

Obesity and Metabolic Syndrome: Clinical Challenges and Emerging Therapies

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Abstract: Obesity and metabolic syndrome have become major global public health concerns because of their strong association with type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, and premature mortality. The prevalence of obesity has increased dramatically over recent decades owing to changes in dietary patterns, reduced physical activity, urbanization, genetic susceptibility, and environmental influences. Metabolic syndrome, characterized by central obesity, hypertension, dyslipidemia, insulin resistance, and impaired glucose metabolism, substantially increases the risk of both cardiovascular and metabolic complications. Advances in understanding adipose tissue biology, chronic inflammation, gut microbiota, hormonal regulation, and energy metabolism have transformed approaches to prevention and treatment. Contemporary management combines lifestyle intervention, pharmacotherapy, bariatric surgery, and multidisciplinary long-term care. Recently developed anti-obesity medications, particularly glucagon-like peptide-1 receptor agonists and dual incretin therapies, have demonstrated substantial improvements in weight reduction and metabolic health. This review summarizes current evidence regarding the pathophysiology, diagnosis, and management of obesity and metabolic syndrome while highlighting emerging therapeutic strategies.

Keywords: Obesity; Metabolic syndrome; Insulin resistance; Weight management; GLP-1 receptor agonists; Bariatric surgery.

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INTRODUCTION

Obesity has evolved into one of the most significant global health challenges of the twenty-first century. Once considered primarily a consequence of excessive caloric intake, obesity is now recognized as a complex chronic disease resulting from interactions among genetic, metabolic, hormonal, behavioral, environmental, and socioeconomic factors. The rapid increase in obesity prevalence has contributed substantially to the worldwide burden of type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, obstructive sleep apnea, osteoarthritis, infertility, and several forms of cancer [1].

Metabolic syndrome represents a cluster of interconnected metabolic abnormalities including abdominal obesity, elevated blood pressure, impaired glucose metabolism, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol. Individuals meeting diagnostic criteria for metabolic syndrome have a markedly increased risk of developing diabetes mellitus, atherosclerotic cardiovascular disease, stroke, and premature mortality. Because obesity serves as the central driving factor for many of these abnormalities, early identification and comprehensive management remain essential components of preventive healthcare.

The pathophysiology of obesity extends beyond simple accumulation of excess body fat. Adipose tissue functions as an active endocrine organ that secretes numerous hormones, cytokines, and inflammatory mediators influencing appetite regulation, insulin sensitivity, vascular function, and systemic metabolism. Excess visceral adiposity promotes chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances that contribute directly to cardiovascular disease and multiple organ dysfunction [2].

Recent scientific advances have transformed obesity management. Lifestyle intervention remains fundamental; however, growing understanding of appetite regulation and neuroendocrine signaling has led to the development of highly effective pharmacological therapies capable of producing clinically meaningful weight reduction. Simultaneously,

bariatric and metabolic surgery continue to provide durable improvements in obesity-related complications among carefully selected patients. These advances have established obesity as a treatable chronic disease requiring long-term multidisciplinary management rather than short-term weight loss alone.

Pathophysiology of Obesity and Metabolic Syndrome

Body weight is regulated through a complex interaction among central nervous system pathways, gastrointestinal hormones, adipose tissue, skeletal muscle, liver, pancreas, and environmental influences. Under physiological conditions, appetite and energy expenditure remain tightly controlled through hormonal signals including leptin, ghrelin, insulin, peptide YY, glucagon-like peptide-1 (GLP-1), and numerous hypothalamic neuropeptides. Disruption of these regulatory systems contributes to excessive energy storage and progressive weight gain.

Visceral adipose tissue plays a central role in metabolic syndrome. Unlike subcutaneous fat, visceral fat demonstrates greater metabolic activity and releases increased amounts of free fatty acids, inflammatory cytokines, tumor necrosis factor-alpha, interleukin-6, and adipokines that impair insulin signaling. Progressive insulin resistance develops as skeletal muscle, liver, and adipose tissue become less responsive to insulin, resulting in hyperglycemia, compensatory hyperinsulinemia, dyslipidemia, and endothelial dysfunction [3].

Chronic low-grade inflammation has emerged as a key mechanism linking obesity with metabolic disease. Activation of macrophages within adipose tissue promotes continuous production of inflammatory mediators that contribute to vascular injury, oxidative stress, hypertension, and accelerated atherosclerosis. Alterations in gut microbiota composition, intestinal permeability, circadian rhythm disruption, and genetic susceptibility further influence metabolic homeostasis and may contribute to obesity development.

Table 1. Major Components of Metabolic Syndrome

Component	Clinical Significance
Central obesity	Major driver of metabolic dysfunction
Hypertension	Increased cardiovascular risk
Hyperglycemia	Development of type 2 diabetes mellitus
Elevated triglycerides	Accelerated atherosclerosis
Reduced HDL cholesterol	Increased cardiovascular events

Clinical Evaluation and Diagnosis

Diagnosis of obesity should extend beyond body mass index (BMI) because BMI alone does not accurately reflect body fat distribution or metabolic risk. Comprehensive evaluation should include waist circumference, assessment of visceral adiposity, blood pressure measurement, fasting blood glucose or glycated hemoglobin, lipid profile, liver function tests, and evaluation for obesity-related complications.

A detailed clinical history should explore dietary habits, physical activity, sleep quality, psychological health, medication use, family history, and previous weight management attempts. Physical examination should assess cardiovascular risk factors, endocrine disorders, musculoskeletal complications, and evidence of obesity-associated comorbidities including non-alcoholic fatty liver disease and obstructive sleep apnea.

Increasing attention has focused on early identification of metabolic syndrome because timely intervention substantially reduces progression toward diabetes mellitus and cardiovascular disease. Contemporary risk assessment therefore integrates anthropometric measurements with laboratory evaluation and comprehensive cardiovascular risk stratification.

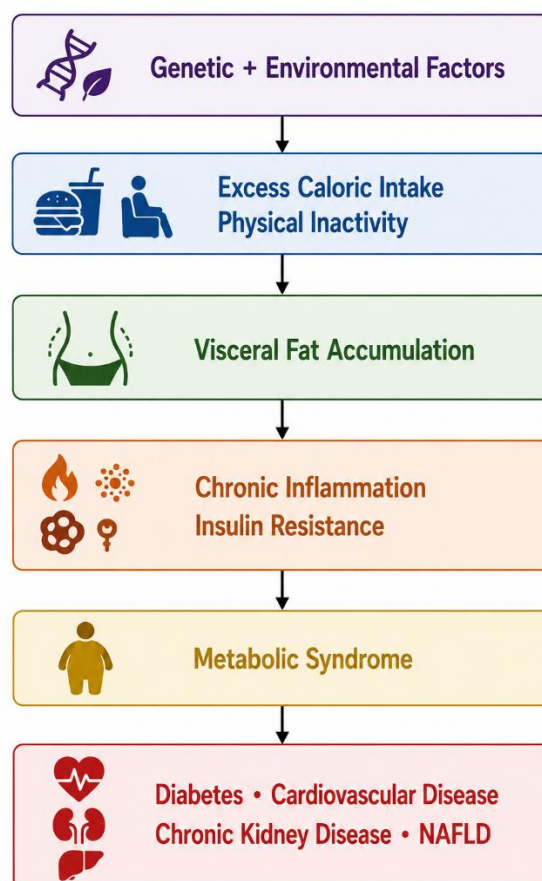


Figure 1. Development of Obesity-Associated Metabolic Syndrome

Figure 1. Simplified overview illustrating the progression from obesity to metabolic syndrome and associated chronic diseases.

Contemporary Management and Emerging Therapies

Management of obesity and metabolic syndrome requires a comprehensive, long-term strategy that addresses excess adiposity, metabolic abnormalities, cardiovascular risk factors, and associated comorbidities. Modern treatment emphasizes sustainable lifestyle modification combined with individualized pharmacological therapy and metabolic surgery for selected patients. Because obesity is now recognized as a chronic relapsing disease, management should focus on improving overall metabolic health rather than achieving rapid short-term weight loss alone [4].

Lifestyle intervention remains the cornerstone of treatment and should be recommended for every patient regardless of body mass index or metabolic status. Nutritional therapy aims to establish a sustainable caloric deficit while ensuring adequate intake of essential nutrients. Dietary patterns such as the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), and plant-based dietary strategies have consistently demonstrated improvements in body weight, insulin sensitivity, lipid profile, and cardiovascular health. Rather than promoting restrictive diets, current recommendations emphasize individualized meal planning that patients can maintain over the long term.

Regular physical activity complements dietary intervention by increasing energy expenditure, preserving lean muscle mass, improving insulin sensitivity, and enhancing cardiovascular fitness. International guidelines recommend at least 150–300 minutes of moderate-intensity aerobic exercise per week together with resistance training on two or more days each week. Even modest increases in daily physical activity contribute to clinically meaningful improvements in metabolic health independent of substantial weight loss.

Behavioral modification forms another essential component of obesity treatment. Structured counseling, cognitive behavioral therapy, self-monitoring of dietary intake, stress management, sleep optimization, and psychological support significantly improve long-term adherence to lifestyle interventions. Addressing emotional eating, depression, anxiety, and other psychological factors often enhances treatment success and reduces weight regain.



Pharmacological therapy should be considered for individuals who fail to achieve adequate weight reduction through lifestyle intervention alone or who possess obesity-related comorbidities. The development of glucagon-like peptide-1 (GLP-1) receptor agonists has transformed obesity management by producing clinically significant and sustained weight reduction while simultaneously improving glycemic control and cardiovascular risk factors. Medications such as semaglutide have demonstrated average weight reductions exceeding those achieved with earlier pharmacological therapies. More recently, dual glucose-dependent insulintropic polypeptide (GIP) and GLP-1 receptor agonists, including tirzepatide, have demonstrated even greater improvements in body weight and metabolic outcomes across multiple clinical trials [5].

Other approved pharmacological options include orlistat, naltrexone-bupropion, and phentermine-topiramate, each acting through different mechanisms to reduce caloric intake or nutrient absorption. Medication selection should be individualized according to patient characteristics, cardiovascular risk profile, metabolic abnormalities, contraindications, and treatment preferences. Pharmacotherapy should always complement rather than replace lifestyle intervention.

Table 2. Current Therapeutic Approaches for Obesity

Intervention	Primary Clinical Benefit	Suitable Patient Population
Lifestyle modification	Weight reduction and improved metabolic health	All patients
GLP-1 receptor agonists	Significant weight loss and improved glycemic control	Obesity with or without diabetes
Dual GIP/GLP-1 agonists	Greater weight reduction	Moderate to severe obesity
Bariatric surgery	Long-term weight loss and remission of metabolic disease	Severe obesity with comorbidities
Behavioral therapy	Improved long-term adherence	All stages of obesity management

Metabolic and bariatric surgery remains the most effective treatment for severe obesity and its associated metabolic complications. Procedures including sleeve gastrectomy and Roux-en-Y gastric bypass produce substantial and durable weight reduction while frequently improving or resolving type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, and non-alcoholic fatty liver disease. Long-term follow-up is essential because patients require nutritional monitoring, vitamin supplementation, and continued lifestyle support following surgery [6].

Management of metabolic syndrome also requires aggressive treatment of associated cardiovascular risk factors. Blood pressure optimization, glycemic control, lipid-lowering therapy, smoking cessation, and management of non-alcoholic fatty liver disease should be integrated into comprehensive patient care. This multifaceted approach substantially reduces cardiovascular events while improving overall survival.



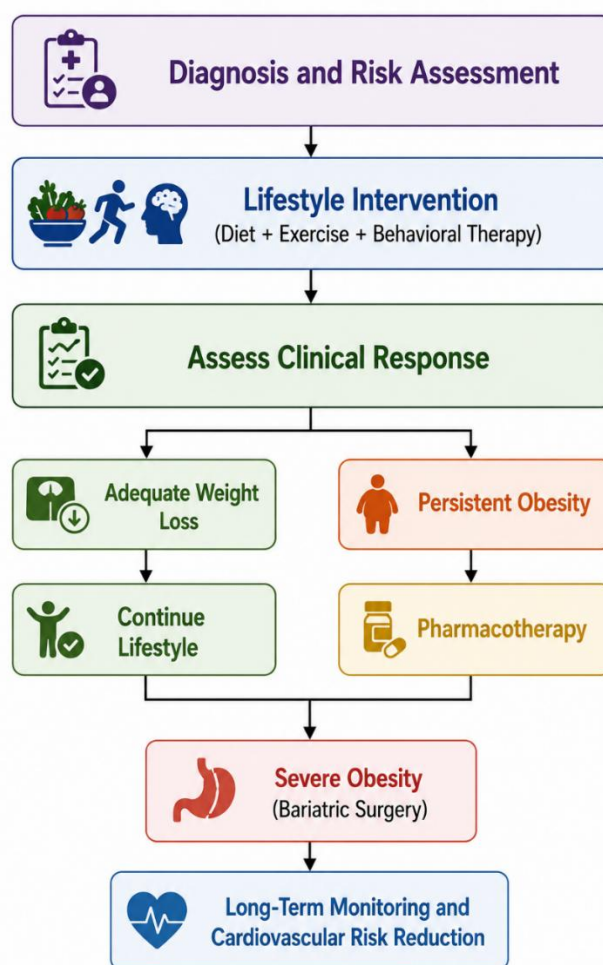


Figure 2. Comprehensive Management of Obesity and Metabolic Syndrome

Figure 2. Contemporary management pathway demonstrating the stepwise approach to obesity treatment, beginning with lifestyle intervention and progressing to pharmacotherapy or bariatric surgery when clinically indicated.

Increasing interest has also focused on precision medicine in obesity management. Genetic profiling, metabolic phenotyping, microbiome analysis, and biomarker-guided therapy may eventually enable clinicians to identify the most effective treatment for individual patients. Artificial intelligence-supported dietary counseling, wearable health technologies, continuous glucose monitoring, and digital weight-management platforms are also improving long-term patient engagement and treatment adherence.

Table 3. Emerging Innovations in Obesity Management

Innovation	Current Status	Potential Clinical Benefit
Dual incretin therapies	Clinical implementation	Greater weight loss than previous medications
Triple hormone agonists	Advanced clinical trials	Improved metabolic regulation
Artificial intelligence-based lifestyle coaching	Increasing clinical use	Personalized weight management
Gut microbiome therapies	Experimental	Improved metabolic function
Precision nutrition	Ongoing research	Individualized dietary recommendations
Digital health monitoring	Widely expanding	Improved adherence and long-term follow-up

These emerging therapeutic strategies indicate that obesity management is transitioning from generalized treatment recommendations toward individualized, mechanism-based care. Continued advances in pharmacology, metabolic research, digital health technologies, and precision medicine are expected to further improve long-term outcomes while reducing the global burden of obesity and metabolic syndrome.



DISCUSSION

Obesity and metabolic syndrome represent complex chronic disorders that have become major contributors to the global burden of non-communicable diseases. Current evidence indicates that obesity is far more than excessive accumulation of body fat; it is a multifactorial metabolic disease involving genetic susceptibility, neuroendocrine regulation, chronic inflammation, environmental influences, and behavioral factors. This broader understanding has fundamentally changed clinical management by emphasizing long-term disease control rather than short-term weight reduction alone [1].

One of the most significant advances in obesity research has been recognition of adipose tissue as an active endocrine organ rather than a passive energy storage site. Excess visceral adipose tissue secretes inflammatory cytokines, adipokines, and free fatty acids that promote insulin resistance, endothelial dysfunction, hypertension, dyslipidemia, and systemic inflammation. These metabolic disturbances collectively contribute to cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, and non-alcoholic fatty liver disease, highlighting the need for early intervention before irreversible complications develop [2].

Lifestyle modification remains the cornerstone of treatment and continues to provide substantial improvements in metabolic health. Sustained dietary modification, increased physical activity, behavioral counseling, and long-term patient support have consistently demonstrated reductions in body weight and cardiometabolic risk. However, maintaining long-term adherence remains one of the greatest clinical challenges because biological mechanisms frequently promote weight regain after initial weight loss. Consequently, obesity management should be viewed as lifelong chronic disease care rather than temporary lifestyle intervention.

Pharmacological therapy has undergone remarkable evolution during recent years. Earlier anti-obesity medications generally produced modest weight reduction and were often limited by adverse effects. In contrast, newer glucagon-like peptide-1 receptor agonists and dual incretin therapies have demonstrated unprecedented improvements in body weight, glycemic control, blood pressure, and cardiovascular risk. These medications have shifted therapeutic expectations by providing clinically meaningful weight reduction that approaches outcomes previously achievable only through bariatric surgery. Continued investigation of triple hormone agonists and combination therapies may further expand treatment options in the future [5].

Metabolic and bariatric surgery remains the most effective intervention for severe obesity and has demonstrated durable improvements in diabetes remission, hypertension, dyslipidemia, obstructive sleep apnea, and overall survival. Nevertheless, surgical treatment requires careful patient selection, multidisciplinary evaluation, and lifelong nutritional follow-up to minimize postoperative complications and maintain long-term health. Modern obesity management therefore integrates surgical and non-surgical approaches according to individual patient characteristics and treatment goals.

Another important development is the growing emphasis on precision medicine. Increasing evidence suggests that obesity consists of multiple biological subtypes differing in genetic background, appetite regulation, metabolic phenotype, gut microbiota composition, and treatment responsiveness. Future individualized treatment strategies based on molecular profiling may enable clinicians to select the most appropriate dietary intervention, pharmacological therapy, or surgical procedure for each patient rather than applying a uniform management approach.

Despite encouraging progress, important challenges remain. Global obesity prevalence continues to rise because of sedentary lifestyles, increased consumption of highly processed foods, socioeconomic inequalities, inadequate access to preventive healthcare, and environmental influences. Furthermore, weight stigma and misconceptions regarding obesity as solely a lifestyle choice continue to delay diagnosis and treatment. Comprehensive public health policies addressing nutrition, physical activity, urban planning, food regulation, and health education will therefore remain essential for reversing current trends.



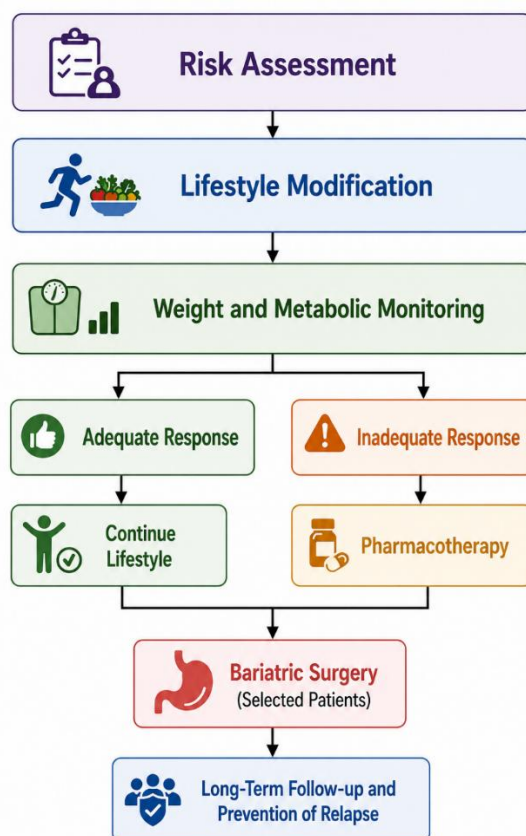


Figure 3. Long-Term Management Framework for Obesity and Metabolic Syndrome

Figure 3. Comprehensive long-term management model demonstrating continuous assessment, individualized treatment escalation, and sustained follow-up for obesity and metabolic syndrome.

Future Perspectives

Future obesity management is expected to become increasingly individualized through advances in precision medicine, genomics, metabolomics, artificial intelligence, and digital healthcare technologies. Identification of genetic and metabolic profiles may allow clinicians to predict therapeutic response and personalize dietary, pharmacological, and behavioral interventions.

Research into gut microbiota modulation, microbiome transplantation, triple incretin receptor agonists, gene-based therapies, and appetite-regulating neural pathways continues to expand rapidly. These innovations may provide more effective and durable weight reduction while improving metabolic health with fewer adverse effects.

Artificial intelligence-assisted nutritional counseling, wearable activity monitors, continuous metabolic monitoring, and digital lifestyle coaching platforms are expected to enhance long-term treatment adherence by providing real-time feedback and individualized recommendations. Integration of these technologies into routine clinical practice may significantly improve patient engagement and sustained weight management.

CONCLUSION

Obesity and metabolic syndrome remain among the most important contributors to chronic disease and premature mortality worldwide. Contemporary evidence demonstrates that these conditions result from complex interactions among genetic, hormonal, metabolic, behavioral, and environmental factors rather than excessive caloric intake alone.

Lifestyle intervention remains the foundation of treatment, while recent advances in pharmacotherapy, particularly GLP-1 receptor agonists and dual incretin therapies, have significantly improved long-term weight management. Bariatric surgery continues to provide the most effective treatment for carefully selected patients with severe obesity and associated metabolic complications.

Future progress will depend upon early identification of high-risk individuals, implementation of multidisciplinary long-term care, expansion of preventive public health strategies, and continued development of precision medicine approaches. Through coordinated clinical management and population-based prevention, the growing global burden of obesity and metabolic syndrome can be substantially reduced.

Conflict of Interest

The authors declare that there are no conflicts of interest related to this review.

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Author Contributions

Both the author contributed to the conception, literature review, manuscript drafting, critical revision, and approval of the final manuscript.

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