role of the IGF-1 Signaling Cascade in Muscle Protein Synthesis	<ul style="list-style-type: none"> <li>• Loss of muscle mass occurs due to acute changes in protein balance.</li> <li>• Reduced muscle protein synthetic response affects exercise, availability of amino acids</li> </ul>



	and Anabolic Resistance in Aging Skeletal Muscle (Barclay <i>et al.</i> , 2019)	from food, or insulin resistance. Insulin like growth factor 1 (IGF-1), Akt/Protein Kinase B and the mechanistic target of the rapamycin pathway (mTOR) are the main drivers between mechanical contraction and protein synthesis.
2019	Mechanisms Underlying Metabolic Syndrome-Related Sarcopenia and Possible Therapeutic Measures (Rubio-Ruiz <i>et al.</i> , 2019)	<ul style="list-style-type: none"> <li>• High-intensity exercise is considered the protocol of choice in combating age-related muscle decline, as compared to low- and moderate-intensity exercise</li> </ul>
2020	Metabolic aspects of muscle wasting during critical illness (Van Gassel <i>et al.</i> , 2020)	<ul style="list-style-type: none"> <li>• Skeletal muscle wasting during critical illness is the result of impaired metabolism. Immobilization, inflammation and impaired muscles</li> <li>• Energy and nutrient metabolism are the main drivers of muscle protein loss.</li> <li>• Basic research should focus on ways to further increase the anabolic potency of nutrition by uncovering the mechanisms that regulate anabolic and catabolic pathways and energy metabolism.</li> </ul>
2020	Mechanisms of IGF-1-Mediated Regulation of Skeletal Muscle	<ul style="list-style-type: none"> <li>• Insulin-like growth factor-1 (IGF-1) is a growth factor that regulates both anabolic pathways and catabolic pathways in skeletal muscle.</li> </ul>



	Hypertrophy and Atrophy (Yoshida and Delafontaine, 2020)	<ul style="list-style-type: none"> <li>• IGF-1 increases skeletal muscle protein synthesis via PI3K/Akt/mTOR and PI3K/Akt/GSK3<math>\beta</math> lines. PI3K/Akt can also inhibit FoxOs and suppress transcription of the E3 ubiquitin ligase that regulates the - mediated ubiquitin proteasome system (UPS) protein degradation.</li> <li>• Evidence suggests that IGF-1/Akt can inhibit muscle atrophy activation Cytokine and myostatin signaling via inhibition of the NF-kB and Smad pathways.</li> </ul>
2020	Implications of Insulin-Like Growth Factor-1 in Skeletal Muscle and Various Diseases (Ahmad <i>et al.</i> , 2020)	<ul style="list-style-type: none"> <li>• Insulin-like growth factor-1 (IGF-1) is a hormone found in the blood that plays an important role in skeletal and important myogenesis related to mass entities, strength development and degeneration and increase the proliferative capacity of muscle satellite cells (MSCs).</li> <li>• IGF-1 synthesis is increased in injured muscle MSCs and triggers MSC proliferation and myogenic differentiation.</li> <li>• Mechanical loading also affects the frame muscle production by IGF-1, and low levels of IGF-1 with low grip strength and poor physical performance.</li> </ul>
2020	Physical activity and exercise: Strategies to manage frailty (Angulo	<ul style="list-style-type: none"> <li>• Physical activity/exercise is considered as one of the main strategies to counter the associated weakness</li> </ul>



	<i>et al.</i> , 2020)	<ul style="list-style-type: none"> <li>• physical disorders in the elderly. Exercise reduces age-related oxidative damage and chronic inflammation enhance autophagy, and improve mitochondrial function, myokine profile, insulin-like growth factor-1 (IGF-1) signaling pathway, and insulin sensitivity.</li> <li>• Exercise interventions target resistance (strength and power), aerobics, balance, and work flexibility.</li> </ul>
2021	IGF-1 and IGFBP-3 in Inflammatory Cachexia (Martín <i>et al.</i> , 2021)	<ul style="list-style-type: none"> <li>• inhibition of the hypothalamic-GH-IGF-1 axis contributes to catabolic processes, with muscle atrophy and cachexia</li> <li>• changes in pituitary GH secretion, IGF-1, and IGF-1 binding protein-3 (IGFBP-3), and the mechanisms that mediate this response. GH and IGF-1 expression contribute to muscle wasting during inflammation</li> </ul>
2021	Mechanisms of exercise as a preventative measure to muscle wasting (Graham <i>et al.</i> , 2021)	<ul style="list-style-type: none"> <li>• Exercise will encourage the process of recovery of muscle mass and function even though the duration required is quite long, the intervention is a structured exercise</li> <li>• Resistant Training prevents a decrease in cycle creatine kinase and FGF levels and increases protein synthesis. Preventive measures such as exercise therapy in combination with neuromuscular electrical stimulation (NMES) and protein supplementation from the 5-day study are</li> </ul>



		good for those with atrophy.
2021	Molecular Mechanisms of Muscle Fatigue (Constantin-Teodosiu, D Constantin, 2021)	<ul style="list-style-type: none"> <li>• Rehabilitation programs such as resisted exercise, together with interventional protein-rich diets are practical and hands-on approaches to increasing muscle mass and function.</li> </ul>
2021	Metabolic Remodeling in Skeletal Muscle Atrophy as a Therapeutic Target (Renzini <i>et al.</i> , 2021)	<ul style="list-style-type: none"> <li>• Low-intensity exercise induces oxidative lipid metabolism, whereas high-intensity exercise activates glycolytic pathway metabolism. exercise increases the clearance of damaged mitochondria.</li> <li>• Moderate-intensity exercise (15 minutes done twice a day) delays deterioration of motor function and weakens the decrease in muscle strength.</li> </ul>
2021	Results of the use of physical therapy for metabolic syndrome according to anthropometric studies (Kalmykova <i>et al.</i> , 2021)	<ul style="list-style-type: none"> <li>• Physical exercise is considered as a factor to increase mobility in physiological processes, therapeutic massage and manipulation can be used in the complex treatment process of metabolic syndrome (obesity).</li> <li>• The intensity and duration of massage on each part of the body directly depends on the location and amount of adipose tissue deposition</li> <li>• physiotherapy is quite recommended in the management of metabolic syndrome, 4 months of comprehensive exercise therapy program provides a significant comparison of</li> </ul>



		effects in comparison of anthropometric indices related to abdominal circumference
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#### 4. Discussion

##### 4.1. Mechanisme of Muscle Wasting

The balancing mechanism in reducing the incidence of muscle wasting is controlled by an intracellular signaling cascade that controls protein synthesis and translational efficiency/capacity while also coordinating the regulation of proteolytic and autophagic degradation systems (Graham *et al.*, 2021).

Muscle mass is maintained by balancing the levels of protein synthesis and protein degradation. When synthesis exceeds degradation, the result is an increase in muscle fiber size and performance. Conversely, when the long-term balance supports protein degradation, muscle size and performance will decrease (Graham *et al.*, 2021). Bed rest or prolonged immobilization results in a rapid 3%-5% loss of muscle mass in the first week, and can be more severe when accompanied by severe burns or SCI injuries (Dirks *et al.*, 2016)

##### 4.1.1. Protein synthesis in skeletal muscle

Regulation of protein synthesis is closely related to nutrient availability, mechanotransduction, intracellular, stress, and several other factors. One of the main mechanisms of protein synthesis in skeletal muscle is the mechanistic (or mammalian) target of rapamycin (mTOR). mTOR is a serine/threonine kinase that is a key mediator of many anabolic signals in skeletal muscle. There are two main mTOR complexes, each defined by its main regulatory protein: mTORC1 contains raptors (rapamycin sensitive) whereas



mTORC2 contains ritors (insensitive to rapamycin). In mouse animal trials, the best described role for mTORC1 is regulating protein synthesis in skeletal muscle, phosphorylation to increase capacity (ribosome biogenesis) and efficiency (initiation, elongation, and termination) of mRNA translation. Growth signaling factors such as IGF-1 activate mTORC1 via a PI3K/PDK1/Akt-mediated process. Activated Akt will then phosphorylate and absorb transcription factors from muscle atrophy such as FOXO1 and 3a in the cytosol and then inactivate GSK3b. The branched-chain amino acid leucine, also activates mTORC1, stimulating protein synthesis events. PI3K activation through insulin receptor binding also initiates signaling through Akt which leads to GLUT4 translocation or can be called the main mode of glucose uptake in skeletal muscle. Calorie intake and proper nutrition will also affect the response of mTORC1/C2 activation and protein synthesis in skeletal muscle (Graham *et al.*, 2021)

#### **4.1.2. Protein degradation in skeletal muscle**

Proteolysis via the proteasome is the main way muscles carry out the process of protein catabolism. The process of protein degradation is multistep. E1 enzyme first activates ubiquitin, then E2 (conjugation) transfers the enzyme and the chaperone activates ubiquitin. and finally E3 (ligase) transfers activated ubiquitin to the targeted substrate. The chain of polyubiquitinated lysine residues is a key requirement for proteins to be degraded by the proteasome. Ligase enzymes are most commonly associated with muscle wasting, one of which is muscle ting finger1 (MuRF1) and atrogin-1. Atrophic



events can activate different pathways that result in upregulation of MuRF1 and atrogen-1 such as prolonged immobilization, inflammatory events, glucocorticoids, oxidative stress and caloric deficit. Exercise appears to reduce the expression of the genes encoding both atrogen-1 and MuRF1. Another major degradation system present in muscle fibers is the autophagic system. Autophagy is associated with nutritional stress events, it works through a combined regulatory system involving AMPK and mTOR, especially mTORC1. This system is a recycling system that can use autophagosome formation to take up useless (dysfunctional) organelles and proteins to cause degradation that occurs in the Lysosomes (Graham *et al.*, 2021).

#### **4.2 Gene expression Muscle Wasting**

Gene expression mediators of protein degradation pathway events such as TRIM63, FBX032 and CAPN1 (Murf1/Atrogen-1 and Calpain 1) are usually elevated in debilitated/critical patients. It is known that insulin-like growth factor-1 (IGF-1) through the PI3K/Akt/mTOR and PI3K/Akt/GSK3 pathways will increase protein synthesis in skeletal muscle and is also able to inhibit FoxOs and suppress transcription of the ubiquitin E3 ligase which regulates the ubiquitin proteasome system (UPS). in the process of protein degradation. IGF-1 via mTOR and FoxO signaling is likely to inhibit autophagy, which contributes to autophagy regulation to inhibit the occurrence of muscle atrophy. In another signaling pathway, IGF-1 is also able to inhibit the triggering of muscle atrophy events by inhibiting cytokine and myostatin signaling that are involved in inflammatory pathways such as NF-B and Smad. IGF-1 has the potential to



regenerate skeletal muscle through skeletal muscle stem (satellite) activity which can cause muscle hypertrophy and inhibit muscle atrophy.

High-intensity exercise is generally considered the protocol of choice for combating age-related muscle decline when compared to low- and moderate-intensity exercise. PGC-1 is a key mediator of the beneficial effects of endurance exercise and is a molecular target that may be a promising candidate for alleviation of metabolic inefficiency. Protection against mitochondrial disorders (apoptosis, oxidative damage, etc.) may be due to increased production of PGC-1. Increased PGC-1 expression in muscle improves metabolic fitness and prevents sarcopenia in aging mice (Rubio-Ruiz *et al.*, 2019).

#### **4.3 Insulin-like growth factor-1 (IGF-1)**

Insulin-like growth factor-1 (IGF-1) is a key growth factor that regulates both anabolic and catabolic pathways in skeletal muscle. IGF-1 increases skeletal muscle protein synthesis via the PI3K/Akt/mTOR and PI3K/Akt/GSK3 pathways. PI3K/Akt can also inhibit FoxOs and suppress transcription of the ubiquitin ligase E3 which regulates the protein degradation-mediated ubiquitin proteasome (UPS) system. Autophagy is likely inhibited by IGF-1 via mTOR and FoxO signaling, although the contribution of autophagy regulation in IGF-1-mediated inhibition of skeletal muscle atrophy remains to be determined. Evidence suggests that IGF-1/Akt can inhibit muscle atrophy triggers cytokine and myostatin signaling through inhibition of the NF- $\kappa$ B and Smad pathways. IGF-1 also potentiates skeletal muscle regeneration through skeletal muscle stem (satellite) activation, which can lead to muscle hypertrophy and/or inhibit atrophy (Yoshida and Delafontaine, 2020).



IGF-1 is mostly secreted in the liver, IGF-1 also circulates relatively stable and has significantly greater concentrations in young adults than in older individuals. There was a significant but transient increase in IGF-1 expression during exercise induction. In muscle, IGF-1 is stimulated by mechanical load and contraction whereby the IGF receptor (IGFR) is activated in the cell to allow membrane binding protein signaling pathways to be activated (Barclay *et al.*, 2019). Insulin significantly stimulates muscle protein synthesis in the case of MetS, one of which is sarcopenia, there will be a decrease in muscle protein synthesis as part of the response to a decrease in insulin which is known as anabolic resistance (Rubio-Ruiz *et al.*, 2019). IGF-1 is also a biomarker of health and fitness; in fact, higher circulating IGF-1 concentrations are positively related to health factors associated with body structure and cardiovascular strength, and negatively related to body fat levels. Aerobic fitness and muscular stamina are positively associated with circulating IGF-1 concentration (Ahmad *et al.*, 2020)

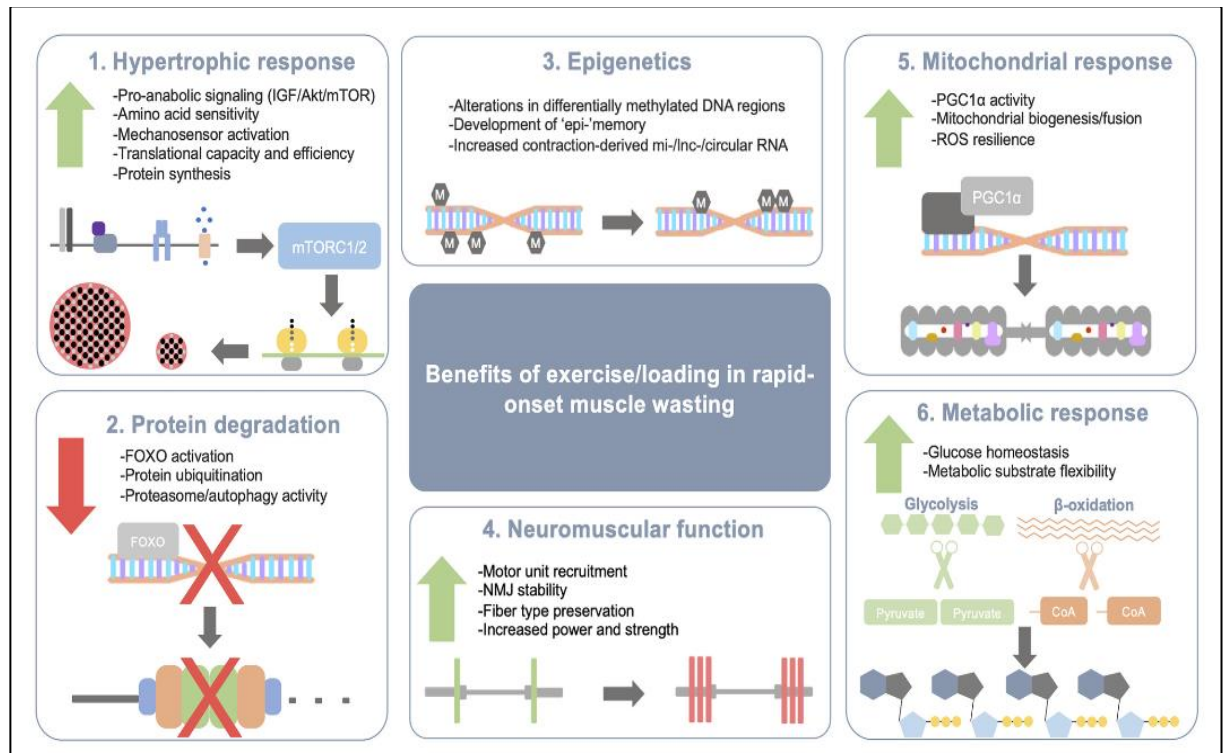
#### **4.4 Exercise therapy mechanism in muscle wasting**

Exercise Therapy is known as one of the modalities of choice for a physiotherapist in providing physiotherapy management to patients with muscle weakness/muscle atrophy disorders. (Graham *et al.*, 2021).

Exercise plays a role in the process of regulating muscle mass which involves complex biochemistry, any imbalance strongly opposes the process of protein homeostasis. exercise therapy in various modes and recipes is a strong stimulus that can reduce the incidence of muscle atrophy, it is also known that exercise can change the molecular profile which is considered the key to changes in gene expression. Exercise acts on signaling pathways involved in the maintenance of muscle mass. such as the IGF-1/Akt/mTOR axis which



is active in the catabolic pathway so as to weaken muscle atrophy (Scicchitano *et al.*, 2018).



Gambar 1. Benefits of exercise on muscle wasting disorders

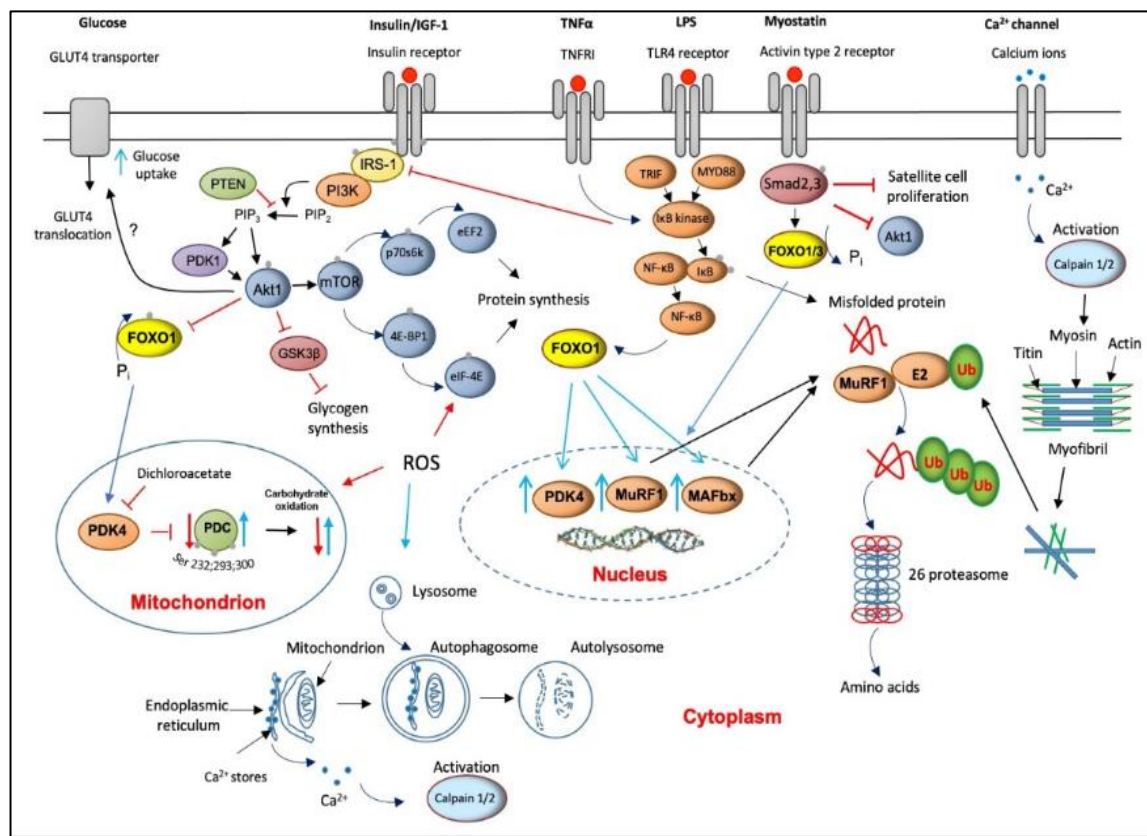
Sumber : Graham *et al.*, 2021

Muscle mass is needed to balance the levels of protein synthesis and protein degradation. Muscle protein synthesis is important for increasing muscle fiber size and performance whereas protein degradation in muscle will result in reduced muscle size and performance, excess protein breakdown during muscle wasting can occur rapidly even in healthy individuals. Bed rest or immobilization results in a rapid loss of 3%-5% muscle mass in the first week and this loss may be exacerbated when sustained after a severe injury from burns or following SCI. Exercise is an important anabolic stimulus and



a need to get muscle protein under normal conditions, through direct activation of the mTOR pathway (Van Gassel *et al.*, 2020).

Early mobilization Fifty patients with a SOFA score of 9 within 72 hours after admission to the ICU were randomized for action. Exercise therapy that focuses on skeletal muscle training will be able to improve metabolic function, coordination, inflammatory response and protect muscle mass (Wollersheim *et al.*, 2019). The liver as the site of IGF-1 expression has an important secretory role in the exercise response which will have an effect on skeletal muscle. In acute conditions, exercise therapy can be an option and the main modality for overcoming muscle atrophy, which with proper exercise volume regulation will affect the metabolic origin of muscle wasting.



Gambar 2. Schematic of the main molecular mechanisms underlying muscle wasting

Sumber : Constantin-Teodosiu, D Constantin, 2021

There is a process of adaptation to exercise with muscle wasting conditions, will make exercise therapy very personal, exercise recipes to optimize recovery. Exercise therapy is widely proposed as an intervention strategy in the treatment of MetS, because it can increase anti-inflammatory cytokines (such as IL-10, IL1 and TNF $\alpha$  receptors), exercise will have a negative impact on the process of tumor mass growth and will significantly increase muscle metabolism. Aerobic exercise, resistance and combination training have been shown to be beneficial for muscles experiencing muscle



wasting (Renzini *et al.*, 2021). Recent literature highlights that the combination of exercise with increased protein intake may represent a strategy against muscle wasting. Supported by research that has been documented by Schicchitono and friends, protein supplementation combined with aerobic and resistance training can increase muscle mass, strength, and physical performance in elderly participants.

The main goals of treatment for the metabolic syndrome are: normalization of body weight, increased physical activity, antihypertensive therapy, decreased drug use, lipid lowering and disaggregation therapy. The therapeutic effect of exercise therapy on the body is exerted by the neural and humoral regulation of motor-visceral reflexes. Each muscle contraction irritates the many nerve endings within it and the flow of impulses provides information to the musculoskeletal system, being sent to the central nervous system. Changing the functional state through the vegetative center will regulate and restructure the activities of internal organs. At the same time, the humoral system will produce metabolic products that appear in the muscles enter the bloodstream and act on the nervous system (directly in the center and through the chemoreceptors) and endocrine glands, causing the release of hormones. Thus, information about muscle work along the nervous and humoral pathways enters the central nervous system (CNS), is integrated, and then this system regulates the function and trophism of internal organs and endocrine glands affecting every activity in the metabolic system processes that occur (Kalmykova *et al.*, 2021).

Based on an intervention study with an objective measure of physical exercise that was tested for differences with those who did not perform on the severity of NAFLD, it showed a recommendation of at



least 30 minutes of moderate physical activity every day of the week, or vigorous intensity at least 3 times per week for > 20 minutes at a time (Montesi *et al.*, 2013). In human clinical trials showing many beneficial effects of exercise, to obtain health benefits, a combination of intensive aerobic exercise protocols of at least 75 minutes/week, or moderate exercise of at least 150 minutes/week, with resistance training of major muscle groups 2-3 days per week for people adults, has been recommended by the American College of Sports Medicine so that it will improve physical and psychosocial function including muscle wasting and fatigue and metabolic dysfunction.

## 5. Conclusion

A vicious cycle between muscle wasting and intramuscular fat accumulation may be associated with MetS through a complex interaction of factors including: nutritional intake, physical activity, body fat, oxidative stress, proinflammatory cytokines, insulin resistance, hormonal changes, and mitochondrial dysfunction. MetS-related muscle wasting contributes to the health impact. Although currently, no pharmacotherapy results are able to provide a direct effect on the incidence of muscle wasting, lifestyle changes including diet and exercise therapy, especially in increasing strength seem to be the best option.

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