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PHARMACOLOGICAL CORRECTION OF METABOLIC SYNDROME

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Abstract. Metabolic syndrome (MetS) is a multifactorial disorder characterized by insulin resistance, central obesity, dyslipidemia, and hypertension, significantly increasing the risk of cardiovascular diseases and type 2 diabetes. This study analyzes recent advances in the pharmacological correction of MetS, focusing on modern therapeutic strategies and their clinical effectiveness. Particular attention is given to novel drug classes, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, which demonstrate pleiotropic effects beyond glycemic control. The findings indicate that combination therapy provides superior outcomes compared to monotherapy by targeting multiple metabolic pathways simultaneously. Despite promising results, challenges such as safety, cost, and patient variability remain. The study highlights the importance of integrated and personalized approaches for improving long-term clinical outcomes in metabolic syndrome management.

Keywords: metabolic syndrome, pharmacological treatment, SGLT2 inhibitors, GLP-1 receptor agonists, insulin resistance, obesity, cardiovascular risk, combination therapy, precision medicine, metabolic disorders.

Introduction. Metabolic syndrome (MetS) represents a complex cluster of interrelated metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension, which collectively increase the risk of cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and overall mortality. Recent epidemiological data indicate that MetS affects approximately 12–30% of the global adult population, with a steadily rising prevalence driven by sedentary lifestyles, unhealthy dietary habits, and increasing obesity rates . The syndrome is not a single disease entity but rather a multifactorial condition characterized by chronic low-grade inflammation, hormonal dysregulation, and metabolic imbalance involving lipid, carbohydrate, and protein metabolism. The clinical importance of MetS lies in its strong association with adverse health outcomes. Individuals with MetS have approximately a twofold higher risk of developing atherosclerotic cardiovascular disease and a fivefold increased risk of progressing to T2DM compared to healthy individuals . Furthermore, the syndrome contributes significantly to global healthcare burden due to its link with multiple comorbidities, including renal dysfunction, cancer, and non-alcoholic fatty liver disease. Given its systemic nature, MetS requires a comprehensive and multifaceted therapeutic approach that targets both underlying mechanisms and individual risk factors.

Traditionally, the management of metabolic syndrome has relied heavily on lifestyle interventions, such as dietary modification, weight reduction, and increased physical activity.

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These strategies remain the cornerstone of therapy and have demonstrated effectiveness in improving metabolic parameters and reducing disease progression . However, lifestyle modifications alone are often insufficient for achieving sustained remission, particularly in patients with advanced metabolic disturbances or high cardiovascular risk. As a result, pharmacological interventions have become an essential component of MetS management, especially in cases where non-pharmacological measures fail to achieve therapeutic goals. One of the major challenges in the pharmacological correction of metabolic syndrome is the absence of a single approved drug that specifically targets the syndrome as a whole. Instead, current therapeutic strategies focus on treating individual components of MetS using drugs originally developed for related conditions such as hypertension, dyslipidemia, obesity, and diabetes . For instance, antihypertensive agents are used to control blood pressure, statins and other lipid-lowering drugs address dyslipidemia, while antidiabetic medications such as metformin improve insulin sensitivity and glycemic control. These interventions, although effective in reducing individual risk factors, may not fully address the complex pathophysiology of MetS.

Recent advances in pharmacotherapy have introduced novel drug classes that show promise in the integrated management of metabolic syndrome. Among these, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and dual incretin-based therapies have gained significant attention due to their ability to simultaneously improve glycemic control, promote weight loss, and reduce cardiovascular risk . Emerging evidence also highlights the role of combination therapies targeting multiple metabolic pathways, including lipid metabolism, inflammation, and insulin signaling, which may offer a more comprehensive therapeutic effect. Moreover, the growing understanding of the molecular mechanisms underlying metabolic syndrome has opened new avenues for targeted pharmacological interventions. Key pathogenic processes such as insulin resistance, adipose tissue dysfunction, oxidative stress, and chronic inflammation are now recognized as potential therapeutic targets . In this context, precision medicine approaches are being explored to tailor pharmacotherapy based on individual metabolic profiles, genetic predisposition, and comorbidity patterns. Despite these advancements, several challenges remain in the pharmacological management of MetS. These include variability in patient response, potential side effects of long-term drug use, and the need for combination therapy to achieve optimal outcomes. Additionally, the heterogeneity of the syndrome complicates the development of standardized treatment protocols. Therefore, there is a growing need for continued research to identify novel therapeutic targets and develop more effective and safer pharmacological strategies.

Metabolic syndrome represents a major global health challenge requiring an integrated therapeutic approach. While lifestyle modification remains fundamental, pharmacological correction plays a critical role in managing the complex and multifactorial nature of the syndrome. Ongoing advancements in drug development and a deeper understanding of pathophysiological mechanisms hold promise for improving clinical outcomes and reducing the burden of metabolic syndrome worldwide.

Literature review. The pharmacological correction of metabolic syndrome (MetS) has become a major focus of contemporary biomedical research due to the syndrome's multifactorial pathophysiology and its strong association with cardiovascular, renal, and metabolic disorders. Recent literature highlights that the complexity of MetS requires therapeutic approaches that go beyond targeting individual risk factors, emphasizing integrated pharmacological strategies capable of addressing multiple metabolic pathways simultaneously. Traditionally, pharmacological management of MetS has relied on the use of drugs targeting its individual components, including antihypertensive agents, lipid-lowering medications, and antidiabetic

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drugs. However, growing evidence suggests that such fragmented approaches may not fully address the underlying pathophysiological mechanisms, such as insulin resistance, chronic inflammation, endothelial dysfunction, and adipose tissue dysregulation. As a result, recent research has shifted toward identifying drug classes with pleiotropic effects that can simultaneously influence multiple components of the syndrome.

Among the most extensively studied pharmacological agents in recent years are sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). These drug classes have demonstrated not only glycemic control but also significant cardiovascular and renal protective effects. SGLT2 inhibitors act by promoting renal glucose excretion, leading to improved glycemic control, reduced blood pressure, and favorable effects on cardiac preload and afterload. In addition, they have been shown to reduce hospitalization rates for heart failure and slow the progression of chronic kidney disease . On the other hand, GLP-1 receptor agonists improve insulin secretion, delay gastric emptying, and promote satiety, thereby contributing to weight loss and improved metabolic profiles. Recent systematic reviews and meta-analyses emphasize the complementary mechanisms of these drug classes. GLP-1 RAs primarily reduce atherosclerotic cardiovascular events, while SGLT2 inhibitors exert stronger effects on heart failure and renal outcomes . This distinction has led to increasing interest in combination therapy, which aims to exploit the synergistic effects of both drug classes. Evidence from randomized controlled trials and observational studies suggests that combined therapy results in superior improvements in glycated hemoglobin (HbA1c), body weight, and systolic blood pressure compared to monotherapy. Furthermore, large-scale meta-analyses involving over one million patients have demonstrated that the combination of SGLT2 inhibitors and GLP-1 receptor agonists significantly reduces the risk of major adverse cardiovascular events (MACE), all-cause mortality, and progression of kidney disease . These findings support the hypothesis that integrated pharmacological strategies targeting multiple metabolic pathways can provide superior clinical outcomes in patients with metabolic syndrome and related disorders. In addition to their cardiovascular and metabolic benefits, recent studies have explored the role of these agents in the treatment of metabolic-associated steatotic liver disease (MASLD), which is frequently associated with MetS. GLP-1 receptor agonists, particularly semaglutide, have shown promising results in reducing liver fat content and inflammation, indicating their potential role in managing hepatic manifestations of metabolic syndrome . Similarly, SGLT2 inhibitors have demonstrated beneficial effects on liver steatosis and metabolic parameters, further supporting their use in a broader spectrum of metabolic disorders.

Another emerging area of research focuses on dual incretin therapies, such as GLP-1/GIP receptor agonists (e.g., tirzepatide), which have shown enhanced efficacy in improving glycemic control and promoting weight loss compared to traditional therapies. These agents represent a new generation of pharmacological interventions that target multiple hormonal pathways involved in metabolic regulation. Recent studies suggest that such therapies may offer superior outcomes in patients with obesity and type 2 diabetes, key components of metabolic syndrome. Despite these promising advancements, several limitations and challenges remain in the pharmacological management of MetS. One of the major concerns is the safety profile of long-term pharmacotherapy. For example, SGLT2 inhibitors have been associated with an increased risk of genitourinary infections and, in rare cases, euglycemic diabetic ketoacidosis. Similarly, GLP-1 receptor agonists may cause gastrointestinal side effects and potential reductions in lean body mass, particularly in older populations . These adverse effects necessitate careful patient selection and monitoring.

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Another important challenge highlighted in recent literature is the issue of accessibility and cost-effectiveness. Although SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated significant clinical benefits, their high cost limits widespread use, particularly in low- and middle-income countries. Studies indicate that these medications are often underutilized in populations that could benefit the most, due to economic constraints and disparities in healthcare access . This underscores the need for healthcare policies that improve the affordability and availability of these therapies. Moreover, the heterogeneity of metabolic syndrome poses a significant challenge for standardized treatment approaches. Patients with MetS exhibit diverse clinical profiles, which may require individualized therapeutic strategies. In this context, precision medicine has emerged as a promising approach for optimizing pharmacological interventions. Advances in machine learning and metabolic phenotyping have enabled the identification of distinct metabolic subtypes, allowing for more targeted and personalized treatment strategies. Such approaches may improve treatment efficacy by aligning pharmacological interventions with the specific pathophysiological mechanisms present in individual patients.

Recent research also highlights the importance of targeting underlying molecular pathways involved in metabolic syndrome, including insulin signaling, AMP-activated protein kinase (AMPK), and peroxisome proliferator-activated receptors (PPARs). These pathways play critical roles in regulating energy metabolism, inflammation, and cellular homeostasis, making them attractive targets for future drug development. Novel pharmacological agents targeting these pathways are currently under investigation, with the potential to provide more effective and comprehensive treatment options for MetS. The literature indicates a significant shift in the pharmacological management of metabolic syndrome from isolated treatment of individual components to integrated, multi-targeted therapeutic strategies. The emergence of SGLT2 inhibitors, GLP-1 receptor agonists, and dual incretin therapies represents a major advancement in this field, offering improved metabolic, cardiovascular, and renal outcomes. However, challenges related to safety, cost, and patient heterogeneity remain, highlighting the need for continued research and innovation. Future studies focusing on precision medicine and novel molecular targets are expected to further enhance the effectiveness of pharmacological interventions for metabolic syndrome.

Resarch discussion. The present analysis of recent literature demonstrates that pharmacological correction of metabolic syndrome (MetS) has evolved significantly over the past decade, shifting from a fragmented, component-based approach toward a more integrated and pathophysiology-oriented strategy. This transition reflects an improved understanding of the complex interactions between insulin resistance, inflammation, adipose tissue dysfunction, and cardiovascular risk factors that characterize MetS. One of the most important findings across contemporary studies is the growing role of novel antidiabetic drug classes, particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). These agents have demonstrated benefits that extend beyond glycemic control, including improvements in cardiovascular and renal outcomes. Evidence indicates that SGLT2 inhibitors significantly reduce the risk of heart failure, chronic kidney disease progression, and cardiovascular mortality, while GLP-1 receptor agonists are more effective in reducing atherosclerotic events such as myocardial infarction and stroke . This distinction highlights the complementary nature of these drug classes and supports their use in combination therapy.

The findings of recent meta-analyses further reinforce the superiority of combined pharmacological approaches. Combination therapy with SGLT2 inhibitors and GLP-1 receptor agonists has been associated with a reduced risk of major adverse cardiovascular events, all-

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cause mortality, and kidney-related complications compared to monotherapy . Additionally, improvements in key metabolic parameters such as glycated hemoglobin (HbA1c), body weight, and blood pressure have been consistently reported. These results suggest that targeting multiple metabolic pathways simultaneously may be more effective in managing the complex and multifactorial nature of MetS. Another important aspect highlighted in the literature is the pleiotropic effect of modern pharmacological agents. SGLT2 inhibitors, for example, exert beneficial effects on hemodynamic parameters, oxidative stress, and inflammation, while GLP-1 receptor agonists influence appetite regulation, insulin secretion, and lipid metabolism. This multi-targeted mechanism of action is particularly relevant in MetS, where multiple physiological systems are dysregulated. The ability of these drugs to act on interconnected metabolic pathways provides a strong rationale for their increasing use in clinical practice. Despite these advancements, several challenges remain in the pharmacological management of metabolic syndrome. One of the key issues is the variability in patient response to treatment. Clinical studies indicate that individual outcomes may differ depending on factors such as genetic predisposition, baseline metabolic profile, and the presence of comorbid conditions. This variability underscores the importance of personalized medicine approaches in optimizing treatment strategies. Emerging evidence suggests that machine learning and metabolic phenotyping can help identify patient subgroups that may benefit most from specific pharmacological interventions, thereby improving therapeutic efficacy.

Safety considerations also play a critical role in the long-term use of pharmacological therapies. Although SGLT2 inhibitors and GLP-1 receptor agonists are generally well tolerated, they are associated with certain adverse effects. For instance, SGLT2 inhibitors may increase the risk of genitourinary infections, while GLP-1 receptor agonists are commonly associated with gastrointestinal symptoms. These potential side effects must be carefully balanced against the clinical benefits, particularly in patients requiring long-term therapy. Another important limitation is related to accessibility and cost. Advanced pharmacological agents, including GLP-1 receptor agonists and combination therapies, remain expensive and may not be widely доступны in low- and middle-income countries. Studies have shown that despite strong clinical evidence supporting their use, these therapies are often underutilized due to economic barriers and disparities in healthcare systems . Addressing these challenges will require coordinated efforts from healthcare providers, policymakers, and pharmaceutical industries to improve affordability and accessibility. Furthermore, the heterogeneity of metabolic syndrome complicates the development of standardized treatment guidelines. Patients with MetS may present with different combinations and severities of metabolic abnormalities, making it difficult to apply a one-size-fits-all approach. As a result, current clinical guidelines increasingly emphasize individualized treatment plans based on patient-specific risk profiles and comorbidities.

In addition to established pharmacotherapies, emerging research is exploring new therapeutic targets, including pathways related to AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and inflammatory mediators. These targets represent promising avenues for future drug development and may lead to more effective and comprehensive treatment strategies. The discussion of recent findings highlights that pharmacological correction of metabolic syndrome is moving toward a more integrated, multi-targeted, and personalized approach. The use of SGLT2 inhibitors, GLP-1 receptor agonists, and their combination has demonstrated significant improvements in metabolic, cardiovascular, and renal outcomes. However, challenges related to safety, cost, and patient heterogeneity remain significant barriers to optimal treatment. Future research should focus on developing novel

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therapeutic agents, improving accessibility, and implementing precision medicine approaches to enhance the effectiveness of pharmacological interventions in metabolic syndrome.

Conclusion. Metabolic syndrome remains a major global health challenge due to its complex pathophysiology and strong association with cardiovascular and metabolic diseases. This study highlights that pharmacological correction has shifted from targeting individual components toward integrated, multi-targeted therapeutic strategies. Modern drug classes, particularly SGLT2 inhibitors and GLP-1 receptor agonists, demonstrate significant benefits not only in glycemic control but also in reducing cardiovascular risk, improving renal outcomes, and promoting weight loss. The evidence suggests that combination therapy provides superior clinical outcomes compared to monotherapy, supporting a more comprehensive approach to managing metabolic syndrome. However, several challenges persist, including variability in patient response, potential side effects, high treatment costs, and limited accessibility in certain regions. Therefore, future directions should focus on the development of novel pharmacological agents targeting underlying molecular mechanisms, as well as the implementation of personalized treatment strategies based on individual metabolic profiles. Enhancing affordability and accessibility of effective therapies will also be crucial. Overall, a multidisciplinary and patient-centered approach is essential for improving long-term outcomes in metabolic syndrome management.

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