



Review Article

A comprehensive review on current strategies and developments in treatment of skeletal muscle atrophy

Shubhada V Mangrulkar^{1,*}, Dinesh Chaple², Sukanya Korewar¹, Priyanka Mazumdar¹, Twinkle Charde¹

¹Dept. of Pharmacology, Priyadarshini J L College of Pharmacy Rashtasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India

²Dept. of Pharmaceutical Chemistry, Priyadarshini J L College of Pharmacy Rashtasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India



ARTICLE INFO

Article history:

Received 30-06-2020

Accepted 11-07-2020

Available online 25-07-2020

Keywords:

Skeletal muscle atrophy

Emerging treatment

Ultrasound therapy

Herbal drugs

Nutraceuticals

ABSTRACT

Background: Skeletal muscle atrophy is most remarkable example of multiple changes in physiological state and leads to morbidity. The predominance of skeletal muscle atrophy and the effect of this issue on the patient and family underscore the requirement for effective treatment strategies. Skeletal muscle has the capability of restoration after injury but can be evoked by various pathological conditions.

Main body: Treatments that can increase muscle mass and physical performance might be a promising alternative. The aim of review is to give comprehensive overview over the epidemiology of current potential treatment strategies of muscle atrophy. This review is focused on various treatments strategies like herbal treatment, synthetic drugs, physical therapy, focused ultrasound therapy, and emerging medication etc. which promotes skeletal muscle repair and functional regeneration.

Conclusion: The fact is that the reported drugs are not efficiently targeting every proteolytic system. There is the need for combinational treatment and developing a novel approach to treat skeletal muscle wasting.

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1. Introduction

Skeletal muscle is the most abundant tissue in human body, which has the ability of rejuvenation up to the certain threshold of injury. Muscle atrophy is one of the social problem detected. Muscle atrophy is the loss of muscle mass fiber and its strength which losses its capability of regeneration after muscle injuries like high energy traffic accidents, blast distress, combat injuries, surgical and orthopedic situations, etc.¹ Many pathological conditions like cachexia, diabetes, sepsis, starvation, metabolic acidosis, chronic kidney disease, immobilization, obesity etc. leads to muscle atrophy.² There is imbalance between catabolic and anabolic signaling pathways.³ The increased prevalence of muscle atrophy is observed over

the population due to age, metabolic disorders and changed lifestyle many peoples of rural and urban are in misery with muscle atrophy.⁴

Various pathological conations alters the anabolic and catabolic signaling pathways. In muscle, IGF-1 is stimulated by mechanical stacking and contraction to which IGF receptor (IGFR) is activated in the cell to allow for membrane bound protein signaling pathways to become active. IGF-1 is secreted from muscle fibers into the extracellular matrix (ECM) to which it is bound by IGF binding proteins (IGFBPs). 18135–18140. The half-life of IGF-1 is just 5–10 min, these pools of IGFBPs must be local to the ECM. Upon binding to IGFBPs, IGF-1 stimulates its receptor to which intracellular signaling processes driving MPS can occur.⁵ GF-1 enters the cell via IGFR, it triggers phosphoinositide 3-kinase (P13-K) to generate phosphatidylinositol -bisphosphate (PIP2), leading to the production of phosphatidylinositol 3, 4, 5-trisphosphate

* Corresponding author.

E-mail address: shubhadamangrulkar@gmail.com (S. V. Mangrulkar).

(PIP3). PIP3 is then free to bind to phosphoinositide-dependent kinase-1 (PDK1) which binds to the pleckstrin homology (PH) domain of Akt, allowing for translocation to the cell membrane preceding phosphorylation at Akt.^{6,7}

Phosphatidylinositol -3, 4, 5 – triphosphate is one of the major signalling pathway which disturbs in protein synthesis and degradation which provides membrane-binding site for serine/threonine kinase. On activation, Akt phosphorylates an array of protein and alters protein synthesis. In order to induce muscular atrophy, various diseases were used in the studies⁸ another signaling pathway that controls skeletal muscle growth involves myostatin, a member of the transforming growth factor β (TGF β) superfamily. Myostatin is produced by skeletal muscle and acts as a negative regulator of muscle growth, as shown by the finding that myostatin mutations in various mammalian species cause muscle hypertrophy.⁹ Muscle hypertrophy may also be prompted by inhibitory extracellular binding proteins, such as follistatin, whose effect is even greater than the lack of myostatin, because it binds to other TGF β superfamily members, such as activin A, that act as negative regulators of muscle growth like myostatin does. Myostatin and activin A intermingle and activate a heterodimeric receptor complex with serine–threonine kinase activity, comprising a type II receptor, activin receptor 2 (ACVR2 and ACVR2B), and a type I receptor, activin receptor-like kinase 4 and 5 (ALK4 and ALK5). A soluble form of ACVR2B acts as a myostatin/activinA inhibitor that is accomplished.

2. Current treatment strategies for muscle atrophy

Muscle atrophy which is characterized by a deteriorated quantity and quality of muscle which results in gradual slowing of movement and a decline in strength and power. Number of approaches has been tried and proved to have promising beneficial effect in treatment of muscle atrophy; Figure 1 compiles various triggering factors resulting in muscle atrophy and treatment strategies.

3. Herbal treatment and Nutraceuticals

Herbals have the potential to improve the blood circulation along with repairing of damaged tissue. It is observed that many botanicals have the effect on skeletal muscle atrophy which helps in reduction of muscle atrophy. Cichoriumintybus(Cii) commonly known as blue daisy extract reduced H₂O₂-induced viability loss in C₂C₁₂ myoblasts, inhibited oxidative stress-induced apoptosis and increased intracellular heat shock protein 70 (Hsp 70) expression. Cii also inhibited the level of intracellular ceramide. These results indicate that Cii may prevent skeletal muscle atrophy by inducing the expression of Hsp 70 and inhibiting the level of ceramide.¹⁰ Inflammation and oxidative stress induce muscle damage and muscle pain and

several botanicals.¹¹

Citrus aurantium, Coffea Arabica, Zingiberofficinale, Eugenia punicifolia, Panax ginseng, Go-sha-jinki-Gan, Vitisvinifera, and Curcuma longa L. have a significant role in the prevention of this phenomenon. Coffea decreases the levels of interleukins IL-1 α and IL-6 and TNF- α , which are correlated with muscle weight and grip strength. Using mice cells in vitro, coffee increases the number of proliferating cells and augmented DNA synthesis through the Akt signaling pathway. There is a combination of augmented satellite cell activation and decreased inflammatory levels by coffee treatment; it has anti-inflammatory effects both because it has antioxidant properties and because it has compounds, such as kahweol, with immunomodulatory properties.¹²

The anti-inflammatory effect of flavonoids isolated from Citrus aurantium, Coffeearabica, and Zingiberofficinale on interleukins such as IL-1 α and IL-6 and TNF- α on skeletal muscle cells.

Specifically, the flavonoids (hesperidin, nobiletin, and naringin of Citrus aurantium, also known as sour orange) inhibit the inflammatory response in lipopolysaccharide-(LPS-) induced L6 skeletal muscle cells. In addition, the flavonoids isolated from Korean Citrus aurantiumL.inhibit significantly inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-6, and TNF- α by blocking the nuclear factor-kappa B (NF- κ b) and by blocking mitogen-activated protein kinases (MAPKs) signal pathways. Another study in the same muscle cells demonstrates the anti-inflammatory role of flavonoids isolated from Citrus aurantium through the modulation in protein related to the immune response. Furthermore, the pretreatment with flavonoids resulted in a decreased level of cleaved caspase-3, which is induced by muscle inflammation and is involved in muscle proteolysis and atrophy.¹³ Also, Zingiberofficinale, commonly known as ginger, showed interesting anti-inflammatory and analgesic effects in humans who ingested 2 grams of ginger or placebo after exercise; however, this extract has no remarkable effect after single administration. A moderate reduction in the progression of muscle pain from 24 h to 48 h following eccentric exercise was observed in participants who consumed ginger 24 h after exercise, and this effect was not enhanced by heat-treated ginger.¹⁴

Go-sha-jinki-Gan (GJG) maintains the area of muscle fibers in the soleus via normalizing signal transduction through the insulin-growth factor (IGF-1) Akt axis, the suppression of inflammation, and the maintenance of mitochondrial-related transcription factors.¹⁵

A positive effect on cell atrophy caused by TNF- α was shown with resveratrol (in Vitisvinifera) supplementation in a muscle cell line (regulating the Akt/mTOR/FoxO1 signaling pathways together with inhibition of the atrophy-related ubiquitin ligase).¹⁶ Curcuma longa can prevent

muscle atrophy. It stimulates glucose-regulated protein 94 kDa (Grp94) expression in myogenic cells, whose levels decrease significantly in unloaded muscle, and it is involved in attenuation of myofiber atrophy in rats.¹⁷ Curcumin, a constituent of turmeric (*Curcuma longa* L.), exerts its beneficial effect on muscle, curcumin acts by mechanism by suppressing the activation of NF- κ B, an effect of critical relevance in DOMS relief, since NF- κ B appears to be involved in the regulation of proteolysis and inflammation in muscle. Therefore, inhibition of NF- κ B by curcumin may result in a muscle-protective effect. Consistently, it has been suggested that curcumin may prevent loss of muscle mass during sepsis and endotoxaemia and may stimulate muscle regeneration after traumatic injury. Other mechanisms potentially responsible for the anti-inflammatory and antioxidant properties of curcumin include induction of heat-shock response,¹⁸ reduction in the expression of the pro-inflammatory enzyme cyclooxygenase-2 (COX-2), and promotion of the antioxidant response by activation of the transcription factor Nrf2. More recent studies confirm that curcumin can reduce inflammation and decrease some of the negative effects associated with eccentric exercise-induced muscle damage, including the release of pro-inflammatory cytokines and markers of muscle injury like creatine kinase (CK).¹⁹ It stimulates glucose-regulated protein 94 kDa (Grp94) expression in myogenic cells, whose levels decrease significantly in unloaded muscle, and it is involved in attenuation of myofiber atrophy.^{17,20} Nutraceutical compounds by *C. sinensis* in mice decrease myostatin and β -galactosidase and increase levels of markers of muscle; instead, in humans, they (epicatechin) increase hand grip strength and the ratio of plasma follistatin/myostatin.²⁰ and regulate NF- κ B activity in regenerating muscle fibers.²¹ Camellia also induces changes in satellite cell number and it improves muscle recovery following a period of atrophy in old rats and decreases oxidative stress, but this is insufficient to improve muscle recovery following a period of atrophy.²²

GRb1 improves the maintenance of normal pH range in muscle tissue by reducing the accumulation of lactic acid (LA) and attenuates LA induced side effects of various biochemical and physiological processes, which impair bodily performance.²³ In skeletal muscles, it checks muscle wasting by down-regulating the TNF mRNA expression without showing any significant effects on insulin-like growth factor-1 (IGF-1) mRNA in gastrocnemius muscle in a burn injury. Ghrelin precursor peptide (des-acyl ghrelin, DAG) also has regulatory effect on TNF and IFN-induced skeletal muscle atrophy. This study shows that DAG attenuates the cytokine induced reduction in phosphorylation of Akt, FoxO1 and glycogen synthase kinase-3 beta (GSK3) in C₂C₁₂ myotubes. This, DAG also inhibits the activation of NFB and down-regulates atrogen1/MuRF1 mRNA.²⁴

Fish oil (abundant in 3 PUFAs such as EPA and docosahexaenoic acid) is also very effective in regulating muscle pathophysiology. Studies have shown that dietary supplementation of fish oil prevents the LPS-induced inhibition of Akt signaling by decreasing forkhead box O1 (FoxO1) and FoxO4 abundance along with decreasing mRNA expression of muscle-specific E3 ubiquitin ligases i.e. muscle-specific F-box protein (MAFbx; atrogen1) and MuRF1, markers of the Ub-proteasome system in gastrocnemius and latissimus dorsi muscles. This treatment reduced the TNF and cyclooxygenase2 (Cox2) mRNA abundance in myofibers via regulation of muscle toll-like receptor (TLR) and nucleotide-binding oligomerization domain protein (NOD) signaling pathways, leading to improved skeletal muscle mass.²⁵ A large number of studies performed in vitro and in vivo have confirmed that resveratrol treatment can prevent protein degradation induced by PIF, Angiotensin I and II, phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), dexamethasone. In addition, resveratrol has observed its protective effect on muscle wasting under diverse catabolic conditions including cachexia and disuse.²⁶ Eicosapentaenoic acid (EPA) is a naturally occurring long-chain polyunsaturated fatty acid (PUFA) of omega-3 (-3) family mainly found in deep-sea fish and certain algae. EPA exhibits diverse pharmacological actions including anti-genotoxic, anti-oxidant and chemopreventive effects. Numerous studies showed that in cancer patients there is a progressive muscle wasting (75% decrease in skeletal muscle protein mass) which makes it a key reason for the cause of cachexia. This is due to up-regulation in the level of various pro-inflammatory cytokines and their mediated activation of skeletal muscle specific proteolytic system. One of those systems is the NFB-dependent ubiquitin-proteasome pathway which is responsible for degradation of myofibrillar proteins and thus skeletal muscle wasting.²⁷

4. Synthetic Agents

Cox2 inhibitor: cyclooxygenase exists in multiple isoforms i.e. Cox1, Cox2 and Cox3. Of all these isoforms, Cox2 has pro-inflammatory actions and is induced by cytokines and mitogens not only in immune cells but also in other tissues including skeletal muscles. Cox2, a bifunctional enzyme, has both cyclooxygenase and peroxidase activities. The cyclooxygenase activity is responsible for the synthesis of prostaglandins (PGE2) from arachidonic acid while peroxidase activity can generate proximate carcinogens. These prostaglandins perform various actions via specific G-protein coupled receptors and nuclear peroxisome proliferator-activated receptors (PPARs). Cox2 and PGE2 both are the downstream effectors of cytokine activity and mediate cachexia.²⁸

Preclinical and clinical trials strongly support the potential role for Cox2 inhibitors in the treatment of

cancer.²⁹ Celecoxib showed its anti-cachectic role in diverse pathophysiological conditions. Rheumatoid arthritis cachectic rabbits when treated with celecoxib showed reduction in the weight loss as well as in the level of inflammatory molecules (such as IL-6 and NFB).³⁰ Meloxicam is another Cox2 inhibitor that inhibits the growth of murine adeno-carcinoma tumors (MAC 13, MAC16). Studies have shown that meloxicam treatment inhibits the LPS induced expression of Cox2, atrogin1 and MuRF1 and regulates the loss in muscle mass of rats by attenuating protein catabolism.³¹

5. Exercise

Exercise induces a hormetic response in humans. That is, an appropriate dose of exercise over time leads to beneficial cellular adaptations to withstand the stress of exercise. This process of adaptation is at the essence of evolutionary biology. At extreme or high dosages, exercise can be toxic. When appropriate dosages of exercise are applied to an organism, the hormetic response plays a role in the prevention of pathological conditions. Exercise has been suggested to increase mitochondrial volume by up to 40%.³² This is due to factors of mitochondrial biogenesis being increased with exercise, signaling the increase in mitochondrial proteins to be synthesized in aging skeletal muscle, a rapid decline in muscle mass and muscle performance parameters are observed as are decreases in mitochondrial volume and biogenesis. Moderate exercise reverses or attenuates the decline in mitochondrial biogenesis markers and reduce the age-associated reduction in skeletal muscle mass.³³

Exercise induces mitochondrial biogenesis and efficient mitophagy, increases the ability to create ATP and neutralize ROS, reduces cell apoptosis, increases growth and protein synthesis signaling, and decreases protein degradation pathways. These effects reveal the role exercise plays in skeletal muscle atrophy prevention and its potential use as a treatment prior to atrophic situations, such as prescribing exercise pre-surgery to a patient that will be on bedrest or immobilized post-surgery. TFAM protects mtDNA from degradation via ROS and initiates mitochondrial protein transcription while improving mitochondrial function. This reveals the role TFAM plays in preventing mitochondrial dysfunction and highlights the connection this dysfunction has with skeletal muscle atrophy. This knowledge can lead to targeting of the mitochondria as a method of treating the negative effects associated with skeletal muscle disuse. Further, combination of exercise training with the overexpression of TFAM will synergistically enhance mitochondrial function and prevent skeletal muscle atrophy.³⁴

6. Focused ultrasound therapy

Therapeutic ultrasound is the technique of using sound waves to try and relieve pain or disability. It is done by using a round-headed wand or probe on the skin of the painful area. Ultrasound gel is used on the wand and on your skin to make it more comfortable and help the sound waves reach the affected area.³⁵ Therapeutic ultrasound produces both thermal and non-thermal effects. The thermal effect has the similar effects like general thermal therapy which shows pain relief and also accelerates the tissue repair.³⁶

Therapeutic ultrasound applied with temperature of tissue greater than 3° to 4°. The frequency for US is MHz, beam uniformity ratio should be 5.0 for effective radiating area should be of 0.7 cm² and modulating frequency should be of Hz 15%. Aqueous gel used in US serves as coupling media. The area was exposed up to 15 minutes with sound waves. Ultrasound with continuous mode is a method for the application of deep heat to connective tissue.³⁷

Low-intensity pulsed ultrasound (LIPUS) is a common treatment for skeletal muscle injury and is effective in accelerating the rate of muscle growth. In muscle tissues, LIPUS can stimulate the proliferation of myogenic precursor cells and myogenic cells in muscle treated with ultrasound, an aligned and more regular disposition of collagen fibers and myotubes is observed, enabling increased functionality. LIPUS can increase the differentiation of muscular lineage cells and favor tissue regeneration.³⁸

LIPUS therapy can lead to significant improvements in T1DM-induced muscle atrophy and later improve the ability of skeletal muscle to utilize glucose to stabilize blood glucose concentration.

These effects' mechanisms may be associated with the MSTN/Akt/mTOR and Foxo1 pathway in the skeletal muscle.³⁹

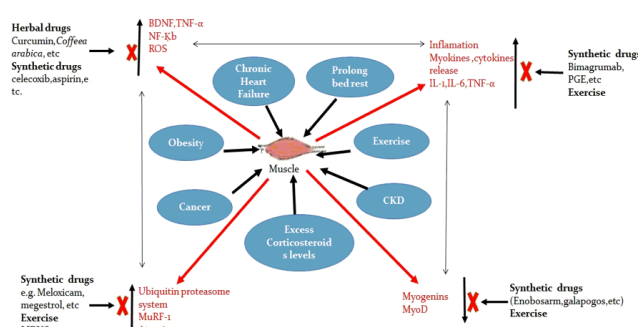


Fig. 1: Potential treatment strategies for skeletal muscle atrophy with various triggering factors.

7. Emerging Treatment Strategies

Enobosarm (also called ostarine, GTx-024) is non-steroidal, orally bio-available and a selective androgen receptor

modulator (SARM). It has shown a dose-dependent improvement in total lean body mass and physical function in healthy elderly men and postmenopausal women.⁴⁰ Enobosarm is also useful in the prevention of muscle wasting associated with cancer cachexia. Data from Phase II clinical trial where cancer patients were administered with ostarine showed improvement in muscle performance (measured by stair climb) and insulin resistance without any visible side effect and toxicity. Hence enobosarm possesses a strong efficacy and safety in cancer cachexia conditions to regulate muscle loss.⁴¹

GLPG0492 (galapagos) is another non-steroidal SARM that has shown its efficacy on muscle by increasing muscle fiber size and skeletal muscle function in the hindlimb of immobilized and in duchenne muscular dystrophy (DMD) patients respectively. This drug is in preclinical trial to treat DMD.^{42,43} OHR/AVR118 is a broad-spectrum peptide-nucleic acid immune-modulator with anti-inflammatory activity that targets both cellular pro-inflammatory chemokine and cytokine synthesis (such as TNF and IL-6). A Phase II trial of this drug on patients with advanced cancer and cachexia achieved stabilization of body weight, body fat and muscle mass with a significant increase in appetite without showing any adverse effect.⁴⁴ Bimagrumab (BYM338) and REGN1033 are two human monoclonal antibodies against myostatin. The treatment with BYM338 enhances differentiation of primary human skeletal myoblasts and increases skeletal muscle mass in mice by blocking the activin type II B receptors (ActRIIB). However REGN1033 administration prevents loss of muscle mass in dexamethasone or immobilization within 2 weeks. This soluble receptor is also very effective in preventing cardiac muscle atrophy in tumor-bearing patients.⁴⁵ Megestrol acetate this significantly improves appetite and the lean body mass. This drug is being used either alone or as a supplement along with meloxicam for cachectic cancer patients where it has shown positive effects in regulating the loss of body mass.⁴⁶ The studies have shown that in MA-treated rats, the food and water intake significantly increased when compared to untreated group. The levels of NY in the lateral hypothalamic area increased indicating that NY may be responsible for this orexigenic (appetite-stimulating) effect. Another study has shown that administration of MA in tumor (Yoshida AH-130 asciteshepatoma)-bearing rats results in reversal of muscle wasting process by decreasing the mRNA level of ubiquitin, E2 and atrogin1 which are the key biomarkers of Ub-proteasome proteolytic system.⁴⁷

8. Conclusion

Up-regulation of skeletal muscle protein breakdown is the hallmark of atrophy and as a result, all potential drugs target the proteolytic systems to cure or prevent the skeletal muscle atrophy. All the drugs have displayed positive effects

in diverse atrophic models either by inhibiting particular molecules/cytokines/proteolytic systems involved in the protein catabolic pathway or by improving the satellite cell function during muscle injury and aging. The fact is that the reported drugs are not efficiently targeting every proteolytic system. It can be safely inferred that skeletal muscle atrophy being a multi-factorial syndrome, needs a multi-targeted approach to yield success. There are reports in the literature regarding the use of some non-pharmacological therapies (such as nutritional supplement and rehabilitation) to delay the onset of disease and ease its symptoms at least up to some extent and improve the quality of life. Thus there is the need for combinational treatment and developing a novel approach to treat skeletal muscle wasting.

9. Abbreviations

IGF-1-Insulin -like growth factor-1, IGFR-IGF receptor, ECM-Extracellular matrix, IGFbPs-IGF binding proteins, MPS-Muscle protein synthesis, GF-1-Growth factor - 1, P13-K-Phosphoinositide 3-kinase, PIP2-Phosphatidylinositol -bisphosphate, PIP3-Phosphatidylinositol 3, 4, 5-trisphosphate, PDK1-Phosphoinositide-dependent kinase-1, PH-Pleckstrin homology, Akt-Serine threonine kinase, HS-Hindlimb suspension, CKD-Chronic kidney disease, COPD-Chronic obstructive pulmonary disease, CIA-Collagen-induced arthritis, TGF β -Transforming growth factor β , ACVR2-Activin receptor 2, ACVR2B-Activin receptor 2 B, mTOR-Mammalian target of rapamycin, Fzd7-Frizzled 7, nNOS-Neuronal nitric oxide synthase, MAFbx-Muscle atrophy F-box, MuRF1-Muscle RING finger 1, US-Ultrasound, LIPUS-Low-intensity pulsed ultrasound, Cii-Cichoriumintybus, Hsp 70-Heat shock protein 70, COX-2-Cyclooxygenase-2, MAPKs-Mitogen-activated protein kinases, NF- κ B-Nuclear factor-kappa B, GJG-Go-sha-jinki-Gan, Grp94-Glucose-regulated protein 94 kDa, Ck-Creatine kinase, DAG-des-acyl ghrelin, GSK3-Glycogen synthase kinase-3 beta, TLR-Toll-like receptor, FoxO1-Forkhead box O1, NOD-Nucleotide-binding oligomerization domain protein, EPA-Eicosapentaenoic acid, PGE 2-Prostaglandins, MAC-Murine adenocarcinoma tumors, DMD-Duchenne muscular dystrophy, BYM338-Bimagrumab.

10. Source of Funding

None.

11. Conflict of Interest

None.

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Author biography

Shubhada V Mangrulkar Assistant Professor

Dinesh Chaple Principal

Sukanya Korewar Research Scholar

Priyanka Mazumdar Research Scholar

Twinkle Charde Research Scholar

Cite this article: Mangrulkar SV, Chaple D, Korewar S, Mazumdar P, Charde T. **A comprehensive review on current strategies and developments in treatment of skeletal muscle atrophy.** *IP Int J Comprehensive Adv Pharmacol* 2020;5(2):77-83.