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REVIEW

Obesity and Metabolic Syndrome: Current Insights and Future Directions

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Abstract

Obesity and metabolic syndrome are global health challenges, significantly increasing risks for type 2 diabetes, cardiovascular and cerebrovascular diseases, and overall mortality. This narrative review aims to discuss the relationship between obesity and metabolic syndrome; the past, present and future of anti-obesity medications including new advances in incretin-based therapies which have enabled patients to achieve significant weight loss and improvement in metabolic parameters; and the role of metabolic/bariatric surgery which remains the most effective durable treatment for severe obesity, with high remission rates of metabolic comorbidities like type 2 diabetes. Multimodal approaches involving the combination of lifestyle, medical and surgical advances will revolutionise our approach to treating obesity and metabolic syndrome in the future.

Key words: obesity; metabolic syndrome; incretins; glucagon-like peptide-1 receptor agonist; metabolic/bariatric surgery; weight loss

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Introduction

Obesity and metabolic syndrome are closely interconnected, with obesity serving as a major risk factor for metabolic syndrome. Obesity has been conventionally defined as a body mass index (BMI, the weight in kilograms divided by the square of the height in metres) $\geq$30.0 kg/m^2 (WHO, 2000). As of 2022, approximately 890 million adults worldwide, 16% of the global adult population, were classified as living with obesity (WHO, 2024). More than one in four people in the United Kingdom are living with clinical obesity (NHS England, 2024), while in the United States the figure rises to two in five (NIDDK, 2021). Although included in the International Classification of Diseases in 1948 (James, 2008), obesity has more recently gained wider acceptance as a disease in its own right. It is further classified into clinical and pre-clinical obesity (Rubino et al, 2025). Pre-clinical obesity is considered a state of excess adiposity with increased risk of developing clinical obesity and several non-communicable diseases such as type 2 diabetes (T2D) and cardiovascular disease. Clinical obesity is associated with end-organ dysfunction and causes limitations to daily activities.

Metabolic syndrome, since its first description as "Syndrome X" (Reaven, 1988), has emerged as a significant global health challenge. Described as a cluster of interrelated risk factors that collectively increases the risk of cardiovascular disease,

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T2D, and overall mortality, its prevalence has risen in parallel with the obesity epidemic (Saklayen, 2018). Although estimates of metabolic syndrome prevalence vary due to differing definitions, data suggests that more than 60% of individuals with obesity also have metabolic syndrome (Shi et al, 2020).

The most widely recognized definitions of the metabolic syndrome are provided by the International Diabetes Federation (IDF), the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III), and the World Health Organization (WHO) (Table 1). Common among these definitions is the key role of central obesity—measured by waist circumference—as a defining criterion. For example, the IDF requires central obesity as a mandatory component, defined as a waist circumference $\geq$94 cm in men and $\geq$80 cm in women (with lower ethnicity-specific cutoffs) (Ford, 2005). In contrast, the NCEP ATP III includes central obesity as one of five criteria, with a threshold of $>$102 cm for men and $>$88 cm for women, requiring the presence of at least three out of five criteria for diagnosis (Grundy et al, 2005).

In this review, we aim to explore the relationship and pathophysiology of obesity and metabolic syndrome. We discuss the past, present and future of anti-obesity medications (AOMs) which have advanced significantly over the past decade. We highlight the role of established metabolic/bariatric surgery (MBS) and the emerging role of endoscopic and minimally invasive procedures in treating severe obesity and metabolic syndrome. We discuss how multimodal approaches involving the combination of lifestyle, medical and surgical advances will revolutionise our approach to treating obesity and metabolic syndrome in the future.

Methods

We undertook a focused, non-systematic, narrative review of the literature with searches of the published literature in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/) with a broad range of combinations of the medical subject headings (MeSH) terms: "Obesity", "Metabolic Syndrome", "Anti-Obesity Agents", "Bariatric Surgery", "Gastric Bypass", "Gastrectomy" and "Gastroplasty", and terms and phrases relevant to this review; English language articles retrieved up to February 2025 were included.

Obesity and Metabolic Syndrome

Obesity is traditionally attributed to an imbalance between caloric intake and expenditure. However, the metabolic complications associated with obesity are largely driven by the accumulation of fat in ectopic sites, such as the liver, heart, and skeletal muscles. This visceral fat is metabolically active and contributes to elevated free fatty acids (FFAs) and inflammatory mediators which are secreted by dysfunctional adipose tissue (Tchernof and Després, 2013).

Whilst the full pathophysiology of metabolic syndrome and obesity is complex and extensive due to their heterogeneity, we discuss the causal roles of FFAs, proinflammatory adipokines, chronic inflammation and insulin resistance, and maladaptation of central reward pathways in subsequent sections.

Table 1. Definitions of metabolic syndrome.

	NCEP ATP III (2001, updated 2005)	WHO (1998)	IDF (2005)
Diagnosis criteria	Three out of five criteria below	Insulin resistance plus two of the five criteria below	Obesity, plus two of the four criteria below
Central obesity defined by	Waist ≥102 cm (Male), ≥88 cm (Female)	BMI >30 kg/m^2 or waist-to-hip ratio >0.90 (Male), >0.85 (Female)	Waist >94 cm (Male), >80 cm (Female)
Hyperglycaemia	Fasting glucose ≥5.6 mmol/L or on treatment	Either diagnosed with T2D, IGT or IFG	Fasting glucose ≥5.6 mmol/L or T2D
Dyslipidaemia (Triglyceride)	≥1.7 mmol/L or on lipid-lowering therapy	≥1.7 mmol/L	≥1.7 mmol/L or on lipid-lowering therapy
Dyslipidaemia (HDL cholesterol)	<1.0 mmol/L (Male) <1.3 mmol/L (Female)	<0.9 mmol/L (Male) <1.0 mmol/L (Female)	<1.0 mmol/L (Male) <1.3 mmol/L (Female)
Hypertension	≥130/85 mmHg or on hypertensive treatment	≥140/90 mmHg	≥130/85 mmHg or on hypertensive treatment

Table adapted from (Alberti and Zimmet, 1998; Alberti et al, 2005; Grundy et al, 2005).
NCEP ATP III, National Cholesterol Education Program's Adult Treatment Panel III; WHO, World Health Organization; IDF, International Diabetes Federation; BMI, body mass index; T2D, type 2 diabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL, high density lipoprotein.

Adipose Tissue Dysfunction and Chronic Inflammation

Adipose tissue stores energy in the form of triglycerides, which can be hydrolysed into glycerol and FFA during lipolysis. Beyond acting as a mere storage, adipose tissue is also an immunologically and endocrinologically active organ whereby, in obesity, infiltrating leukocytes and adipocytes produce adipokines which causes a state of metabolic inflammation (Tilg et al, 2025). This "metainflammation" leads to metabolic complications such as insulin resistance, metabolic dysfunction-associated steatotic liver disease (MASLD), and cardiovascular disease (Tilg et al, 2025). There are several emerging concepts regarding initiation of metainflammation such as release of toxic cargo including cell-free DNA from dying adipocytes which engages immune effectors and initiates inflammatory response (Nishimoto et al, 2016); obesity-induced genotoxicity and related stress response (Minamino et al, 2009); and adipocyte hypertrophy and hypoxia further exacerbate this inflammatory state, impairing metabolic homeostasis (Lefere et al, 2016; Trayhurn et al, 2010).

Proinflammatory Adipokines and Insulin Resistance

Proinflammatory adipokines affect insulin sensitivity. Tumour necrosis factor-alpha (TNF-α) directly impairs insulin signalling by promoting the phosphorylation of insulin receptor substrate-1 (IRS-1) at serine residues, thereby inhibiting downstream signalling pathways necessary for glucose uptake (Hotamisligil et al, 1996). Interleukin-6 (IL-6) exacerbates insulin resistance by altering hepatic glucose metabolism and increasing systemic inflammation (Sabio et al, 2008). Monocyte chemoattractant protein-1 (MCP-1) recruits macrophages to adipose tissue, amplifying inflammation through the release of reactive oxygen species (ROS) and additional cytokines (Weisberg et al, 2003). This chronic low-grade inflammatory state contributes to insulin resistance (Hotamisligil et al, 1996).

Brain and Reward Pathways

The brain's reward system, particularly in the hypothalamus and mesolimbic pathways, regulates appetite and energy homeostasis. The hypothalamus integrates signals from peripheral hormones such as leptin, ghrelin and insulin to regulate energy intake. Dysregulation in these pathways promotes overconsumption of high-calorie foods (Morton et al, 2014). Chronic overstimulation of these pathways alters dopamine signalling, further reinforcing maladaptive eating behaviours.

Treatment of Obesity and Metabolic Syndrome

The cornerstones of the treatment of obesity are lifestyle, dietary and behavioural modifications, supplemented by AOMs and MBS as discussed in subsequent sections.

Lifestyle, Diet and Behavioural Interventions

Lifestyle modifications such as diet and exercise are integral part of obesity treatment. Diet modification alone can induce about 5% weight loss in 2 years (Kheniser et al, 2021). When exercise is combined with diet, clinically significant

weight loss of –6.29 (95% confidence interval, –7.33 to –5.25) kg is observed after 12 to 18 months (Johns et al, 2014). By incorporating cognitive behavioural therapy with lifestyle modification, patients experience further weight loss of –4.9 (95% confidence interval, –7.3 to –2.4) kg when compared to diet and exercise alone (Kheniser et al, 2021). Although lifestyle changes are effective in the short term, their role in long term weight loss/maintenance is complicated by poor sustainability and weight regain (Hartmann-Boyce et al, 2021; Hartmann-Boyce et al, 2023).

Medical Therapy

The medical management of obesity has advanced significantly in recent years. Achieving clinically significant weight loss—typically at least 5% of body weight—is often necessary to improve cardiometabolic risk (Bays et al, 2022). Research indicates that for every 1 kg/m^2 increase in BMI, the risk of heart failure rises by 5% in men and 7% in women (Syed et al, 2025a). AOMs facilitate weight reduction whilst also improving metabolic parameters such as glycaemic control, lipid profiles, and blood pressure (Table 2).

Conventional AOMs

The past few decades have seen the marketing and subsequent withdrawal of several AOMs such as aminorex (pulmonary hypertension), fenfluramine and dexfenfluramine (cardiac valvulopathy), phenylpropanolamine (stroke), rimonabant (psychiatric adverse effects including suicidal ideation), sibutramine (cardiovascular events), and lorcaserin (cancer risk) (Tak and Lee, 2021).

Orlistat

A semisynthetic derivative of lipstatin, Orlistat is a selective inhibitor of gastric and pancreatic lipases. As Orlistat blocks fat absorption, users can find it difficult to tolerate due to steatorrhoea, frequent bowel movements, flatulence with discharge, and faecal incontinence (Tak and Lee, 2021). A daily multivitamin supplement is advisable as deficiencies of fat-soluble vitamins A, D, E and K can arise. Orlistat is best avoided in patients with chronic kidney disease as there is a risk of hyperoxaluria and oxalate nephropathy (Weir et al, 2011).

Phentermine and Phentermine/Topiramate

Phentermine is a sympathomimetic amine that acts as an appetite suppressant, primarily through the release of norepinephrine in the hypothalamus, leading to decreased hunger (Woodard et al, 2020). When combined with topiramate, an anticonvulsant drug, the combination has shown an average weight loss of 8.4% over 12 weeks (Patel and Stanford, 2018). Side effects include paraesthesia, dry mouth, dysgeusia, constipation, anxiety, depression, insomnia, tachycardia, electrolyte disturbances, metabolic acidosis and nephrolithiasis (because of carbonic anhydrase inhibition by topiramate); contraindications include uncontrolled hypertension, cardiovascular disease, chronic kidney disease, hyperthyroidism, glaucoma, and treatment with of monoamine oxidase inhibitors (Syed et al, 2025b). It is not recom-

Table 2. Anti-obesity medications for long term use.

	Medication	Mode of action	Mean weight loss	Metabolic effect and cardiovascular outcome	Side effects
Long term conventional AOM therapy	Orlistat	Inhibit pancreatic and gastric lipase	4% at 1 year	No established cardiovascular outcome	Steatorrhea, faecal urgency, and fat-soluble vitamin deficiency
	Phentermine/Topiramate extended release	In addition to phentermine effect, also activates GABA receptor and inhibit carbonic anhydrase (topiramate)	9% at 1 year	No established cardiovascular outcome	Same as phentermine and paraesthesia, altered taste, memory loss, depression
	Naltrexone/Bupropion	Stimulation of POMC neuron Central control of appetite; via opioid receptor antagonist action (naltrexone); and dopamine and noradrenaline reuptake inhibitor (bupropion)	5% at 1 year	Improved HbA1c No established cardiovascular outcome	Nausea, vomiting, diarrhoea, constipation, dry mouth, irritability, headache, insomnia, dizziness, elevated blood pressure and seizures
Incretin-based AOM therapy	Liraglutide	GLP-1 receptor activation in the hypothalamus and hindbrain regulates the appetite, combined with peripheral effects such as delayed gastrointestinal transit and lowered glucose levels	8–10% of body weight	LEADER trial showed 13% reduction in major adverse cardiovascular events in patients with type 2 diabetes	Nausea, vomiting, diarrhoea, constipation, dyspepsia, abdominal pain, and headache

Table 2. Continued.

	Medication	Mode of action	Mean weight loss	Metabolic effect and cardiovascular outcome	Side effects
	Semaglutide	Same as Liraglutide	12–15% of body weight	Improvement in BP, HbA1c and non-HDL cholesterol in T2D patients SUSTAIN-6 trial also showed a 26% reduction in major adverse cardiovascular events in patients with type 2 diabetes	Same as Liraglutide
	Tirzepatide	GLP-1/GIP dual agonist. GIP receptor activation enhances insulin secretion, and may improve fat metabolism and insulin sensitivity synergistically with GLP-1	15–20 % of body weight	Reduction in waist circumference, fasting serum glucose, systolic and diastolic BP and prevalence of Triglyceride >150 mg/dL Cardiovascular outcome in progress	Nausea, diarrhoea and constipation
Clinical trial	Retatrutide	GLP-1/GIP/Glucagon agonist. In addition to Tirzepatide mode of action, glucagon has the added action of reducing meal size and increasing energy expenditure	8.7%–24% of body weight	Improvement in waist circumference, systolic and diastolic blood pressure, HbA1c, fasting glucose, insulin, and lipid levels (Except for HDL cholesterol) Cardiovascular outcome in progress	Nausea, diarrhoea, vomiting and constipation

Adapted from (Jastreboff et al, 2023; Nicholls et al, 2024; Perdomo et al, 2023).

AOM, anti-obesity medication; POMC, pro-opiomelanocortin; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; GABA, gamma-aminobutyric acid; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; T2D, type 2 diabetes; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes trial 6.

mended for clinical use in the NHS (National Health Service) by the National Institute for Health and Care Excellence (NICE) (2012).

Naltrexone/Bupropion

Naltrexone, an opioid antagonist, does not have an effect on its own but when combined with bupropion, a norepinephrine and dopamine reuptake inhibitor, it augments bupropion effect on the pro-opiomelanocortin (POMC) neurons in the hypothalamus to cause appetite suppression (Booth and Clements, 2016). Clinical trials indicate that this combination can lead to a mean weight loss of about 4% over 24 weeks (Greenway et al, 2009). Common side effects include nausea, vomiting, constipation, dizziness and dry mouth; contraindications include uncontrolled hypertension, seizure, abrupt discontinuation of alcohol, anorexia or bulimia nervosa, and use of benzodiazepines, barbiturates, antiepileptic drugs or monoamine inhibitors (Syed et al, 2025b). It is not recommended for clinical use in the NHS by NICE (2017).

Novel Incretin-Based AOMs

Obesity management has entered a new era of potent incretin-based AOMs. These currently include glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists.

Glucagon-Like Peptide-1 Receptor Agonists

Liraglutide and Semaglutide, two of the GLP-1RAs to be approved for the treatment of obesity, have transformed the management of obesity and metabolic syndrome (Table 2). These agents replicate the activity of GLP-1, an incretin hormone that enhances insulin secretion in response to glucose intake. Additionally, GLP-1RAs delay gastric emptying and act on the hypothalamus to suppress appetite and increase satiety. Semaglutide, with its once-weekly subcutaneous dosing, has demonstrated superior weight loss efficacy compared to daily subcutaneous Liraglutide, achieving average weight loss up to 15% (Wilding et al, 2021). Common side effects include nausea, vomiting, bloating, diarrhoea, constipation, abdominal pain and headache; less common but more severe adverse effects include gallbladder disorders, acute pancreatitis and acute intestinal obstruction (Ghusn and Hurtado, 2024; Müller et al, 2022; Sodhi et al, 2023; Tak and Lee, 2021). The incretin class of AOMs carry a product warning of a theoretical risk of medullary thyroid cancer. Observational data suggests an increased risk of medullary as well as all-cause thyroid cancers (Bezin et al, 2023). These medications are, therefore, contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia.

Higher doses of injectable Semaglutide up to 7.2 mg weekly and oral Semaglutide 50 mg daily have also been developed, both currently in phase 3 trials. In a recent phase 3 randomised controlled trial (RCT) in adults with overweight or obesity without T2D, oral Semaglutide 50 mg once per day has shown significant

weight loss compared with placebo (Knop et al, 2023). Two other oral GLP-1RAs, Danuglipron and Orforglipron, are also undergoing phase 2/phase 3 trials.

Beyond weight loss, GLP-1RAs enhance glucose-dependent insulin secretion while suppressing glucagon release, leading to improved glycaemic control (Nauck and Meier, 2018), and improvements in blood pressure and lipid profile in patients with T2D (Ji et al, 2023).

However, sustaining long term weight loss and metabolic benefits of GLP-1 based therapy is challenging due to low rate of adherence. One study reported that 64% of patients without and 46% of patients with T2D discontinued therapy within one year (Rodriguez et al, 2025). Discontinuation leads to patients regaining two-thirds of their prior weight loss and reverses the cardiometabolic improvements that were initially achieved (Wilding et al, 2022).

Incretin-Based Dual Agonists

Tirzepatide, a groundbreaking advancement in the treatment of T2D and obesity, is a dual agonist that activates both GLP-1 and GIP receptors, synergistically enhancing insulin secretion, improving glycaemic control, and reducing food intake. The dual mechanism targets multiple metabolic pathways, providing comprehensive benefits including improvements in lipid profiles, reduced visceral fat, and enhanced insulin sensitivity. The SURMOUNT-1 trial reported an average 20.9% weight loss with the highest dose of 15 mg of Tirzepatide, making it one of the most effective pharmacological options available (Jastreboff et al, 2022). A recent *post hoc* analysis from the SURPASS trial has also shown that Tirzepatide at all doses studied was associated with a greater reduction in the prevalence of metabolic syndrome compared to placebo, Semaglutide 1 mg, insulin Glargine, and insulin Degludec (Nicholls et al, 2024). Tirzepatide treatment led to significant reductions in waist circumference, fasting glucose, systolic and diastolic blood pressures, and triglyceride levels when compared to comparators (Nicholls et al, 2024).

Pharmacotherapy Under Development

There are now several novel AOMs in development that incorporate actions at more than one level, such as dual agonists (GLP-1-glucagon, GIP-GLP-1 and amylin-calcitonin) and tri-agonists (GIP-GLP-1-glucagon) (Müller et al, 2022). Other combination products that are in development include CagriSema which is a combination of Semaglutide and Cagrilintide (a dual amylin and calcitonin receptor agonist), and oral Amycretin which is a combination of amylin and GLP-1 agonist (Melson et al, 2025). Several other combination products are also in development, such as Survodutide, Efinopegdutide, Mazdutide and Pemvidutide (Melson et al, 2025).

Triple Agonist Incretin Therapy

Retatrutide, a newer incretin-based molecule that combines the agonistic effect of GLP-1, GIP and glucagon receptors, has shown greater average weight loss than existing AOMs in a phase 2 trial with a dose dependent mean weight reduction of 24% at 48 weeks of treatment (Jastreboff et al, 2023). The weight loss is accom-

Table 3. Bariatric operative procedures for the treatment of obesity and the metabolic syndrome.

	Mechanism of action	Total body weight loss (%) at 2 years	Metabolic impact	Common side effects
One-anastomosis gastric bypass (OAGB)	Increases GLP-1, insulin secretion and satiety while reducing hunger, insulin resistance and hepatic gluconeogenesis	37%	Improvement in T2D, reduction in triglycerides and LDL cholesterol, increase in HDL cholesterol, reduction in systolic and diastolic blood pressure	Nutritional deficiency risk, diarrhoea, steatorrhea and internal hernia
Roux-en-Y gastric bypass	Increases GLP-1, PYY, bile acid and insulin secretion and satiety while reducing insulin resistance and hepatic gluconeogenesis	30–35%		Chronic abdominal pain, nutritional deficiency and chronic abdominal pain
Sleeve gastrectomy	Increases GLP-1, PYY, satiety, bile acid and insulin secretion while reducing ghrelin, insulin resistance and hunger	26%		GORD, nutritional deficiency risk, Barret's oesophagus
Endoscopic sleeve gastrectomy	Early satiety, slow gastric emptying without significant change in PYY, GLP-1 and leptin hormone	13–20% at 1 year	Improvement in dyslipidaemia, hypertension and diabetes	Nausea, vomiting and abdominal pain
Adjustable gastric banding	Restricts food calorie intake, hunger and frequency of meal	15–20%	Improvement in T2D	Band slippage, intolerance or erosion, GORD, dysphagia

Adapted from (Wolfe et al, 2016; Docimo et al, 2023; Sudlow et al, 2020).
GLP-1, glucagon-like peptide-1; PYY, peptide YY; GORD, gastro-oesophageal reflux disorder; LDL, low density lipoprotein; T2D, type 2 diabetes.

panied by improvements in metabolic parameters such as waist circumference, systolic and diastolic blood pressures, glycated haemoglobin (HbA1c), fasting glucose, insulin, and lipid levels (Jastreboff et al, 2023). The main side effects and adverse events are similar to other incretin-based therapies (Jastreboff et al, 2022). One explanation for greater weight loss is the added glucagon effect whereby its presence stimulates the vagus nerve to reduce meal size (Woods et al, 2006), and increases in energy expenditure (Conceição-Furber et al, 2022).

Gut Microbiome Therapy

Disruption of the gut microbiome—comprising commensal symbiotic and pathogenic microorganisms that exist in the gastrointestinal tract—has been associated with chronic inflammation, insulin resistance, obesity, T2D and cardiovascular disease. There is increasing interest in supplements, classified as prebiotics, probiotics, synbiotics or postbiotics, reviewed elsewhere (Antony et al, 2023), that can improve the profusion of beneficial gut microbiota and to reduce harmful ones in patients with metabolic syndrome.

Metabolic/Bariatric Surgery

MBS remains the most effective long-term treatment for severe obesity and metabolic syndrome, offering durable weight loss and significant metabolic benefits (Table 3). It achieves maximum weight reduction between 12 and 24 months post-surgery, with average percentage total weight loss (%TWL) >30% within two years regardless of the presence of metabolic syndrome at baseline (Ragavan et al, 2024). Moreover, MBS consistently leads to substantial remission rates of T2D, hypertension, and dyslipidaemia, further improving patients' quality of life and reducing mortality (Ammori et al, 2020; Bashir et al, 2023). By modifying gastrointestinal anatomy (Fig. 1), these procedures address the underlying pathophysiology of obesity beyond mere caloric restriction by altering hormonal pathways. Endoscopic weight loss interventions such as intragastric balloon (IGB) and duodenal-jejunal bypass liner (DJBL) have also emerged as less invasive alternatives for selected patients but effectiveness is lesser compared to definitive bariatric surgery and weight regain common after removal of the device (Crossan and Sheer, 2025; Ryder et al, 2023).

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is one of the procedures with the most robust level 1 evidence showing its efficacy in inducing weight loss and treating T2D (Sudlow et al, 2020). It involves surgical creation of a small gastric pouch and rerouting the small intestine to bypass most of the stomach and duodenum (Fig. 1A). The reduced stomach capacity, combined with altered nutrient absorption, leads to significant caloric restriction. RYGB also alters neurohormonal signalling by gut hormones such as ghrelin, GLP-1 and peptide YY (PYY), and bile acid metabolism (Sudlow et al, 2020). Patients achieve mean %TWL of 28% to 35% (Uhe et al, 2022), and experience resolution or improvement of comorbidities such as T2D,

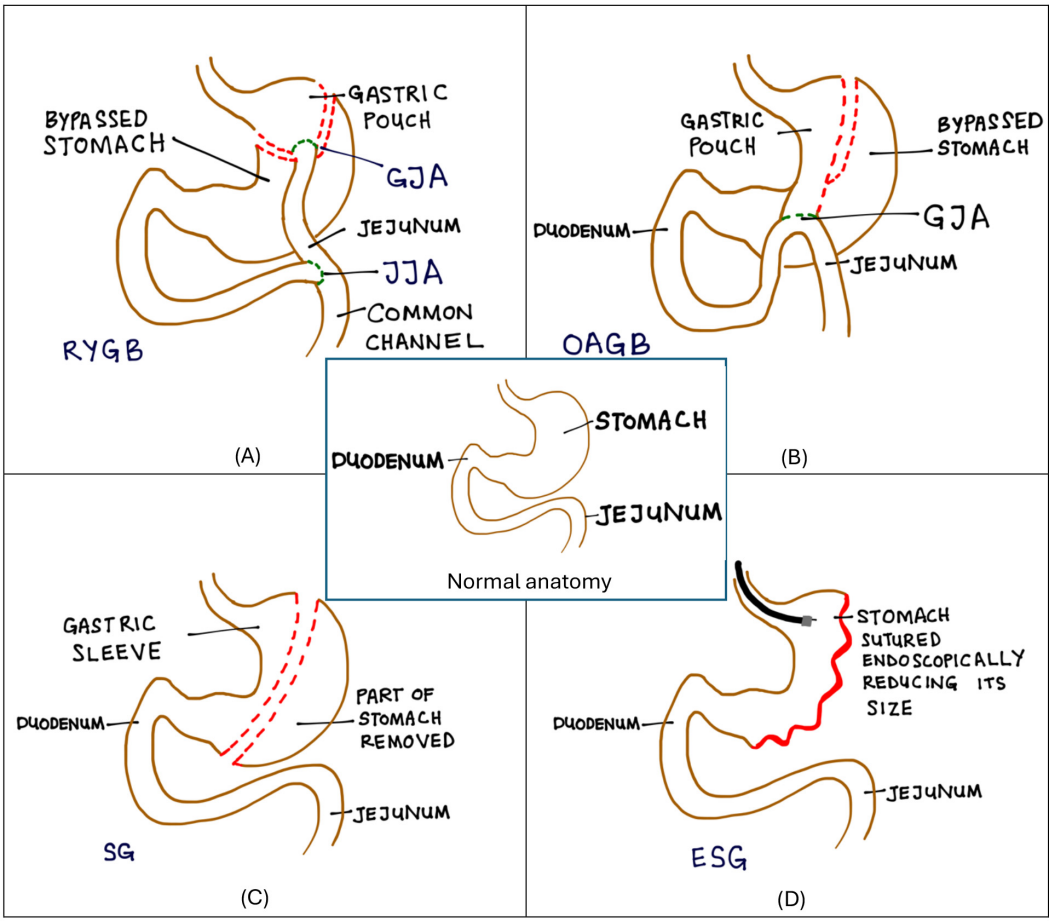

Fig. 1. Metabolic/bariatric surgery. (A) RYGB, Roux-en-Y gastric bypass. (B) OAGB, one anastomosis gastric bypass. (C) SG, sleeve gastrectomy. (D) ESG, endoscopic sleeve gastroplasty. Centre inset, normal anatomy. GJA, gastrojejunal anastomosis; JJA, jejunojejunal anastomosis. The figure was hand-drawn by the first author.

dyslipidaemia, hypertension and obstructive sleep apnoea (OSA), as well as improvement in life expectancy (Carlsson et al, 2020; Kashyap et al, 2010).

One Anastomosis Gastric Bypass

One anastomosis gastric bypass (OAGB) is technically less challenging to perform than RYGB but shares similar bypassing of proximal small bowel (Fig. 1B). Its metabolic effects are largely similar on gut hormones (De Bandt et al, 2022). Although the rate of weight loss and T2D remission of OAGB and RYGB are comparable as shown in the YOMEGA trial, the rate of gastric complications such as diarrhoea and steatorrhea and nutritional deficiency are higher in OAGB (Robert et al, 2019). There is also a concern of bile acid reflux due to the configuration of the anastomosis, resulting in higher rates of oesophagitis when compared to RYGB (Esparham et al, 2023).

Sleeve Gastrectomy

Sleeve gastrectomy (SG), one of the most commonly performed bariatric procedures, involves the removal of approximately 80% of the stomach, resulting in

a tubular gastric remnant (Fig. 1C). This significantly reduces stomach volume, promoting early satiety and reducing caloric intake. The metabolic effect of SG is thought to be due to a reduction in ghrelin due to the resection of the fundus, and increased secretion of GLP-1 and PYY which enhances satiety and insulin sensitivity (Esparham et al, 2023). Weight loss at 1 year and beyond is lesser with SG compared to gastric bypass (Uhe et al, 2022), with higher rates of weight regain. It has been shown that SG improves HbA1c, triglycerides, and blood pressure (Łukaszewicz et al, 2024). This procedure arguably has fewer complications compared to other bariatric operations. Its popularity is reflected in global surveys whereby SG accounted for 45.9% of bariatric surgery in 2018, compared to 37% in 2013 (Sudlow et al, 2020). However, some studies have shown significant reoperation rate due to reflux compared to RYGB (Peterli et al, 2018; Salminen et al, 2018).

Endoscopic Sleeve Gastroplasty

Endoscopic sleeve gastroplasty (ESG) is an endoscopic procedure whereby endoluminal stiches are performed to plicate the anterior and posterior walls of the stomach to replicate a luminal version of SG (Fig. 1D) (Docimo et al, 2023). Since all the suturing is done endoscopically, it has the advantage of lowering the surgical risk in patients with prior abdominal surgery, older adults, and those with significant comorbidities. The total body weight loss via ESG is about 13% to 20% after 12 months, with the weight loss sustained for 3 years (Docimo et al, 2023). It is associated with improvements of metabolic diseases such as hypertension, T2D and dyslipidaemia; but data are mainly for patients with BMI of 30 to 40 kg/m^2 with less evidence for patients with higher BMI (Docimo et al, 2023). The International Federation for the Surgery of Obesity and Metabolic Disorders has recently published an evidence-based review and position statement wherein it endorses ESG as an effective and valuable treatment for obesity, particularly for patients with class I and II obesity, as well as for those with class III obesity who are not suitable candidates for metabolic bariatric surgery (Dayyeh et al, 2024). ESG could also be considered for patients who may not be suitable for AOMs due to contraindications, intolerance, or lack of efficacy (Syed et al, 2025b).

Medical Therapy vs Bariatric Surgery

Although there is no head-to-head trial comparing incretin-based therapy and bariatric surgery, there is considerable evidence that bariatric surgery is superior in metabolic outcomes and weight loss compared to lifestyle and medical management in T2D population. The Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) study showed that MBS was superior to medical/lifestyle intervention for achieving T2D remission as well as lowering HbA1c, fasting glucose, BMI, and other cardiovascular risk factors using substantially fewer medications at 3 years of follow-up in patients with T2D (Kirwan et al, 2022). In a long-term study, after 7 to 12 years of follow-up, individuals originally randomized to undergo bariatric surgery compared with medical/lifestyle intervention had superior glycaemic control with less diabetes medication use and higher

rates of diabetes remission (Courcoulas et al, 2024). Even after 12 years, patients in the bariatric surgery group had superior weight loss at 19% compared to 11% in the medical/lifestyle group (Courcoulas et al, 2024). In a large observational cohort study of matched pairs of patients who were followed up for a median 7 years, mortality was lower in those who underwent MBS than in those treated with GLP-1RAs among those with a diabetes duration of less than 10 years (Dicker et al, 2024). This is likely due to the greater weight loss achieved in MBS (Dicker et al, 2024).

Metabolic Impact of Weight Loss

Weight loss has profound effects on improving metabolic parameters. MBS has been shown to induce reductions in HbA1c, non-high density lipoprotein (non-HDL) cholesterol, and systolic and diastolic blood pressures by 12 months and sustained over 5 years after surgery in individuals with metabolic syndrome (Ragavan et al, 2024). These improvements are critical in mitigating the risk of cardiovascular and metabolic complications. Weight reduction also alleviates adipose tissue dysfunction by decreasing adipocyte size and reducing inflammatory cytokine secretion (Tilg et al, 2025). Improvements in insulin sensitivity often accompany these changes, leading to better glucose uptake and lipid metabolism (Norton et al, 2022). Additionally, weight loss reduces visceral fat, which is particularly implicated in metabolic dysfunction as discussed earlier.

Future Directions

The effectiveness of incretin-based therapies in improving metabolic parameters may also lead to their use in treating MASLD, which is the hepatic manifestation of metabolic syndrome. A recent large cohort study showed that the use of GLP-1RAs in patients with MASLD is associated with a lower risk of developing liver cirrhosis and its complications, including hepatocellular cancer and liver decompensation (Kanwal et al, 2024).

While OSA is common in people with severe obesity and metabolic syndrome, a recent RCT in people with moderate-to-severe OSA and obesity showed that Tirzepatide reduces the apnoea/hypopnoea index, hypoxic burden and systolic blood pressure, and improved sleep-related patient-reported outcomes (Malhotra et al, 2024). Tirzepatide has thus recently received FDA (USA Food and Drug Administration) approval of license for the treatment of moderate or severe OSA.

New advances in targeted treatment of cardiovascular disease and heart failure, which are significant issues in people with obesity and metabolic syndrome, include sodium-glucose cotransporter inhibitors, incretin-based AOMs and bariatric surgery (Syed et al, 2025a). Further advances in the treatment of obesity and metabolic syndrome will include multimodal approaches combining lifestyle and dietary management, AOMs and traditional and minimally invasive bariatric operations.

Conclusion

Advances in obesity treatment encompassing both medical and surgical modalities have significantly transformed the management landscape for this complex disease. Incretin-based therapies have emerged as groundbreaking interventions, offering substantial weight reduction, approaching the efficacy of metabolic bariatric surgery while maintaining its metabolic benefits. However, metabolic bariatric surgery, with its well-documented durability in achieving profound and sustained weight loss and metabolic improvements, continues to have a significant role, especially in those with severe obesity. Future innovations may render it less invasive and safer for patients.

Key Points

- Obesity causes adipose tissue dysfunction which leads to metainflammation and subsequently metabolic dysfunction and insulin resistance.
- Approved current incretin-based therapy induces weight loss of up to 20%, approaching the efficacy of metabolic/bariatric surgery.
- Novel incretin-based therapies currently in development target multiple receptors synergistically.
- Metabolic/bariatric surgery remains the most efficacious and durable treatment for severe obesity.

Availability of Data and Materials

Not applicable.

Author Contributions

ZZ and AAS conceived the review article. ZZ carried out the literature searches and wrote the first draft. RNM and WAM made contributions to the conception and design of the study. All authors reviewed and critically revised the article, approved the final manuscript, and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Professor Syed is a former honorary member of the Leadership & Development Awards committee at the Society for Endocrinology (UK), and reports receiving an honorarium from the Endocrine Society (USA) as an invited speaker at the Clinical Endocrinology Update 2024. Other authors declare no conflict of interest.

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