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Sarcopenia Risk Associated with GLP-1 Receptor Agonist Therapy: Mechanisms, Clinical Implications, and Management Strategies

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La sarcopenia, caracterizada por la pérdida progresiva de masa y fuerza muscular esquelética, se ha convertido en una preocupación importante en el contexto del tratamiento de la obesidad y la diabetes, especialmente con el uso cada vez mayor de agonistas del receptor GLP-1. Si bien estos agentes ofrecen beneficios sustanciales en el control glucémico y la reducción de peso, la evidencia acumulada sugiere una posible relación entre la terapia con agonistas GLP-1 y la exacerbación de los procesos sarcopénicos. Este artículo examina críticamente los mecanismos subyacentes a través de los cuales los agonistas del receptor GLP-1 pueden contribuir a la pérdida muscular, incluyendo alteraciones en las vías de señalización anabólica y catabólica, la distribución de nutrientes y las adaptaciones metabólicas. Presentamos una revisión de los datos preclínicos y clínicos, destacando la interacción fisiológica entre la señalización del GLP-1 y el metabolismo muscular. Se analizan las implicaciones para las poblaciones de pacientes en riesgo, como los adultos mayores y las personas con trastornos metabólicos crónicos, junto con las estrategias para el seguimiento, la prevención y el tratamiento de la sarcopenia en pacientes que reciben agonistas del GLP-1. Uno de los objetivos era subrayar la importancia de equilibrar los objetivos terapéuticos en el tratamiento de la obesidad y la diabetes con la preservación de la salud del músculo esquelético, con el fin de informar la práctica clínica y orientar la investigación futura en este campo en evolución.

Resumen

Este artículo analiza el vínculo emergente entre el tratamiento con agonistas del receptor GLP-1 y el riesgo de sarcopenia, una condición caracterizada por la pérdida progresiva de masa y fuerza muscular. Aunque los agonistas GLP-1 ofrecen beneficios notables en el control glucémico y la reducción de peso en pacientes con obesidad y diabetes, la evidencia actual sugiere que podrían contribuir a procesos sarcopénicos al alterar vías anabólicas y catabólicas, así como la partición de nutrientes y la adaptación metabólica. Se revisan datos preclínicos y clínicos que exploran el impacto de la señalización GLP-1 sobre el metabolismo muscular, especialmente en poblaciones vulnerables como adultos mayores y personas con enfermedades metabólicas crónicas. Finalmente, el artículo subraya la importancia de monitorizar la salud muscular en estos pacientes, proponiendo estrategias para prevenir y gestionar la sarcopenia paralelamente al tratamiento de la obesidad y la diabetes, y destaca la necesidad de futuras investigaciones para optimizar el equilibrio entre eficacia terapéutica y preservación de la masa muscular.

Palabras clave

Agonistas de receptores GLP-1, sarcopenia, pérdida muscular, tratamiento de la obesidad y la diabetes.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

This article analyses the emerging link between treatment with GLP-1 receptor agonists and the risk of sarcopenia, a condition characterised by progressive loss of muscle mass and strength. Although GLP-1 agonists offer notable benefits in glycaemic control and weight reduction in patients with obesity and diabetes, current evidence suggests that they may contribute to sarcopenic processes by altering anabolic and catabolic pathways, as well as nutrient partitioning and metabolic adaptation. Preclinical and clinical data exploring the impact of GLP-1 signalling on muscle metabolism, especially in vulnerable populations such as older adults and people with chronic metabolic diseases, are reviewed. Finally, the article highlights the importance of monitoring muscle health in these patients, proposing strategies to prevent and manage sarcopenia in parallel with the treatment of obesity and diabetes, and emphasises the need for further research to optimise the balance between therapeutic efficacy and muscle mass preservation.

Key words

GLP-1 receptor agonists, Sarcopenia, Muscle loss, Obesity and diabetes management..

Conflict of interests

This article does not present a conflict of interest.

1. Introduction

Sarcopenia is commonly characterized as a geriatric condition of progressive muscle mass loss and functional loss in daily activities. However, epidemiological data show trends in younger populations, such as those with liver disease, kidney dysfunction, and metabolic disorders (Yuan *et al.*, 2023). The pathophysiology of the disease stems from the disturbance between the anabolic and catabolic balance of protein-producing pathways in skeletal muscles. The number of type II fibers, fatty infiltration, decreased satellite cells, and changes in systemic factors lead to dysregulated growth factor activity and changes in myogenesis (Cho *et al*., 2022). As a result, oxidative stress, energy functions, inflammation, and denervation of muscle fibers lead to generalized loss of muscle mass, which promotes active stagnation in the individual.

Considering that sarcopenia may affect older people, recent data has shown changes in the prevalent pattern of those affected by the disease. Du *et al*., 2018 and other studies have revealed that over the years, the percentage of individuals between ages of 20 and 39 years old affected by sarcopenia has increased, which indicates the interference of other parameters in the epidemiological analysis of the cases (Jung *et al.* 2023). Endocrine metabolic disorders, physical inactivity, poor nutrition, genetic factors, and nutritional deficiencies are among the strongest topics of discussion and are leading the studies for a complete understanding of etiological behavior for contemporary diseases. In this case, the media and other information resources, with the promotion of new weight loss drugs and aesthetic standards, exert influence on public opinion, and the repercussions are roughly noticeable (Arillotta *et al*., 2023).

In the review discussed by Nishikawa *et al.*, 2021, the balance between muscle protein synthesis and biochemical degradation is well described for its crucial contribution to the pathophysiological mechanisms of sarcopenia. Protein synthesis is regulated by the IGF-1/PI3K/Akt/mTOR system, which decreases with age, resulting in lower protein synthesis and greater anabolic resistance. At the same time, there is an increase in protein degradation mediated by the ubiquitin-proteasome system, with greater expression of ubiquitin ligases specific to muscle atrophy. Besides, chronic inflammation in aging involves an increase in several pro-inflammatory cytokines, namely: tumor necrosis factor α (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6). They all impair mitochondrial function, can increase the production of reactive oxygen species (ROS), and activate proteolytic and apoptosis pathways, leading to muscle atrophy. Considering the mTOR pathway, it controls the number of components involved in the initiation and elongation stages of mRNA translation, since its intracellular signaling is involved in the stimulation of the cellular machinery (Wang and Proud, 2006). As described and detailed by Liu *et al.* (2020), signaling of this system occurs through the two distinct complexes mTORC1 and mTORC2 which perform distinct physiological effects in skeletal muscle, liver, and adipose tissue; therefore, they stimulate hypertrophy,

increase glucose and glycogen formation, lipogenesis, and adipogenesis. On the other hand, they can inhibit postprandial ketogenesis and gluconeogenesis. As metabolic syndromes such as obesity alter the body functioning, chronic hyperactivation by excess of nutrients can shut down PI3K–mTORC2 signaling regulated by insulin interaction, and trigger the process of insulin resistance, resulting in lipid accumulation in muscle and liver and type 2 diabetes. Finally, with insulin signaling suppressed, the catabolic and ketogenic processes are stimulated, thus leading to muscle mass loss and large generalized fat deposition in obese and older patients.

The GLP-1, glucagon-like peptide, is an incretin that displays physiological effects on the regulation of the metabolic axis of various pathways, such as bone, muscle, endocrine, and neurological, acting to control bone calcium deposition, increase muscle mass, lipolysis, glycolysis, and induce hunger (Tan *et al*., 2022). Hence, the Glucagon-like peptide-1 (GLP-1) agonists are drugs widely used clinically to control type II diabetes and for weighting loss, which may be considered a risk, however, according to reported adverse drug events (Ghusn and Hurtado, 2024). The first incretins as medicines, a class of molecules that include GLP-1 agonists, were initially isolated from both the canine intestine, where they were characterized as gastric inhibitor polypeptide and preglucagon mRNA. Thus, with further studies, GIP secretion has been shown to be stimulated by the ingestion of carbohydrates and fats by enteroendocrine K cells scattered in the duodenum and jejunum, while GLP-1, the second isolated incretin, is present postprandially and its secretion is stimulated by enteroendocrine L cells distributed

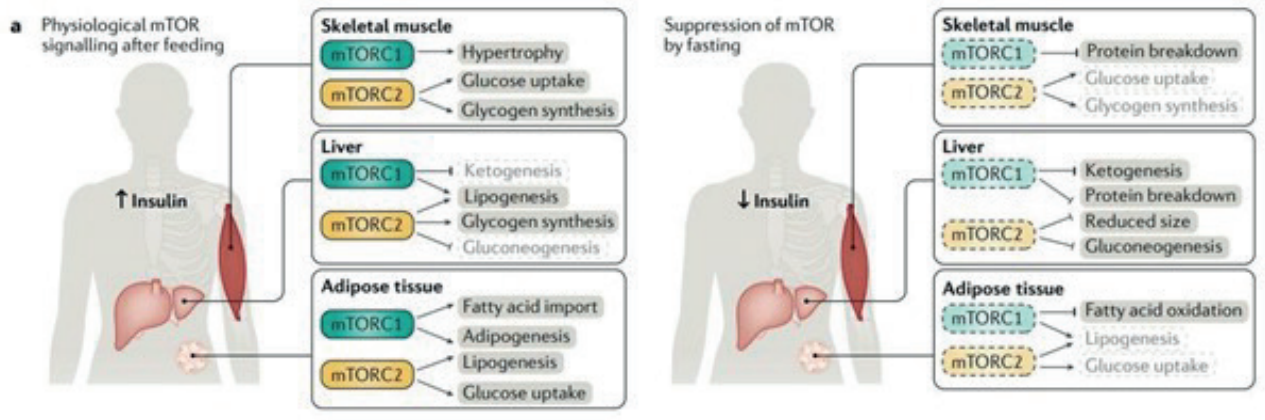

Figure 1. (Post-Feeding Signaling): After feeding, increased insulin activates the mTOR pathway. This activation promotes anabolism: in skeletal muscle, it stimulates hypertrophy and glycogen synthesis. In the liver, it stimulates lipogenesis and glycogen synthesis. In adipose tissue, it stimulates adipogenesis and the influx of fatty acids. (Fasting Suppression): During fasting, insulin decreases, resulting in suppression of the mTOR pathway. This suppression promotes catabolism. Thus, in muscle, protein breakdown is stimulated. In the liver, it stimulates ketogenesis and gluconeogenesis, while in adipose tissue, it stimulates fatty acid oxidation.

Extracted from: Liu, G.Y., Sabatini, D.M. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol 21, 183–203 (2020). https://doi.org/10.1038/s41580-019-0199-y

in the ileum and colon. Liu (2024) has published scientific findings on the GLP-1 agonists effects due to their binding to specific receptors, GIPRs and GLP-1Rs. Such molecules are widely distributed throughout the brain, pancreas, adipocytes, gastrointestinal tract, and liver; they are intended to regulate various physiological functions in an integrated manner. GIP regulates the increase in lipoprotein lipase (LPL) production, thereby increasing triglyceride (TG) clearance from the circulation and stimulating lipogenesis in adipocytes, in addition to increasing glucagon levels in cases of hypoglycemia and increasing insulin production in hyperglycemia. At the central nervous system (CNS), it increases satiety through hypothalamic neurons. Considering the GLP-1, it increases insulin levels, reduces glucagon, and increases somatostatin, thus regulating all types of pancreatic cells. In addition, it decreases vagal activity and increases sympathetic tone, which directly affects gastric emptying and impacts an increase in the time of this process. It is important to note that the metabolic and neurological effects are self-controlled, since at basal concentrations, GLP-1 is produced in parallel with other endocrine regulators such as insulin-like growth factor 1 (IGF-1) and growth hormone (GH), hormones that maintain some similar functions and actions.

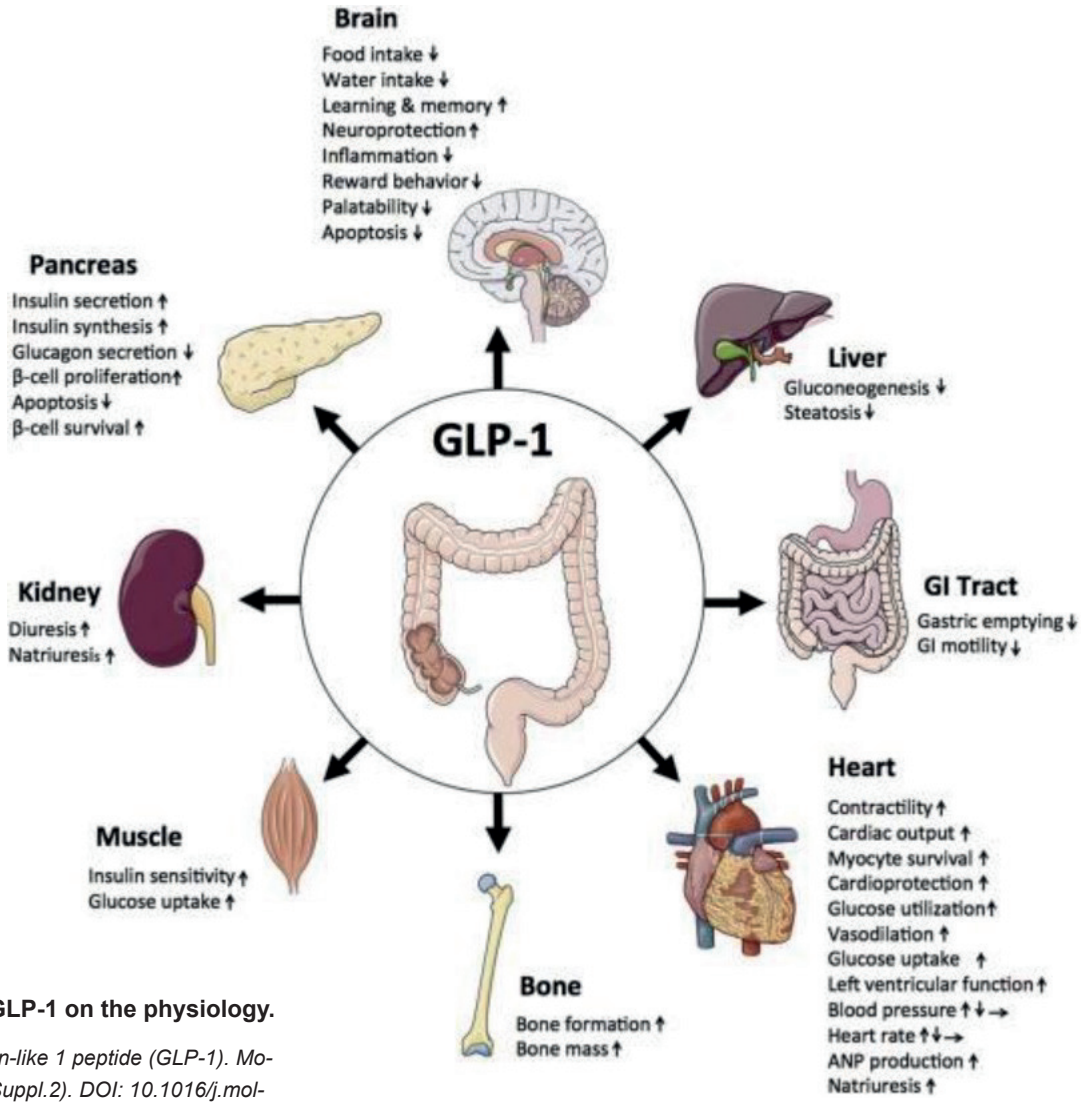

Figure 2. Impact of GLP-1 on the physiology.

Extracted from: Glucagon-like 1 peptide (GLP-1). Molecular Metabolism 30 (Suppl.2). DOI: 10.1016/j.molmet.2019.09.010

GLP-1 receptor agonists have demonstrated significant efficacy in inducing weight loss in obese individuals; however, the use of these drugs is associated with some adverse effects that demand clinical attention (Chow *et al*., 2025). The most common adverse events are gastrointestinal in nature, including nausea, diarrhea, constipation, and vomiting, with mild to moderate intensity. Serious adverse reactions are rare but include acute pancreatitis and gallbladder disorders, such as cholelithiasis and cholecystitis, which are observed more frequently at high doses and with prolonged use (Ghusn and Hurtado, 2024).

Given the role that these hormones play in maintaining vital physiological effects, misuse has become common, and reports of adverse psychological events have been noted (Arillotta *et al*., 2023). In 2023, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), reviewed data on the risk of suicidal thoughts and self-harm resulting from the use of GLP-1 agonists. The review, conducted by the Icelandic Medicines Agency was based on the monitoring of reported effects, around 150 possible cases in a population using liraglutide and semaglutide (EMA, 2023).

2. Discussion

Recent scientific studies have begun to shed light on the connection between GLP-1 receptor agonist therapy and the development or exacerbation of sarcopenia. While GLP-1 agonists are well-recognized for their efficacy in weight loss and glycemic control, emerging evidence indicates that their use -especially in populations with low baseline muscle mass or inadequate nutritional intake- may contribute to unintended lean muscle mass loss. Clinical reports and observational data have documented cases where significant weight reduction induced by GLP-1 agonists was accompanied by a disproportionate decrease in skeletal muscle compared to fat, raising concerns about the risk of sarcopenia, particularly in older adults or those with pre-existing risk factors. Furthermore, pharmacodynamic studies have demonstrated that the appetite-suppressing effects of GLP-1 agonists can lead to reduced protein and caloric intake, both of which are critical for the maintenance of muscle mass. The loss of muscle is not only a cosmetic or functional issue but also correlates with negative outcomes such as decreased mobility, higher fall risk, and increased frailty. While large-scale randomized controlled trials specifically assessing sarcopenia incidence in GLP-1 agonist users are still limited, current scientific data underscore the importance of monitoring muscle health and implementing preventive strategies -such as resistance exercise and adequate protein intake- when prescribing these agents, especially to at-risk populations.

For example, Linge *et al*. (2024) provided data that allow for the interpretation of this correlation, as they describe the total weight loss, but muscle mass ends up being lost as well. Perhaps it is due to the high caloric load that muscle tissue, liver, and other essential organs require to function, which with the large reduction in body mass, also

suffer a reduction in size and compromise the physiological functions that help maintain muscles.

Some pharmacologic treatments to maintain or improve muscle mass designed in combination or not with GLP-1-based therapies are under development, with some other pharmacological targets emerging. Perhaps they may offer new perspectives for the treatment and the reversal of the addressed sarcopenia. Myostatin, a member of the transforming growth factor β (TGF-β) family, is a potent inhibitor of muscle hypertrophy, whose increased expression is associated with sarcopenia and muscle atrophy (Wetzlich; Nyakundi; Yang, 2024). The binding of myostatin to the activin type II receptor triggers a cascade of cell signaling that reduces protein synthesis, contributing to muscle mass loss. The inhibition of myostatin, through specific antibodies or agents that block its receptors, has been shown to promote muscle mass and strength gain (Muramatsu *et al*., 2021).

Activin, another protein in the TGF-β family, is involved in inflammatory processes and muscle mass regulation, as it increases Akt levels and influences mTOR pathway regulation (Nunn *et al*., 2024). Activin A negatively regulates skeletal muscle mass by activating the type IIB activin receptor in skeletal muscle, promoting signaling pathways that cause muscle protein degradation (Lach-Trifilieff; Minetti; Sheppard *et al*., 2014). Anti-ActRII antibodies, type II activin receptors, are beneficial in promoting muscle hypertrophy in both naive mice and mice with myostatin gene deletion (Morvan *et al*., 2017).

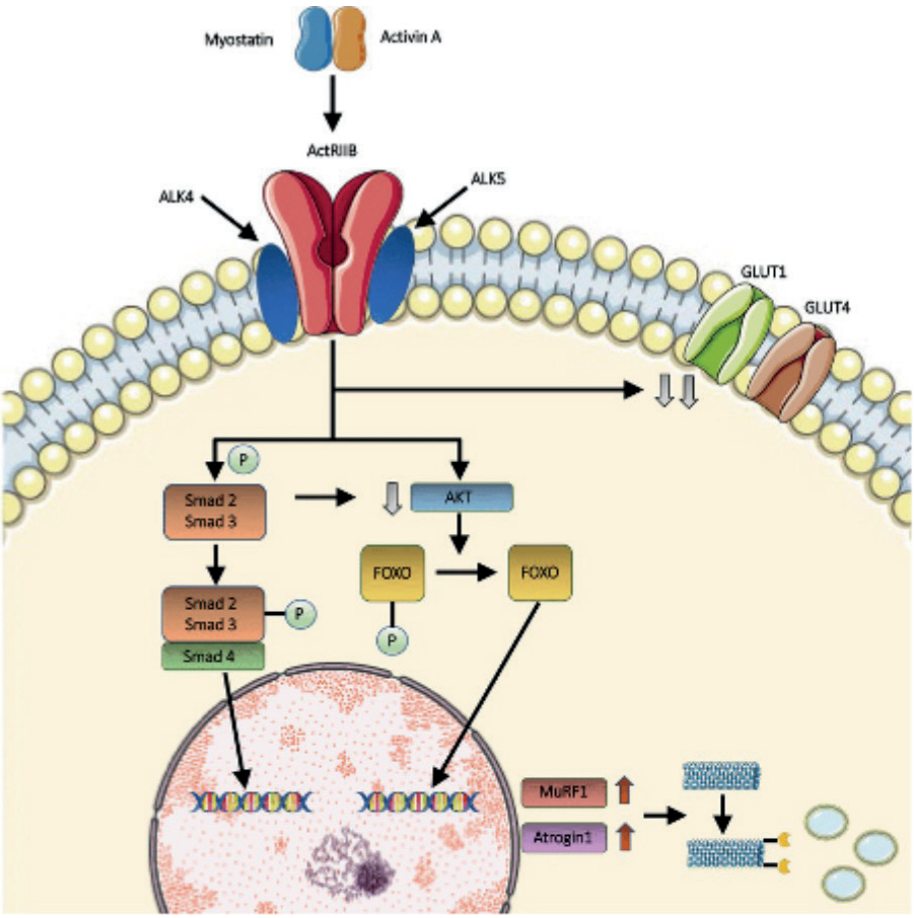

Figure 3. The binding of myostatin or activin to the ActRIIB receptor activates the Smad2/3/4 complex and inhibits the AKT pathway, preventing FOXO phosphorylation. The translocation of FOXO and the Smad complex to the nucleus promotes the transcription of atrophy genes that mark muscle proteins for degradation via the proteasome. Additionally, signaling reduces GLUT1 and GLUT4 levels, impairing glucose homeostasis.

Extracted from ABATI, E. et al. Inhibition of myostatin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases. Cellular and Molecular Life Sciences, [s. l.], v. 79, n. 7, art. 374, jun. 2022. DOI: https://doi.org/10.1007/s00018-022-04408-w.

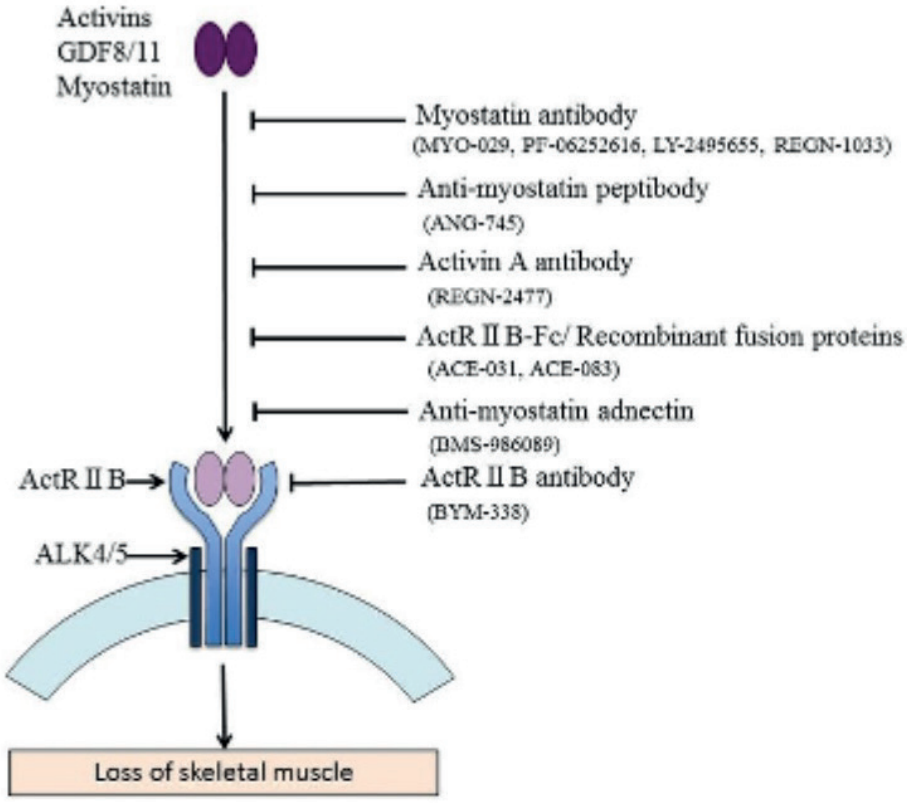

Figure 4. Signaling through the ActRIIB and ALK4/5 complex inhibits muscle growth and differentiation. Myostatin inhibitors reverse this process by acting in the extracellular space through ligand neutralization, binding directly to myostatin and other members of the TGF-β family (such as activin A), or through receptor blockade, binding to the ActRIIB complex to prevent the activation of downstream catabolic signaling.

Extracted from: SAITOH, M. et al. Myostatin inhibitors as pharmacological treatment for muscle wasting and muscular dystrophy. JCSM Clinical Reports, v. 2, n. 1, art. e00037, out. 2017. DOI: https://doi.org/10.17987/jcsm-cr.v2i1.37.

Despite their potential, these therapies still require further clinical evidence regarding their long-term efficacy and safety, especially in geriatric populations with comorbidities. Recent studies have provided relevant data comparing the use of GLP-1 agonists in conjunction with activin type II receptor blockers, such as Bimagrumab (BYM338). It is a human monoclonal antibody that acts as an antagonist of activin type II receptors (ActRIIA and ActRIIB), exhibiting a higher binding affinity for the ActRIIB subtype compared to ActRIIA (Lach-Trifilieff *et al*., 2014). Its mechanism is based on blocking ligands that negatively regulate skeletal muscle growth, such as myostatin and activins A and B (Heymsfield *et al*., 2021). By blocking these receptors, Bimagrumab prevents the formation of the signaling complex that would stimulate the phosphorylation of the transcription factors Smad2 and Smad3, which would normally activate genes associated with atrophy and degradation (Lach-Trifilieff *et al*., 2014). With these findings, albeit

in mice, it was possible to understand that the use of both classes of drugs can bring benefits for the effective combat of sarcopenia through the use of agonists, as well as metabolic syndrome caused and aggravated by obesity, because they preserve and increase muscle mass gain while increasing fat loss (Nunn *et al*., 2024). Simultaneously, inhibition of this signaling pathway results in the restoration and activation of the Akt/mTOR axis, which is an essential process for promoting protein synthesis and muscle fiber hypertrophy (Lach-Trifilieff *et al*., 2014). In addition to lean mass gain, clinical evidence shows that this modulation results in a significant reduction in total fat mass and improved insulin sensitivity, highlighting Bimagrumab as a potential therapeutic intervention for the treatment of obesity and associated metabolic disorders (Heymsfield *et al*., 2021).

On the other hand, Trevogrumab (REGN1033) is a human monoclonal antibody characterized by its affinity and specificity in blocking circulating myostatin (Latres *et al*., 2015). Trevogrumab acts selectively on myostatin, preventing its signaling and consequently promoting skeletal muscle hypertrophy, increased contractile strength, and accelerated recovery in models of preexisting atrophy (Latres *et al*., 2015). Recently, the clinical application of this molecule has gained prominence in the management of obesity through phase 2 clinical trials. The results demonstrated that the addition of Trevogrumab to Semaglutide therapy is capable of significantly mitigating lean mass loss, preventing approximately half of this muscle loss (Regeneron, 2024). Thus, Trevogrumab emerges as a promising therapeutic strategy to optimize the quality of weight loss and treat diseases associated with loss of muscle mass and function (Latres *et al*., 2015; Regeneron, 2024).

3. Conclusion

While the agents show potential, it is important to note that their long-term safety and efficacy, particularly in populations with multiple comorbidities or those experiencing muscle loss due to GLP-1 agonist use, remain under investigation. Ongoing and future clinical trials will provide more definitive evidence regarding their role in mitigating sarcopenia associated with GLP-1 receptor agonist therapy.

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