Obesity Updates: Understanding Obesity as a Disease and Its Management

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Abstract

Obesity is now recognized as a chronic disease requiring long-term care to treat or prevent adiposity-induced and obesity-related complications. This article discusses the biology of weight regulation as a basis for understanding obesity as a disease, and for appreciating the complex and multifactorial nature of the obesity problem. Finally, the article highlights a clinical approach to obesity care that starts with accurate diagnosis and severity assessment (including clinical vs preclinical obesity), then outlines a multi-pronged treatment strategy, and provides brief updates on pharmacotherapy and the future direction of obesity care.

Keywords: Obesity. Chronic Disease. Body Weight Regulation. Obesity Management.

Introduction

Over the last 40 years, the prevalence of obesity has risen substantially in almost all regions of the world, such that there are now more than 600 million people with obesity worldwide (1,2). This increasing burden of obesity affects all regions (1), including Singapore. The National Health Survey (NHS 1992 – 2010) reports that 10.8% of adult Singaporeans had obesity in 2010, more than double the prevalence in 1992 (3). Results from recent national health surveys, including the latest National Population Health Survey (NPHS 2023 – 2024), suggest a continuation of this trend after a brief period of stabilisation from 2010 to 2017 (4).

Biology of Weight Regulation

The body's adipose tissue represents energy stores to survive energy-scarce conditions. Hence, it would not be surprising that that body weight (or more accurately, adipose tissue in the body) is tightly regulated by an extremely complex neuroendocrine energy balance circuitry, which is composed of specific nuclei in various brain regions, most prominently the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus, the lateral hypothalamic area and the nucleus of solitary tract of the hindbrain (5–7) (**Figure 1**). Under relatively constant environmental conditions, this regulatory system senses and processes various metabolic signals regarding the current energetic status and adjusts the metabolic responses to maintain a stable weight without conscious control (5,8). This homeostatic regulation of body weight is similar to the regulation of other physiologic parameters, such as body temperature, blood pressure, or blood glucose, where a 'set point' seems to exist and deviation from this 'set point' elicits a compensatory response in an opposite direction to restore this body weight 'set point'. Therefore, weight regain after weight loss is physiological (9,10) and not necessarily due to a failure of conscious efforts (to lose weight).

Figure 1: Key hypothalamic nuclei involved in the regulation of appetite and energy balance. Figure taken from (7).

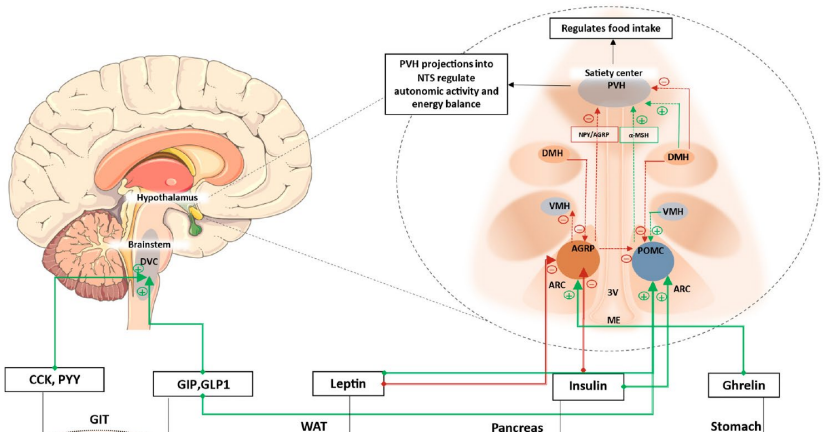


Figure 1. Key hypothalamic nuclei involved in the regulation of appetite and energy balance. ARC, comprising AGRP and POMC neurons, is located next to the median eminence. This region comprises permeable capillaries, thereby allowing access to circulating signals. These signals can modulate ARC neuronal populations, which then have extensive projections to PVH and other hypothalamic nuclei. PVH is the major hypothalamic satiety center. POMC neurons activate MC4R neurons in the PVH to decrease appetite, while AGRP neurons inhibit PVH-MC4R neurons to increase appetite. Additionally, AGRP neurons also inhibit POMC neurons via stimulation of inhibitory GABAergic input to POMC neurons. Anorexigenic signals such as leptin and GLP1 increase satiety by acting on POMC neurons, whereas orexigenic signals such as ghrelin can increase appetite by acting on AGRP neurons. Other hypothalamic neuronal populations have extensive projections to and from adjacent nuclei. While DMH has predominantly inhibitory projections to PVH and POMC, it also has been shown to also have activate inhibitory GABAergic neurons projecting to the AGRP neurons in the ARC. VMH mainly has excitatory projections to the POMC neurons, while AGRP neurons has inhibitory projections to VMH. Additionally, postprandial satiety signals from the enteroendocrine cells of the GIT can also act on DVC located in the brainstem to suppress appetite. AGRP: Agouti-related protein; POMC: Pro-opiomelanocortin; ARC: Arcuate nucleus; ME: median eminence; VMH: Ventromedial nucleus of the hypothalamus; DMH: Dorsomedial hypothalamus; PVH: Paraventricular nucleus; 3V: Third ventricle; DVC: Dorsal vagal complex; CCK: cholecystokinin; GIP: Glucose-dependent insulinotropic polypeptide; GLP1: Glucagon-like peptide-1; WAT: White adipose tissue; GIT: Gastrointestinal tract. Green dotted lines/arrows represent activation. Red dotted

Additionally, there exist a different set of neuroendocrine signals which guides food intake based upon the reward value of the food, also known as the reward or 'hedonic' system (5,11). The brain regions responsible for this reward system are dispersed in the corticolimbic structures, and a primary characteristic of this system is its ability to override the signals from the homeostatic circuits as described (5). Hence, the reward system is non-homeostatic with regard to energy balance. This system integrates basic midbrain and hindbrain functions with more complex cortical functions involving arousal at the sight of palatable food items and the procurement of food, mediating the 'liking' (level of pleasure or reward) and 'wanting' (the motivation or drive to consume food), which are subconscious processes (5). In human studies, functional MRI (fMRI) studies have shown overactivation of reward-encoding brain regions and/or deficiency in cortical inhibitory networks in people with obesity (5).

Obesity as a Disease: Pathophysiology and Health Consequences

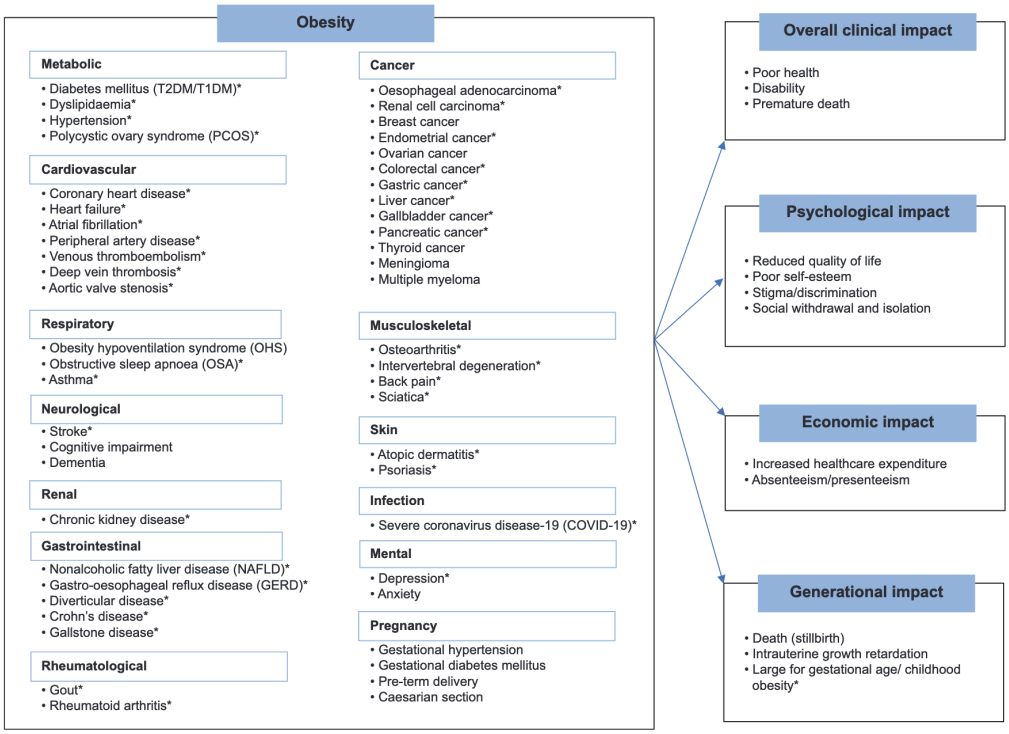
With the understanding of the biology of weight regulation, obesity (defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue (12)) is now understood to signify an abnormal physiological state whereby there has been a surplus intake of energy and an elevated body weight set point is now defended (5,13). The factors known to cause this are complex and multiple, and they range from genetic to environmental to emotional factors, which are well-known to be potent modulators of appetite (11). Twin, family, and adoption studies show that the rate of heritability of BMI is high, ranging from 40 to 70% (14), demonstrating a major genetic component. In addition to syndromic and monogenic forms of obesity, genome-wide association studies (GWAS) have identified more than 700 independent loci associated with BMI and/or obesity (15–17). Environmental and lifestyle factors favouring a positive energy balance and weight gain include increasing per capita food supplies and consumption, particularly of highly processed, energy-dense and palatable food that are often served in large portions; decreasing time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities such as television watching and use of electronic devices; growing use of medicines that have weight gain as a side effect; stress and inadequate sleep (14).

More recent studies have identified a potential role for the microbial content of the gut in determining a broad range of metabolic abnormalities, including obesity (18,19). The evidence supporting causation includes animal studies which show that obesity, as a phenotype, is transmittable via the transfer of gut microbiota from the obese (mice/humans) to germ-free mice (20,21), and mechanistic studies which demonstrate the possible mechanisms linking the gut microbiota with obesity (18,22). These specific obesogenic factors can, in turn, be influenced by broader environmental context, such as the physical environment (built environment, atmospheric temperature), socio-economic conditions (education, income), the psychosocial environment, cultural influences, and biological factors such as age, menopause, and coexisting health conditions (23,24). In addition, gene-environment interactions can occur, such as environmental and lifestyle factors modifying gene expression (25,26), lifestyle and genetic factors attenuating each other (27,28), and genetic factors influencing the propensity for certain lifestyle traits (29). Therefore, the development of obesity is truly complex, potentially involving a multitude of interactions between genetic and environmental/lifestyle factors.

Obesity is not benign. The failure of adipose tissues to continually expand leads to pathological changes in the adipose tissue which is characterized by macrophage invasion and/or increased release of pro-inflammatory adipokines and decreased release of anti-inflammatory adipokines such as adiponectin (12). Also, this failure to further expand and act as a 'metabolic sink' results in harmful ectopic fat deposition in lean tissues such as the heart, liver, pancreas and kidneys (12). These two phenomena contribute to a pro-inflammatory and insulin-resistant milieu, giving rise to metabolic complications such as type 2 diabetes mellitus (T2DM), metabolic-dysfunction associated steatotic liver disease (MASLD, previously known as non-alcoholic fatty liver disease) and cardiovascular disease (CVD) (12,30,31). Additionally, the physical forces as a result of excessive adipose tissue can give rise to biomechanical

consequences (such as Obstructive Sleep Apnea (OSA) and low back pain), and obesity as a condition has been associated with various psychosocial issues, impacting on mental health (31,32). All these adverse consequences affect quality of life, increase healthcare costs, and finally, increase mortality (31,33) (**Figure 2**). Therefore, based on the current knowledge that the development of obesity results from established pathophysiology, with attending health consequences (adiposity-induced/obesity-related complications, and mortality), obesity fulfils the criteria for a disease state and is now determined to be a disease (13), rather than just a lifestyle risk factor. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease (**Box 1**), and this is an important first step to tackling the problem of obesity, which has emerged as an epidemic that poses an unprecedented public health challenge (13).

Figure 2: Summary of diseases and conditions associated with obesity and the potential impacts. Figure taken from (31).



*Supported by Mendelian randomisation studies. T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus.

Figure 3 : Associations or organisations that have declared obesity is a disease. Figure taken from (13).

Box 1
Associations or organizations that have declared obesity is a disease

- National Institutes of Health
- US Food and Drug Administration
- Federal Trade Commission
- American Medical Association
- World Health Organization
- American College of Physicians
- American Association of Clinical Endocrinologists
- American College of Cardiology
- The Endocrine Society
- American Academy of Family Physicians
- Institute of Medicine
- The Obesity Society
- World Obesity Federation
- American Heart Association
- American Diabetes Association
- American Academy of Family Physicians
- American Society for Reproductive Medicine
- American Urologic Association
- American College of Surgeons

Data from Kahan S, Zvenyach T. Obesity as a disease: current policies and implications for the future. Curr Obes Rep 2016;5(2):291–7; and Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 2017;18(7):715–23.

Clinical Approach to Obesity Care

As with any disease, effective obesity care starts with an accurate diagnosis. Obesity is fundamentally a state of excess adiposity, so diagnosis should not rely on BMI alone (34), which is best used as a screening tool or population-level risk marker (34). Where feasible, excess adiposity should be confirmed using direct body-fat assessment, or at least one additional anthropometric measure such as waist circumference or waist-to-height ratio alongside BMI (34); in people with very high BMI ($\geqslant$40 kg/m^2), excess adiposity can generally be assumed, so additional adiposity measurement is usually not required to confirm the diagnosis (34). This emphasis on diagnosing obesity based on adiposity rather than BMI alone is a key point highlighted in the recently published 'The Lancet Diabetes & Endocrinology Commission on the definition and diagnostic criteria of clinical obesity' (34).

After diagnosis, as with the management of other chronic diseases, complications and health impact should be assessed to determine disease severity and guide treatment intensity. Since 2013, the field has been shifting from a BMI-centric model (treat to a generic 5–10% weight-loss target) toward a complications-centric approach, where treatment intensity is driven by the risk, presence, and severity of both adiposity-induced and obesity-related complications, and weight loss is primarily a means to improve those outcomes (35). This direction is reinforced by the recently published 'The Lancet Diabetes & Endocrinology Commission on the definition and diagnostic criteria of clinical obesity', which proposes a more clinically meaningful framework—distinguishing preclinical obesity (excess adiposity with preserved organ function) from clinical obesity (a chronic, systemic illness with adiposity-related organ dysfunction and/or substantial functional limitation) (34). Clinical obesity, by definition, warrants active treatment, and the aggressiveness of therapy should scale with the number, severity, and trajectory of complications (34,35). For example, when MASLD and/or OSA are present, $\geqslant$10% weight loss may be needed for meaningful improvement (35), making "modest" loss (5–10%) potentially inadequate and supporting escalation to more intensive options when the expected benefit outweighs risk.

Building on this paradigm, management should increasingly address the underlying obesity as a driver of many adiposity-driven cardiometabolic conditions, rather than treating each complication in isolation. This is consistent with a consensus document published by the Working Group on Obesity, Diabetes and the High-risk Patient from the European Society for Hypertension and the European Association

for the Study of Obesity, which highlights practice guidance for obesity-related hypertension, diabetes, and dyslipidaemia, and calls for treating obesity itself in affected individuals (36). For some patients, this means the first-line pharmacotherapy may reasonably be an anti-obesity medication rather than, for example, an antihypertensive, when obesity is a major contributor to the condition. Equally important, medications used to treat these conditions should not worsen obesity, so clinicians should consider weight effects when selecting agents; for instance, sulphonylureas can promote weight gain and should be avoided where possible in people with obesity (36).

Importance of a Multi-level and Individualized Multi-pronged Approach to Treat Obesity

It is now known that the simple calculations underlying the traditional adage of 'eat less, exercise more' are fatally flawed (37). Aiming for a 500 kcal deficit (energy expenditure more than energy intake) per day, cumulating to 3,500 kcal per week (equivalent to ~0.5kg of fat) will not result in a 0.5kg/week weight loss indefinitely, because this calculation does not consider the homeostatic mechanisms that will resist further weight loss, and in fact, will conspire to regain weight to restore the original 'set point' (9,10,37). Also, it is important to note that the same diet and exercise plan (often prescribed once in the beginning) will not suffice to maintain that 500kcal deficit per day as a declining weight will mean declining energy expenditure (37). Nonetheless, the point here is that asking all people with obesity to just 'eat less and exercise more' overly simplifies the obesity problem. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution (38) and would necessitate a multi-level and individualized multi-pronged approach to treating obesity. Multi-level, apart from the individual, would include the social and community, physical (environment) and economic levels of interventions (38), while a multi-pronged approach at the individual level would encompass not just the lifestyle and behavioural modifications, which remain the cornerstone, but also the possible combination with pharmacologic, and even bariatric surgical procedures based on individualized risk-benefit assessment (12,35).

Dietary strategies with RCT-level evidence that can be routinely advised include reducing sugar-sweetened beverages and practising portion control (e.g., the plate concept) (39). More structured approaches can be grouped into energy-focused (meal replacements, low/very low energy diets), macronutrient-focused (low carbohydrate, low fat), dietary pattern–focused (DASH, Mediterranean), and timing-focused (intermittent fasting, time-restricted feeding) interventions (39). When adhered to, most approaches produce weight loss, and long-term trials have not shown consistent superiority of one diet over another—making adherence the key determinant of outcomes (12,39). However, weight loss activates homeostatic counter-regulation (increased hunger and cravings), which undermines long-term adherence and weight maintenance; therefore, the satiating quality of the diet becomes particularly important. Higher-protein, low–glycaemic index diets appear more favourable for weight-loss maintenance (37), and individuals with impaired glucose metabolism may experience weaker satiety from carbohydrate-containing meals and potentially benefit from relatively higher fat/protein patterns (40,41). Timing-focused regimens, such as time-restricted feeding, are increasingly popular and, across available human data, can yield some weight loss and cardiometabolic improvements with no clear signal of harm (42–44). Yet evidence is still limited by small trials and observational designs, and larger, longer-duration RCTs (>1 year) are needed before firm recommendations can be made (42). Beyond diet, lifestyle management should also prioritise regular physical activity—combining aerobic training with resistance exercise—to support fat loss, preserve lean mass, and improve cardiometabolic fitness (45); adequate sleep duration and quality (45), given consistent associations between short/poor sleep and higher adiposity (46–48); and practical stress-management strategies (e.g., mindfulness, problem-solving, social support) (45), as chronic stress can undermine healthy eating, sleep, and activity routines (49,50).

Update on the Pharmacologic Management of Obesity

For many years, obesity pharmacotherapy achieved only modest weight loss, including the first glucagon-like peptide-1 receptor agonist (GLP-1RA) indicated for obesity, liraglutide (51). More recently, higher-potency incretin therapies have shown markedly greater efficacy, with semaglutide and tirzepatide—a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist—achieving ~15% and ~20% mean weight loss, respectively, in pivotal trials (52,53). These agents reduce energy intake by slowing gastric emptying (increasing post-meal fullness) and by acting on appetite centres in the hypothalamus and brainstem to increase satiety and reduce hunger (54). The most common adverse

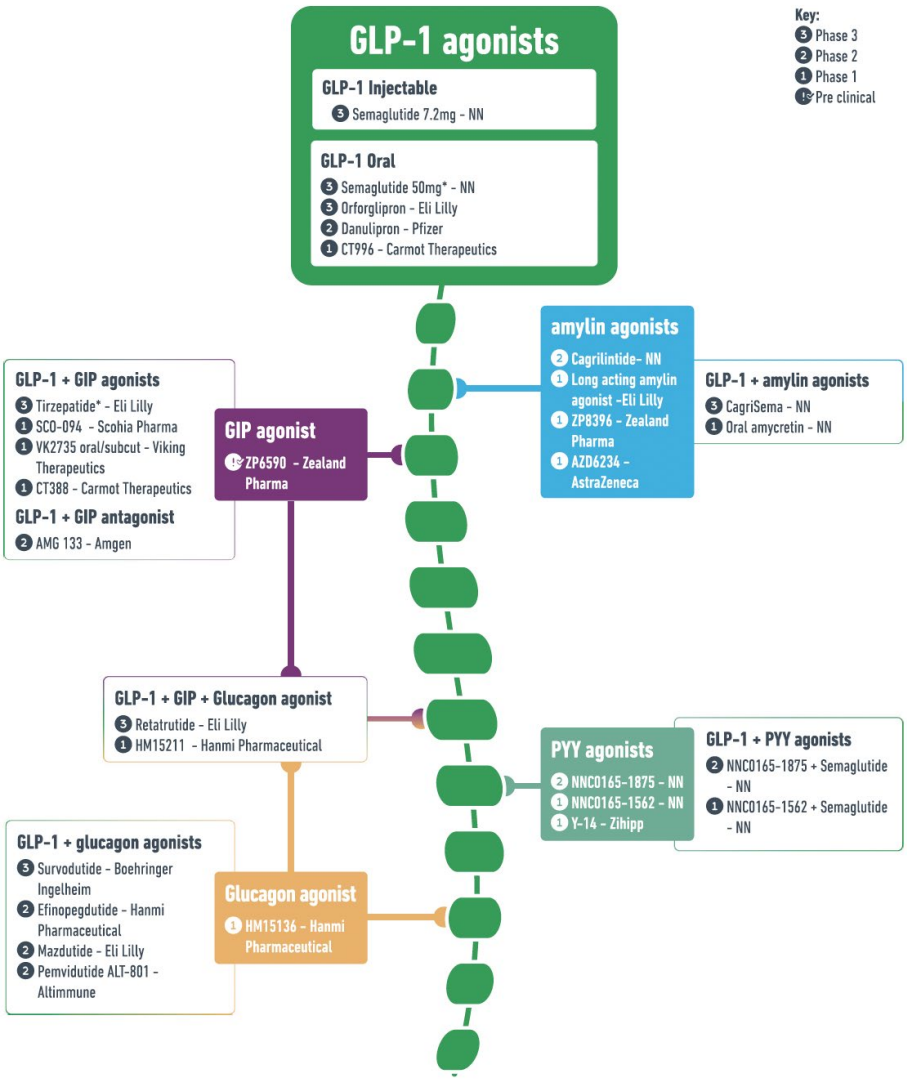
effects are gastrointestinal (nausea, vomiting, diarrhoea/constipation), while key cautions include avoidance in people with personal or family history of medullary thyroid carcinoma (MTC), in people with multiple endocrine neoplasia syndrome type 2 (MEN2), and in those with a history of pancreatitis (54). Reassuringly, although thyroid C-cell tumours are seen in rodents, a causal increase in human thyroid cancer risk remains unproven (54). Suicidality was previously highlighted as a caution, but accumulated evidence has not supported a causal link (55), prompting the U.S. Food and Drug Administration (FDA) to request removal of suicidal ideation/behaviour warnings from GLP-1RA weight-management labels (56).

Two frequently cited concerns are lean-mass reduction and durability of treatment. Some lean-mass reduction is expected with substantial weight loss, but emerging data suggest part of the observed change reflects reduced intramuscular fat (potentially improving muscle quality), rather than a simple loss of functional muscle tissue (57). Weight regain is common after stopping therapy, consistent with the idea that GLP-1RAs are treating an ongoing pathophysiology, and may be more rapid than after behavioural programmes, possibly because behavioural programmes leave patients with coping skills that persist beyond treatment (58). Importantly, the clinical value of GLP-1–based therapy extends beyond weight loss, with benefits across cardiometabolic and obesity-related disease (including liver outcomes, heart failure, and sleep apnoea) (54) and emerging signals for reduced risks in areas such as dementia (59), obesity-associated cancers (60), and alcohol/substance abuse (54,55,61).

Future of Obesity Management

The obesity-treatment pipeline is expanding rapidly, with glucagon-like peptide-1 (GLP-1)–based therapy remaining the “backbone” for many next-generation agents (**Figure 4**) (62). Newer multi-agonists are pushing efficacy closer to (and in some cases beyond) what was historically seen with bariatric surgery—for example, retatrutide (a GIP/GLP-1/glucagon triple agonist) achieved ~24.2% mean weight loss at 48 weeks in phase 2 data (63). In parallel, oral GLP-1 options are advancing beyond oral semaglutide; in a phase 2 obesity trial, the oral non-peptide GLP-1RA orforglipron produced dose-dependent weight loss up to ~14.7% at 36 weeks (64), potentially improving scalability and long-term acceptability. The pipeline is also diversifying beyond entero-pancreatic hormones, with agents targeting central appetite/reward pathways and other mechanisms in various phases of development (62,65). As efficacy increases, newer strategies are also aiming to optimise body composition, including approaches designed to mitigate excessive lean-mass loss (e.g., via myostatin–activin pathway modulation) (66). Procedural innovation is advancing alongside pharmacotherapy (67), including modified operations such as “sleeve-plus” procedures that build on sleeve gastrectomy to improve durability and metabolic outcomes (68). The likely end-state is not “drug vs surgery”, but combination, stepped, complications-driven care—pairing lifestyle therapy with pharmacotherapy (often in combinations) and using endoscopic/surgical options when needed to achieve durable, individualised health goals. In summary, deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

Figure 4: Glucagon-like peptide-1 as the backbone of the pipeline for gut hormone-based obesity treatments. Figure taken from (62).



GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: novo nordisk, *completed phase 3 trials for obesity.

Conclusion

Obesity is now recognized as a disease and has been described as a complex, chronic medical condition with a major negative impact on human health. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease, and this is an important first step to tackling the problem of obesity. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution and would necessitate a multi-level and individualized multi-pronged approach to treating obesity and its related conditions. Lifestyle intervention remains the cornerstone of obesity management and should be integrated with pharmacologic, endoscopic, and surgical options when indicated. Finally, a deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

References:

1. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. The Lancet. 2016;387(10026):1377–96.

2. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019 Mar;92:6–10.

3. Ministry of Health S, Epidemiology & Disease Control Division. National Health Survey 2010. 2011.

4. Disease Policy and Strategy Division, and Health Analytics Division, Ministry of Health Singapore, Policy, Research & Surveillance Group, Health Promotion Board, Singapore. National Population Health Survey 2024. 2025.

5. Yu YH, Vasselli JR, Zhang Y, Mechanick JI, Korner J, Peterli R. Metabolic vs. hedonic obesity: a conceptual distinction and its clinical implications. Obesity Reviews. 2015;16(3):234–47.

6. Morton GJ, Blevins JE, Williams DL, Niswender KD, Gelling RW, Rhodes CJ, et al. Leptin action in the forebrain regulates the hindbrain response to satiety signals. J Clin Invest. 2005 Mar;115(3):703–10.

7. Haspula D, Cui Z. Neurochemical Basis of Inter-Organ Crosstalk in Health and Obesity: Focus on the Hypothalamus and the Brainstem. Cells. 2023 Jul 7;12(13):1801.

8. Fasano A. The Physiology of Hunger. Ingelfinger JR, Lee CD, editors. N Engl J Med. 2025 Jan 23;392(4):372–81.

9. Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. Clinical science. 2013 Feb;124(4):231–41.

10. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. American journal of physiology Regulatory, integrative and comparative physiology. 2011 Sep;301(3):R581-600.

11. Farr OM, Li CS, Mantzoros CS. Central nervous system regulation of eating: Insights from human brain imaging. Metabolism. 2016 May;65(5):699–713.

12. Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, Despres JP, Matsuzawa Y, Loos RJF, et al. Obesity. Nat Rev Dis Primers. 2017 Jun 15;3:17034.

13. Upadhyay J, Farr O, Perakakis N, Ghaly W, Mantzoros C. Obesity as a Disease. Medical Clinics of North America. 2018;102(1):13–33.

14. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. The New England journal of medicine. 2017 Jan 19;376(3):254–66.

15. Tam V, Turcotte M, Meyre D. Established and emerging strategies to crack the genetic code of obesity. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2019 Feb;20(2):212–40.

16. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. Hum Mol Genet. 2018 Oct 15;27(20):3641–9.

17. Singh RK, Kumar P, Mahalingam K. Molecular genetics of human obesity: A comprehensive review. C R Biol. 2017 Feb;340(2):87–108.

18. Boulange CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016 Apr 20;8(1):42.

19. Rial SA, Karelis AD, Bergeron KF, Mounier C. Gut Microbiota and Metabolic Health: The Potential Beneficial Effects of a Medium Chain Triglyceride Diet in Obese Individuals. Nutrients. 2016 May 12;8(5).

20. Stephens RW, Arhire L, Covasa M. Gut Microbiota: From Microorganisms to Metabolic Organ Influencing Obesity. Obesity (Silver Spring, Md). 2018 May;26(5):801–9.

21. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science (New York, NY). 2013 Sep 6;341(6150):1241214.

22. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007 Jul;56(7):1761–72.

23. Garvey WT. Is Obesity or Adiposity-Based Chronic Disease Curable: The Set Point Theory, the Environment, and Second-Generation Medications. Endocr Pract. 2022 Feb;28(2):214–22.

24. Campbell CL, Wagoner TB, Foegeding EA. Designing foods for satiety: The roles of food structure and oral processing in satiation and satiety. Food Structure. 2017;13:1–12.

25. Catalan V, Aviles-Olmos I, Rodriguez A, Becerril S, Fernandez-Formoso JA, Kiortsis D, et al. Time to Consider the 'Exposome Hypothesis' in the Development of the Obesity Pandemic. Nutrients. 2022 Apr 12;14(8).

26. Mahmoud AM. An Overview of Epigenetics in Obesity: The Role of Lifestyle and Therapeutic Interventions. Int J Mol Sci. 2022 Jan 25;23(3).

27. Heianza Y, Qi L. Gene-Diet Interaction and Precision Nutrition in Obesity. Int J Mol Sci. 2017 Apr 7;18(4).

28. Brunkwall L, Chen Y, Hindy G, Rukh G, Ericson U, Barroso I, et al. Sugar-sweetened beverage consumption and genetic predisposition to obesity in 2 Swedish cohorts. The American journal of clinical nutrition. 2016 Sep;104(3):809–15.

29. Wang Z, Emmerich A, Pillon NJ, Moore T, Hemerich D, Cornelis MC, et al. Genome-wide association analyses of physical activity and sedentary behavior provide insights into underlying mechanisms and roles in disease prevention. Nat Genet. 2022 Sep;54(9):1332–44.

30. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, et al. What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? International journal of obesity. 2017 Jun;41(6):853–65.

31. Lam BCC, Lim AYL, Chan SL, Yum MPS, Koh NSY, Finkelstein EA. The impact of obesity: a narrative review. Singapore Medical Journal. 2023;64(3):163–71.

32. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i–xii, 1–253.

33. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014;384(9945):766–81.

34. Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, et al. Definition and diagnostic criteria of clinical obesity. The Lancet Diabetes & Endocrinology. 2025 Mar;13(3):221–62.

35. Cefalu WT, Bray GA, Home PD, Garvey WT, Klein S, Pi-Sunyer FX, et al. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From aDiabetes CareEditors' Expert Forum. Diabetes care. 2015;38(8):1567–82.

36. Kotsis V, Jordan J, Micic D, Finer N, Leitner DR, Toplak H, et al. Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part A: mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment. Journal of hypertension. 2018 Jul;36(7):1427–40.

37. Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. Medical Clinics of North America. 2018;102(1):183–97.

38. Amarasinghe A, D'Souza G. Individual, Social, Economic, and Environmental Model: A Paradigm Shift for Obesity Prevention. ISRN Public Health. 2012;2012:1–10.

39. Raynor HA, Champagne CM. Position of the Academy of Nutrition and Dietetics: Interventions for the Treatment of Overweight and Obesity in Adults. Journal of the Academy of Nutrition and Dietetics. 2016 Jan;116(1):129–47.

40. Hjorth MF, Due A, Larsen TM, Astrup A. Pretreatment Fasting Plasma Glucose Modifies Dietary Weight Loss Maintenance Success: Results from a Stratified RCT. Obesity (Silver Spring, Md). 2017 Dec;25(12):2045–8.

41. Hwang JJ, Jiang L, Hamza M, Sanchez Rangel E, Dai F, Belfort-DeAguiar R, et al. Blunted rise in brain glucose levels during hyperglycemia in adults with obesity and T2DM. JCI Insight. 2017 Oct 19;2(20).

42. Patterson RE, Sears DD. Metabolic Effects of Intermittent Fasting. Annual review of nutrition. 2017 Aug 21;37:371–93.

43. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing research reviews. 2017 Oct;39:46–58.

44. Dong TA, Sandesara PB, Dhindsa DS, Mehta A, Arneson LC, Dollar AL, et al. Intermittent Fasting: A Heart Healthy Dietary Pattern? The American journal of medicine. 2020 Aug;133(8):901–7.

45. Nadolsky K, Garvey WT, Agarwal M, Bonnecaze A, Burguera B, Chaplin MD, et al. American Association of Clinical Endocrinology Consensus Statement: Algorithm for the Evaluation and Treatment of Adults with Obesity/Adiposity-Based Chronic Disease – 2025 Update. Endocrine Practice. 2025 Nov;31(11):1351–94.

46. Miller MA, Bates S, Ji C, Cappuccio FP. Systematic review and meta-analyses of the relationship between short sleep and incidence of obesity and effectiveness of sleep interventions on weight gain in preschool children. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2021 Feb;22(2):e13113.

47. Bacaro V, Ballesio A, Cerolini S, Vacca M, Poggiogalle E, Donini LM, et al. Sleep duration and obesity in adulthood: An updated systematic review and meta-analysis. Obes Res Clin Pract. 2020 Aug;14(4):301–9.

48. Fatima Y, Doi SA, Mamun AA. Sleep quality and obesity in young subjects: a meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2016 Nov;17(11):1154–66.

49. Hill D, Conner M, Clancy F, Moss R, Wilding S, Bristow M, et al. Stress and eating behaviours in healthy adults: a systematic review and meta-analysis. Health Psychology Review. 2022 Apr 3;16(2):280–304.

50. Schultchen D, Reichenberger J, Mittl T, Weh TRM, Smyth JM, Blechert J, et al. Bidirectional relationship of stress and affect with physical activity and healthy eating. British J Health Psychol. 2019 May;24(2):315–33.

51. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015 Aug 18;314(7):687–99.

52. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine. 2021 Mar 18;384(11):989.

53. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205–16.

54. Drucker DJ. GLP-1-based therapies for diabetes, obesity and beyond. Nat Rev Drug Discov. 2025 Aug;24(8):631–50.

55. Xie Y, Choi T, Al-Aly Z. Mapping the effectiveness and risks of GLP-1 receptor agonists. Nat Med. 2025 Mar;31(3):951–62.

56. FDA Requests Removal of Suicidal Behavior and Ideation Warning from Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) Medications. 2026 [cited 2026 Feb 10]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-suicidal-behavior-and-ideation-warning-glucagon-peptide-1-receptor-agonist-glp

57. Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with GLUCAGON-LIKE PEPTIDE-1-based therapies and mitigation strategies. Diabetes Obesity Metabolism. 2024 Sep;26(S4):16–27.

58. West S, Scragg J, Aveyard P, Oke JL, Willis L, Haffner SJP, et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. BMJ. 2026 Jan 7;392:e085304.

59. Seminer A, Mulihano A, O'Brien C, Krewer F, Costello M, Judge C, et al. Cardioprotective Glucose-Lowering Agents and Dementia Risk: A Systematic Review and Meta-Analysis. JAMA Neurol. 2025 May 1;82(5):450.

60. Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes. JAMA Netw Open. 2024 Jul 5;7(7):e2421305.

61. Gonzalez-Rellan MJ, Drucker DJ. New Molecules and Indications for GLP-1 Medicines. JAMA. 2025 Oct 14;334(14):1231.

62. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity? Int J Obes. 2025 Mar;49(3):433–51.

63. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, et al. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. N Engl J Med. 2023 Aug 10;389(6):514–26.

64. Wharton S, Aronne LJ, Stefanski A, Alfaris NF, Ciudin A, Yokote K, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. N Engl J Med. 2025 Nov 6;393(18):1796–806.

65. Kokkorakis M, Chakhtoura M, Rhayem C, Al Rifai J, Ghezzawi M, Valenzuela-Vallejo L, et al. Emerging pharmacotherapies for obesity: A systematic review. Pharmacological Reviews. 2025 Jan;77(1):100002.

66. Ryan DH. New drugs for the treatment of obesity: do we need approaches to preserve muscle mass? Rev Endocr Metab Disord. 2025 Oct;26(5):805–13.

67. Perdomo CM, Cohen RV, Sumithran P, Clément K, Frühbeck G. Contemporary medical, device, and surgical therapies for obesity in adults. The Lancet. 2023 Apr;401(10382):1116–30.

68. Kurahashi Y, Hojo Y, Shinohara H. Sleeve Plus Procedures: A Review of Technical Evolution Along a Schematic Diagram. OBES SURG. 2025 Nov;35(11):4806–13.

Learning Points

1. Obesity is now recognized as a chronic disease requiring long-term care to treat or prevent adiposity-induced and obesity-related complications.
2. The complex and multifactorial nature of obesity means that there is no one-size-fits-all intervention or solution, and would necessitate a multi-level and individualized multi-pronged approach to treating obesity and its related conditions.
3. A deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

Dietary strategies with RCT-level evidence that can be routinely advised include reducing sugar-sweetened beverages and practising portion control (e.g., the plate concept) (31). More structured approaches can be grouped into energy-focused (meal replacements, low/very low energy diets), macronutrient-focused (low carbohydrate, low fat), dietary pattern–focused (DASH, Mediterranean), and timing-focused (intermittent fasting, time-restricted feeding) interventions (31). When adhered to, most approaches produce average weight loss, and long-term trials have not shown consistent superiority of one diet over another—making adherence the key determinant of outcomes (12,29). However, weight loss activates homeostatic counter-regulation (increased hunger and cravings), which undermines long-term adherence and weight maintenance; therefore, the satiating quality of the diet becomes particularly important. Higher-protein, low–glycaemic index diets appear more favourable for weight-loss maintenance (29), and individuals with impaired glucose metabolism may experience weaker satiety from carbohydrate-containing meals and potentially benefit from relatively higher fat/protein patterns (32,33). Timing-focused regimens, such as time-restricted feeding, are increasingly popular and, across available human data, can yield some weight loss and cardiometabolic improvements with no clear signal of harm (35–37). Yet evidence is still limited by small trials and observational designs, and larger, longer-duration RCTs (>1 year) are needed before firm recommendations can be made (35).