

COMMENTARY

Addressing the burden of obesity: Commentary to “Obesity management: An update on the available pharmacotherapy”

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Abstract

Obesity is a complex systemic condition with significant sexual dimorphism, increasing the risks of disorders such as type 2 diabetes mellitus, arterial hypertension, dyslipidemia, metabolic dysfunction-associated steatotic liver disease, chronic kidney disease, premature cardiovascular disease, and certain types of cancers. A recent publication by Christaki *et al.* on the comprehensive overview of obesity management in *Innovative Medicines and Omics* highlights the multifactorial nature of obesity, as well as the importance of lifestyle changes, alongside pharmacological treatments and bariatric surgery. This commentary advocates for precision medicine strategies to effectively address the challenges posed by obesity. By highlighting the potential health and economic benefits of reducing obesity, we call for a holistic approach that integrates behavioral, medical, and policy interventions. We also identify research gaps, suggesting that future studies explore endocrine connections in obesity and assess endoscopic techniques targeting the duodenum as adjunct therapies in the context of tailored care.

Keywords: Endocrine connections; Endoscopy; Lifestyle interventions; Metabolic disorders; Pharmacotherapy; Precision medicine approaches

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1. Background

Pragmatically defined based on classes of body mass index (BMI), obesity is a systemic condition with complex pathogenic determinants and significant sexual dimorphism.^{1,2} Alarming, obesity often acts as the precursor of a cluster of self-aggregating metabolic disorders, including type 2 diabetes mellitus (T2DM), arterial hypertension (HTN), atherogenic dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD; previously known as nonalcoholic fatty liver disease, NAFLD), and chronic kidney disease (CKD).³⁻⁵ These metabolic conditions are interrelated and collectively impact cardio-metabolic health, the risk of hepato-renal failure, and certain types of cancer.^{3,6-8} Over the past few decades, the burden of T2DM and obesity has rapidly increased, while the rise in HTN and dyslipidemia has slowed, and the burden of MASLD burden has remained stable.⁹

According to a recent survey, from 1990 to 2021, global deaths and disability-adjusted life years (DALYs) attributed to high BMI have more than doubled in both sexes.¹⁰ The

age-standardized death rates remained steady for females, increased by 15.0% for males, and the age-standardized DALY rates increased by 21.7% for females and 31.2% for males.¹⁰ In 2021, the six leading causes of high BMI-attributable DALYs were T2DM, ischemic heart disease, hypertensive heart disease, CKD, low back pain, and stroke.¹⁰ From 1990 to 2021, the highest annual percentage changes in age-standardized DALY rates were observed in countries of low-middle socio-demographic index (SDI), with high SDI countries showing the lowest changes.¹⁰

To combat obesity, a wide range of therapeutic interventions are available, including lifestyle changes, pharmacological approaches, and, ultimately, endoscopic techniques and bariatric surgery.¹¹⁻¹⁴ Lifestyle changes are affordable and easily accessible, but they can be difficult to sustain over long periods of time.¹¹ Pharmacological treatment, although usually effective and safe for most patients, may cause financial burdens and potential side effects for a small group of individuals.¹² Endoscopic techniques are less invasive than bariatric surgery, but their availability and risk-benefit profile are still uncertain.¹³ Metabolic bariatric surgery results in long-term weight loss and improvement in certain obesity-related conditions, but it necessitates lifelong lifestyle changes and comes with risks of complications and potential weight regain.¹⁴

2. Summary of the paper by Christaki *et al.*

With this complex background, Christaki *et al.*¹⁵ recently published a comprehensive overview of drug therapy for obesity management in *Innovative Medicines and Omics*. The review provides a thorough analysis of childhood obesity, a growing concern exacerbated by the COVID-19 pandemic due to its long-term health and psychosocial impacts, lifestyle interventions, and supplements. Christaki *et al.*, highlight the global prevalence of obesity, its socioeconomic consequences, and the economic burden it places on healthcare systems. The authors emphasize the multifactorial nature of obesity, influenced by genetic, behavioral, and hormonal factors, which pose significant health risks such as cardiovascular diseases, diabetes, and certain cancers. They also note that while BMI is commonly used to classify obesity severity, alternative metrics such as waist-to-hip ratio and body fat percentage provide more detailed insights.

Reducing obesity can yield significant health, social, and economic benefits, including lower healthcare costs, improved quality of life, and enhanced productivity. Various strategies are available to achieve this goal, such as lifestyle changes, including dietary modifications, physical activity, behavioral therapy, stress management, and sleep optimization. While these are foundational options, they

are often challenging to sustain in the long run in most cases.

According to Christaki *et al.*,¹⁵ pharmacological treatments include food and drug administration-approved drugs such as orlistat, liraglutide, semaglutide, phentermine/topiramate, naltrexone/bupropion, metreleptin, setmelanotide, and tirzepatide. These medications act through suppression of appetite, inhibition of fat absorption, and metabolic regulation, with each individual drug having a specific profile of safety, efficacy, mechanisms, and dosages. Supplements such as L-carnitine, conjugated linoleic acid, ginseng, glucomannan, psyllium, melatonin, and cannabidiol are also being explored for their potential in weight management. The chapter on supplements adds to the accuracy of the review article, although additional clinical data are needed before utilizing these drugs in clinical practice. Bariatric surgery is recommended for more advanced cases of obesity, particularly in the presence of comorbidities and if other treatments have failed.

Ongoing research into genetic and metabolic factors promises more targeted and effective treatments. Obesity management requires a multifaceted approach that combines lifestyle changes, pharmacotherapy, and, in severe cases, surgical interventions.¹⁵

3. Strengths and limitations

This review provides a comprehensive overview of obesity pharmacotherapy, covering established treatments like orlistat and newer to emerging options like tirzepatide. One of its strengths is recognizing that obesity is a complex issue that requires a combination of behavioral, medical, and policy interventions. The wide range of therapies discussed allows clinicians and researchers to understand the ongoing advancements in personalized obesity management. However, a limitation is the focus on weight-centric outcomes, while future studies should consider including “visceral endpoints,” such as biomarkers of hepatic health and renal function, to better understand the impact of obesity on multiple organs. This would provide more accurate evaluations of treatment effectiveness and safety. In addition, while the review effectively summarizes current interventions, there is a need for systematic comparisons of cost-effectiveness and real-world adherence, considering genetic, cultural, and socioeconomic factors.

4. Research agenda

Further investigation should focus on the mutual and bi-directional endocrine connections in obesity. These connections can range from obesity resulting from primary endocrine deficiencies, such as those seen in hypothalamic

obesity,¹⁶ to hypogonadism resulting from primary obesity.¹⁷ In addition, the potential role of concurrent endoscopic techniques, such as duodenal mucosa resurfacing,¹⁸ as an add-on option to pharmacological treatment should be explored further through randomized controlled trials. Moreover, the significant role of sex differences,¹⁹ as well as the various genetic and metabolic forms of MASLD in determining the progression from healthy to unhealthy obesity and its complications,^{19,20} needs to be more thoroughly investigated. This includes examining the impact of obesity treatment on crucial visceral outcomes such as MASLD and CKD.^{2,21,22}

5. Conclusion

In conclusion, this paper lays a solid foundation for expanding obesity research to include holistic endpoints and precision medicine approaches.

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Conflict of interest

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The author, Amedeo Lonardo retired from Azienda Ospedaliero-Universitaria of Modena, Modena, Italy in 2023.

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