Interpretation and Implications of the 2024 Italian Guidelines for the Management of Behavioral Treatment Resistance in Adult Overweight, Obesity and Metabolic Comorbidities: Postprint

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Abstract

Obesity is frequently complicated by metabolic-related diseases, which constitute important etiological factors or risk factors and are associated with poor prognosis; effective weight loss can improve and even remit these comorbidities. Lifestyle intervention alone demonstrates suboptimal efficacy, and behavioral resistance is prevalent; currently, China lacks guidelines specifically targeting patients with behavioral resistance. In 2024, the Italian Society of Endocrinology published the "Guidelines for the Management of Behavioral Treatment Resistance in Adult Overweight, Obesity, and Metabolic Comorbidities" based on the latest evidence-based medical research, with a focus on the application of pharmacological and surgical treatments in these patients. This article, in conjunction with relevant Chinese guidelines, focuses on analyzing the assessment and treatment of obesity within these guidelines, aiming to provide references for the management of overweight or obese patients with behavioral resistance in China.

Full Text

Interpretation and Clinical Implications of the 2024 Italian Guidelines for the Management of Adult Individuals with Overweight and Obesity and Metabolic Comorbidities That Are Resistant to Behavioral Treatment

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【Abstract】 Obesity is frequently accompanied by metabolism-related diseases, serving as a critical etiological factor or risk factor and being associated with adverse clinical outcomes. Effective weight reduction has been demonstrated to ameliorate or even alleviate these comorbidities. However, lifestyle interventions alone often yield suboptimal efficacy, and behavioral resistance is often observed. In China, there are currently no specific guidelines targeting patients with behavioral resistance. In 2024, the Italian Association of Clinical Endocrinologists released the Guidelines for the management of adult individuals with overweight and obesity and metabolic comorbidities that are resistant to behavioral treatment, grounded in the latest evidence-based research. The guidelines primarily focus on pharmacological and surgical interventions in this patient population. This paper, in conjunction with Chinese guidelines, delves into the obesity evaluation and treatment strategies from the Italian guidelines, aiming to offer a reference for managing Chinese overweight or obese patients with behavioral resistance.

【Key words】 Obesity management; Overweight; Metabolic comorbidities; Behavioral therapy resistance; Drug therapy; Metabolic-bariatric surgeries

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1 Guideline Recommendations and Related Content

Obesity is not only a complex chronic disease but also a critical risk factor for multiple chronic conditions, with its prevalence continuing to increase globally. According to the 2022 World Health Organization (WHO) European report, nearly 60% of adults are overweight or obese [1]. By Chinese standards, over half of adults and one-fifth of children are overweight or obese, making China the country with the largest number of overweight or obese individuals worldwide [2-3]. Obesity has become a major cause of mortality and disability in China [4], imposing a tremendous burden on the national healthcare system. The rising prevalence of obesity is associated with sedentary lifestyles and dietary habits [2]. Initial treatment for overweight or obese individuals should involve comprehensive lifestyle interventions, including diet, exercise, and behavioral modification [5]. However, for most obese patients, lifestyle changes alone are insufficient to achieve and maintain target weight, and behavioral resistance is common. Currently, China lacks guidelines specifically for such patients. In 2024, the Italian Association of Clinical Endocrinologists developed management guidelines for overweight or obese adult patients with metabolic complications who are resistant to lifestyle changes [6] (hereinafter referred to as "the guidelines"), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. These guidelines focus on pharmacological and surgical interventions in this patient population. Based on the GRADE method, evidence certainty is classified into four levels: high, moderate, low, and very low, and recommendation strength is categorized as "strong" or "conditional" support/opposition for interventions, according to the balance between effects, evidence certainty, patient values and preferences, economic resources, equity, acceptability, and feasibility.

Obesity is frequently complicated by metabolic comorbidities such as abnormal glucose metabolism, dyslipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), obstructive sleep apnea syndrome, polycystic ovary syndrome, and cardiovascular disease [7]. Obesity is not only an important cause and/or risk factor for these comorbidities but is also closely associated with poor prognosis [10-11]. Effective weight loss can improve and even alleviate these comorbidities [12-15]. The guidelines primarily address metabolic comorbidities in forming recommendations.

Table 1 Comparison of Obesity Classifications and Pharmacotherapy Indications

Table 2 List of Recommendations

Table 3 Comparison of Weight-Loss Medications

Table 4 Indications for Metabolic and Bariatric Surgery Based on the Chinese Clinical Guideline for Obesity Management

1.1 Definition, Classification, and Comorbidities of Obesity

WHO defines obesity as a chronic, complex disease of abnormal or excessive fat accumulation that impairs health [8]. In recent years, some academic organizations have proposed defining obesity as "adiposity-based chronic disease" (ABCD) [9]. There are certain differences in obesity classification between domestic and international standards. The guidelines classify obesity into grade I, II, and III based on body mass index (BMI) (see Table 1). Considering the characteristics of the Chinese population, Chinese guidelines use different BMI cutoff values, categorizing obesity into mild, moderate, severe, and very severe (see Table 1). Obesity is often complicated by metabolic diseases, serving as an important etiological factor and/or risk factor, and is closely associated with poor prognosis of these comorbidities [10-11]. Effective weight loss can improve and even alleviate these comorbidities [12-15]. The guidelines primarily focus on metabolic comorbidities.

1.2 Assessment of Obesity

Regarding obesity assessment, Chinese guidelines share many similarities with the Italian guidelines but also have some differences. The Italian guidelines emphasize the integration of comprehensive information, while Chinese guidelines provide more detailed specific assessment methods and examination items. Both highlight the importance of investigating etiology, psychological evaluation, physical examination, laboratory tests, obesity comorbidities, and functional assessment. Additionally, Chinese guidelines mention body fat and visceral fat content measurement, family and social resource support assessment, and weight loss motivation and goal setting. The Italian guidelines stress the critical role of clinical history, including weight gain trends over time, potential triggers, previous weight loss attempts (methods and outcomes), medication history (drugs that may cause weight gain), lifestyle, and family history. They also emphasize the need to assess whether specialized psychological evaluation is required. Chinese guidelines recommend initial psychological screening to identify potential mental health issues and list commonly used screening scales [7], such as the 9-item Patient Health Questionnaire for depressive symptoms, the 7-item Generalized Anxiety Disorder scale for anxiety symptoms, and the Eating Disorder Inventory for eating disorders.

BMI alone does not provide information on body fat distribution and should be combined with waist circumference measurement. Clinicians should also note signs related to obesity-associated diseases or conditions causing secondary obesity, such as acanthosis nigricans, moon face, and goiter [7]. Laboratory evaluation and imaging examinations should be performed to understand comorbidities such as glucose and lipid metabolism, uric acid metabolism, and hepatic and renal function, and to assess secondary causes. For example, serum TSH should be tested to exclude hypothyroidism. Both male and female patients should be clinically evaluated for symptoms and signs of hypogonadism [6], while specific hormone tests should only be performed in symptomatic pa-

tients [16]. Chinese guidelines also emphasize screening for Cushing' s syndrome or hypogonadism when clinically suspected [7].

By integrating information on comorbidities, physical and psychological symptoms, and functional limitations, the stage of obesity can be determined using the Edmonton Obesity Staging System (EOSS). Chinese guidelines also list two other staging systems: cardiometabolic disease staging and ABCD staging, which aim to more precisely diagnose and manage obesity patients through an "obesity-related disease-centered" approach [7].

1.3 Treatment of Obesity

The guidelines clarify that the core objectives of multidisciplinary obesity treatment should be weight reduction and comorbidity prevention. Lifestyle modification is the first step. Nutritional therapy should be personalized and combined with other treatments. Combining nutritional therapy with physical activity is crucial for treating overweight and obese populations and reducing morbidity and mortality. Since lifestyle intervention is not the focus of these guidelines, they concisely provide timeframes, dietary goals, dietary approaches, exercise time targets, and exercise modalities to facilitate goal management and self-monitoring for patients and physicians. The dietary goal is to achieve 5% weight loss within 3-6 months by reducing daily caloric intake by 600-1,000 kcal while maintaining protein intake and limiting carbohydrates to 60% of total calories. To achieve weight loss goals of 2.0-3.0 kg or 5.0-7.5 kg within 4-6 months, aerobic exercise should be increased to 150-225 min/week and 250-420 min/week, respectively [6]. Using appropriate exercise modalities, aerobic exercise appears more effective than resistance exercise. Chinese guidelines also emphasize the importance of multidisciplinary treatment, nutritional and exercise guidance, and psychological counseling for obese patients, providing more detailed clinical applications of various dietary and exercise approaches [7] that are suitable for clinical practice. Combined use of both guidelines can provide more comprehensive and personalized treatment plans for obese patients.

The guidelines define lifestyle intervention resistance as overweight or obese patients who have received standardized lifestyle intervention (including diet and exercise) for 6 months but have not achieved at least 5% weight loss [6]. At this point, other treatment options should be considered (see Table 2). Chinese guidelines only state that weight-loss medications may be used when lifestyle interventions fail to achieve weight loss goals. The Italian guidelines explicitly define the threshold for lifestyle intervention resistance, providing an actionable efficacy evaluation time point that helps Chinese clinicians more accurately identify and manage obese patients who do not respond to lifestyle interventions.

1.3.1 Pharmacotherapy The guidelines state that pharmacotherapy, as part of a comprehensive plan, is indicated for patients with BMI $ $30kg/m^{2}$ or BMI $ $27kg/m^{2}$ with overweight-related risk factors who are resistant to lifestyle interventions [6]. Chinese guidelines have broadly similar indications

for weight-loss medications (Table 1), but it should be noted that the Italian guidelines use BMI $ 27kg/m^{2}$ rather than the BMI $ 25kg/m^{2}$ overweight threshold, likely based on evidence from available literature and resource optimization. The guidelines list four long-term obesity treatment drugs approved by the European Medicines Agency and the Italian Medicines Agency, along with their research evidence: orlistat, naltrexone/bupropion combination, liraglutide, and semaglutide [6]. Their applications and recommendation strengths are detailed in Table 2 .

Currently, five drugs are approved for adult primary obesity in China, including orlistat, liraglutide, benaglutide, semaglutide, and tirzepatide [7]. Drugs for genetic obesity have not been approved. Table 3 summarizes the mechanisms of action, weight-loss efficacy, adverse effects, and contraindications of these medications based on both guidelines. Additionally, these weight-loss medications can improve metabolic indicators such as waist circumference, fasting glucose, glycated hemoglobin, and triglycerides. Except for orlistat, the other medications also improve quality of life. The clinical value of weight-loss drugs extends beyond metabolic benefits (weight reduction and comorbidity improvement) to helping reduce psychological resistance to behavior change, making it easier to establish a positive cycle of "negative energy balance → metabolic improvement → behavioral reinforcement." However, weight regain occurs after discontinuing these medications. Furthermore, caution is needed when using weight-loss drugs in patients with sarcopenic obesity, as evidence regarding the efficacy and potential risks of these drugs in sarcopenic obesity is currently lacking, and there is concern they may exacerbate sarcopenia [7].

1.3.2 Surgical Treatment Metabolic and bariatric surgery reduces body weight by decreasing gastric volume and/or shortening the effective length of the small intestine to limit food intake and/or reduce nutrient absorption [7]. Such surgery not only effectively improves and even alleviates obesity-related comorbidities but also works through mechanisms independent of weight loss, hence the term "metabolic surgery" [7]. The guidelines classify metabolic and bariatric surgery into three categories based on mechanism: "restrictive,""malabsorptive," and "mixed."They outline various surgical procedures and their evolution, including laparoscopic sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB) and its variant one-anastomosis gastric bypass (OAGB), adjustable gastric banding (AGB), biliopancreatic diversion (BPD) and its modified procedures [such as biliopancreatic diversion with duodenal switch (BPD-DS)]. The guidelines analyze the technical characteristics of each procedure (such as gastric pouch volume, limb length, and anastomosis methods) and development trends (for example, LSG and RYGB, the two most commonly performed procedures globally from 2014-2018, have similar weight-loss and complication outcomes; OAGB has become more popular due to improved weight-loss efficacy; AGB has decreased in use due to complications and poor efficacy [24]; technical improvements have driven the optimization of malabsorptive procedures). They focus on research evidence for SG, RYGB, AGB, and OAGB, emphasizing the importance of thor-

ough preoperative evaluation and postoperative care (such as education on diet and medication adjustments).

Chinese guidelines classify surgical procedures into three categories based on mechanism: those primarily restricting food intake, those primarily reducing nutrient absorption, and those balancing both approaches. They recommend procedures such as SG, RYGB, OAGB, and BPD-DS [7], and provide detailed information on surgical indications (Table 4), contraindications, preoperative preparation, discharge criteria, postoperative nutritional management, and follow-up [7]. Chinese guidelines for obesity and metabolic disease surgery provide detailed discussions on the characteristics and selection of recommended procedures in China [25]. In comparison, Chinese guidelines are more comprehensive but lack detailed evidence summaries for procedures. The Italian guidelines provide evidence-based support for procedure selection in China, helping to optimize surgical strategies and improve treatment efficacy and safety.

The guidelines recommend that individuals who meet surgical indications without contraindications should actively consider surgery, with comprehensive preoperative evaluation of obesity and related diseases, surgical safety, and active management of related issues. The guidelines mention that preoperative weight loss of 5%-10% can improve surgical outcomes and reduce postoperative complications. Chinese guidelines do not require preoperative weight loss for all patients, but for severe and above obesity, especially those with severe fatty liver disease, preoperative weight loss of 5%-10% can help reduce surgical difficulty and perioperative complications [7]. Both the volume and quality of metabolic and bariatric surgery have improved in China, with the three most common procedures in 2023 being SG, OAGB, and RYGB [26].

2 Summary and Implications

Obesity is a global health challenge with continuously rising prevalence, and the situation is particularly severe in China [2], yet subsequent management measures lag behind [27]. To address this, China has issued a series of obesity-related policies and guidelines [7,25,28] to standardize obesity diagnosis and treatment. Obesity treatment includes multiple approaches such as psychological intervention, lifestyle intervention, pharmacotherapy, and surgical treatment, with lifestyle intervention as the cornerstone [7]. However, most obese patients struggle to adhere long-term and achieve or maintain ideal results, and behavioral resistance is common. China currently lacks specific guidelines for such patients. Building upon lifestyle interventions, adjunctive measures such as pharmacotherapy and surgery can achieve more significant and durable weight loss while improving various obesity-related health issues. In fact, pharmacotherapy and surgical treatment are already widely used internationally, but their application in China is limited by factors such as drug availability, surgical expertise, and economic considerations [29].

The 2024 guidelines from the Italian Association of Clinical Endocrinologists,

based on evidence-based medicine, provide detailed recommendations on pharmacological and surgical treatment for overweight or obese adults with metabolic complications who are resistant to lifestyle interventions. Therefore, this article analyzes the core content of these guidelines in the context of China' s national conditions and existing guidelines, aiming to provide evidence-based support and practical references for managing overweight or obese Chinese patients with behavioral resistance.

Weight loss goals for obesity should be stratified based on the degree of obesity and the risk and severity of comorbidities [6,28], with stage-specific goals established (such as intensive treatment and maintenance phases [28]), and time-efficacy dual-dimension criteria implemented to avoid treatment delays due to lack of quantitative indicators. The intensive treatment phase extends from treatment initiation to approaching individual optimal weight and can be divided into multiple short-term stages based on individual circumstances, with specific goals set for each stage (such as changes in body weight and waist circumference), typically lasting 3-6 months [28]. For example, most overweight and mildly obese patients are recommended to reduce body weight by 5%-15% within 3-6 months and maintain it; moderately to severely obese patients may set higher weight loss goals to improve metabolic abnormalities and clinical outcomes [28]. For younger patients with few or no complications, the initial stage goal may be set at 10%-15% weight loss within 3-6 months, while for older patients with multiple complications, a more moderate goal such as 5%-10% weight loss within 3-6 months may be set to ensure safety [28]. The rate of weight loss should be appropriate for obesity severity and the weight loss method, with close monitoring for dehydration, sarcopenia, and endocrine system changes. Weight loss efficacy and metabolic indicators should be evaluated every 3-6 months, with the next goal set after achieving each stage goal, gradually reaching and maintaining individual optimal weight [28]. Earlier intervention in weight management yields greater benefits, and the focus should be shifted to earlier stages, initiating management when weight begins to increase rather than waiting for obesity or complications to develop [28].

Obesity treatment requires comprehensive application of multiple modalities. Lifestyle intervention remains the foundation, but most patients achieve suboptimal results with this approach alone and experience rebound, necessitating combination with other treatments. Pharmacotherapy can be applied, and metabolic and bariatric surgery performed when necessary. When using pharmacotherapy, factors such as drug mechanism, weight-loss efficacy, and adverse effects should be comprehensively considered to develop personalized regimens, while remaining vigilant about risks in special populations. Metabolic and bariatric surgery yields significant results, and surgical indications and contraindications should be strictly followed. Individuals who meet surgical indications without contraindications may actively consider surgery, with enhanced preoperative evaluation and postoperative care and promotion of preoperative weight loss strategies. The long-term and comprehensive nature of obesity management must be recognized, as scientific comprehensive lifestyle interven-

tion and/or pharmacotherapy remains necessary even after pharmacotherapy or surgery. Additionally, traditional Chinese medicine and acupuncture therapy with Chinese characteristics may be considered, including dietary therapy based on syndrome differentiation, traditional Chinese exercise (Daoyin), "mindfulness intervention," and acupuncture-related therapies [7].

Weight loss strategies should involve full communication with patients to understand their motivation, needs, concerns, expected goals, and family/social resources, with shared decision-making with patients and families to develop the most reasonable individualized weight loss plan and guide its implementation, monitoring, and follow-up. With technological development, digital health tools such as wearable devices, mobile health applications, and remote monitoring equipment show promising prospects in obesity management, enabling real-time patient data monitoring, personalized recommendations, behavioral interventions, and remote interaction between patients and healthcare providers to improve treatment adherence and self-management capabilities. Obesity is a complex chronic disease requiring integration of multidisciplinary expertise. A multidisciplinary collaborative diagnosis and treatment model should be advocated, encouraging participation of physicians from multiple specialties (such as general practice, endocrinology, cardiology, psychology, rehabilitation, surgery, and traditional Chinese medicine), dietitians, nurses, and others in obesity management. Continuous attention should be paid to the latest clinical advances in related fields to provide patients with standardized, comprehensive, personalized, and continuous services based on evidence-based medicine [29], thereby effectively curbing the epidemic of obesity and related comorbidities and achieving long-term goals and benefits. Furthermore, it is recommended to gradually integrate obesity management into the public health system, improving public awareness and attention to obesity through policy guidance and health education, increasing medical resource investment, and enhancing the capacity of primary care physicians in obesity diagnosis and treatment through training and telemedicine to promote accessibility and equity in obesity treatment.

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