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Therapeutic Myostatin Inhibitors in Sarcopenia – A Review of Their Effects on Muscle Mass, Strength, and Function

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Abstract

Background. Sarcopenia is an age-related syndrome characterized by progressive loss of skeletal muscle mass, strength, and physical performance, leading to increased risks of disability, falls, hospitalization, and mortality. Myostatin, a negative regulator of muscle growth, has emerged as a potential therapeutic target in sarcopenia.

Aim. The aim of this review was to evaluate the current evidence regarding the use of myostatin inhibitors in sarcopenia, with particular emphasis on their effects on muscle mass, strength, and physical function.

Material and methods. A narrative review of the literature was conducted, including experimental studies, randomized controlled trials, systematic reviews, and meta-analyses investigating myostatin inhibition in sarcopenia and related muscle-wasting conditions.

Results. Available evidence indicates that myostatin inhibitors increase lean body mass and promote skeletal muscle hypertrophy. Clinical studies, particularly those involving bimagrumab, demonstrated significant gains in muscle volume and lean mass. However, improvements in muscle strength and physical performance were generally limited and not always proportional to increases in muscle mass. Current evidence is constrained by heterogeneous study populations and short follow-up periods.

Conclusions. Myostatin inhibitors may represent a useful pharmacological strategy for increasing muscle mass in sarcopenia. Nevertheless, their effects on functional outcomes remain uncertain. Further studies are needed to assess long-term clinical benefits and the effectiveness of combining pharmacological treatment with exercise and nutritional interventions.

Keywords: sarcopenia, myostatin inhibitors, bimagrumab, muscle mass, muscle strength, physical function

1. Introduction

Sarcopenia is one of the most significant health issues facing an aging population. Its prevalence in people over 60 is estimated to range from 10% to 27%, depending on the diagnostic criteria used, while in hospitalized patients or those in nursing homes, it can exceed 40%. This means that as societies age, the problem of muscle mass and function loss will grow. Sarcopenia is not merely a morphological change; it is a syndrome leading to decreased muscle strength, impaired physical performance, and an increased risk of falls, disability, and mortality (1,2).

In recent years, its definition has been refined, emphasizing that the key element of diagnosis is not only low muscle mass but, above all, reduced strength and functionality (3,4). This represents a significant shift from structural to clinical parameters. In practice, this means that an increase in muscle mass does not necessarily equate to an improvement in the patient's functional capacity.

Sarcopenia often coexists with chronic diseases. In patients with liver cirrhosis, its prevalence ranges from 30 to 70%, and its presence is associated with a poorer prognosis and higher

mortality (5,6). Similar associations are observed in hospitalized elderly populations, where the coexistence of frailty and sarcopenia significantly increases the risk of complications (7). This phenomenon therefore has not only geriatric but also internal medicine and rehabilitation implications.

The cornerstone of treatment remains resistance training and nutritional interventions (8). However, their effectiveness may be limited in patients with severe comorbidities, advanced muscle mass loss, or limited capacity for physical exertion. For this reason, pharmacological strategies targeting molecular regulators of muscle homeostasis are being developed (9,10).

One of the key negative regulators of muscle growth is myostatin (GDF-8). It inhibits the proliferation and differentiation of satellite cells by activating the ActRIIB/Smad pathway, thereby limiting muscle fiber hypertrophy. Molecular studies indicate that its expression may be regulated, among other things, by the HDAC6 and FoxO3a pathways (11). Importantly, elevated myostatin levels correlate with impaired functional parameters and a state of malnutrition (12,13). This suggests that its role extends beyond the regulation of muscle mass alone.

In preclinical studies, myostatin blockade led to a significant increase in muscle mass and strength (14,15). However, in clinical trials, the results proved to be more complex. Randomized phase II trials using bimagrumab demonstrated an increase in lean body mass (16,17), and a meta-analysis confirmed its effect on body composition (18) Nevertheless, functional improvement was moderate and not always proportional to the increase in muscle mass.

The difference between muscle hypertrophy and actual functional improvement is currently one of the key issues in assessing the efficacy of myostatin inhibitors. It appears that an increase in muscle mass is a necessary but insufficient condition for functional improvement. There is a growing emphasis on the need to combine pharmacotherapy with exercise interventions and to personalize therapy (10).

The aim of this study is to provide a critical review of current data on the therapeutic use of myostatin inhibitors in the treatment of sarcopenia, with particular emphasis on their impact on muscle mass, strength, and functionality in patients.

2. Diagnostic criteria for sarcopenia

Sarcopenia is currently recognized as a clinical syndrome encompassing not only muscle mass loss but, above all, a decline in muscle strength and a deterioration in physical performance. In recent years, there has been a significant shift in the diagnostic approach, with the emphasis shifting from morphological to functional parameters. According to current recommendations, low muscle strength is the primary criterion for diagnosing sarcopenia, while reduced muscle mass confirms the diagnosis, and limited physical performance helps determine the severity of the condition (1,4).

Assessment of muscle strength is most often based on handgrip strength measurement or the chair stand test. These are simple, reproducible methods with documented prognostic value that correlate with the risk of falls, hospitalization, and mortality (1). It is worth noting that reduced muscle strength can occur even with relatively preserved muscle mass, which confirms its key diagnostic significance.

Muscle mass is typically assessed using dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). The parameter most commonly used in clinical practice is the lean muscle mass index (ASM/height^2). Reduced muscle mass confirms the diagnosis of sarcopenia, but by itself does not allow for an assessment of its clinical significance (1,4). This limitation is particularly important in the context of therapies aimed at increasing muscle mass.

The third diagnostic component is the assessment of physical performance, which includes measurement of walking speed, the Short Physical Performance Battery (SPPB) test, or the 6-minute walk test. These parameters enable the assessment of the severity of sarcopenia and the prediction of the risk of clinically adverse events. In clinical practice, limited physical fitness is one of the strongest predictors of loss of independence (1).

In Asian populations, different threshold values for muscle strength and mass have been proposed, taking into account anthropometric and metabolic differences (4). These differences underscore the need to adapt diagnostic criteria to the specific characteristics of the study population and to exercise caution when comparing the results of clinical trials conducted in different regions of the world.

The use of functionality-based diagnostic criteria has significant implications for the evaluation of new pharmacological therapies. In the case of myostatin inhibitors, an increase in muscle mass should be interpreted in the context of concurrent improvements in strength and physical

performance. The absence of such improvements may limit the clinical significance of the observed changes.

3. The role of myostatin in the pathogenesis of sarcopenia

Myostatin (growth differentiation factor 8, GDF-8) belongs to the transforming growth factor β (TGF-β) family and acts as a "brake" on skeletal muscle growth. Under normal conditions, it controls the proliferation and differentiation of myoblasts and limits excessive muscle fiber hypertrophy. Animal models with myostatin gene knockouts exhibit significant muscle mass gain, confirming its function as a potent inhibitor of myogenesis (1,19). However, in the context of aging and chronic diseases, this physiological regulatory function may transform into a factor promoting progressive muscle loss.

The mechanism of myostatin action is primarily based on the activation of type II activin receptors (ActRIIA and ActRIIB). Upon binding to the receptor, Smad2/3 proteins are phosphorylated, which then form a complex with Smad4 and translocate to the cell nucleus, where they regulate the expression of genes associated with the inhibition of muscle protein synthesis and the intensification of proteolytic processes (15,19). The ActRIIA/ActRIIB/Smad pathway influences, among other things, the activity of the ubiquitin–proteasome system and the expression of muscle atrophy factors, such as atrogin-1 and MuRF-1. As a result, anabolism is inhibited and the degradation of contractile proteins is enhanced. This pathway interacts with other signaling axes, including insulin-like growth factor 1 (IGF-1) and the mTOR pathway, which further exacerbates metabolic imbalances in aging muscle (1,2).

The regulation of myostatin expression is a multilevel process dependent on the metabolic context. Experimental studies have shown that transcription factors, such as FoxO3a, can enhance myostatin expression under catabolic conditions, promoting muscle atrophy (11). At the same time, histone deacetylase 6 (HDAC6) participates in the epigenetic regulation of this process by modulating the activity of transcription factors and chromatin accessibility (11). These data suggest that the increased expression of myostatin in sarcopenia is not a random phenomenon but results from specific molecular changes associated with aging, oxidative stress, and metabolic disorders. It is worth noting, however, that most of these observations come from cellular or animal models, and their direct translation to the elderly population requires further clinical studies.

The role of myostatin in sarcopenia is also supported by clinical data. In studies involving patients meeting the diagnostic criteria for sarcopenia, a correlation was found between myostatin levels and reduced muscle mass and impaired physical function (12). Similar observations have been reported in populations with chronic diseases, where elevated myostatin levels correlated with the severity of muscle mass loss and indicators of malnutrition (13). At the same time, not all studies unequivocally demonstrate higher myostatin concentrations in older adults with sarcopenia compared to control groups. These discrepancies may result from methodological differences (various assay techniques, lack of measurement standardization), heterogeneity of the study populations, and the influence of comorbid factors, such as inflammation or liver disease (12,13).

A critical analysis of the available data indicates that myostatin is an important, but not the only, component of the complex regulatory network responsible for the development of sarcopenia. Its role may be modulated by environmental (physical activity, diet), hormonal, and genetic factors (1,2). Furthermore, some studies have observed paradoxical relationships in which myostatin levels did not correlate linearly with the severity of muscle mass loss, suggesting the existence of compensatory mechanisms or differences in the protein's biological activity (12). For this reason, the interpretation of myostatin levels as a standalone biomarker of sarcopenia should be approached with caution.

Despite these limitations, understanding the role of myostatin in the pathogenesis of sarcopenia has significant translational implications. As a central regulator of the muscle growth-inhibiting pathway, it represents an attractive therapeutic target, as evidenced by recent reviews analyzing the development of myostatin inhibitors and type II activin receptors (19). Theoretically, inhibiting ActRIIA/ActRIIB/Smad signaling could restore the balance between anabolism and catabolism, increase muscle mass, and improve physical function. However, the key question remains whether modulation of a single molecular pathway is sufficient to effectively inhibit the multifactorial process of sarcopenia.

In summary, myostatin plays a central role in the regulation of skeletal muscle mass and function, and its excessive activity may contribute to the development and progression of sarcopenia (1,2,19). The ActRIIA/ActRIIB/Smad pathway and transcriptional regulatory mechanisms involving FoxO3a and HDAC6 constitute the molecular basis of this phenomenon (11,15). Clinical data confirm the association between myostatin and the loss of muscle mass and function, although their interpretation requires caution (12,13).

4. Therapeutic strategies for the treatment of sarcopenia

Therapeutic management of sarcopenia encompasses a broad spectrum of interventions aimed at both halting the progression of muscle mass loss and improving skeletal muscle strength and function. Current strategies focus primarily on non-pharmacological methods, such as resistance training and nutritional interventions, which form the basis of clinical management. At the same time, intensive research is underway on pharmacological therapies targeting molecular mechanisms regulating muscle metabolism, including the modulation of anabolic pathways and the inhibition of factors that negatively regulate muscle growth, such as myostatin (3,9).

Resistance training remains the best-documented and most recommended method for treating sarcopenia. Regular physical activity leads to increased muscle protein synthesis, improved mitochondrial function, and stimulation of anabolic pathways, particularly those dependent on mTOR kinase (8,20). Intervention studies have shown that systematic strength training in older adults can lead to a significant increase in both muscle mass and muscle strength, as well as improved functional capacity (18). Importantly, these benefits are observed even in patients of very advanced age, which underscores the importance of physical activity as a fundamental component of sarcopenia therapy (10).

In clinical practice, training programs combining resistance exercises with endurance training and balance exercises prove particularly effective. Such multifaceted rehabilitation programs not only increase muscle mass but also reduce the risk of falls and improve patients' overall functional fitness (21). Despite clear evidence confirming the effectiveness of physical training, its implementation in the elderly population is often hindered by comorbid chronic diseases, mobility limitations, or low patient motivation (5).

The second key element in the treatment of sarcopenia is nutritional intervention. With age, muscle sensitivity to anabolic stimuli decreases, a phenomenon known as "anabolic resistance." Consequently, older adults require increased protein intake to maintain a positive protein balance (7). Current guidelines suggest that daily protein intake in patients at risk of sarcopenia should be approximately 1.0–1.5 g/kg of body weight, which exceeds standard recommendations for the healthy adult population (6).

The quality of the protein consumed also plays a significant role. Particular attention is paid to essential amino acids, especially leucine, which is a potent activator of the mTOR pathway and stimulates muscle protein synthesis (22). Clinical studies have shown that supplementation with

leucine or its metabolite—β-hydroxy-β-methylbutyrate (HMB)—may lead to moderate improvements in muscle mass and function in older adults, especially when combined with physical activity (16).

Despite the growing number of studies on nutritional supplementation, the results remain somewhat inconsistent. Some meta-analyses have observed only a slight effect of protein supplementation on muscle strength, particularly in the absence of concurrent training intervention (17). This suggests that the effectiveness of nutritional strategies is largely dependent on their integration with physical activity programs.

In addition to non-pharmacological interventions, pharmacological strategies are also being developed to directly modulate anabolic and catabolic processes in muscles. The approaches under investigation include, among others, selective androgen receptor modulators (SARMs), hormone therapy, and drugs affecting muscle metabolism (23). To date, however, none of these methods has been widely accepted as a standard treatment for sarcopenia, mainly due to limited efficacy or potential side effects.

In recent years, therapies aimed at inhibiting myostatin—a protein that is one of the key negative regulators of muscle growth—have attracted particular interest. Blocking the myostatin signaling pathway leads to increased muscle mass in animal models, which has formed the basis for the development of new therapeutic strategies (24).

One of the most advanced drugs in this class is bimagrumab—a monoclonal antibody targeting type II activin receptors. The mechanism of action of this drug involves blocking catabolic signals transmitted by myostatin and other ligands from the TGF-β family, which leads to an increase in anabolic processes in skeletal muscle (25). Clinical trials have shown that administration of bimagrumab can lead to a significant increase in lean body mass in patients with sarcopenia or muscle loss associated with chronic diseases (26). The increase in muscle mass did not always translate into a proportional improvement in muscle strength or physical function. In some studies, only moderate improvements in functional parameters, such as walking speed or the chair stand test, were observed (27). This phenomenon suggests that muscle hypertrophy alone is not sufficient to restore full functional capacity, which also depends on neurological and metabolic factors as well as the quality of muscle structure.

Limitations of studies on new therapies include relatively short follow-up periods, small sample sizes, and significant heterogeneity in patient populations. Furthermore, many studies focus

primarily on changes in muscle mass, whereas clinically relevant parameters are primarily functional measures such as muscle strength or the ability to perform activities of daily living. The treatment of sarcopenia requires a multifaceted approach combining behavioral, nutritional, and—potentially—pharmacological interventions. Currently, resistance training and adequate protein intake remain the cornerstones of therapy, as they have the best-documented efficacy. The development of therapies targeting molecular mechanisms regulating muscle metabolism, particularly myostatin inhibitors, opens up new therapeutic prospects.

5. Myostatin inhibitors as a potential therapy for sarcopenia

In recent years, therapeutic strategies targeting the modulation of molecular regulators of skeletal muscle growth have garnered increasing interest. One of the most important of these is myostatin (growth differentiation factor-8, GDF-8), which belongs to the transforming growth factor-β (TGF-β) family. This protein acts as a potent negative regulator of muscle development, limiting the proliferation and differentiation of satellite cells and inhibiting muscle protein synthesis. Consequently, inhibiting myostatin activity has become an attractive therapeutic target in diseases characterized by muscle mass loss, including sarcopenia (24).

Myostatin exerts its biological effects by binding to type II activin receptors—ActRIIA and ActRIIB—present on the surface of muscle cells. Upon ligand-receptor binding, the intracellular Smad2/3 signaling pathway is activated, leading to the inhibition of gene expression responsible for muscle growth and regeneration. Activation of this pathway results in reduced myoblast proliferation and increased catabolic processes in muscle tissue. Consequently, this leads to a reduction in muscle mass and impaired skeletal muscle function (24). For this reason, blocking myostatin signaling at the ligand or ActRIIA/ActRIIB receptor level may reverse these processes and stimulate muscle hypertrophy.

Based on this, several pharmacological strategies have been developed to inhibit myostatin's action. One approach involves the use of monoclonal antibodies that directly neutralize myostatin. Drugs in this group bind the myostatin molecule in the extracellular space, preventing it from interacting with activin receptors. Another strategy involves blocking the ActRIIA or ActRIIB receptors themselves using monoclonal antibodies or fusion proteins that act as so-called "ligand traps" to capture myostatin and other ligands from the TGF-β family. This approach may lead to a stronger anabolic effect, as it simultaneously inhibits the action of several factors that limit muscle growth (25).

The most clinically advanced representative of myostatin pathway inhibitors is bimagrumab—a human monoclonal antibody directed against type II activin receptors. This drug blocks signal transduction via the ActRIIA and ActRIIB receptors, preventing activation of the Smad2/3 pathway and thereby counteracting myostatin's inhibitory effect on skeletal muscle growth (25). Preclinical studies have shown that blocking activin receptors leads to a significant increase in muscle mass and an improvement in body composition by increasing lean body mass while simultaneously reducing body fat.

The first clinical trials involving bimagrumab showed promising results regarding its effect on body composition. In randomized controlled trials, a significant increase in muscle volume and lean body mass was observed in patients with muscle wasting. At the same time, some studies reported a reduction in body fat, suggesting a beneficial effect of the drug on overall body metabolism (16,17). Meta-analyses of available studies indicate that bimagrumab therapy may lead to significant changes in body composition, particularly in terms of increased muscle mass (18).

However, these results should be interpreted with some caution. Although an increase in muscle mass is one of the key goals of sarcopenia therapy, it does not always translate directly into improved muscle function. In some clinical trials, only moderate improvements in functional parameters such as muscle strength, walking speed, or the ability to perform activities of daily living were observed (17,23). This suggests that an increase in muscle volume does not necessarily imply a simultaneous improvement in muscle quality and neuromuscular coordination.

This phenomenon may result from several factors. First, sarcopenia is a complex clinical syndrome involving not only a reduction in muscle mass but also changes in muscle fiber structure, mitochondrial dysfunction, and impaired neuromuscular conduction. Second, many studies on myostatin inhibitors involve relatively short follow-up periods, which may not be sufficient to demonstrate full functional improvement. Furthermore, studies often include heterogeneous groups of patients with varying degrees of sarcopenia and different comorbidities (24,26).

A significant limitation of previous studies is also the fact that most of them focus primarily on changes in body composition, such as muscle mass or muscle volume assessed via imaging studies. Meanwhile, from a clinical perspective, functional parameters such as muscle strength, mobility, and the ability to function independently are of key importance. The lack of clear

improvement in these parameters in some studies suggests that therapy with myostatin inhibitors should be considered rather as part of combination therapy, combined with physical activity and appropriate nutritional interventions (27).

Despite these limitations, myostatin inhibitors remain one of the most promising avenues for the development of pharmacotherapy for sarcopenia. Advances in understanding the biology of the TGF-β pathway and the interactions between myostatin and other regulators of muscle metabolism may enable the development of more selective and effective therapies in the future. In particular, further clinical trials are needed to evaluate the long-term efficacy and safety of myostatin inhibitors and their impact on functional aspects of physical performance in older adults (19).

Given the growing interest in these therapies, it is particularly important to thoroughly analyze the results of existing clinical trials on myostatin inhibitors, especially bimagrumab. The following chapter provides an overview of the most important clinical trials evaluating the efficacy and safety of these therapies in a population of patients with sarcopenia.

6. Clinical Trials of Myostatin Inhibitors in the Treatment of Sarcopenia

The growing interest in myostatin inhibitors as a potential therapeutic strategy for sarcopenia has led to the initiation of a series of clinical trials in recent years aimed at evaluating the efficacy and safety of these therapies. These studies primarily focus on evaluating the impact of drugs that modulate the myostatin signaling pathway on clinically relevant parameters for patients with sarcopenia, such as muscle mass, body composition, muscle strength, and the ability to perform activities of daily living. In this context, randomized controlled trials (RCTs) are a key tool for assessing the true therapeutic value of new drugs and their potential role in future treatment strategies for this condition (9).

One of the most extensively studied myostatin pathway inhibitors is bimagrumab—a monoclonal antibody that blocks type II activin receptors. Clinical trials have evaluated its impact on body composition and muscle function in patients with age-related or chronic disease-related muscle loss. One of the first randomized Phase II trials evaluated the efficacy of bimagrumab in an elderly population with sarcopenia. The study was double-blind and placebo-controlled, and its primary objective was to assess changes in muscle volume and functional parameters during treatment (16).

The results of this study showed that administration of bimagrumab led to a significant increase in skeletal muscle volume compared to the placebo group. An increase in lean body mass was observed after just a few weeks of therapy, suggesting a rapid anabolic effect resulting from the inhibition of signaling via activin receptors. At the same time, a reduction in body fat was noted in some analyses, indicating a potentially beneficial effect of the therapy on patients' overall body composition (16).

Another randomized clinical trial evaluated the efficacy of bimagrumab compared to optimal standard care in community-dwelling older adults living independently. The study design included a multicenter RCT with a control group and a longer follow-up period, allowing for a more comprehensive assessment of the therapy's impact on functional parameters. The study analyzed, among other things, changes in muscle mass, muscle strength, and physical performance tests (17).

The results of this study confirmed that bimagrumab therapy leads to a significant increase in lean body mass compared to standard treatment. However, the improvement in functional parameters was less clear-cut. In some analyses, only a moderate improvement in muscle strength and a limited change in functional test results, such as walking speed or the chair stand test, were observed. This suggests that an increase in muscle mass does not always directly translate into a proportional improvement in physical fitness (17).

Interesting data were also provided by a study evaluating the effect of bimagrumab on muscle volume and composition in men with immobilization-induced muscle atrophy. Although this study involved an experimental model of muscle atrophy, its results provide valuable insights into the mechanisms of action of myostatin inhibitors. It was demonstrated that bimagrumab therapy led to a significant increase in thigh muscle volume and an improvement in muscle structure as assessed by imaging methods (23). These results confirm the strong anabolic potential of blocking type II activin receptors.

A meta-analysis encompassing the results of several clinical trials on bimagrumab provided a comprehensive assessment of the available studies. This analysis demonstrated that treatment with this drug consistently leads to an increase in lean body mass and an improvement in body composition through a reduction in body fat. This effect was observed in various patient populations, suggesting a relatively universal mechanism of action for the drug (18). At the same time, the meta-analysis indicated that the impact of therapy on functional parameters, such as muscle strength or the ability to perform daily activities, remains less clear-cut.

The discrepancy between a marked increase in muscle mass and a relatively limited improvement in muscle function is one of the most frequently discussed issues in research on myostatin inhibitors. Sarcopenia is, in fact, a complex clinical syndrome involving not only a reduction in muscle mass but also changes in muscle fiber quality, mitochondrial dysfunction, and impaired neuromuscular transmission. For this reason, muscle hypertrophy alone does not necessarily lead to an improvement in patients' functional abilities.

An additional limitation of the available studies is the relatively small size of the patient groups analyzed and the relatively short duration of follow-up. In many studies, the treatment period lasted only a few months, which may be insufficient to fully assess the impact of treatment on long-term physical performance. Furthermore, the studies often included heterogeneous patient populations with varying degrees of sarcopenia and different comorbidities, which may complicate the interpretation of results and their generalization to the general population (18,17).

Despite these limitations, clinical trials to date provide important evidence suggesting that modulation of the myostatin pathway may lead to significant changes in body composition and increased muscle mass. These results suggest that myostatin inhibitors may in the future constitute an important element of sarcopenia therapy, particularly in combination with non-pharmacological interventions such as resistance training and an appropriate nutritional strategy.

In summary, clinical trials of myostatin inhibitors, particularly bimagrumab, indicate their clear anabolic potential and ability to increase muscle mass in patients with muscle wasting. At the same time, results regarding functional improvement remain inconclusive, underscoring the need for further studies involving larger patient populations and longer follow-up periods. A better understanding of the relationship between changes in muscle mass and improvements in physical function will be crucial for determining the true role of myostatin inhibitors in future strategies for treating sarcopenia.

7. Limitations of myostatin inhibitor therapy and future research directions in the treatment of sarcopenia

Despite growing interest in myostatin inhibitors as a potential strategy for treating sarcopenia, clinical studies to date indicate a number of significant limitations related to both study design and the interpretation of the results obtained. Although modulation of the myostatin pathway

represents a biologically sound therapeutic target, current clinical data do not yet allow for a clear determination of the role of these therapies in the standard management of patients with sarcopenia (9,18).

One of the most frequently highlighted issues is the discrepancy between the observed increase in muscle mass and the relatively limited functional improvement. Many clinical trials have demonstrated that myostatin inhibitors, including bimagrumab, lead to a significant increase in lean body mass and skeletal muscle volume (16,17). However, improvements in functional parameters, such as muscle strength, walking speed, or the ability to perform activities of daily living, often remain moderate or fail to reach statistical significance. This phenomenon suggests that an increase in muscle volume does not always translate into an improvement in muscle quality and functional performance (18).

The explanation for this discrepancy is complex. Sarcopenia is a multifactorial clinical syndrome involving not only a reduction in muscle mass but also changes in muscle fiber structure, disturbances in energy metabolism, and deterioration of neuromuscular function. Consequently, therapy targeting only one aspect of the disease's pathophysiology may not be sufficient to achieve full functional recovery. Furthermore, some studies suggest that pharmacologically induced muscle mass gain may primarily lead to an increase in muscle fiber volume without a proportional improvement in their ability to generate force (9).

A significant limitation of the available clinical studies is also their methodology. Many studies involved relatively small groups of patients, which limits the statistical power of the analyses and makes it difficult to detect subtle differences in functional parameters. Furthermore, the observation period in most studies was relatively short, often covering only a few months of therapy. In the case of chronic diseases associated with the aging process, such as sarcopenia, the assessment of long-term treatment effects is crucial for determining the actual therapeutic value of new interventions (17,18).

Another issue is the significant heterogeneity of the study populations. Clinical trials often include individuals with varying degrees of sarcopenia, different comorbidities, and differing levels of physical activity. These factors can significantly influence treatment response and make it difficult to compare results across studies. Additionally, the diagnostic criteria for sarcopenia used are not always identical, introducing an additional source of variability in the analyzed populations (9).

Potential clinical limitations associated with biologic therapies must also be considered. Drugs such as monoclonal antibodies typically require parenteral administration, which may limit their availability and patient acceptance in long-term therapy. Furthermore, the costs of biological therapy are typically high, which in clinical practice may constitute a significant barrier to the widespread use of these therapies in the elderly population. Although existing studies indicate a relatively good safety profile for myostatin inhibitors, further observations are necessary to assess their long-term safety (16,18).

In light of these limitations, increasing attention is being paid to the possibility of using combination therapies. Combining pharmacological modulation of anabolic pathways with non-pharmacological interventions, such as resistance training and appropriately tailored nutritional strategies, may potentially lead to more pronounced improvements in functional parameters. Physical training remains one of the strongest stimuli for muscle protein synthesis, while an adequate supply of protein and essential amino acids supports regenerative processes in muscle tissue. Integrating these strategies with pharmacological therapy may therefore represent a promising direction for further research (8,10).

In the future, the development of more precise methods for patient selection for therapy will also be particularly important. Sarcopenia is characterized by significant clinical heterogeneity; therefore, identifying patient subgroups that may benefit most from myostatin inhibitor therapy could enhance treatment efficacy. In this context, biomarkers related to muscle metabolism may become increasingly important, as they will allow for better prediction of treatment response and monitoring of therapeutic effects (22).

Long-term clinical trials involving larger patient populations and a more comprehensive assessment of treatment outcomes are also necessary. In addition to traditional parameters such as muscle mass and muscle strength, future studies should also consider indicators of quality of life, physical activity levels, and the ability to function independently. This approach will allow for a better assessment of the actual clinical and social significance of these new therapies (9,18).

In summary, myostatin inhibitors represent a promising class of drugs for the treatment of sarcopenia; however, the current state of knowledge indicates a need for further research to more accurately determine their efficacy and safety. It is particularly important to conduct long-term, well-designed clinical trials and to develop therapeutic strategies combining pharmacotherapy with behavioral and nutritional interventions. The results of such studies may

contribute to better utilization of myostatin inhibitors in the treatment of sarcopenia in the future and provide an important backdrop for the final conclusions of this paper.

8. Conclusions

Sarcopenia poses a significant challenge to modern medicine, particularly in the context of an aging population and the growing burden on healthcare systems. Its multifactorial nature, encompassing both muscle mass loss and impaired muscle function, requires a comprehensive diagnostic and therapeutic approach. In this context, myostatin, as a key negative regulator of muscle growth, emerges as a promising target for pharmacological intervention.

To date, studies indicate that myostatin inhibitors, including bimagrumab, demonstrate significant potential for increasing lean body mass and improving body composition in patients with sarcopenia. These effects are relatively consistent across different study populations, confirming the importance of the myostatin pathway in regulating muscle metabolism. At the same time, however, clinical trial results reveal significant limitations of these therapies, particularly regarding improvements in muscle function. In many cases, the observed increase in muscle mass does not translate into a proportional improvement in strength or physical performance, which underscores the complexity of the pathophysiology of sarcopenia.

Limitations of the available studies, such as small patient groups, short follow-up periods, and population heterogeneity, further complicate the unambiguous assessment of myostatin inhibitor efficacy in clinical practice. This points to the need for further, well-designed clinical trials involving larger populations and longer follow-up periods, as well as incorporating functional parameters as key endpoints.

In the future, the development of combination therapies—combining pharmacological modulation of anabolic pathways with non-pharmacological interventions, such as resistance training and an appropriate nutritional strategy—appears to be a particularly promising direction. Such an approach may allow for a more comprehensive impact on the mechanisms underlying sarcopenia. In summary, myostatin inhibitors represent a promising, though still research-intensive, component of future strategies for treating sarcopenia.

Disclosure:

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References

[1] Cho, M. R., Lee, S., & Song, S. K. (2022). A Review of Sarcopenia Pathophysiology, Diagnosis, Treatment and Future Direction. *Journal of Korean medical science*, *37*(18), e1469.https://doi.org/10.3346/jkms.2022.37.e146

[2] Kim, J. W., Kim, R., Choi, H., Lee, S. J., & Bae, G. U. (2021). Understanding of sarcopenia: from definition to therapeutic strategies. *Archives of pharmacal research*, *44*(9-10), 876–889. https://doi.org/10.1007/s12272-021-01349-z

[3] Liu, D., Wang, S., Liu, S., Wang, Q., Che, X., & Wu, G. (2024). Frontiers in sarcopenia: Advancements in diagnostics, molecular mechanisms, and therapeutic strategies. *Molecular aspects of medicine*, *97*, 101270. https://doi.org/10.1016/j.mam.2024.101270

[4] Huang, W. F., Chen, Y. C., Chang, C. S., & Wu, C. H. (2025). Definition and diagnosis of sarcopenia: Asia-Pacific perspectives. *Osteoporosis and sarcopenia*, *11*(2 Suppl), 2–10. https://doi.org/10.1016/j.afos.2025.05.004

[5] Leunis, S., Vandecruys, M., Van Craenenbroeck, A. H., Cornelissen, V., Bogaerts, S., De Smet, S., & Monbaliu, D. (2023). Sarcopenia in end-stage liver disease and after liver transplantation. *Acta gastro-enterologica Belgica*, *86*(2), 323–334. https://doi.org/10.51821/86.2.11412

[6] Fox, R., Stenning, K., Slee, A., Macnaughtan, J., & Davies, N. (2022). Sarcopenia in liver cirrhosis: Prevalence, pathophysiology and therapeutic strategies. *Analytical biochemistry*, *647*, 114581. https://doi.org/10.1016/j.ab.2022.114581

[7] Echeverria, I., Besga, A., Sanz, B., Amasene, M., Hervás, G., Barroso, J., Rodriguez-Larrad, A., & Irazusta, J. (2021). Identification of frailty and sarcopenia in hospitalised older people. *European journal of clinical investigation*, *51*(4), e13420. https://doi.org/10.1111/eci.13420

[8] Sakuma, K., Hamada, K., Yamaguchi, A., & Aoi, W. (2023). Current Nutritional and Pharmacological Approaches for Attenuating Sarcopenia. *Cells*, *12*(19), 2422. https://doi.org/10.3390/cells12192422

[9] Rolland, Y., Dray, C., Vellas, B., & Barreto, P. S. (2023). Current and investigational medications for the treatment of sarcopenia. *Metabolism: clinical and experimental*, *149*, 155597. https://doi.org/10.1016/j.metabol.2023.155597

[10] Liu, X., Chen, X., & Cui, J. (2025). Therapeutic advances in sarcopenia management: From traditional interventions to personalized medicine. *Clinical nutrition (Edinburgh, Scotland)*, *51*, 187–197. https://doi.org/10.1016/j.clnu.2025.06.007

[11] Kang, M. J., Moon, J. W., Lee, J. O., Kim, J. H., Jung, E. J., Kim, S. J., Oh, J. Y., Wu, S. W., Lee, P. R., Park, S. H., & Kim, H. S. (2022). Metformin induces muscle atrophy by transcriptional regulation of myostatin via HDAC6 and FoxO3a. *Journal of cachexia, sarcopenia and muscle*, *13*(1), 605–620. https://doi.org/10.1002/jcsm.12833

[12] de Luis, D., Primo, D., Izaola, O., & Gómez, J. J. L. (2024). Role of irisin and myostatin on sarcopenia in malnourished patients diagnosed with GLIM criteria. *Nutrition (Burbank, Los Angeles County, Calif.)*, *120*, 112348. https://doi.org/10.1016/j.nut.2023.112348

[13] Alexopoulos, T., Vasilieva, L., Kontogianni, M. D., Tenta, R., Georgiou, A., Stroumpouli, E., Mani, I., & Alexopoulou, A. (2021). Myostatin in combination with creatine phosphokinase or albumin may differentiate patients with cirrhosis and sarcopenia. *American journal of physiology. Gastrointestinal and liver physiology*, *321*(5), G543–G551. https://doi.org/10.1152/ajpgi.00184.2021

[14] Malerba, A., Harish, P., & Popplewell, L. (2023). Systemic Delivery of a Monoclonal Antibody to Immunologically Block Myostatin in the A17 Mouse Model of OPMD. *Methods in molecular biology (Clifton, N.J.)*, *2587*, 557–568. https://doi.org/10.1007/978-1-0716-2772-3_30

[15] Cano-Martínez, A., Méndez-Castro, J. A., García-Vázquez, V. E., Carreón-Torres, E., Díaz-Díaz, E., Sánchez-Aguilar, M., Castrejón-Téllez, V., & Rubio-Ruíz, M. E. (2025). A Combination of Resveratrol and Quercetin Prevents Sarcopenic Obesity: Its Role as a Signaling Inhibitor of Myostatin/ActRIIA and ActRIIB/Smad and as an Enhancer of Insulin Actions. *International journal of molecular sciences*, *26*(10), 4952. https://doi.org/10.3390/ijms26104952

[16] Rooks, D., Praestgaard, J., Hariry, S., Laurent, D., Petricoul, O., Perry, R. G., Lach-Trifilieff, E., & Roubenoff, R. (2017). Treatment of Sarcopenia with Bimagrumab: Results from a Phase II, Randomized, Controlled, Proof-of-Concept Study. *Journal of the American Geriatrics Society*, *65*(9), 1988–1995. https://doi.org/10.1111/jgs.14927

[17] Rooks, D., Swan, T., Goswami, B., Filosa, L. A., Bunte, O., Panchaud, N., Coleman, L. A., Miller, R. R., Garcia Garayoa, E., Praestgaard, J., Perry, R. G., Recknor, C., Fogarty,

C. M., Arai, H., Chen, L. K., Hashimoto, J., Chung, Y. S., Vissing, J., Laurent, D., Petricoul, O., … Roubenoff, R. (2020). Bimagrumab vs Optimized Standard of Care for Treatment of Sarcopenia in Community-Dwelling Older Adults: A Randomized Clinical Trial. *JAMA network open*, *3*(10), e2020836. https://doi.org/10.1001/jamanetworkopen.2020.20836

[18] Kanbay, M., Siriopol, D., Copur, S., Hasbal, N. B., Güldan, M., Kalantar-Zadeh, K., Garfias-Veitl, T., & von Haehling, S. (2024). Effect of Bimagrumab on body composition: a systematic review and meta-analysis. *Aging clinical and experimental research*, *36*(1), 185. https://doi.org/10.1007/s40520-024-02825-4

[19] Samali, S. A., Hosseini, S. F., Mohammadi, Y., Sadri, F., & Rezaei, Z. (2025). Myostatin inhibitors in sarcopenia treatment: A comprehensive review of mechanisms, efficacy and future directions. *Molecular biology reports*, *53*(1), 224. https://doi.org/10.1007/s11033-025-11390-6

[20] Kim, Y. C., Ki, S. W., Kim, H., Kang, S., Kim, H., & Go, G. W. (2023). Recent Advances in Nutraceuticals for the Treatment of Sarcopenic Obesity. *Nutrients*, *15*(17), 3854. https://doi.org/10.3390/nu15173854

[21] Marques, M., & Baptista, F. (2025). Pediatric Sarcopenia: What do We Know?. *Acta medica portuguesa*, *38*(12), 800–807. https://doi.org/10.20344/amp.23301

[22] Kim, J. Y., Gil, T. H., Lee, H. G., Shin, J. W., Jang, D. H., Kim, H. S., Park, S. S., Kim, S. W., Shin, C. S., Kong, S. H., & Jeon, O. H. (2025). Plasma Extracellular Vesicles Biomarkers Linked to Lower Muscle Mass, Function and Physical Performance in Sarcopenia. *Journal of cachexia, sarcopenia and muscle*, *16*(2), e13784. https://doi.org/10.1002/jcsm.13784

[23] Rooks, D. S., Laurent, D., Praestgaard, J., Rasmussen, S., Bartlett, M., & Tankó, L. B. (2017). Effect of bimagrumab on thigh muscle volume and composition in men with casting-induced atrophy. *Journal of cachexia, sarcopenia and muscle*, *8*(5), 727–734. https://doi.org/10.1002/jcsm.12205

[24] Kanbay, M., Siriopol, D., Copur, S., Hasbal, N. B., Güldan, M., Kalantar-Zadeh, K., Garfias-Veitl, T., & von Haehling, S. (2024). Effect of Bimagrumab on body composition: a systematic review and meta-analysis. *Aging clinical and experimental research*, *36*(1), 185. https://doi.org/10.1007/s40520-024-02825-4

[25] Kaur, M., & Misra, S. (2024). Bimagrumab: an investigational human monoclonal antibody against activin type II receptors for treating obesity. *Journal of basic and clinical physiology and pharmacology*, *35*(6), 325–334. https://doi.org/10.1515/jbcpp-2024-0065

[26] Kaiser, M., Parikh, M. A., Turitto, G., Frishman, W. H., & Peterson, S. J. (2025). Bimagrumab: Novel Medical Therapy for Inclusion Body Myositis, Sarcopenia, and Medication-Induced Lean Body Mass Loss. *Cardiology in review*, 10.1097/CRD.0000000000001113. Advance online publication. https://doi.org/10.1097/CRD.0000000000001113

[27] Baik, J., & Lee, Y. S. (2025). Emerging Role of Myostatin Inhibitors in the Management of Glucagon-Like Peptide-1-Associated Sarcopenia and Metabolic Disorders. *Journal of bone metabolism*, *32*(4), 263–275. https://doi.org/10.11005/jbm.25.919