The Obesity Puzzle: Mechanisms, Consequences, and Cutting Edge Treatments

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Abstract

Obesity is now recognized as a chronic, relapsing, and multifactorial disease with profound implications for global health. Its prevalence has surged across all ages and populations, driving the epidemic of noncommunicable diseases, disability, and rising health care costs. This review summarizes current understanding of obesity from measurement and classification to epidemiology and underlying mechanisms, including neuroendocrine, genetic, developmental, adipose tissue-derived, microbiome, and environmental contributors. Major clinical consequences, cardiometabolic disease, cancer, and impaired quality of life, are highlighted alongside approaches for risk assessment and stratification. Evidence-based prevention and treatment strategies are examined, spanning lifestyle modification, pharmacotherapy, device-based therapies, and metabolic surgery. Particular attention is given to special populations (children, older adults, and pregnant women) and to issues of health system integration and equity. The recent advent of highly effective incretin-based therapies has transformed treatment paradigms, while raising questions about long-term safety, accessibility, and sustainability. We conclude by outlining the key research priorities necessary to translate these scientific advances into sustainable, population-level improvements in metabolic health.

Keywords. obesity, BMI, adiposity, GLP-1, bariatric surgery, NAFLD.

Introduction

Obesity is increasingly recognized as a chronic, relapsing, and multifactorial disease that substantially affects individual and public health. Rather than merely representing an elevated body mass index (BMI), obesity involves abnormal or excessive fat accumulation that carries significant metabolic and cardiovascular risks (1). Clinical assessment often relies on BMI, with thresholds of ≥25 kg/m² for overweight and ≥30 kg/m² for obesity, although additional measures, such as waist circumference and body composition, offer more precise evaluation of cardiometabolic risk. Framing obesity as a chronic disease emphasizes the importance of long-term, multi-modal management strategies, including lifestyle modification, pharmacotherapy, and surgical interventions. This review aims to offer a brief, clinician and researcher-focused overview of current evidence on epidemiology, mechanisms, complications, and treatments.

Global epidemiology and trends

Prevalence and population burden. The prevalence of overweight and obesity has risen dramatically over the past three decades, affecting populations across all age groups. In 2022, approximately 2.5 billion adults were classified as overweight, with nearly 890 million meeting criteria for obesity (1). Childhood and adolescent obesity have also surged, with worrying implications for lifelong cardiometabolic risk. In 2024, 35 million children under the age of 5 were overweight. Over 390 million children and adolescents aged 5–19 years were overweight in 2022, including 160 million who were living with obesity (1). The absolute number of individuals with severe obesity (BMI ≥35 or ≥40 kg/m^2) has risen as well, increasing the demand for high-intensity interventions.

Regional variation and drivers. Prevalence varies markedly by region and socioeconomic status: high-income countries have historically had the highest prevalence, but middle-income countries have experienced rapid increases driven by urbanization, dietary transitions to energy-dense processed foods, reduced physical activity, and obesogenic built environments (2). Social determinants, poverty, education, food deserts, and marketing shape exposure and vulnerability. The epidemiologic transition also shifts noncommunicable disease (NCD) burdens in low- and middle-income countries, where undernutrition and obesity may coexist within populations and even within households.

Temporal trends and burden metrics. Over the past three decades, trends reflect both rising incidence and reduced mortality from competing causes, producing increased years lived with disability and disability adjusted life years (DALYs) attributable to high BMI. The global age-standardized DALY rates associated with being overweight and obesity increased by over 15%, placing it as one of the top risk factors, and the risk with the steepest increase in attributable burden (3). Economic costs include health care expenditures for obesity related conditions and indirect costs from lost productivity.

Measurement and classification

Limitations of BMI and alternative measures. BMI is practical for population surveillance but imperfect for individual risk assessment: it does not distinguish between fat and lean mass or reveal fat distribution (4,5). To detect obesity, BMI has a very high specificity (97%) but poor sensitivity (42%) and sometimes misclassifies individuals (6). Waist circumference and waist-to-hip ratio are better indicators of abdominal adiposity and cardiometabolic risk (6). Imaging (CT, MRI, DXA) enables the quantification of visceral adipose tissue and ectopic fat (hepatic, pancreatic), but it is costly and not routinely performed (7).

Staging systems and personalized risk. Clinical staging systems, such as the Edmonton Obesity Staging System (EOSS), integrate comorbidities and functional status to prioritize treatment intensity (8). Combining anthropometry, cardiometabolic markers, and functional measures supports individualized management plans.

Pathophysiology of obesity

Energy balance and neuroendocrine regulation. At the simplest level, obesity results from chronic positive energy balance. However, biologic systems tightly regulate energy homeostasis via hypothalamic and brainstem circuits integrating peripheral signals (leptin, insulin, ghrelin, peptide YY, GLP-1, cholecystokinin) (9). Hedonic pathways (mesolimbic dopamine) and food reward substantially influence intake and are modulated by environmental cues (10). Set-point and defended-weight theories explain why weight loss often triggers compensatory increases in appetite and reductions in energy expenditure, thereby favoring weight regain.

Adipose tissue biology and inflammation. Adipose tissue is an active endocrine organ that releases adipokines (leptin, adiponectin, resistin) and serves as a source of proinflammatory cytokines (TNF-α, IL-6), contributing to systemic low-grade inflammation, insulin resistance, and atherogenesis. Adipose tissue expandability and the depot-specific propensity for visceral versus subcutaneous storage influence metabolic outcomes; visceral and ectopic fat are more closely linked to cardiometabolic risk than subcutaneous fat (11).

Genetics, epigenetics, and developmental contributors. Genetic variation explains some interindividual susceptibility: monogenic forms (e.g., MC4R mutations) illustrate severe, early-onset phenotypes, while polygenic risk scores capture common variant contributions (12). Epigenetic programming mediated by prenatal nutrition, maternal obesity, and early life exposures can predispose to later obesity. Interactions between genetic predisposition and obesogenic environments are central to contemporary epidemics.

Gut microbiome, circadian biology, and environmental obesogens. Emerging evidence suggests that the gut microbiome plays a role in energy harvesting, bile acid metabolism, and inflammation; dysbiosis may also influence weight and metabolic phenotype (13). Circadian disruption (shift work, irregular sleep) alters appetite regulation and metabolism. Environmental

chemicals (endocrine disrupting obesogens) may perturb adipogenesis and metabolic signaling (14).

Behavioral and psychosocial factors. Hedonic feeding, driven by food reward, stress, emotional eating, adverse childhood experiences, and socioeconomic constraints (including food insecurity and limited access to safe physical activity spaces), strongly influences intake patterns and the ability to maintain behavior change (10). Weight stigma and discrimination can worsen psychological distress and create barriers to care.

Complications and associated diseases (comorbidities) (Fig.1)

Cardiometabolic disease. Obesity is a major risk factor for type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and atherosclerotic cardiovascular disease (ASCVD) (15,16). Weight reduction, even modest (5–10%), improves glycemic control, blood pressure, and lipid profiles (17).

Respiratory and sleep disorders. Obstructive sleep apnea (OSA) is highly prevalent among people with obesity and contributes independently to cardiovascular risk and daytime dysfunction (18).

Musculoskeletal and quality of life impacts. Excess weight accelerates joint degeneration, notably knee and hip osteoarthritis, increasing pain and disability (19). Reduced physical function and weight stigma also impair mental health and social participation.

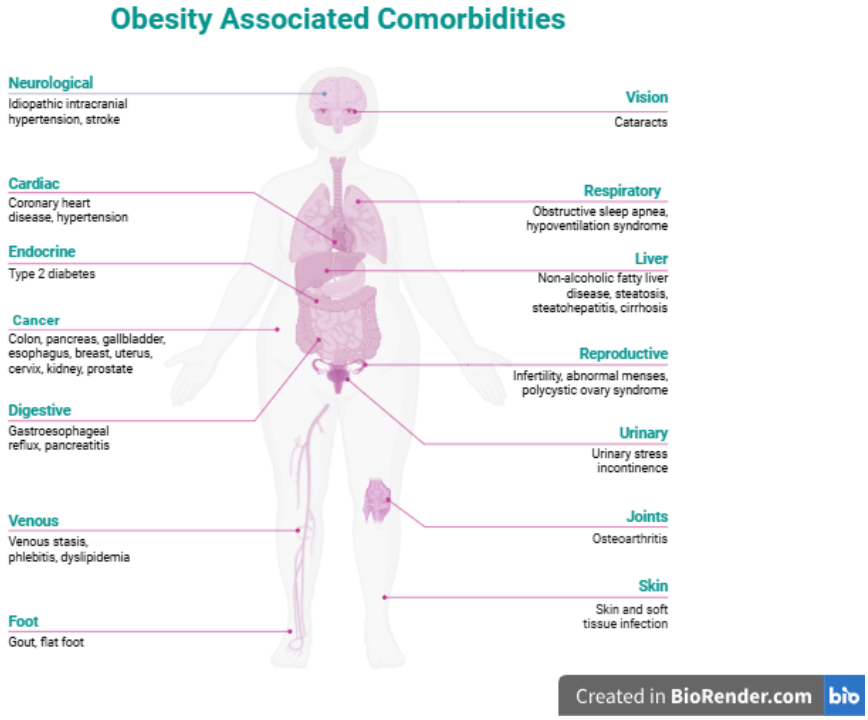

Figure 1. Comorbidities associated with obesity. (Images realized by the author with BioRender)

Hepatic, oncologic, and reproductive consequences. Nonalcoholic fatty liver disease (NAFLD) and its progressive form, nonalcoholic steatohepatitis (NASH), are closely linked to obesity and metabolic dysfunction (20). Obesity increases risk for several cancers (postmenopausal breast, colorectal, endometrial, pancreatic) and is associated with reproductive disorders, including polycystic ovary syndrome (PCOS) and subfertility (21,22).

Infectious disease interactions and COVID-19 example. Obesity has been associated with increased risk of severe outcomes from infectious diseases (e.g., COVID-19), likely via cardiopulmonary compromise, chronic inflammation, and altered immunity (23).

Mental health, stigma, and quality of life. Depression, anxiety, disordered eating, and poor body image frequently coexist with obesity. Weight stigma in healthcare settings undermines care-seeking, adherence, and mental well-being (24).

Assessment and risk stratification in clinical practice

Clinical evaluation. A thorough history should include weight trajectory, diet, physical activity, sleep, stress, medication-induced weight gain, family history, and psychosocial factors, including eating disorders and weight stigma. Physical exams should assess anthropometry (BMI, waist circumference) and signs of comorbidity.

Investigations and risk calculators. Baseline labs commonly include fasting glucose/HbA1c, lipid profile, liver enzymes, and thyroid function, where indicated. Consider assessment for OSA, NASH, and cardiovascular risk stratification. Use staging tools (EOSS) to align treatment intensity with health risk (8).

When to refer. Referral to specialists (endocrinology, bariatric surgery, sleep medicine, multidisciplinary obesity clinics) is warranted for severe obesity, complex comorbidities, or when advanced therapies (surgery, device, combination pharmacotherapy) are considered.

Prevention strategies

Population-level interventions. Addressing obesity at scale requires policy actions, including fiscal measures (such as sugar-sweetened beverage taxes), front-of-package labeling, restrictions on unhealthy food marketing (especially to children), urban design that promotes active transportation, and improvements to the food environment. Effective prevention integrates multisectoral policies to shift defaults toward healthier choices.

Community and school programs. School-based interventions that improve nutrition, increase physical activity, and foster health literacy show modest benefits. Community programs tailored to local contexts and addressing social determinants are essential.

Individual-level prevention. Clinician-delivered counseling, behavioral support, and digital health tools can support behavior change; however, individual approaches are limited if structural barriers persist.

Treatment approaches

Lifestyle modification. Lifestyle interventions remain the foundation of obesity management. Multicomponent programs incorporating dietary changes, increased physical activity, and behavioral strategies (such as goal setting, self-monitoring, and stimulus control) achieve average weight losses of 5–10% at 6–12 months (25). Different dietary patterns (Mediterranean, low-carbohydrate, low-fat, time-restricted feeding) can be effective when sustained; individual preferences and comorbidities should guide choices. Physical activity enhances weight maintenance and improves cardiometabolic fitness. Digital and remotely delivered programs can extend reach.

Pharmacotherapy

Indications and Principles. Pharmacotherapy is advised for individuals with a BMI of ≥30 kg/m2 or those with a BMI of ≥27 kg/m2 who have obesity-related comorbidities and have not achieved adequate weight loss through lifestyle therapy alone (26). Medications should be used as adjuncts to lifestyle modifications and typically require long-term use with ongoing monitoring.

Key drug classes and recent advances

- GLP-1 receptor agonists: Semaglutide and liraglutide mimic incretin hormones to reduce appetite and food intake while improving glycemic control (27). Semaglutide (2.4 mg weekly) has demonstrated substantial placebo-subtracted weight loss (~15% in STEP trials) and improvements in cardiometabolic markers (28).

- GIP/GLP dual agonists: Tirzepatide (GIP and GLP-1 receptor agonist) has produced even larger weight losses in clinical trials (SURMOUNT programme), generating considerable enthusiasm (29).

- Other agents: Naltrexone/bupropion, orlistat, and older sympathomimetic agents have demonstrated more modest effects; combination strategies are under investigation (30).

Efficacy, safety, and long-term considerations. New incretin-based therapies have transformed expectations, but questions remain about long-term cardiovascular and metabolic outcomes, durability after treatment cessation (weight regain is common), gastrointestinal side effects, cost, and access. Ongoing cardiovascular outcomes trials and real-world safety data are crucial. Shared decision making should discuss benefits, side effects (nausea, gallbladder disease, potential pancreatitis risk), and the likelihood of chronic use.

Device-based and endoscopic therapies. Minimally invasive procedures (intragastric balloons, aspiration therapy, endoscopic sleeve gastroplasty) offer intermediate options for patients who prefer non-surgical but more intensive interventions (31). Weight loss is generally intermediate between pharmacotherapy and surgery; device-related safety and durability vary.

Table 1. Comparative overview of current therapeutic options for obesity management.

Therapy option	Mean weight loss (% body weight)	Target BMI / Indications	Common adverse effects	Advantages	Limitations / Considerations
Lifestyle modification (diet + exercise + behavioral therapy)	5–10%	BMI ≥ 25 kg/m²	Minimal (GI discomfort, fatigue)	Non-invasive, improves overall metabolic health	Limited long-term adherence, modest weight loss
Pharmacotherapy (e.g., Semaglutide, Liraglutide, Orlistat)	8–15% (agent-dependent)	BMI ≥ 30 kg/m² or ≥ 27 with comorbidities	GI symptoms, headache, nausea	Adjunct to lifestyle change, can reduce cardiometabolic risk	Cost, adherence, contraindications
Endoscopic interventions (e.g., intragastric balloon)	10–15%	BMI 30–40 kg/m²	Nausea, vomiting, abdominal pain	Reversible, minimally invasive	Temporary effect, procedure-specific risks
Bariatric surgery (e.g., sleeve gastrectomy, gastric bypass)	20–35%	BMI ≥ 40 or ≥ 35 with comorbidities	Surgical complications, micronutrient deficiencies	Greatest and sustained weight loss, improvement of comorbidities	Invasive, lifelong follow-up required
Emerging therapies (e.g., dual/triple agonists like Tirzepatide)	Up to 20% (early trials)	BMI ≥ 30 kg/m² or ≥ 27 with comorbidities	GI side effects, still under evaluation	High efficacy potential, promising cardiometabolic outcomes	Limited long-term data, cost, regulatory approval pending

Legend: BMI = body mass index; GI = gastrointestinal; RA = receptor agonist. Data summarized from international guidelines and pivotal clinical trials (2021–2024). Sources include the World Health Organization, the American Diabetes Association, the American Association of Clinical Endocrinology.

Bariatric/metabolic surgery

Efficacy and indications. Bariatric surgery remains the most effective and durable therapy for severe obesity and produces substantial and sustained weight loss, remission of T2DM in many patients, and reductions in long-term mortality for selected cohorts (32). Common procedures include sleeve gastrectomy and Roux-en-Y gastric bypass; biliopancreatic diversion with duodenal switch offers greater weight loss but higher malabsorption risk (33).

Risk, benefit, and long-term care. Surgical risks include perioperative complications and long-term nutritional deficiencies requiring lifelong monitoring and supplementation (33). Patient selection, multidisciplinary preoperative evaluation, and long-term follow-up are crucial for maximizing outcomes.

Special populations

Children and adolescents. Pediatric obesity requires family-centered prevention and treatment, emphasizing lifestyle modification and psychosocial support. Pharmacotherapy and bariatric surgery have roles in carefully selected adolescents with severe obesity and comorbidities, guided by specialist centers and ethical considerations (34).

Older adults and sarcopenic obesity. In older adults, unintentional weight loss and preservation of lean mass are key concerns. Interventions should prioritize functional outcomes and sarcopenia prevention, combining resistance training with nutrition strategies.

Pregnancy. Preconception and antenatal weight optimization can reduce pregnancy complications. Management during pregnancy focuses on appropriate weight gain, nutritional adequacy, and managing obesity related risks; many pharmacotherapies are contraindicated (35).

Health systems, policy, and equity considerations

Access to effective obesity care is uneven. Many health systems classify obesity as a lifestyle issue rather than a treatable chronic disease, limiting insurance coverage for pharmacotherapy, multidisciplinary care, and surgery. Weight stigma in healthcare settings reduces care-seeking and the quality of care. Equity-focused policies should expand access, subsidize effective treatments, and address social determinants of health to reduce disparities.

Future directions and research gaps

Long-term outcomes of new therapies. Large, long-duration trials are needed to assess cardiovascular, oncologic, neurocognitive, and safety outcomes of chronic incretin and combination therapies.

Precision obesity medicine. Research into obesity phenotypes (metabolic, immunologic, behavioral), polygenic risk, and biomarker-guided therapy could enable precision approaches, matching patients to the intervention most likely to succeed (36,37).

Combination therapies and sequencing. Combining lifestyle, pharmacotherapy, devices, and surgery in rational sequences or combinations may improve outcomes; comparative effectiveness research is needed.

Implementation of science and policy evaluation. Translating efficacious interventions into population-level health gains requires implementation research, economic evaluation, and policy experiments (e.g., taxation, marketing restrictions) with robust evaluation frameworks.

Microbiome and novel biologics. Microbiome-targeted therapies, anti-inflammatory agents, and new biologics acting on central or peripheral pathways offer promising areas for future interventions (36,37).

Conclusions

Obesity is a complex, chronic disease with profound individual and societal consequences. Advances in understanding pathophysiology have catalyzed the development of highly effective pharmacotherapies and improved surgical techniques, expanding the clinical toolkit. Nonetheless, prevention at the population level and equitable access to effective treatments remain critical. A comprehensive strategy requires integration of clinical care, public health policy, and research priorities focused on long-term safety, personalized approaches, and implementation at scale. Clinicians should adopt a compassionate, evidence-based approach that integrates lifestyle support with medical and procedural therapies tailored to individual risk profiles and preferences.

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Conflicts of Interest. None

References

1. World Health Organization. Obesity and overweight: fact sheet. WHO; 2025. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Ng, Marie et al. Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. The Lancet, Volume 405, Issue 10481, 813 – 838

3. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet.* 2024; 403:2162-2203

4. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Roundtable on Obesity Solutions; Callahan EA, editor. Translating Knowledge of Foundational Drivers of Obesity into Practice: Proceedings of a Workshop Series. Washington (DC): National Academies Press (US); 2023 Jul 31. 10, The Science, Strengths, and Limitations of Body Mass Index. Available from: https://www.ncbi.nlm.nih.gov/books/NBK594362/
5. Byker Shanks, C., Bruening, M. & Yaroch, A.L. BMI or not to BMI? Debating the value of body mass index as a measure of health in adults. Int J Behav Nutr Phys Act **22**, 23 (2025). https://doi.org/10.1186/s12966-025-01719-6
6. Zhang X, Lu X, Pan X, Shen S, Tong N. Role of waist circumference-to-height ratio in assessing adiposity, predicting type 2 diabetes mellitus and other cardiometabolic diseases. 2024;49(7):1062-1072. doi:10.11817/j.issn.1672-7347.2024.240259
7. Crabtree CD, LaFountain RA, Hyde PN, Chen C, Pan Y, Lamba N, Sapper TN, Short JA, Kackley ML, Buga A, et al. Quantification of Human Central Adipose Tissue Depots: An Anatomically Matched Comparison Between DXA and MRI. *Tomography*. 2019; 5(4):358-366. https://doi.org/10.18383/j.tom.2019.00018
8. Swaleh R, McGuckin T, Myroniuk TW, et al. Using the Edmonton Obesity Staging System in the real world: a feasibility study based on cross-sectional data. *CMAJ Open*. 2021;9(4):E1141-E1148. Published 2021 Dec 7. doi:10.9778/cmajo.20200231
9. Liu J, Jing C, Guo Y, et al. The central signaling pathways related to metabolism-regulating hormones of the gut-brain axis: a review. *J Transl Med*. 2025;23(1):648. Published 2025 Jun 11. doi:10.1186/s12967-025-06656-3
10. Zhenggang Zhu *et al.* Hedonic eating is controlled by dopamine neurons that oppose GLP-1R satiety.Science **387**,eadt0773(2025). DOI:10.1126/science.adt0773
11. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al. The Role of Adipokines in Health and Disease. *Biomedicines*. 2023;11(5):1290. Published 2023 Apr 27. doi:10.3390/biomedicines11051290
12. Mohammed I, Haris B, Al-Barazenji T, et al. Understanding the Genetics of Early-Onset Obesity in a Cohort of Children From Qatar. J Clin Endocrinol Metab. 2023;108(12):3201-3213. doi:10.1210/clinem/dgad366
13. Montenegro J, Armet AM, Willing BP, et al. Exploring the Influence of Gut Microbiome on Energy Metabolism in Humans. *Adv Nutr*. 2023;14(4):840-857. doi:10.1016/j.advnut.2023.03.015
14. Marta Jaskulak, Malwina Zimowska, Marta Rolbiecka, Katarzyna Zorena, Understanding the role of endocrine disrupting chemicals as environmental obesogens in the obesity epidemic: A comprehensive overview of epidemiological studies between 2014 and 2024, Ecotoxicology and Environmental Safety, Volume 299, 2025, 118401, https://doi.org/10.1016/j.ecoenv.2025.118401
15. Sidhu SK, Aleman JO, Heffron SP. Obesity Duration and Cardiometabolic Disease. Arterioscler Thromb Vasc Biol. 2023;43(10):1764-1774. doi:10.1161/ATVBAHA.123.319023
16. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143(21):e984-e1010. doi:10.1161/CIR.0000000000000973
17. Garvey, W.T.; Umpierrez, G.E.; Dunn, J.P.; Kwan, A.Y.M.; Varnado, O.J.; Konig, M.; Levine, J.A. Examining the evidence for weight management in individuals with type 2 diabetes. Diabetes Obes. Metab. 2022, 24, 1411–1422.
18. Esmaeili, Neda et al.The relationship between obesity and obstructive sleep apnea in four community-based cohorts: an individual participant data meta-analysis of 12,860 adults eClinicalMedicine, Volume 83, 103221
19. Shumnalieva R, Kotov G, Monov S. Obesity-Related Knee Osteoarthritis-Current Concepts. Life (Basel). 2023;13(8):1650. Published 2023 Jul 28. doi:10.3390/life13081650
20. Sheila Gato, Vanessa García-Fernández, Antonio Gil-Gómez, Ángela Rojas, Rocío Montero-Vallejo, Rocío Muñoz-Hernández, Manuel Romero-Gómez, Navigating the Link Between Non-alcoholic Fatty Liver Disease/Non-alcoholic Steatohepatitis and Cardiometabolic Syndrome, European Cardiology Review 2024;19:e03. https://doi.org/10.15420/ecr.2023.26
21. Claudia Reytor-González, Emilia Jiménez-Flores, Natalí González & Daniel Simancas-Racines. (2025) Redefining Chemoresistance: Natural Bioactives as Molecular Modulators at the Cancer–Tumor Microenvironment Interface. *International Journal of Molecular Sciences* 26:16, pages 8037.

22. Mili, N., Paschou, S.A., Goulis, D.G. *et al.* Obesity, metabolic syndrome, and cancer: pathophysiological and therapeutic associations. *Endocrine* **74**, 478–497 (2021). https://doi.org/10.1007/s12020-021-02884-x

23. Jang S, Hong W, Moon Y. Obesity-compromised immunity in post-COVID-19 condition: a critical control point of chronicity. *Front Immunol*. 2024;15:1433531. Published 2024 Aug 12. doi:10.3389/fimmu.2024.1433531

24. David Sánchez-Carracedo, Obesity stigma and its impact on health: A narrative review, Endocrinología, Diabetes y Nutrición (English ed.),Volume 69, Issue 10,2022,Pages 868-877,ISSN 2530-0180, https://doi.org/10.1016/j.endien.2021.12.007.

25. World Health Organization. Obesity and Overweight: World Health Organization Global Strategy on Diet, Physical Activity and Health; WHO: Geneva, Switzerland, 2025.

26. Rodrigues Silva Sombra L, Anastasopoulou C. Pharmacologic Therapy for Obesity. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK562269/

27. Zheng, Z., Zong, Y., Ma, Y. *et al.* Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Sig Transduct Target Ther* **9**, 234 (2024). https://doi.org/10.1038/s41392-024-01931-z

28. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, et al: Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 2021, 384(11): 989-1002

29. Horn DB, Kahan S, Batterham RL, et al. Time to weight plateau with tirzepatide treatment in the SURMOUNT-1 and SURMOUNT-4 clinical trials. *Clin Obes*. 2025;15(3):e12734. doi:10.1111/cob.12734

30. Telci Caklili O, Cesur M, Mikhailidis DP, Rizzo M. Novel Anti-obesity Therapies and their Different Effects and Safety Profiles: A Critical Overview. *Diabetes Metab Syndr Obes*. 2023;16:1767-1774. Published 2023 Jun 14. doi:10.2147/DMSO.S392684

31. Ghusn W, Calderon G, Abu Dayyeh BK, Acosta A. Mechanism of action and selection of endoscopic bariatric therapies for treatment of obesity. Clin Endosc. 2024;57(6):701-710. doi: 10.5946/ce.2024.005

32. Ram Sohan P, Mahakalkar C, Kshirsagar S, et al. Long-Term Effectiveness and Outcomes of Bariatric Surgery: A Comprehensive Review of Current Evidence and Emerging Trends. *Cureus*. 2024;16(8):e66500. Published 2024 Aug 9. doi:10.7759/cureus.66500

33. Ganipisetti VM, Naha S. Bariatric Surgery Malnutrition Complications. [Updated 2023 May 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan; https://www.ncbi.nlm.nih.gov/books/NBK592383/

34. Järvholm K, Janson A, Henfridsson P, Neovius M, Sjögren L, Olbers T. Metabolic and bariatric surgery for adolescents with severe obesity: Benefits, risks, and specific considerations. *Scandinavian Journal of Surgery*. 2024;114(1):95-106. doi:10.1177/14574969241297517

35. Kalantari E, Tajvar M, Naderimagham S, Takian A. Maternal obesity management: a narrative literature review of health policies. *BMC Womens Health*. 2024;24(1):520. Published 2024 Sep 18. doi:10.1186/s12905-024-03342-2

36. Art Muijsenberg, Emanuel E Canfora, Ellen E Blaak, Metabolic Phenotypes, Genotypes, and Gut Microbiome Signatures in Obesity: Implications for Precision Nutrition Strategies in Type 2 Diabetes Prevention, *Nutrition Reviews*, 2025;, nuaf088, https://doi.org/10.1093/nutrit/nuaf088

37. F. Carbone, J.P. Despres, J.P.A. Ioannidis, *et al.* Bridging the gap in obesity research: A consensus statement from the European Society for Clinical Investigation Eur. J. Clin. Invest. (2025), Article e70059