Review

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Obesity: current developments in mechanisms, diagnosis, classification and the evolution of personalized management

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Abstract: In recent years, the global prevalence of overweight and obesity has exhibited a sustained upward trajectory. As an independent entity within the spectrum of chronic diseases, obesity serves as a significant pathogenic factor for multiple chronic conditions and ranks as the sixth leading risk factor for mortality and disability nationwide. It poses a severe threat to public health while imposing a considerable socioeconomic burden. The etiology of obesity is multifactorial; however, primary diagnostic modalities and therapeutic approaches remain relatively undiversified, and long-term weight maintenance remains challenging. Similar to other chronic diseases, obesity management demands a long-term multimodal strategy. This strategy must incorporate individualized treatment goals and balance the benefits and risks of different interventions to formulate personalized management plans. These plans aim to reduce body weight through multifaceted interventions, alleviate obesity-related comorbidities, enhance quality of life, and optimize overall health outcomes.

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Introduction

Obesity, defined as abnormal or excessive fat accumulation that impairs health [1], is a chronic, progressive, and relapsing disease influenced by genetic, environmental, and behavioral factors. The global number of people with overweight or obesity has increased from 0.929 billion in 1990 to 2.6 billion in 2021, with the obesity prevalence more than doubling in both adult males and females [2]. Among high-income countries, the United States has the highest obesity rate, where over 40 % of adults are affected by obesity [3]. The prevalence of overweight and obesity among Chinese adults has reached 50.7 % and is projected to rise to 65.3 % by 2030 [4]. Obesity is linked to a higher risk of premature death [3] and elevated risks of multiple severe diseases, including type 2 diabetes (T2D), cardiovascular disease (CVD), stroke and certain types of cancer [5–8]. Given its association with diabetes, CVD, stroke and cancer, obesity demands urgent attention in healthcare policy and clinical practice [9]. While obesity increases mortality risks, some studies report an "obesity paradox" where higher body mass index (BMI) correlates with lower post-PCI mortality [10]. A study of 1,033 patients with ischemic stroke revealed a negative correlation between BMI and mortality: each 1-unit increase in BMI was associated with a 23.9 % reduction in mortality. Compared with normal weight individuals, those with obesity and severe obesity (BMI≥35 kg/m^2) exhibited a 62% and 46 % lower mortality, respectively [11]. Similarly, among cancer patients receiving immune checkpoint inhibitor (ICI) therapy, those with obesity (BMI≥30 kg/m^2) were found to have better 5-year overall survival (36.2 % vs. 25.5 %), with a 30 % reduction in the risk of death [12]. However, as BMI fails to reflect body composition and fat distribution, and evaluating obesity solely based on BMI tends to overlook patients' actual metabolic status, it may lead to misjudgment of disease prognosis and the true risk of death [12]. Thus, the

obesity paradox remains controversial. The management of obesity primarily encompasses lifestyle intervention, pharmacotherapy and surgical intervention. Nevertheless, conventional obesity treatments are associated with certain limitations, necessitating an urgent need for effective, non-invasive novel weight loss strategies with relatively mild adverse effects. Furthermore, with the increasing attention and in-depth understanding of obesity, this condition has been categorized into multiple subtypes, and targeted therapeutic approaches have been developed based on distinct obesity subtypes. This offers a more rationalized and tailored treatment paradigm for clinical obesity management in the future.

Diagnostic

BMI (kg/m^2) is a universal criterion for evaluating general obesity, correcting body weight by height to reduce the influence of height on obesity assessment. In the adult population of China, a BMI below 18.5 kg/m^2 is defined as underweight, 18.5 kg/m^2 to less than 24 kg/m^2 as normal weight, 24 kg/m^2 to less than 28 kg/m^2 as overweight, and 28 kg/m^2 or higher as obesity [13]. To better guide clinical diagnosis and treatment, based on the international classification of obesity and the characteristics of Asian populations, it is recommended that a BMI of 28.0 kg/m^2 to less than 32.5 kg/m^2 be defined as mild obesity, 32.5 kg/m^2 to less than 37.5 kg/m^2 as moderate obesity, 37.5 kg/m^2 to less than 50 kg/m^2 as severe obesity, and 50 kg/m^2 or higher as morbid obesity [14, 15]. However, although BMI is the most commonly used metric for obesity, it has certain limitations as it cannot reflect body composition and fat distribution. This shortcoming is particularly pronounced with age, as the gradual decline in lean body mass (fat-free mass) and concurrent increase in body fat content give rise to divergent body fat ratios between young and elderly individuals with identical BMI values. Moreover, at the same BMI threshold, individuals engaged in high-intensity physical activity or professional athletics consistently exhibit lower body fat percentages compared to the general population [16].

Adipose tissue distribution in humans is highly heterogeneous. In Chinese populations, central accumulation of intra-abdominal visceral fat is a key trait, predisposing to abdominal obesity. Excessive visceral fat strongly correlates with metabolic dysfunction, increased cardiovascular/cerebrovascular disease risk [17], and premature mortality [18]. Waist circumference is a commonly used indicator for assessing central obesity. Based on the characteristics of Chinese adults and health risk evaluations, normal waist circumference is defined as <85 cm in males and <80 cm in females, while central obesity is diagnosed when waist circumference reaches ≥90 cm in males and ≥85 cm in females [13]. The waist-hip ratio (WHR) is another indicator for central obesity, with central obesity diagnosed at WHR ≥0.90 in males and ≥0.85 in females [19]. Body fat percentage (BFP) refers to the proportion of fat mass in total body weight. It can be measured via methods such as bioelectrical impedance analysis (BIA) [20] and dual-energy X-ray absorptiometry (DEXA). In China, excessive body fat is defined as body fat percentage exceeding 25 % in males or 30 % in females; however, its limitation lies in the difficulty of fully reflecting the distribution of adipose tissue in the body, making it not a routine clinical diagnostic method. Notably, computed tomography (CT)-measured visceral adipose area, as the gold standard for diagnosing abdominal obesity, enables precise visualization and quantification of intra-abdominal fat deposition.

Obesity phenotypes

Obesity is classified differently depending on etiology, presence or absence of metabolic abnormalities, and pathophysiological mechanisms (Figure 1). Obesity is commonly categorized into primary and secondary types based on etiology. Primary obesity, the most common form, arises from combined environmental and genetic factors like sedentary behavior, high-calorie/imbalanced diets, lack of exercise, and sleep insufficiency. Secondary obesity, conversely, stems from endocrine disorders, medication use, or genetic defects, addressing the root cause often leads to substantial weight loss and possible weight normalization.

The diagnosis of obesity should not rely solely on anthropometric parameters, but should also include precise assessment of metabolic status. Metabolic classification includes metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), and sarcopenic obesity (SO) [21]. Moreover, normal weight obesity (NWO) is a distinct subtype of obesity characterized by a normal body mass index alongside significantly elevated body fat percentage, particularly excessive visceral fat accumulation. Despite presenting as “normal weight” outwardly, individuals with NWO exhibit imbalanced body composition and heightened metabolic health risks [22] (Table 1).

Pathophysiological subtypes consist of hungry brain, hungry gut, emotional hunger and slow burn [35]. Among them, the cerebral hunger type refers to *ad libitum* food intake exceeding the 75th percentile of the intake in the same-sex population, i.e., >894 kcal per meal in females and

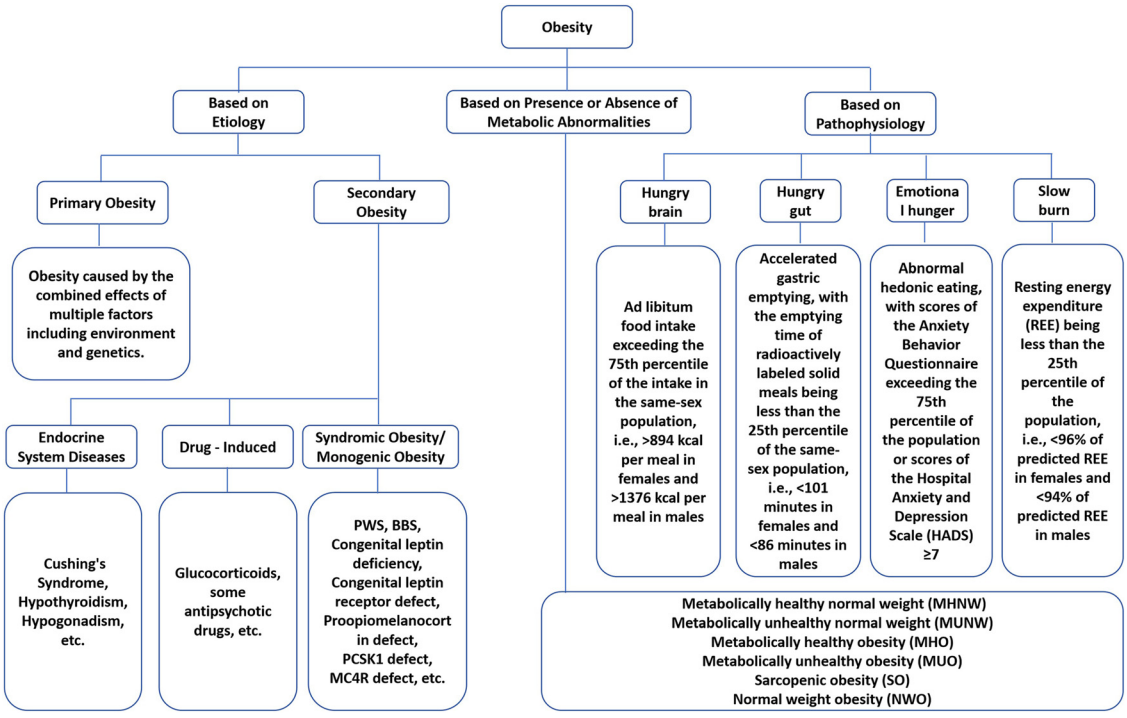

Figure 1: Classification of obesity.

Table 1: Characteristics of different obesity subtypes.

Characteristics	MHNW	MUNW	MHO	MUO	SO	NWO
Definition	Absence of metabolic disorders, normal body weight	Metabolic disorders, normal body weight	Absence of metabolic disorders, obesity	Metabolic disorders, obesity	Low muscle mass and weak muscle strength lack physical exercise	Metabolic disorders, normal body weight
Waist circumference	Normal	Normal/high	Normal	High	High WC and/or >28	Normal/high
BMI, kg/m^2	18.5–24.9	18.5–24.9	>28	>28		18.5–24.9
Visceral fat	Low	High fat mass	Low	High	High fat mass	High
Lean mass	–	–	High	–	Low	–
Metabolic disorder	Absent	Present	Absent	Present	Present	Present
BFP	–	–	–	–	–	Male ≥23.5 %; female ≥29.2 % [23]
HF (vs. normal weight lean)	–	Increased risk [24]	Increased risk [25]	Increased risk vs normal weight lean post-menopausal woman [26]	Decrease risk CRF vs. non-sarcopenic HFrEF [27]	–
AF (vs. normal weight lean)	–	Increased risk [24]	Increased risk [25]	Increased risk [28]	Increased risk [29]	–
CV events/mortality (vs. normal weight lean)	–	Increased risk [30]	Increased risk [31]	Increased risk [30]	Increased risk vs. non-sarcopenic HF and elderly [32]	Increased risk vs. normal weight lean [23, 33]
Metabolic syndrome	Three or more of the following: waist circumference ≥88 cm for women, ≥102 cm for men; triglycerides ≥150 mg/dL; fasting plasma glucose ≥100 mg/dL; blood pressure ≥130/85 mm Hg; HDL-C <40 mg/dL in men, <50 mg/dL in women [34].					

MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; SO, sarcopenic obesity; NOW, normal weight obesity; BMI, body mass index; BFP, Body fat percentage.

>1,376 kcal per meal in males. The gastrointestinal hunger type is defined as accelerated gastric emptying, with the emptying time of radioactively labeled solid meals being less than the 25th percentile of the same-sex population, i.e., <101 min in females and <86 min in males. The emotional hunger type is characterized by abnormal hedonic eating, with scores of the Anxiety Behavior Questionnaire exceeding the 75th percentile of the population or scores of the Hospital Anxiety and Depression Scale (HADS) ≥7. The hypometabolic type refers to resting energy expenditure (REE) being less than the 25th percentile of the population, i.e., <96 % of predicted REE in females and <94 % of predicted REE in males [35]. This classification is conducive to guiding pathophysiology-based treatment of obesity [36]. These classifications are critical for personalized obesity management, as treatment strategies ranging from pharmacotherapy to lifestyle interventions – vary by subtype.

Mechanisms

Unhealthy lifestyle

Obesity is driven by increased energy intake, insufficient physical activity, and reduced energy expenditure, and is synergistically mediated by biological-socio-psychological factors through mechanisms including abnormal neuroendocrine regulation, epigenetic modulation, and behavioral pattern alteration. Poor dietary habits, excessive intake of ultra-processed foods, sedentary behavior, and reduced physical activity are established causes of obesity. Stress-related mental disorders may also induce changes in eating habits, thereby contributing to obesity [37].

Genetics

Furthermore, genetic factors exert a critical influence on shaping an individual's response to obesogenic environments. Preliminary evidence from family [38], twin [39], and adoption [40] studies has estimated the heritability of obesity/BMI to be 70 %–80 % [41]. From a genetic perspective, obesity is categorized into monogenic and polygenic forms. Monogenic obesity is classified into monogenic syndromic obesity and monogenic non-syndromic obesity. Monogenic syndromic obesity is often associated with abnormalities in other organ systems. Typical cases include Prader–Willi Syndrome (PWS), which is characterized by obesity and intellectual developmental delay [42], and Bardet–Biedl Syndrome (BBS), which has a higher prevalence of obesity and is accompanied by retinitis pigmentosa, renal dysfunction and cognitive impairment [43]. Monogenic non-syndromic obesity, caused by specific gene mutations, is characterized by excessive adipose accumulation, primarily involving genes encoding the leptin-melanocortin pathway, which is critical for appetite regulation. Studies show that Leptin gene mutations lead to rapid weight gain, severe early-onset obesity and extreme hyperphagia [44]. Autosomal recessive defects in proopiomelanocortin may induce red hair and severe obesity via dual effects of a-MSH on pigmentation and appetite [41]. The Melanocortin 4 Receptor (MC4R) mutation drives increased appetite and feeding behavior in children, accompanied by other comorbidities [45]. Polygenic inheritance of obesity refers to the collaborative effect of multiple minor-effect genes and environmental factors in driving obesity susceptibility, representing the most common form of obesity. Quantified indices of individual cumulative genetic risk can be calculated based on risk loci identified by genome-wide association studies (GWAS).

Epigenetics

Epigenetics refers to the phenomenon where the primary sequence of DNA (i.e., the base sequence of genes) remains unchanged, while gene expression is regulated via specific molecular modifications – with such regulatory patterns stably inheritable during cell division. Epigenetic regulation encompasses DNA methylation, histone modification, non-coding RNA regulation and chromatin remodeling, disruption of this balance can lead to a variety of diseases and is associated with the development of obesity and T2D. Back in 2017, Wahl et al. identified 187 CpG sites significantly associated with BMI from 450,000 DNA methylation data points derived from over 10,000 whole blood samples [46]. They demonstrated that DNA methylation alterations in blood are typically driven by obesity but may occasionally contribute to it – a finding later validated in adipose tissue. Importantly, obesity-associated DNA methylation sites can predict the future risk of T2D [46]. Researchers have also discovered that body weight in adult individuals with obesity is associated with the methylation status of the leptin (LEP) promoter and adiponectin gene [47]. Additionally, the methylation status of members of the insulin signaling pathway (including INS, IRS1, and PIK3R1) is positively associated with obesity and metabolic diseases [48]. At the level of histone modification, altered levels of histone-modifying enzymes – such as histone methyltransferases, histone demethylases, histone deacetylases (HDACs), and histone acetyltransferases – are linked to obesity. Specific enzymes, including HDACs and Jhdm2a, have been shown in clinical studies to promote the progression of obesity [49]. Collectively, DNA methylation,

histone modification differences are observed in obesity and may offer new avenues for diagnostic approaches and therapeutic interventions.

Gut microbiota alteration

Beyond genetic factors, the gut microbiome functions as a critical adaptive consequence of environmental influences, and its dysbiosis has been identified as a prominent contributor to the development of obesity [50, 51]. Extensive metagenomic studies have linked specific gut microbes to human obesity, with inverse correlations observed for *Akkermansia muciniphila* [52, 53], *Bacteroides thetaiotaomicron* [54] and *Faecalibacterium prausnitzii* [55, 56], and positive correlations for certain species of Ruminococcus, Desulfovibrio [57] and Megamonas [58]. Animal studies, by demonstrating the anti-obesity effects of specific Lactobacillus [59, 60] and other microbes, further affirm the non-negligible role of gut microbiota intervention in obesity and other metabolic diseases, advancing the potential application of microbes in the management of such disorders.

Obesity management

In the management of obesity, a standardized comprehensive assessment process is essential (Figure 2). Firstly, etiological investigation and assessment are carried out to fully understand the patient's past history, family history and personal history. Subsequently, psychiatric and psychological assessments are performed by specialized clinicians using tools such as the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Eating Disorder Inventory (EDI). Next, a physical examination is performed, including measurements of height, weight, waist/hip circumference, BMI, waist-to-hip ratio and relevant signs.

For laboratory testing, obesity-associated conditions are first assessed, involving at least measurements of blood glucose, glycated hemoglobin, insulin, lipid profile, serum uric acid, liver function, and renal function. Second, secondary causes of obesity are evaluated, including thyroid function tests, Cushing's syndrome screening, and gonadal function assessments, followed by measurements of total body fat and visceral fat content.

In addition, initial screening for obesity-related comorbidities employs tools such as the SF-36 Health Survey, Moorehead-Ardelt Quality of Life Questionnaire, Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Self-Rating

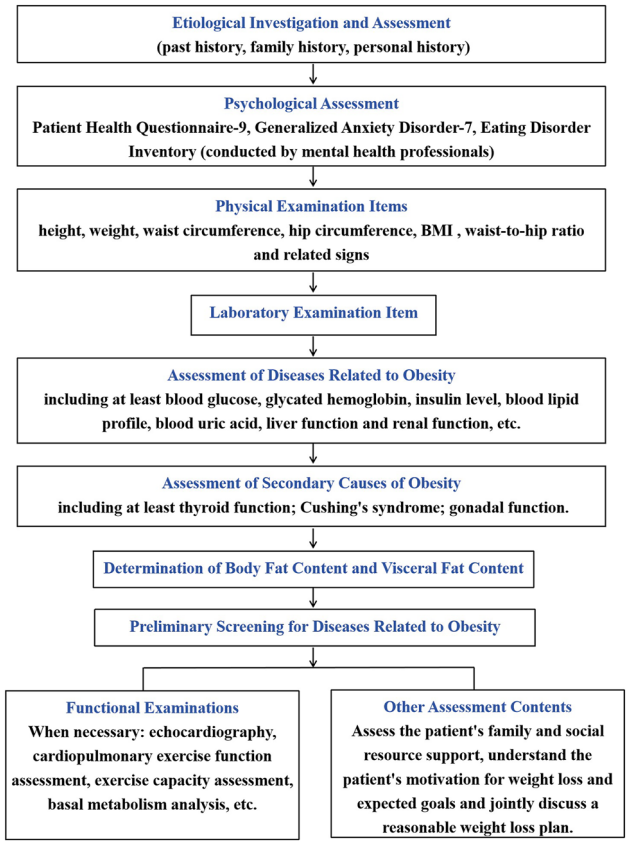

Figure 2: Diagnostic and therapeutic process of obesity.

Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), Epworth Sleepiness Scale, STOP-BANG Questionnaire (for sleep apnea screening), and Gastroesophageal Reflux Disease Questionnaire (GERD-Q). For suspected obstructive sleep apnea syndrome (OSAS), polysomnography (PSG) is performed if clinically indicated. For non-alcoholic fatty liver disease (NAFLD), evaluations include abdominal liver ultrasound, transient elastography, CT or MRI, along with assessments using the Fibrosis-4 (FIB-4) index and NAFLD Fibrosis Score (NFS); liver biopsy may be required to further evaluate disease progression when necessary.

Meanwhile, screening for secondary etiologies includes – but is not limited to – thyroid ultrasound for suspected thyroid disorders, adrenal CT/ultrasound for suspected adrenal conditions, and pituitary MRI for suspected pituitary abnormalities. Additionally, functional tests (e.g., echocardiography, cardiopulmonary exercise testing, exercise capacity assessments, basal metabolic analysis) may be warranted. Finally, the patient's family and social support, weight-loss motivation, and expected goals should be evaluated to collaboratively develop an individualized weight-loss plan.

Lifestyle intervention

Earlier initiation of weight management interventions is associated with greater benefits [61]. In the field of obesity management, lifestyle intervention-changing behaviors around diet and physical activity-should be implemented throughout the entire process. All other treatment modalities, including medications, medical devices and surgical procedures, must be based on the foundation of lifestyle modifications [62]. The importance of dietary management lies not only in reducing energy intake and effectively promoting weight loss, but also in improving metabolic problems such as blood pressure, blood glucose, blood lipids and insulin resistance. Restricting total calorie intake and maintaining a negative balance between energy intake and expenditure are crucial for achieving clinically significant weight loss. Additionally, dietary composition, eating patterns, and meal timing are also significant factors influencing weight reduction [63]. Currently, various dietary patterns exist, including energy-restricted diets, high-protein diets, low-carbohydrate diets, intermittent fasting, low-fat diets, and meal replacements. However, their weight-lowering effects vary greatly among individuals, resulting in short-term weight loss ranging from 1 to 16.1 %. Moreover, a single dietary management approach is often insufficient to maintain an individualized optimal weight in the long term, and most patients experience weight regain 6–12 months after the intervention [64–66]. Single dietary intervention shows suboptimal efficacy and high rebound tendency, necessitating combination with exercise. Although exercise alone achieves only modest weight loss (approximately 2.4 % body weight reduction), it confers additional benefits in long-term weight maintenance and reduction of obesity-related metabolic and cardiovascular complications [67, 68].

Social and psychological factors

Beyond lifestyle interventions, there is a close association between the built environment and metabolic health [69]. Social and environmental drivers are known to influence an individual's decisions about healthy behaviour. Data derived from UK Biobank revealed that compared with car-only commuters, mixed public transport and active commuters had significantly lower percentage body fat (men: −1.32 % to −1.12 %], p<0.0001; women: −1.10 % to −0.81 %], p<0.0001), as did cycling or cycling and walking commuters (men: −2.75 % to −2.48 %], p<0.0001; women: −3.26 % to −2.71 %], p<0.0001) [70]. Residential greenness was independently and consistently negatively associated with lower obesity prevalence, and this association remained robust after adjusting for multiple confounders [71]. Large-scale population studies have found that regions with fewer fast-food restaurants, lower levels of air pollution and greater proximity to green spaces are associated with reduced risks of obesity and diabetes [69]. In summary, neighborhood characteristics such as walkability/bikeability, mixed land use, accessible destinations, and public transportation can increase residents' physical activity levels, while the availability of high-calorie foods and convenience stores increases the risk of overweight and obesity [72]. The incidence rates of obesity and type 2 diabetes are the highest in regions characterized by the lowest educational attainment, income levels and the most deprived areas [73]. This phenomenon underscores the robust association between socioeconomic status and the prevalence of these metabolic disorders. Unequal access to nutritious food is one mechanism by which socioeconomic factors influence the diet and health of a population. Under conditions of economic constraint, food selection is predominantly driven by cost-effectiveness rather than nutritional adequacy. As income declines, foods with low nutritional density but high energy content emerge as the primary option for meeting daily caloric requirements at an affordable cost. In contrast, nutrient-dense, high-quality food items and nutritionally optimal dietary patterns are not only cost more but are consumed by more affluent groups [73]. At the psychological level, additional psychosocial support should be provided to obese patients. Individuals with obesity often experience low self-esteem, self-blame, and even depression or bipolar disorder due to body shape/appearance changes and physical complications, which further exacerbate eating disorders and form a vicious cycle. Family-based weight management programs facilitate the establishment of healthy dietary, exercise, and lifestyle habits, enabling weight loss ranging from 5 % to 20 % [74].

Probiotic preparations

Dysbiosis of the gut microbiota is one of the key mechanisms driving obesity and metabolic disorders, and targeted modulation of the gut microbiota can significantly improve obesity phenotypes and related metabolic abnormalities. Currently, various gut microbial preparations have been applied in the treatment of obesity. *Lactobacillus paracasei* K56, validated by clinical studies, can reduce body fat, visceral fat and waist circumference [75]. Mechanistically, it may inhibit fatty acid synthase activity, promote brown adipose tissue thermogenesis, and modulate gut microbiota homeostasis to reduce energy absorption [76]; This strain is now widely incorporated into probiotic supplements and

fermented dairy products. *Bifidobacterium animalis* CP-9, derived from the breast milk of healthy Chinese mothers, has been confirmed by relevant clinical trials to reduce BMI, improve blood lipid profiles, decrease body fat thickness in different regions, and increase the abundance of beneficial gut bacteria [77]. Findings from multicenter clinical trials have demonstrated that *A. muciniphila* AKK-WST01 exerts a significant therapeutic effect in obese subjects with low baseline concentrations of *A. muciniphila*, which is manifested as reductions in body weight and visceral fat, alongside improvements in glucose and lipid metabolism [78].

Pharmacotherapy

Overweight individuals with at least one weight-related comorbidity such as hyperglycemia, hypertension, dyslipidemia, fatty liver disease, OSAS and CVDs fail to achieve weight loss goals through lifestyle interventions, anti-obesity pharmacotherapy can be combined with lifestyle interventions. With the in-depth understanding of the pathophysiological mechanisms of obesity, innovation in pharmaceutical Research & Developing technologies and the continuous pursuit of the "efficacy-safety" balance, anti-obesity drugs have gradually evolved from "single central nervous system inhibition" to "multi-targeted precise regulation" (Figure 3).

Currently, medications approved in China for weight loss in adult patients with primary obesity include Orlistat and nutrient-stimulated hormone receptor agonists (MuSH). Within the MuSH class, the dual-receptor agonist Tirzepatide exhibits superior weight loss efficacy compared to the single-receptor agonist Semaglutide (Table2). Specifically, in overweight or obese individuals with type 2 diabetes, semaglutide 2.4 mg administered subcutaneously once weekly resulted in a mean weight loss of 10.6 % after 68 weeks of treatment [82]. Retrospective observational cohort studies have shown that the rates of achieving ≥5 %, ≥10 %, and ≥15 % weight loss in the Tirzepatide group were 1.76, 2.54, and 3.24 fold those in the Semaglutide group, respectively, with favorable safety profiles and similar incidences of gastrointestinal adverse events. Additionally, the highest dose group of the MuSH triple-receptor agonist Retatrutide achieved a 24.2 % weight reduction [86], demonstrating favorable weight loss efficacy. Furthermore, this class of agents has exhibited protective effects against obesity-associated complications. A phase 3 cardiovascular outcome study based on the SELECT trial showed that, in patients with a history of CVD and overweight or obesity but without diabetes, subcutaneous injection of 2.4 mg semaglutide once weekly reduces the incidence of cardiovascular death, non-fatal myocardial infarction or nonfatal stroke after a median follow-up of 39.8 months [87]. Semaglutide modulates the "metabolism-inflammation-fibrosis" triple pathway to reduce hepatic steatosis, suppress inflammatory responses and retard the progression of liver fibrosis [88]. As highlighted by Drucker DJ et al., glucagon-like peptide-1 receptor agonists (GLP-1RA), including semaglutide, exert pleiotropic benefits across multiple organ systems. Specifically, in patients with type 2 diabetes mellitus (T2DM) complicated by chronic kidney disease (CKD), these agents reduce the risk of composite renal outcomes (encompassing renal failure and a significant decline in renal function) by 24 %. In trials involving heart failure with preserved ejection fraction (HFpEF), they decrease the risk of cardiovascular death and heart failure-related intensive therapy by 31 %. Additionally, GLP-1RA improve liver histological parameters in patients with metabolic dysfunction-associated steatohepatitis (MASLD) [89]. The protective effects of this class of medications against obesity-associated complications, which transcend mere weight loss, are of great clinical importance.

Operation surgery

The consensus from the European Association for the Study of Obesity (EASO) in its new framework for the diagnosis, staging, and management of adult obesity recommends bariatric surgery (BS) for individuals with BMI≥40 kg/m^{2}or BMI≥35 kg/m^2 with obesity-related comorbidities or BMI≥35 kg/m^2 with

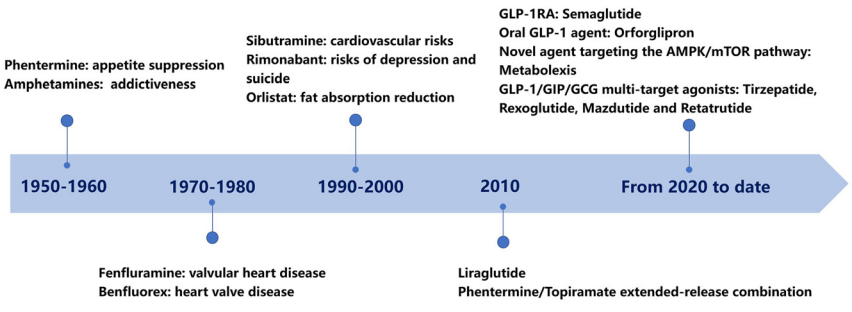

Figure 3: The evolution of anti-obesity drugs.

Table 2: Weight-loss efficacy comparison of GLP-1 RAs.

GLP-1 RA	Target group	Therapeutic dose	Treatment duration	Treatment effect
Liraglutide	Overweight/obese + non-diabetic population	3.0 mg once a day	56 weeks	An average weight loss of 8 % (higher than the 2.6 % in the placebo group) [79]
	Overweight/obese + type 2 diabetic population	3.0 mg once a day	56 weeks	An average weight loss of 6 % (higher than the 4.7 % in the placebo group) [80]
Semaglutide	Overweight/obese + non-diabetic population	2.4 mg once a day	68 weeks	An average weight loss of 16.9 % (higher than the 2.4 % in the placebo group) [81]
	Overweight/obese + type 2 diabetic population	2.4 mg once a day	68 weeks	An average weight loss of 10.6 % (higher than the 3.1 % in the placebo group) [82]
	Overweight/obesepopulation	2.4 mg once a day	44 weeks	An average weight loss of 12.8 % (higher than the 3.0 % in the placebo group) [83]
Tirzepatide	Adults with at least one weight-related complication (excluding diabetes)	5.0 mg once a day	72 weeks	An average weight loss of 15 % (higher than the 3.1 % in the placebo group) [84]
	Overweight/obese + type 2 diabetic population	10.0 mg once weekly	72 weeks	An average weight loss of 12.8 % (higher than the 3.2 % in the placebo group) [85]
Retatrutide	Overweight/obese with comorbidities	12.0 mg	48 weeks	An average weight loss of 24.2 % (higher than the 3.2 % in the placebo group)

GLP-1RA, glucagon-like peptide-1, receptor agonists.

poorly controlled type 2 diabetes despite optimal pharmacotherapy [90]. Additionally, the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders suggest surgery for those with BMI>35 kg/m^2 or BMI 30–34.9 kg/m^2 accompanied by metabolic diseases [91]. In China, the Guidelines for Long-term Weight Management and Clinical Application of Drugs in Obese Patients (2024) propose that active surgery is recommended for individuals with BMI≥32.5 kg/m^2; surgery is advised for those with BMI 27.5–32.5 kg/m^2 who are difficult to control despite standardized treatment and have ≥2 components of metabolic syndrome [92].

BS typically achieves a sustained 25 % weight loss and rapidly, sustainably improves obesity-related comorbidities [74]. A large matched cohort study followed individuals with severe obesity who underwent BS versus those receiving non-surgical management for 4.3 years. It demonstrated that compared with the control group, the surgical group had a 53 % reduction in all-cause mortality; specifically, the gastric bypass subgroup had a 62 % reduction, the sleeve gastrectomy subgroup 37.5 % and the gastric banding subgroup 50 %, all of which were superior to non-surgical management [93]. Common laparoscopic bariatric surgeries include sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and Intragastric balloon (IGB). Retrospective observational cohort studies have revealed that RYGB achieves the optimal weight loss efficacy, with mean weight reductions of 31.2 %, 29 %, and 25.5 % at 1, 3, and 5 years postoperatively, respectively; however, it also has the highest incidence of major adverse events within 30 days (approximately 5.0 %) [94]. Common complications of BS include anemia, iron deficiency, cholelithiasis, anastomotic ulcers protein malnutrition and so on [95]. Additionally, multiple case reports have indicated that vitamin A deficiency post-BS can lead to xerophthalmia, diffuse punctate keratitis and corneal scarring [96], while deficiencies in vitamins or trace elements may impair the skin barrier and immune function, inducing refractory skin infections [97]. To reduce complications of BS, emphasis should be placed on its rehabilitation care. Preoperatively, comprehensive assessment of patients' nutritional status and implementation of personalized nutritional interventions are crucial [98]. For patients with severe and above obesity, especially those with severe fatty liver, achieving a 5 %–10 % preoperative weight loss can not only reduce surgical complexity but also decrease the incidence of perioperative complications [99]. Adjunctive therapies including low-calorie diet (LCD) and very-low-calorie ketogenic diet (VLCKD) can effectively facilitate weight loss and reduce intraoperative complications [100]. Probiotic supplementation has been demonstrated to lower the risk of liver damage, improve lipid profiles, support weight loss and suppress appetite in BS patients. Consequently, probiotics function as a valuable component in both preoperative preparation and postoperative prevention for BS [101]. Additionally, balanced diet and appropriate physical activity are recommended after BS to achieve long-term weight management. IGB is a minimally invasive and temporary weight loss approach [102], which primarily involves placing saline- or air-filled balloons into the stomach to occupy space, thereby promoting satiety and reducing food intake. After IGB

implantation, 54.3 % of overweight or obese individuals achieve ≥10 % weight loss from baseline, among whom 41.4 % maintain such weight loss at 6–12 months [103]. IGB avoids surgical trauma, but its long-term weight loss efficacy is inferior to metabolic surgery, and it may be associated with short-term adverse effects such as nausea and abdominal distension.

Other interventions

Microneedles (MNs) are arrays of needles with lengths ranging from 150 to 1,500 μm [104]. They penetrate the stratum corneum in a painless and non-invasive manner to deliver substances such as caffeine, ephedrine, green tea [105], and capsaicin [106] through the skin, which possess anti-obesity properties. Additionally, photodynamic therapy (PDT) has emerged as a promising non-invasive approach for obesity management, particularly via MN-mediated targeting and delivery to adipose tissues. Through MN delivery, photosensitizers are activated by specific wavelengths of light to generate reactive oxygen species (ROS), which initiate lipid peroxidation in adipocyte membranes, thereby inducing adipocyte damage and death [107]. Transdermal photothermal therapy (TPTT) is a technique that combines photothermal agents (e.g., nanomaterials) with near-infrared (NIR) light irradiation to selectively disrupt target tissues via localized heat generation. Studies have demonstrated that its synergism with a mirabegron delivery system inhibits obesity progression in high-fat diet-fed mice, reduces subcutaneous and visceral fat accumulation, lowers serum cholesterol and triglyceride levels, and improves insulin sensitivity [108]. Although these non-invasive methods have shown effects in improving obesity, they are still in the preclinical research stage and require large-scale human trials to verify their effectiveness. Additionally, researchers have proposed auricular stimulation (AS) as a therapeutic approach for obesity. In 12 trials with data on the body weight of 655 participants demonstrated that AS led to a significant weight reduction compared with control methods (mean difference [MD]=−0.66 kg, 95 % confidence interval [CI]: −1.12 to −0.20, p=0.005). This finding indicates that AS exerts a certain effect in obesity management; however, the magnitude of this effect does not appear to be of clinical relevance, warranting further validation through large-scale, high-quality randomized controlled trials [109].

Personalized treatment

Weight loss is a prolonged process requiring long-term adherence, with a high rebound rate. However, efforts to lose weight should persist even after rebound. Notably, significant benefits can still be derived from weight loss, even if therapeutic effects are not achieved or sustained long-term. Compared with individuals with minimal or no weight loss, those who initially achieved substantial weight loss but eventually regained all weight showed significantly improved HbA1c levels after 4 years [110]. For the management of obesity, personalized strategies should be implemented based on different obesity phenotypes. MHO patients, despite normal metabolic parameters, still require active intervention for obesity to reduce the risk of long-term adverse cardiovascular events and prevent progression to MUO [111]. For patients with MUNW, optimization of lifestyle and diet is recommended to reduce visceral ectopic fat deposition. Patients with MUO or sarcopenia present with both obesity and metabolic disorders, necessitating comprehensive intervention targeting both conditions. Sarcopenic patients exhibit significant muscle mass loss; a high-protein, low-calorie diet (1.2–1.4 g/kg ideal body weight daily) combined with regular exercise is advised to preserve muscle mass [112, 113]. Patients identified as having a potential NWO phenotype should undergo DXA imaging or expert evaluation. Concurrently, lifestyle counseling ought to give priority to structured physical activities geared toward increasing lean body mass and reducing visceral fat, as well as dietary interventions that restrict ultra-processed foods and augment the intake of anti-inflammatory nutrients [23].

For the hungry brain phenotype, phentermine-topiramate extended-release is used [114]. For emotional hunger, naltrexone/bupropion sustained-release is administered orally: bupropion is a dopamine/norepinephrine reuptake inhibitor, and naltrexone is an opioid receptor antagonist, which together regulate appetite, mood, and cravings [115]. For the hungry gut, the GLP-1 receptor agonist liraglutide is indicated [116]. Phentermine 15 mg is selected for the slow-burning phenotype, with the addition of daily resistance training [115]. Although numerous researchers have proposed the concept of personalized treatment for obesity and developed corresponding personalized regimens tailored to different types of obesity, the current research evidence regarding distinct obesity subtypes remains relatively scarce. Additionally, it remains unclear whether such targeted therapeutic approaches have been widely incorporated into the clinical evaluation of obese patients.

Conclusions

The global population affected by obesity is increasing, rendering scientific weight loss a global imperative. For the

management of obese patients, a comprehensive assessment should first be performed, with personalized diagnosis and treatment protocols developed based on different obesity subtypes to achieve more efficient and sustainable weight loss. Meanwhile, active exploration of new weight loss methods is essential. An ideal new strategy should not only be significantly effective in reducing body weight but also non-invasive, safe and conducive to long-term weight maintenance. The emergence of MN and photothermal therapy has demonstrated great potential for weight loss. These innovative methods are expected to break through the bottlenecks of traditional treatments and provide more feasible options for different types of obese populations.

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