

Current treatments for obesity

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ABSTRACT

Obesity is a major health and economic crisis facing the modern world. It is associated with excess mortality and morbidity and is directly linked to common conditions such as type 2 diabetes mellitus, coronary heart disease and sleep apnoea. The management of obesity and its associated complications has evolved in recent years, with a shift towards more definitive strategies such as bariatric surgery. This review encompasses the dietary, pharmacological and surgical strategies currently available for the management of obesity.

KEYWORDS: Obesity, diabetes, weight

Introduction

Obesity is defined by the World Health Organization (WHO) as an 'abnormal or excessive fat accumulation that presents a risk to health', commonly classified by the body mass index (BMI; Table 1).¹ BMI is simple to calculate, but it does have its limitations where factors such as age, muscle mass and ethnicity can influence its relationship with body fat. Anthropometric measures such as skinfold thickness, waist circumference and waist-to-hip ratio are increasingly used to assess an individual's risk of obesity related conditions such as type 2 diabetes mellitus (T2DM) and cardiovascular disease.^{2–4}

According to WHO, obesity has reached epidemic proportions worldwide, with approximately 1.9 billion overweight and 650 million obese adults. Similarly, 26% of adults and 10% of children in England were classified as obese in 2016, where it is estimated that obesity-related ill health annually costs the UK's NHS up to £6.1 billion, a figure projected to double by 2050.^{5–7} Public Health England recognises the significance of obesity and has dedicated increasing resources and funding into tackling it and its wider impact on society.

The Royal College of Physicians published a report in 2013 entitled *Action on obesity: Comprehensive care for all* in order to raise awareness of this global problem, particularly among healthcare professionals.⁸ The report noted that education in obesity and nutrition is inadequately represented in

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Table 1. World Health Organization adult body mass index classification

Classification	Body mass index (kg/m ²)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese class I	30.0–34.9
Obese class II	35.0–39.9
Obese class III	≥40

undergraduate curricula, and that this issue needs to be addressed. Moreover, it recognised that training for health professionals in obesity matters is inadequate. This review has been written with the findings of this report in mind, with the aim of giving a detailed overview of current strategies in the management of obesity.

Dietary therapy

Weight loss can be achieved by a net deficit of kilocalories (units of energy). The estimated energy expenditure per adult kilogram of body weight is approximately 22 kcal.⁹ Reduction of intake to yield a net energy deficit can be achieved in numerous ways, as outlined below (Table 2).

Macronutrient composition

The three primary dietary macronutrients are fat, carbohydrate and protein, which provide 9, 3.75 and 4 kilocalories per gram, respectively.¹⁰ Fat is the least satiating, most readily absorbed and calorie-dense macronutrient, making it the most appealing target for weight loss intervention. Recent meta-analysis of low-fat diets shows significant weight loss when compared to baseline intake (-5.41 kg), but not when compared to other dietary interventions, including high-fat diets.¹¹ Low carbohydrate diets (LCHDs) yield rapid results with greater initial weight loss compared to low-fat diets (by up to 3.3 kg at 6 months).¹² However, much of this has been attributed to loss of glycogen stores and water, amounting to 1–2 kg within the first 14 days, after which the rate of weight loss slows.¹³ Protein is highly satiating and used in high protein diets (HPDs) with the aim of reducing passive overconsumption of other less satiating and more energy-dense macronutrients.¹⁴ However, recent meta-analyses have concluded that HPDs have either no effect on body weight, or a small effect of questionable benefit.^{15,16}

Table 2. Summary of dietary interventions for weight loss

Diet	Principles	Mechanisms of action	Variants
Low calorie diet	800–1600 kcal/day	Negative energy balance (net deficit of calories)	Cambridge diet Weight Watchers Nutrisystems diet Intermittent Fasting Biggest Loser SlimFast Jenny Craig
Very low calorie diet	200–800 kcal/day		
Low calorie diet: meal replacement	Pre-cooked low calorie meals		
Low fat diet	Fat accounts for <30% of energy intake	Negative energy balance achieved by reduction of dietary fat, which is the most energy-dense macronutrient (9 kcal/g)	LEARN Ornish Rosemary Conley
Low carbohydrate diet	Carbohydrate intake <130 g/day	Negative energy balance achieved by reduction of dietary carbohydrates (3.75 kcal/g) Mobilisation of glycogen stores and associated water loss Ketogenesis	Atkins South Beach Zone
Very-low carbohydrate diet	Carbohydrate intake <60 g/day		
High protein diet	Protein accounts for >30% of energy intake	Increased satiety leading to reduced passive overconsumption of other macronutrients, thus achieving a lower energy balance	
Mediterranean-style diet	High intake of fruits, vegetables, grains; moderate intake of fat (mostly mono-unsaturated) and dairy (mostly cheese), reduced intake of meats (fish and poultry in preference to red meat)	Lipid reduction Lowering of oxidative stress and improved endothelial function Anti-inflammatory effects Gut microbiota changes	Regional variation

Calorie restriction

Another approach to achieving a net energy deficit is by directly limiting calorie ingestion. Low and very low calorie diets (LCD and VLCD) limit energy intake to 800–1600 kcal/day and <800 kcal/day, respectively.¹⁷ VLCDs yield superior short-term weight loss when compared to LCDs (-16.1 kg vs -9.7 kg, respectively).¹⁸ Weight loss from VLCD is achieved primarily through a loss total body fat (7.8% total body fat reduction at 6 months).¹⁹ However, long-term benefits of VLCDs are less pronounced, and weight loss figures are more comparable to LCDs (-6.3% vs -5%, respectively) due to higher rebound weight gain (61% vs 41%, respectively).¹⁸ This long term pattern of weight loss with VLCDs is independent of its initial rate, and is further supported by a systematic review by Franz *et al*, noting a 17.9 kg (16%) weight loss at six months, following which the weight loss benefits of VLCD begin to wane (-10.9 kg or -10% at 12 months and -5.6 kg or -5% at 36 months).^{20,21} There are numerous reasons for the weight re-gain seen with low calorie diets, ranging from metabolic adaptation to practicalities of calorie counting and resultant loss of diet adherence.

Meal replacement

Meal replacement, either full or partial, involves nutritionally replete but low-calorie substitutes for daily meals, offering an easy and convenient method for calorie intake restriction. Significant weight loss benefits of meal replacement compared to conventional calorie restriction were illustrated by a meta-analysis of six studies by Heymsfield *et al*. Partial meal replacement (PMR) yielded greater weight loss at 3 months (-2.54 kg) and 1 year (-2.63 kg), with a lower attrition rate.²² Similar effects were demonstrated by a subsequent systematic review, where PMR yielded a 3.8 kg weight loss benefit over control diets at 1 year.²⁰ Furthermore, although PMR subjects experience more weight re-gain in the long term compared to conventional diets, the overall weight loss remains greater (-7.8% vs -5.9% at 40 weeks).²³

Of note, dietary weight loss is accompanied by improvement and even remission of obesity-associated complications, namely T2DM. The DiRECT study of 298 participants demonstrated remission of T2DM in 73% of participants who lost >10 kg of weight after 12 months of low calorie diet replacement.²⁴

The postulated mechanisms for this include reduced hepatic gluconeogenesis, net hepatic glycogenolysis and improved hepatic insulin sensitivity.²⁵ Further beneficial effects noted by the DiRECT trial include improvements in blood pressure and triglyceride levels.

Dietary styles

The Mediterranean-style diet (MSD) originates from olive-growing regions of the Mediterranean and has a variety of regional differences. The core principles include a high intake of fruits, vegetables and grains, a moderate intake of fat (most of which from mono-unsaturated fats) and dairy (primarily from cheese), and a reduced intake of meat (fish and poultry in preference to red meat). This can result in significant weight loss (-4.1 kg to -10.1 kg weight loss at 12 months) as well as beneficial effects on multiple cardiovascular risk factors, yet it is less restrictive than other diets.²⁶

Diet choice

With no clear leading diet emerging to date, calorie restriction remains the common factor for weight loss, irrespective of macronutrient composition. This is dependent on diet adherence, especially as dietary effects on weight loss plateau with time due to compensatory adaptation.

For the treatment of obesity, the current National Institute for Health and Care Excellence (NICE) guidelines recommend.²⁷

- > A dietary approach with lower energy intake than expenditure is recommended.
- > A deficit of 600 kcal/day (via LCD or LFD) is recommended for sustainable weight loss, together with expert support and intensive follow-up.
- > Consider LCD at 800–1600 kcal/day but ensure it is nutritionally complete.
- > Diets of 200–800 kcal/day are not recommended unless there is a clinical need for rapid weight loss.

Pharmacotherapy

NICE currently recommends pharmacological treatment for weight loss maintenance in addition to a reduced-calorie diet and optimal physical exercise. Pharmacological options currently available on the NHS are fairly limited with most licensed for weight loss maintenance in patients with BMI of >27 kg/m² with associated risk factors, or those with BMI of ≥30 kg/m². Treatment should be discontinued at 3 months if less than 5% weight loss has been achieved whilst on the drug.

Orlistat

Orlistat irreversibly inhibits pancreatic lipases which break down dietary fat to absorbable free fatty acids, preventing the absorption of up to 32% of ingested fats which are excreted in the faeces.²⁸ Gastro-intestinal side effects are thus common leading to oily stool, faecal urgency and incontinence. To combat this, patients are advised to follow a low-fat diet with medication taken during a meal or up to 1 hour after food consumption. A meta-analysis of 33 randomised control trials (RCTs) showed a mean reduction in body weight of 2.12 kg, although mean duration of therapy varied from 2 months to 3 years.²⁹ Orlistat treatment

also led to modest reductions in cholesterol and triglyceride levels. In a 4-year double-blind RCT (XENDOS trial), orlistat resulted in significantly more weight loss than placebo (-10.6 kg vs -6.2 kg at 1 year, respectively; and -5.8 kg vs -3.0 kg after 4 years, respectively), in addition to a reduction in cardiovascular disease risk factors including a 37.3% relative risk reduction of T2DM.³⁰

Liraglutide (Saxenda®)

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist which is administered once daily subcutaneously. GLP-1 is an incretin hormone released from the gastrointestinal (GI) tract in response to glucose and fat ingestion acting both peripherally (slows GI transit, alters glucose homeostasis) and centrally (appetite suppression).^{31,32} Gastrointestinal upset is the most commonly experienced side effect, but cases of acute pancreatitis have also been reported.³³ GLP-1 therapy leads to an average weight reduction of 3.2 kg, and to improvement in glycaemic control (HbA1c reduction of 1%), cholesterol level and blood pressure.³⁴

The efficacy of liraglutide on weight loss has been demonstrated by the Safety and Clinical Adiposity – Liraglutide Evidence (SCALE) trials. The SCALE obesity and pre-diabetes double-blind RCT demonstrated significantly higher weight loss in the liraglutide group vs placebo (-8.4 kg vs -2.8 kg, respectively) at 1 year, with a larger proportion of participants losing >5% of their initial body weight (63.2% vs 27.1%, respectively).³⁵ These findings were supported by the SCALE diabetes RCT, which demonstrated dose-dependent weight loss in overweight patients with T2DM on liraglutide vs placebo (-6%, 3 mg; -4.7%, 1.8 mg; -2%, placebo, respectively).³⁶ Furthermore the LEADER double-blind RCT showed a lower occurrence rate of mortality from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke, when compared with the control arm.³⁷

Naltrexone/bupropion (Mysimba®)

Naltrexone/bupropion is a fixed dose combination drug often prescribed as an adjunct to diet and lifestyle modifications, but is currently not recommended by NICE as the long-term effectiveness of the drug is unknown.³⁸ Naltrexone is an opioid antagonist licensed for the management of alcohol and opioid dependence whereas bupropion (originally developed as an antidepressant) inhibits dopamine and noradrenaline uptake and is licensed as an aid for smoking cessation. In combination they both lead to appetite suppression although the mechanism of its combined action is unclear. It is postulated that both drugs have a synergistic effect on suppressing hunger centers located in the hypothalamus.³⁹ In a multicenter randomised double-blind, placebo-controlled phase 3 study of 1,742 patients, mean change in body weight was -6.1% compared with -1.3% in the placebo group.⁴⁰ However, only 50% of participants completed the 56 weeks of treatment, with nausea, headaches and constipation being the commonest reported adverse events.

Newer agents

Previously available drugs primarily acting on the central nervous system such as rimonabant and sibutramine have now been withdrawn due to unacceptable side effects and safety concerns such as an increased suicide risk, myocardial infarction and

cerebrovascular events.^{35,41} Newer anti-obesity drugs are on the market which include:

- > Lorcaserin (Belviq[®]): a serotonin (5-HT) agonist acting centrally to suppress appetite. It facilitates sustained weight loss without an increase in cardiovascular risk factors when compared with placebo.⁴²
- > Phentermine/topiramate (Qsymia[®]): a combination of phentermine (a centrally acting appetite suppressant) and topiramate (an antiepileptic) that appears to induce weight loss, possibly by increased energy utilisation.⁴³

Neither of these treatments are currently licensed in the UK for obesity management.

Intragastric balloon

The intragastric balloon (IGB) has been a useful anti-obesity intervention since 1985, and commonly consists of an endoscopically-deployed silicone balloon which is filled with saline and inflated in the stomach for a duration of 6 months. IGBs provide an alternative option for weight loss in those patients who decline or are not fit for bariatric surgery. A Cochrane review concluded that there is little data to support its efficacy for weight loss when compared with conventional medical management.⁴⁴

Bariatric surgery

Bariatric surgery is the treatment of choice when all other interventions have failed. Regardless of the type of bariatric surgery performed, its effects on weight loss and associated co-morbidities are superior when compared with non-surgical interventions.⁴⁵

The Swedish Obesity Study (SOS) is one of the largest prospective studies to date providing observational data on the impact of bariatric surgery on obesity and long-term outcomes.⁴⁶ The study reported a greater degree of weight loss in the surgical group (n=2,010) than the control group (n=2,037), as well as major improvements in obesity related co-morbidities. In particular, there was a 72% remission rate of T2DM after 2 years, dropping to 36% at 10 years. More recent RCTs have shown bariatric surgery to have better long-term outcomes in terms of weight loss and diabetes resolution than medical treatment alone for obese diabetic patients.^{47,48} Based on estimates, the reduction in diabetes medications and in length of patient stay from diabetes complications could lead to potential savings of approximately £18.1 million over a 4-year period after

surgery.⁴⁹ Indeed, surgery is emerging as the more cost effective management option for patients with diabetes and other obesity related co-morbidities.⁵⁰

Observations that diabetes remission can result from bariatric surgery independent of weight loss have led increasing focus on the mechanistic effects of enteric gut hormones including GLP-1 and pancreatic polypeptide YY, which are responsible for maintenance of homeostatic mechanisms such as appetite, gut motility, nutrient absorption and plasma nutrient regulation. Indeed, there is increasing evidence that alterations in these hormones significantly contribute to many of the beneficial effects seen post bariatric surgery.⁵¹

Current NICE guidance advises referral of patients for bariatric surgery if the following criteria are fulfilled:

- > BMI ≥ 40 kg/m²
- > BMI ≥ 35 kg/m² with associated co-morbidities that could be improved with weight loss
- > BMI of 30–34.9 kg/m² who have recent-onset T2DM
- > other conservative and medical weight loss options have been explored but have failed
- > patient is receiving or will receive intensive management in a tier 3 service (a service-based weight loss programme)
- > patient is fit for anaesthesia and the surgery proposed
- > patient shows commitment to long-term follow-up.

Furthermore, NICE advises bariatric surgery for patients with BMI > 50 kg/m².

The common types of bariatric surgery performed are described below and depicted in Fig 1.

Laparoscopic adjustable gastric banding

An inflatable silicone band is placed around the upper part of the stomach to narrow its lumen, restricting food passage and forming a small proximal pouch of stomach which limits the quantity of food that can be ingested.⁵² The band's patency and thus degree of narrowing can be further adjusted by injecting fluid through a subcutaneous port. Laparoscopic adjustable gastric banding (LAGB) does not only yield excess weight loss of up to 55% 2 years post-operatively, but also promotes the remission of diabetes (74%), hypertension (54%), dyslipidaemia (40%) and sleep apnoea (94%).⁵³ The Longitudinal Assessment of Bariatric Surgery (LABS) consortium have reported no mortality at 30 days post-LABG (n=1,198).⁵⁴ More common minor complications include oesophageal pouch dilatation (11%) and gastroesophageal reflux, whereas major complications include band slippage (7.9%) and erosion (<1%).^{55–57}

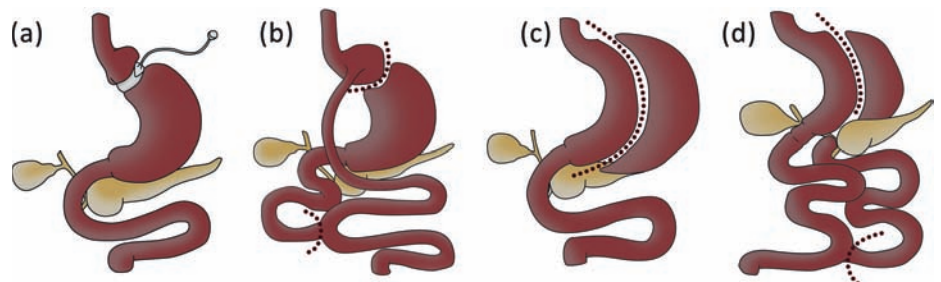


Fig 1. Bariatric surgeries schematic. (a) Adjustable gastric banding. (b) Roux-en-Y gastric bypass. (c) Sleeve gastrectomy. (d) Bilio-pancreatic diversion with a duodenal switch.

Roux-en-Y gastric bypass

In Roux-en-Y gastric bypass (RYGB), the stomach is divided at its upper part, which forms a small proximal stomach pouch.⁵⁸ The small intestine is also separated at the jejunal level, where the distal part of the intestine is attached to the new stomach pouch. As a result, ingested food passes through the small pouch (limiting its amount) and flows directly into the distal part of the small intestine, thus bypassing the proximal part (limiting its absorption). The excised middle fragment of intestine (distal stomach and proximal small intestine) is reattached to the small intestine further down, allowing digestive enzymes to mix with ingested food more distally.

RYGB is mostly done laparoscopically and yields an estimated weight loss of 73% within 1 year, good long-term weight loss maintenance, and remission of comorbidities such as diabetes (95%), dyslipidaemia (80%), hypertension (81%) and sleep apnoea (95%).⁵³ 30-day mortality rates are lower for the laparoscopic vs open approach (0.2% vs 2.1%, respectively).⁵⁴ Serious complications include anastomotic leaks (3–5%) and internal bowel herniation (3.1%) with the potential to lead to bowel obstruction and perforation.^{59–61}

Sleeve gastrectomy

During sleeve gastrectomy (SG), 80% of the stomach is excised, leaving a narrow medial aspect ('sleeve'). The reduced-size stomach has lower motility and restricts the volume of ingested content passing through it, thereby limiting calorie intake. SG is usually performed laparoscopically and can yield excess weight loss (EWL) of up to 70% within 1 year, which is maintained to at least 3 years.⁵³ Like RYGB, SG increases remission rates of diabetes (86%), hypertension (82%), dyslipidaemia (83%) and sleep apnoea (91%). SG has a low mortality rate and its most serious complication is leakage, which occurs in 2–3% of patients.⁶² Others include strictures (4%) and gastro-oesophageal reflux.⁶³

Biliopancreatic diversion with a duodenal switch

Biliopancreatic diversion with a duodenal switch (BPD-DS) is a two-stage, open or laparoscopic procedure which is also usually irreversible. Firstly, a SG-like gastrectomy is performed, leaving a tubular pouch. Secondly, the small intestine is cut in two places; proximally just after the pylorus, and distally approximately 250 cm before the ileocaecal valve. The distal small intestine is brought up and anastomosed to the duodenum. The distal end of the middle fragment is then anastomosed to the small intestine approximately 100 cm before the ileocaecal valve (Fig 1d).⁶⁴ BPD-DS can achieve EWL of up to 73% with maintenance to over 8 years via both restrictive and malabsorptive mechanisms akin to RYGB, with significant effects on comorbidities such as T2DM.⁶⁵ Although mortality rates remain low (<1%), BPD-DS is a more complex procedure, with complications including perioperative anastomotic leaks (3–4%) and splenectomy (<1%), and later malnutrition (4%), internal bowel herniation and small bowel obstruction (2.7%).^{66,67}

Revision and reversal of bariatric surgery

LAGB revision or removal are relatively simple and commonly performed procedures due to high rates of band intolerance

(eg nausea, dysphagia), complications or failure.^{68,69} Despite increasing evidence showing that laparoscopic RYGB reversal is feasible and can result in resolution of complications and their symptoms, RYGB reversal remains uncommon.⁷⁰ Similarly, SG is irreversible and revision/reversal of BPD-DS is possible but carries considerable risk.⁷¹ It is thus vital that patients are well informed of potential side effects and complications prior to undertaking any form of bariatric surgery.

Dumping syndrome

A gastrointestinal complication of malabsorptive surgical procedures is dumping syndrome which arises from rapid gastric emptying leading to gastrointestinal and vasomotor symptoms.⁷² These can be classified into early or late, with early dumping being the most common and which occurs 30 minutes following a meal. This is associated with abdominal symptoms include pain, bloating, diarrhoea and borborygmi. Late dumping typically takes place 1–3 hours after a meal and is related to reactive hypoglycaemia, resulting in more systemic symptoms such as dizziness, fatigue, sweating and weakness.⁷³ The main concern with dumping syndrome is maintaining adequate nutrition as severe cases can lead to protein-wasting and so dietary modifications are essential to combat these risks including smaller, more frequent meals and increasing dietary fibre, fats and protein.⁷⁴

Nutritional deficiencies

All bariatric procedures affect nutritional intake and can also have an impact on the absorption of micro- and macronutrients, in particular procedures which affect absorption (RYGB, SG, BPD-DS). Most patients will require lifelong nutrient supplements in addition to a balanced diet. Multivitamins and minerals (including folate, zinc, copper and selenium), iron, B12, calcium and vitamin D are advised.⁷⁵ Additional fat-soluble vitamins are advised for patients who have undergone a duodenal switch procedure.

Psychological impact

There is a reported increase in harmful behaviours and risk of suicide among post bariatric surgery patients and although the biological and behavioural mechanisms behind this is unclear, possible hypotheses include alterations in absorption of medications and imbalances in peptides, hormones and glucose.^{76,77} There is also accumulating evidence of the development of post-operative eating disorders (anorexia nervosa and bulimia nervosa) and binge eating which may arise as a consequence of the dramatic alteration in eating patterns inherent to bariatric surgery.⁷⁸ Patients undergoing bariatric surgery should be counselled on these uncommon but potentially serious adverse outcomes.

Emerging therapies

New drug treatments

There are numerous pharmacological treatments currently in the clinical trial phase and these include.

- > Central nervous system agents: Monoamine reuptake inhibitors such as tesofensine (initially developed for neurodegenerative

diseases) and zonisamide–bupropion (where zonisamide was initially developed for epilepsy).⁷⁹ Additionally, there are novel D₃ dopamine antagonists, μ -Opioid inverse agonists, AgRP inhibitors and neuropeptide YY5 receptor antagonists such as velneperit.

- > Gut specific agents: Cetilistat (pancreatic lipase inhibitor), oxyntomodulin (dual agonist of GLP-1 receptor and glucagon receptor precursor) and inhibitors of the sodium-dependent glucose co-transporters and diglyceride acyltransferase (DGAT-1).
- > Systemic agents: Resveratrol (activates the caloric restriction driven molecule sirtuin 1) and beloranib (methionine aminopeptidase 2 inhibitor).

Endoscopic interventions

In recent years, we have seen the rapid development of endoscopic therapeutic devices for the treatment of obesity, either as adjuncts to bariatric surgery or as an alternative for individuals who may not be suitable surgical candidates, who decline surgery because of the risks associated, or who would prefer to choose a less invasive therapeutic strategy. Current devices work on a variety of mechanisms including the reduction of gastric capacity or gastric contents, or by excluding the proximal small intestine thus mimicking the effects of surgery.^{80,81} The main limitations of their current use are that the majority of these interventions are only indicated for a finite period after which point they usually require removal so may only provide patients with a transient benefit.

Conclusion

Obesity continues to be a growing epidemic associated with major health and economic implications to society, particularly in low- to middle-income countries and in the youth and adolescent populations. Conventional therapies such as lifestyle modification (diet and exercise) and pharmacotherapy remain important but are limited by their results in terms of weight loss. Bariatric and metabolic surgical interventions are endorsed by many international societies to be an effective treatment for weight loss, which also offers significant improvement in associated comorbidities such as T2DM. Indeed, bariatric services and research in the UK will need to significantly expand to meet the growing demand of the obesity epidemic. ■

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