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CONSENSUS STATEMENT

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

Aim This guideline (GL) is aimed at providing a clinical practice reference for the management of adult patients with overweight or obesity associated with metabolic complications who are resistant to lifestyle modification.

Methods Surgeons, endocrinologists, gastroenterologists, psychologists, pharmacologists, a general practitioner, a nutritionist, a nurse and a patients' representative acted as multi-disciplinary panel. This GL has been developed following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. A systematic review and network meta-analysis was performed by a methodologic group. For each question, the panel identified potentially relevant outcomes, which were then rated for their impact on therapeutic choices. Only outcomes classified as "critical" and "important" were considered in the systematic review of evidence. Those classified as "critical" were considered for clinical practice recommendations. Consensus on the direction (for or against) and strength (strong or conditional) of recommendations was reached through a majority vote.

Results The present GL provides recommendations about the role of both pharmacological and surgical treatment for the clinical management of the adult patient population with BMI > 27 kg/m^2 and < 40 kg/m^2 associated with weight-related metabolic comorbidities, resistant to lifestyle changes. The panel: suggests the timely implementation of therapeutic interventions in addition to diet and physical activity; recommends the use of semaglutide 2.4 mg/week and suggests liraglutide 3 mg/day in patients with obesity or overweight also affected by diabetes or pre-diabetes; recommends semaglutide 2.4 mg/week in patients with obesity or overweight also affected by non-alcoholic fatty liver disease; recommends semaglutide 2.4 mg/week as first-line drug in patients with obesity or overweight that require a larger weight loss to reduce comorbidities; suggests the use of orlistat in patients with obesity or overweight also affected by hypertriglyceridemia that assume high-calorie and high-fat diet; suggests the use of naltrexone/bupropion combination in patients with obesity or overweight, with emotional eating; recommends surgical intervention (sleeve gastrectomy, Roux-en-Y gastric bypass, or metabolic gastric bypass/gastric bypass with single anastomosis/gastric mini bypass in patients with BMI ≥ 35 kg/m^2 who are suitable for metabolic surgery; and suggests gastric banding as a possible, though less effective, surgical alternative.

Conclusion The present GL is directed to all physicians addressing people with obesity—working in hospitals, territorial services or private practice—and to general practitioners and patients. The recommendations should also consider the patient's preferences and the available resources and expertise.

Keywords Obesity · Bariatric surgery · Liraglutide · Semaglutide · Orlistat · Naltrexone–bupropion

Abbreviations

AGB	Adjustable gastric banding
AGREE	The Appraisal of Guidelines for REsearch and Evaluation
AIFA	Agenzia Italiana del Farmaco (Italian agency for drugs)
ALT	Alanine amino-transferase

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AME	Associazione Medici Endocrinologi (Italian Association of Clinical Endocrinologists)
AST	Aspartate amino-transferase
AMSTAR	A measurement tool to assess systematic reviews
BMI	Body mass index
BPD	Biliopancreatic diversion
BPD-DS	BPD with duodenal switch
CI	Confidence interval
COVID-19	Coronavirus disease 19
CV	Cardiovascular
DOI	Digital object identifier
EMA	European Medicine Agency
ERT	Evidence Review Team
EtD	Evidence to Decision
FLI	Fatty liver index
FIB-4	Fibrosis-4
GL	Guideline
GLP-1	Glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LSG	Laparoscopic sleeve gastrectomy
MBS	Metabolic–bariatric surgeries
MD	Mean difference
MESH	Medical subject headings
MSH	Melanocyte stimulating hormone
NAFLD	Non-alcoholic fatty liver disease
NMA	Network meta-analysis
OAGB	One anastomosis gastric bypass
OSAS	Obstructive sleep apnea syndrome
PICO	Population, Intervention, Comparison, Outcome
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
RYGB	Roux-en-Y gastric bypass
SADI	Single-anastomosis duodeno-Ileal bypass
SMD	Standardized mean difference
SoF	Summary of findings
T2DM	Type 2 diabetes mellitus
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
WHO	World Health Organization

Introduction

Definition, epidemiology, and classification

Obesity is a chronic disease characterized by an increased proportion of fat compared to lean mass, as a result of the imbalance between caloric intake and energy expenditure. This condition results from a multifaceted interplay of lifestyle, genetic, and environmental factors. It is only partially modifiable by personal willingness.

According to the 2022 report of WHO Europe, nearly 60% of adults are overweight or affected by obesity [1]. The rise in obesity prevalence is associated with sedentary lifestyles and dietary habits that involve high-fat and fast-absorbing carbohydrate intake [2]. Excess weight impacts patients' quality of life (QoL) and even life expectancy.

The classification of excess weight is based on body mass index (BMI). Individuals fall in the "overweight" category if their BMI is between 25.0 and 29.9 kg/m^2, and in the "obesity" category if their BMI equals or exceeds 30.0 kg/m^2. Within the obesity category, obesity is ranked into first, second, and third degree, if BMI is 30–35 kg/m^2, 35.1–40 kg/m^2, and higher than 40.0 kg/m^2, respectively.

Obesity complications

This guideline (GL) is focused on the medical and surgical management of obesity in adult patients with metabolic comorbidities, such as pre-diabetes, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), dyslipidemia, and hypertension. Non-metabolic complications, such as respiratory, orthopedic, cardiovascular (CV), and oncological issues are not addressed.

Patients with obesity commonly experience glucose metabolism derangements that lead to increased risk for pre-diabetes (reported in over one-third of young patients with obesity) and T2DM, whose risk is reportedly increased 8–14 times compared to subjects with normal weight [3, 4]. The increase in visceral fat deposits is a relevant risk factor for CV disease due to the production of inflammatory cytokines, such as TNF-alpha and interleukin-6. Over one-third of patients with visceral obesity have atherogenic dyslipidemia, marked by high levels of small, dense LDL-cholesterol particles and triglycerides and by low values of HDL cholesterol. Insulin resistance, common in obesity, is a significant contributor to hyperlipidemia.

NAFLD is frequently associated with extra-hepatic clinical manifestations and its link with metabolic disorders such as obesity, type 2 diabetes (T2DM), hypertension, and dyslipidemia is so close that the term MASLD

(metabolic dysfunction-associated steatotic liver disease) has recently been introduced. [5]NAFLD is characterized by the accumulation of dysmetabolic-based fat in liver parenchymal cells and affects approximately 90–95% of patients with severe obesity. In addition, 75% of NAFLD cases occur in patients with overweight or affected by obesity [6].

The association between elevated blood pressure and overweight, or obesity, is widely accepted as a significant CV risk factor [7, 8]. Patients with visceral obesity face an elevated risk of hypertension (range: 60–77%), with an increased differential pressure [9]. Risk of major CV effects is considerably increased by the combination of obesity, hypertension, and other CV risk factors. In patients with obesity, hypertension is associated with heart failure with preserved ejection fraction, due to hypertrophy, remodeling, and dilatation of the heart chambers that lead to diastolic dysfunction. The American Heart Association highlights how, in these patients, the reduction of body weight strongly decreases their risk of developing hypertension [10, 11].

Physical disability, such as osteoarthritis and backache, as well as medical comorbidities that include T2DM, hypertension, and obstructive sleep apnea syndrome (OSAS), significantly impact QoL, regardless of the severity of obesity. However, for patients with grade III obesity, the mental component appears to be a critical factor in defining QoL. It is worth noting that obesity is often associated with psychological distress, including an increased risk of depression with higher BMI. Eating disorders such as Binge Eating Disorder and Night Eating Syndrome play a primary role in the psychological disorders related to obesity; however, dysfunctional behaviors, such as emotional eating, grazing, gorging and prandial overeating, equally contribute to the development and maintenance of obesity even in the absence of objective eating disorders [12–15]. The cognitive profile of patients with obesity includes reduced cognitive and inhibitory control skills, attention bias toward food, and impulsivity toward immediate reward from food. These factors contribute to the maintenance of dysfunctional eating patterns. In addition, neuroinflammation and cerebrovascular disease, which are associated with adiposity and metabolic diseases, are risk factors for neurological abnormalities contributing to the development of cognitive decline with age, mild cognitive impairment, or Alzheimer's disease [16]. These components challenge the efficacy of treatments for obesity and highlight the need of personalized treatment options for these patients [17, 18].

Clinical approach to obesity

When approaching a patient with overweight or obesity, various factors, such as anthropometric, biochemical, clinical, and psychological parameters should be considered. The clinical history plays a pivotal role in this process. The trend of weight gain over time, its initial onset, potential triggers, previous weight loss attempts, medication history, lifestyle, and family history should be taken into account. In addition, the need for specialized psychologic investigation should be evaluated [19].

BMI alone does not provide information on body fat distribution and should be integrated by the measurement of waist circumference. In addition, laboratory evaluation and imaging should be performed to investigate glucose and lipid metabolism, renal and liver function, the presence of cholelithiasis, OSAS, inflammatory status, and osteoarthritis. Serum TSH should be assayed to rule out hypothyroidism. Both men and women should be clinically evaluated for signs and symptoms of hypogonadism, while specific hormonal tests, such as dexamethasone suppression test, should be performed only in symptomatic patients [20].

By integrating information regarding comorbidities, physical and psychological symptoms, and functional limitations, the stage of obesity can be identified according to the Edmonton Obesity Staging System classification [21]. During initial patient evaluation, the suspicion of a genetic condition associated to obesity should be ruled out, even if rare. Genetic obesity is historically distinguished into syndromic, monogenic, and polygenic forms, but their management is not addressed in this GL [21].

Treatments for obesity

The multi-disciplinary therapeutic approach to individuals with obesity should aim to achieve weight loss and to prevent, or treat, comorbidities. Lifestyle modification is the initial step. Nutritional therapy should be individually tailored and combined with other treatments. The dietary goal is a 5% weight loss in 3–6 months through a reduction in caloric intake of 600–1000 kcal/day while maintaining the protein intake and limiting carbohydrates to 60% of total calories. The "Mediterranean diet" is a widely used approach that reduces visceral adipose tissue and positively impacts metabolic syndrome. In selected patients, low- and very-low-calorie or ketogenic diets with nutrient supplementation can be effective strategies [22, 23].

The combination of nutritional therapy and physical activity is crucial in treating people with overweight and obesity and reducing morbidity and mortality. To achieve a weight loss of 2.0–3.0 kg or 5.0–7.5 kg within 4–6 months, the aerobic activity should be increased to 150–225 and 250–420 min per week, respectively. The appropriate time of physical activity should be dedicated to suitable modalities of exercise, based on the patient's characteristics and needs. Aerobic activity seems to be more effective than endurance activity [24].

Lifestyle modification alone is not enough to ensure adequate weight loss and its long-term maintenance in most subjects with obesity. In individuals living with overweight or obesity who do not achieve a weight loss of at least 5% after 6 months of lifestyle modification, including diet and physical activity, other treatment options should be considered. A specific anti-obesity drug treatment is indicated, as part of a comprehensive program, in patients with a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 associated with risk factors related to excess weight, who are resistant to lifestyle changes [25, 26]. Currently, four drugs are approved by EMA and AIFA for long-term obesity treatment: orlistat, naltrexone/bupropion combination, liraglutide 3 mg/day, and semaglutide 2.4 mg/week. However, the last is not yet marketed in Italy.

Orlistat is an oral selective inhibitor of pancreatic lipase that decreases dietary fat absorption and increases its fecal excretion [27, 28].

Bupropion is an oral inhibitor of dopamine and norepinephrine reuptake and a stimulator of α-melanocyte-stimulating hormone (α-MSH) secretion. α-MSH binds to Melanocortin-4 Receptors exerting an anorexigenic action. This action is usually blocked by the negative feedback of the co-secreted ß-endorphin. Naltrexone, an inhibitor of the μ receptor of opiates, inhibits this feedback, and thus prolongs the anorexigenic effect of α-MSH. In addition, bupropion and naltrexone exert an action on the mesolimbic circuit of rewarding [29].

Liraglutide is a receptor agonist of human glucagon-like peptide-1 (GLP-1) to be injected subcutaneously. Liraglutide is marketed as an anti-diabetic drug at a daily dose up to 1.8 mg and is also approved and marketed as a weight-loss-inducing drug at a dose of 3.0 mg per day.

Semaglutide is a GLP-1 analogue that requires a once-weekly subcutaneous administration. It is marketed as an anti-diabetic drug at the dose of 0.5–1.0 mg [30]. Semaglutide 2.4 mg/week has been approved by AIFA but is not yet marketed as of GL's publication date.

Bariatric or metabolic–bariatric surgeries (MBS) may be grouped into three categories, according to their prevalent mechanism of action: "restrictive," "malabsorptive," and "mixed." The two most frequently performed procedures worldwide in the 2014–2018 period were the Roux-en-Y gastric bypass (RYGB) and the laparoscopic sleeve gastrectomy (LSG), which yielded similar results in terms of weight loss and complications. LSG involves a partial resection of the stomach to create a gastric tube, while RYGB requires the creation of a "small gastric pouch" (15–20 mL volume) to which an approximately 100–150 cm food loop is anastomosed and an RY reconstruction with a 50–150 cm biliopancreatic loop is packaged. One anastomosis gastric bypass (OAGB), a variant of RYGB, includes the creation of a long gastric pouch. This procedure is growing in popularity in recent years because it is reported to induce an improved weight loss performance. Adjustable gastric banding (AGB), a common bariatric surgery in the early 2000s, is currently less employed due to its complications and the lower efficacy compared to other surgical techniques [31–34]. Biliopancreatic diversion (BPD) has historically been the most commonly utilized malabsorptive surgery in the treatment of severe obesity. This procedure involves a distal gastric resection and cholecystectomy, followed by reconstruction on a looped Y according to Roux. The food loop, approximately 200-cm long, is connected to a common loop of 50–70 cm (last ileal tract before the ileo-cecal valve), while the remaining intestine represents the biliary loop. Over the years, various technical modifications have been introduced, resulting in the development of more popular malabsorptive procedures such as biliopancreatic diversion with duodenal switch (BPD-DS) and single-anastomosis duodeno-ileal bypass (SADI) [35].

Before undergoing MBS, the candidate patients should be thoroughly evaluated by a team of medical professionals with specific expertise. A preoperative diet and weight loss of 5–10% of body weight improves the surgical outcome and reduces postoperative complications. Patients with metabolic, pulmonary, or endocrine comorbidities should receive optimal treatment to decrease peri-operative risks.

Follow-up care involves regular evaluations and tests to monitor progress and includes education on diet and medication adjustment. A structured, multi-disciplinary approach improves patient's QoL.

The most effective and cost-efficient approach to the management of people with obesity has been determined based on the best available evidence using the GRADE method.

Methods

This GL was developed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [36]. In addition, we ensured that the contents of the GL were reported in accordance with the AGREE II (Appraisal of Guidelines for REsearch and Evaluation II) checklist [37]. Appendix 1 lists all members of the panel, Evidence Review Team (ERT), and external reviewers who contributed to this GL.

Clinical question

The focus of recommendations is the answers to a clinical question: what is the recommended treatment for adult individuals with overweight or obesity (BMI > 27 and ≤ 40 kg/m^2) and metabolic weight-related comorbidities (pre-diabetes, T2DM, NAFLD, dyslipidemia or hypertension) when behavioral treatments have proven ineffective? Patients with obesity may be deemed resistant to lifestyle interventions if

they fail to achieve a weight loss of at least 5% of baseline weight after 6 months of properly prescribed and implemented diet and exercise. The panel formulated the question using the PICO (Population, Intervention, Comparison, Outcome) framework and established the criteria for study inclusion and exclusion (Appendix 2).

Selection of outcomes

The panel identified potentially relevant clinical outcomes and rated their importance on a nine-point scale, where 1–3 points indicated outcomes of limited relevance, 4–6 points indicated important but not critical outcomes, and 7–9 points indicated critical outcomes. Only outcomes that were rated as critical or important were considered in the literature review and only the critical ones for the formulation of recommendations.

Literature review and assessment of quality of evidence

We conducted a comprehensive systematic literature search on the Medline/PubMed, Embase, and Cochrane Library databases from inception to May 16, 2022, without language restrictions, to identify relevant evidence on the safety and efficacy of the treatments in question. The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews PROSPERO (number CRD42022351409).

We included randomized controlled trials (RCTs) only.

Four authors independently screened titles and abstracts, full texts, and extracted data. We performed a network meta-analysis (NMA) using a frequentist approach and a random-effects model with graph theory for each outcome. We analyzed the data using STATA version 17 software. The risk of bias in the included studies was assessed using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0) [38].

Certainty of evidence was evaluated using the methodology developed by the GRADE working group, adapted for assessing the results of a NMA. We assessed confidence in effect estimates by considering the limitations of the studies (risk of bias), heterogeneity of the meta-analytic result, direct applicability of literature findings to the PICO of interest, risk of publication-related bias, and imprecision, following a non-contextualized approach. We assigned four levels of certainty of evidence in accordance with the GRADE approach: high, moderate, low, and very low. Strength of recommendations was expressed as strong or conditional (in favor or against an intervention).

Development of recommendations

During several web-based meetings, the ERT team presented the following items to the panel: the list and characteristics of identified studies, the list of excluded studies along with the reasons for their exclusion, the Evidence to Decision (EtD) framework as a tool for making recommendations, and a report on the economic analysis of treatments related to the clinical question. Subsequently, the panel discussed a draft of the recommendations and voted to judge their strength. Recommendations were categorized as either "strong" or "conditional", based on factors such as the balance between effects, certainty of evidence, patients' values and preferences, economic resources, equity, acceptability, and feasibility of the intervention being considered (Table 1).

External review

A multi-disciplinary group of experts conducted a thorough review of GL draft and provided summary judgments, criticisms, and suggestions to improve the document. The panel evaluated the reviewers' feedback and operated the appropriate amendments into the final text, when accepted and needed.

Update

The recommendations outlined in this GL will remain valid for a maximum of 3 years from the publication date.

Table 1 Categorization of recommendations

Strength of recommendation	Strong	Weak
For clinicians	Most patients should follow the recommendation (benefits outweigh harms)	Beneficial effects probably outweigh harmful effects, but there is still relevant uncertainty
For patients	Almost all properly informed patients behave as recommended	A good proportion of properly informed patients behave as recommended
For researchers	The recommendation is supported by reliable evidence or other convincing arguments. On some occasions, a strong recommendation may also be based on evidence with low or very low certainty	The recommendation could be modified by subsequent studies

Thereafter, AME will contact the Scientific Societies involved in the production of the document to update and revise it.

Results: literature analysis

Pharmacological therapies

Orlistat

The analysis included 31 studies on orlistat, conducted between 1999 and 2009, involving a total of 6,699 patients (mean BMI 38.8 kg/m^2) with weight-related comorbidities. Despite the low certainty of evidence, the studies showed that orlistat led to small improvements in different efficacy outcomes, such as weight reduction, waist circumference, HbA1c, fasting blood glucose, and ALT levels, and moderate results in triglyceride reduction. The side effects of orlistat were considered manageable, and thus were not considered a contraindication for its use in selected patients. A cost-effectiveness study demonstrated favorable results, although the high reference willingness-to-pay may pose sustainability issues. The lack of equitable access to pharmacological treatment and the feasibility and acceptability of orlistat were not regarded as significant concerns. Overall, orlistat is suggested for use in patients with hyperlipidemia and hypertriglyceridemia covered by the GL [39, 40].

Liraglutide

The analysis included ten RCTs conducted from 2009 to 2021, focusing exclusively on liraglutide 3 mg/day for treatment of people with obesity. Despite the low certainty of evidence, the results demonstrated small improvements in efficacy outcomes, such as weight reduction, waist circumference, HbA1c, systolic blood pressure, and QoL. Notably, the reduction in HbA1c was small in studies involving patients without T2DM, but liraglutide has shown significant reductions in HbA1c in patients with T2DM with or without obesity at lower doses [41]. The risk of undesirable effects, including death and serious adverse events, was considered negligible or small by the panel. The analysis did not provide sufficient data for a judgment on cost-effectiveness. Despite the potential equity issues related to out-of-pocket cost, the panel considered liraglutide acceptable and feasible. In conclusion, despite the balance of effects and limited evidence, the panel suggests considering liraglutide for obese patients with pre-diabetes and T2DM due to its potential benefits on HbA1c reduction and glyco-metabolic control.

Semaglutide

Three studies, involving a total of two thousand one hundred seventeen patients (mean BMI 37.2 kg/m^2) with at least two comorbidities, were analyzed. Direct evidence with moderate certainty showed moderate improvements in various efficacy outcomes, including reduction of weight, waist circumference, fasting blood glucose, HbA1c, triglycerides, systolic blood pressure, and ALT. QoL improvement was considered large, while reductions in diastolic blood pressure were deemed as small. Undesirable effects were rated insignificant (as about death) or small (as about serious adverse events). The net balance of effects favored the intervention. Regarding cost-effectiveness, no Italian studies were available for semaglutide 2.4 mg, but an American study considered it cost-effective [42]. The panel expressed a favorable opinion based on the applicability of American data to the Italian market, pending the drug's availability in Italy. Equity considerations suggested that semaglutide could reduce equity, as current obesity drugs are fully out-of-pocket for patients and not reimbursable. Semaglutide-induced weight loss improves health status and QoL for patients with obesity. The use of semaglutide was deemed acceptable and feasible by patients and panel members. Based on this evidence, the panel recommends semaglutide use, particularly for patients with obesity and T2DM or pre-diabetes, contingent upon its availability in Italy [42].

Naltrexone–bupropion

Six studies involving three thousand two hundred forty-one patients (mean BMI 36.3 kg/m^2) were analyzed. Despite the low certainty of evidence, the results showed improvements in various efficacy outcomes, including reduction of weight, waist circumference, HbA1c, and triglycerides, and improvement in QoL. The extent of these improvements was considered small. Undesirable effects were rated insignificant (as about death), small (as about adverse events), and moderate (serious iatrogenic events), aligning with panel members clinical practice. Naltrexone–bupropion, like other anti-obesity drugs, is out-of-pocket, reducing equitable access to treatment. It was considered probably acceptable by patients. While the balance of effects is neutral, naltrexone–bupropion remains a useful aid in patients without contraindications, particularly those with emotional feeding. Its effect on food cravings is valuable in this subgroup. Starting this treatment and continuing it in patients with good tolerability is a reasonable option. Considering these aspects, the panel justifies and suggests the use of naltrexone–bupropion in clinical practice, especially for patients with obesity and emotional eating [43].

Surgical therapies

Considering only RCTs, few studies on MBS were retrieved. This scarcity can be attributed to the ethical challenges associated with randomization in surgical procedures, leading to a predominant reliance on observational studies in the existing literature.

Gastric banding (AGB)

Considering both direct and indirect evidence, five studies on this procedure were included, published between 2006 and 2020, involving a total of 139 patients (mean BMI 34.3 kg/m^2) affected by comorbidities included in the PICO. Despite the low certainty of evidence, the results showed improvement in multiple efficacy outcomes (reduction of weight, waist circumference, HbA1c, fasting blood glucose, triglycerides), which were considered "moderate" by the panel. Regarding adverse effects, the panel could only assess the outcome of "death," which was deemed numerically "irrelevant," while data on minor post-surgical complications are not available. Acceptability data are based on studies conducted on a small number of patients. The study by Roh et al. in 2020 [44] showed that only 11.5% of patients preferred AGB due to awareness of long-term complications, the need for better compliance and frequent follow-up visits, and the perceived ineffectiveness of the treatment. As for healthcare professionals, 31.2% of respondents preferred this approach in the study by Sarwer et al. in 2012 [45]. However, on considering the implementation of more advanced surgical techniques, the panel downgrades the current applicability of this 10-year-old study. For this reason, the acceptability is ranked as "variable." The treatment is feasible and implementable in the national territory. The treatment is associated with high costs but, as all MBS procedures, is reimbursed by the national healthcare system, although approximately 50% of surgical treatments are performed in private practice. Based on these considerations, the panel expresses a conditional recommendation in favor of the intervention, considering the limited number of patients in the analyzed studies and the reduced utilization of the technique in current clinical practice [44, 45].

Sleeve gastrectomy

The analysis included 10 studies on this technique, involving a total of 302 patients (mean BMI 38.4 kg/m^2). Despite the low certainty of evidence, the results showed significant improvement in weight reduction, waist circumference, and HbA1c levels. Triglyceride reduction and QoL improvements were also observed but to a lesser extent. Adverse effects were considered minor, including post-surgical complications and mortality risk. Patient acceptability was high, with the majority preferring sleeve gastrectomy over other interventions. The treatment was deemed feasible and implementable. The panel strongly recommended sleeve gastrectomy, considering its substantial benefits and minimal adverse effects, while also being likely acceptable to all stakeholders and improving equity [44, 45].

Roux-en-Y gastric bypass (RYGBP)

The analysis included 10 RCTs on this technique, involving 318 patients (mean BMI 37.2 kg/m^2) with comorbidities such as T2DM and hypertension. The evidence showed significant improvement in multiple efficacy outcomes, including reduction of weight, waist circumference, HbA1c, triglycerides, and blood pressure. Adverse effects were assessed as small (mortality) or minor (post-surgical complications). The treatment was considered feasible and implementable, despite high costs, and was generally accepted by patients, although preferences varied among individuals. Based on these findings, the panel strongly recommended the intervention due to its significant benefits and minor drawbacks, along with its feasibility and potential for improving equity [44, 46, 47].

Other metabolic bypass procedures

This section addresses surgical interventions different from RYGBP. These alternative procedures included omega loop and one-anastomosis gastric bypass (OAGB), which introduces the possibility of indirect evidence due to the inclusion of patients who underwent different types of surgeries. However, this did not affect the strength of the recommendation.

Four RCTs were analyzed, involving a total of one hundred forty-nine subjects (mean BMI 37.1 kg/m^2). All subjects had T2DM as a comorbidity, and 61% also had arterial hypertension. Despite the limited and mixed certainty of evidence, the results showed significant improvements in different efficacy outcomes, such as reduction of weight, waist circumference, HbA1c, and triglyceride levels, which were considered large by the panel. Moderate effects were observed for fasting glucose reduction and QoL improvement, while the reduction in diastolic blood pressure was considered minor. In terms of adverse effects, with low certainty of evidence, minor post-surgical complications and the outcome of death were assessed as small in magnitude. However, the number of studies and population size were limited [48, 49].

The cost-effectiveness analysis indicated a probable advantage for the intervention, and no significant feasibility or implementation issues were identified. Acceptability of the different surgical procedures varied among patients and surgeons. While one study showed mixed preferences among patients, with some favoring the alternative procedures,

surgeons generally considered the gastric bypass procedures superior to sleeve gastrectomy. Therefore, the panel concluded that acceptability varied among stakeholders.

Based on the evidence, the panel strongly recommends the use of gastric bypass procedures in patients targeted by this GL, particularly those with a BMI higher than 35 kg/m^2, as there is a lack of studies involving patients with lower BMIs.

Recommendations and indications for good clinical practice

Table 2 shows the recommendations agreed on by the panel about the clinical question: "What is the best therapy for adult individuals with overweight or obesity and weight-related metabolic comorbidities (pre-diabetes, T2DM, NAFLD, hyperlipidemia, hypertension), when behavioral treatments have proven ineffective?".

A patient with obesity may be deemed resistant to lifestyle interventions if he/she fails to achieve a weight loss of at least 5% of his/her baseline weight after 6 months of properly prescribed and implemented diet and exercise.

The following indications for good clinical practice are complementary to the previous formal recommendations. They are based on extensive clinical experience and have received unanimous consensus among the participants involved in drafting the GL.

1. The patient should be educated about the chronic nature of obesity and the need for its continuous, long-term treatment.
2. When dealing with patients who have not responded to lifestyle intervention for overweight or obesity, the clinical history should focus on identifying the presence of eating disorders, risky behaviors, and environmental factors that can be potentially corrected or modified.
3. A thorough evaluation of the patient's psychological profile should be conducted, and if needed, should be complemented by psychological consultation to assess the patient's experiences and his/her environmental context.
4. Metabolic, CV, respiratory, and musculoskeletal comorbidities, along with potential nutritional deficiencies, should be assessed with appropriate clinical, biochemical, and imaging evaluations.
5. The weight loss goal should be realistic and established in collaboration with the patient. The goal should consider the patient's demographic, clinical, and environmental circumstances.

Table 2 List of recommendations

Quality of evidence	Recommendations	Strength of recommendation
Low	In adult patients with BMI > 27 kg/m^2 and < 40 kg/m^2 with weight-related metabolic comorbidities who are resistant to lifestyle changes, the panel suggests the implementation of further interventions in addition to diet and physical activity	Conditional, in favor of the intervention
Moderate	In adult patients with BMI 27–40 kg/m^2 who are resistant to lifestyle changes and have diabetes or pre-diabetes, the panel recommends using semaglutide 2.4 mg/week	Strong, in favor of the intervention
Low	In adult patients with BMI 27–40 kg/m^2 who are resistant to lifestyle changes and have diabetes or pre-diabetes, the panel suggests using liraglutide 3 mg/day	Conditional, in favor of the intervention
Moderate	In adult patients with BMI 27–40 kg/m^2 who are resistant to lifestyle changes and have NAFLD, the panel recommends using semaglutide 2.4 mg/week	Strong, in favor of the intervention
Moderate	In adult patients with BMI 27–40 kg/m^2 who are resistant to lifestyle changes and require a larger weight loss to reduce comorbidities, the panel recommends using semaglutide 2.4 mg/week as first-line drug	Strong, in favor of the intervention
Low	In adult patients with BMI 27–40 kg/m^2 who are resistant to lifestyle changes and have hypertriglyceridemia and assume high-calorie and high-fat diet, the panel suggests using orlistat	Conditional, in favor of the intervention
Low	In adult patients with BMI 27–40 kg/m^2 and weight-related metabolic comorbidities, resistant to lifestyle changes, who has emotional eating, the panel suggests using naltrexone/bupropion	Conditional, in favor of the intervention
Low	In adult patients with BMI ≥ 35 kg/m^2 and weight-related metabolic comorbidities who are candidate for metabolic surgery, the panel recommends: sleeve gastrectomy, Roux-en-Y gastric bypass, or metabolic gastric bypass/bypass gastric with single anastomosis/mini bypass gastric	Strong, in favor of the intervention
Low	In adult patients with BMI > 27 kg/m^2 and < 40 kg/m^2 and with weight-related metabolic comorbidities who are resistant to lifestyle changes and are candidate for metabolic surgery, the panel suggests gastric banding as a possible surgical alternative, though less effective	Conditional, in favor of the intervention

6. The intensity of therapeutic intervention, as add-on to lifestyle modifications, should be tailored from the beginning according to disease staging. Factors such as the severity of excess weight, the presence of comorbidities, and the patient's psychological state should be considered.
7. When prescribing pharmacological treatment or recommending metabolic–bariatric surgery, physicians should offer comprehensive information, support, and guidance regarding the diet, physical activity, and behavioral strategies to be adopted. In addition, the implementation of appropriate follow-up should be emphasized.
8. In the event of therapeutic failure, the intensification of psychological support, pharmacological therapy, or surgical intervention should be considered, based on clinical indications.

This is the first Italian GL based on GRADE methodology that advises clinicians on the use of pharmacological and surgical treatments for the management of patients affected by overweight and obesity resistant to lifestyle modification, based on their metabolic comorbidities. In light of the rapidly evolving landscape of anti-obesity treatments, it is worth noting that new medications are being endlessly developed and approved. These advancements have the potential to modify significantly therapeutic approaches. As a consequence, it is crucial to revise and regularly update these guidelines to incorporate the latest evidence and to account for the availability of these innovative treatments. Clinicians will, thus, be equipped with the most updated information for decision-making in the management of patients with overweight and obesity, particularly those resistant to lifestyle modifications.

Furthermore, it is reasonable to anticipate that the introduction of second-generation anti-obesity medications, which are both highly effective and well-tolerated, could extend obesity management to a broader segment of the affected population. This expansion is contingent upon the implementation of their availability and reimbursement, taking into account the potential reductions in health complications and associated costs.

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Declarations

Conflict of interest The authors and the members of the panel declare no potential conflict of interest to be disclosed.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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