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Optimal efferent limb length in Single Anastomosis Sleeve Ileal Bypass: a balance between efficacy and safety

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Оглавление

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Abstract

Background: Bariatric and metabolic surgery is considered to be the most effective long-term treatment of morbid obesity and related comorbidities, for instance, diabetes mellitus, hypertension and dyslipidemia. Classic bariatric surgery techniques usually result in restriction and/or malabsorption. Some procedures create obstacles to ingestion of food and may cause dysphagia, vomiting, esophagitis, etc. Other types of bariatric surgery may impair the absorption of vitamins, macro- and microelements, and cause hypoproteinemia. Some procedures involve partial exclusion of digestive system segments, which may trouble endoscopic access.

Potential complications are forcing bariatric surgeons to look for less risky alternative, which could be easy to perform, require no exclusion of any segment, prevent endoscopic blind areas and guarantee predictable weight loss and metabolic result without development of excessive malabsorption. Hypothetically, bariatric procedure should change the neuroendocrine control of hunger and satiety without making any harm to digestive functions such as gastrointestinal motility, peristalsis, and enzyme secretion.

Aim: This study was conducted to evaluate the effects of novel type of bariatric procedure, the single anastomosis sleeve ileal (SASI) bypass, on weight loss, metabolic effect of this type of surgery, and development of possible complications.

Methods: We performed a retrospective study of patients with obesity who underwent SASI bypass between February 2017 and March 2022. Patients who completed one-year follow up were included in the study. Postoperative BMI changes, percent excess weight loss (% EWL), and complications were analyzed, as well as glucose, cholesterol, and protein levels before and after surgery. Additionally, the effects of efferent limb length on weight loss and protein levels were studied.

Results: During the study period, 66 patients underwent laparoscopic SASI bypass, and 59 patients (89.4%) with completed follow-up were included in the study. The

length of the efferent limb, counted from the ileocecal valve, was 250 cm in 30 patients and 350 cm in 29 patients. The mean age was 44.8 ± 9.53 years and the mean BMI was 47.6 ± 8.9 kg/m2; 27 of them (45.8%) had diabetes mellitus. The %EWL reached 79.8%, and all patients with diabetes mellitus had normal blood glucose levels one year after surgery.

There were 3 early postoperative complications: 2 cases of postoperative bleeding and one case of rhabdomyolysis. One patient died 8 months after surgery, and alcoholic cirrhosis was diagnosed postmortem.

We compared the results of SASI bypass in patients with different length of efferent limb (250 cm and 350 cm); BMI (Body mass index) one year after surgery was 29.4±5.3 and 30.8±5.52 (p=0.317) in short and long efferent limbs, respectively. The rate of hypoproteinemia was 10.16% (6 cases) and occurred only in patients with 250 cm efferent limb. Revisional surgery was performed in 3 of them, the length of the common limb was changed from 250 cm to 350 cm in 2 patients, and in one patient with refractory hypoproteinemia, the bypass was restored to normal anatomy.

Conclusion: SASI bypass is a novel operation with promising bariatric and metabolic effects. It is based on digestive adaptation principles and combines moderate restriction with early nutritive stimulation of the distal gut, modulating the neuroendocrine control of hunger and satiety.
The lengthening of efferent limb up to 350 cm can prevent hypoproteinemia without compromising weight loss. To estimate the sustainability of the short-term outcome of SASI bypass longer follow-up is needed.

1.Introduction

1.1 Obesity

1.1.1 Definition and classification

Obesity is a frequent, serious, complex, relapsing, and chronic disease posing a significant public health challenge [1]. It is characterized by an elevation in fat mass beyond the standard level, exerting adverse effects on health.

Quantitatively measuring body fat would be the ideal method for determining obesity directly. Unfortunately, current methods lack the precision, practicality, economy, and reliability required for widespread use. Consequently, definitions of obesity often resort to anthropometric approaches that utilize straightforward clinical measures like weight and height to quantify and define this condition.

The World Health Organization (WHO) has endorsed Body Mass Index (BMI) as the most valuable measure of obesity in adults. BMI is calculated as the quotient of body weight and squared height, measured in kg/m2. According to the WHO classification, individuals with a BMI ranging from 25.0 to 29.9 kg/m2 are categorized as overweight. Obesity is defined by a BMI of ≥30 kg/m2 and is further subdivided into different degrees of severity (Table 1.1).

Table 1.1 Classification of weight according to BMI

	BMI		Waist	
			Waist circumference and comorbidity risk	
Classification	BMI (kg/ m^2)	Comorbidity risk	Men ≤40 inches Women ≤35 inches	Men >40 inches Women >35 inches
Underweight	<18.5	Low but other problems		
Normal weight	18.5–24.9	Average		
Overweight	25–29.9	Increased	Increased	High
Obesity class I	30–34.9	Moderate	High	Very high
Obesity class II	35–39.9	Severe	Very high	Very high
Obesity class III	≥40	Very severe	Extremely high	Extremely high

Secondary disease risk refers to type 2 diabetes, hypertension, and cardiovascular disease. Increased waist circumference can also be a marker for increased risk even in persons of normal weight [2].

The distribution of fat in the body plays a crucial role: a heightened risk for the development of cardiovascular and metabolic diseases is associated with an increase in "visceral" fat mass compared to subcutaneous fat mass [3]. Abdominal (visceral or central) obesity is often referred to as "apple-shaped." Conversely, subcutaneous (gluteal-femoral or peripheral) obesity involves an increase in fat mass, primarily in the hips and thighs, and is known as "pear type." Circumferential measurements can determine the fat distribution pattern. Abdominal obesity is identified when the waist-to-hip ratio exceeds 0.85 for women and 0.90 for men, while a ratio less than this suggests peripheral obesity. Current guidelines recommend measuring and recording both BMI and waist circumference (WC), with distinct cut points for various ethnic groups [4].

While anthropometric classifications of obesity based on BMI and WC have proven valuable in population studies, they exhibit some limitations. Individuals sharing the same BMI may have a nearly twofold difference in total body fat, and conversely, individuals with the same total body fat may present with a wide range of BMI values [5]. Additionally, there is considerable interindividual variation in the amount of visceral fat among people with the same WC.

Another drawback of the existing anthropometric classification of obesity is its failure to assess the presence of concurrent comorbid conditions or disease risk. According to current recommendations, it is imperative to routinely consider these factors when making treatment decisions. This limitation underscores the need for a more comprehensive and individualized approach to obesity evaluation, considering not only physical measurements but also the presence of obesity-associated comorbidities [6].

The limitations of BMI in assessing adiposity have significant clinical implications. While BMI serves for obesity screening, it alone cannot diagnose overweight or

obesity. Clinical interpretation, considering factors like edema, sarcopenia, or high muscle mass in athletes, is crucial (Table 1.2)

Table 1.2 Limitations of BMI in the screening and diagnosis of obesity

1. BMI inter-relates height and weight but does not directly measure adiposity
2. When applied as an index of adiposity, BMI requires interpretation based on individual clinical assessment with attention to the following: Muscularity Volume status – edema and dehydration Sarcopenia Age Gender Pregnancy Third space fluid accumulation (e.g., ascites) Large tumors (e.g., uterine leiomyosarcomas) Lipodystrophy Loss of muscle mass due to denervation or intrinsic myopathy
3. BMI does not indicate location or distribution of fat Intracellular Extracellular but within the tissue (e.g., "marbling") Peri-organ (mesenteric, pericardial, and perinephric) Subcutaneous versus intra-abdominal Adipose tissue depots (omentum and gluteal) Brown fat versus white fat
4. BMI does not indicate the degree to which excess adiposity is adversely affecting the health of the patient.

Methods, which may be useful in more precise quantifying adipose tissue mass, are detailed in Table 1.3. They offer diverse approaches, with some requiring expensive equipment or being more suitable for research settings, like MRI (Magnetic resonance imaging) or bioelectric impedance plethysmography. Bioelectric impedance, though cost-effective, is hydration-dependent and less accurate in highly adipose individuals.

More complicated techniques, including air displacement plethysmography and DXA (Dual-energy X-ray absorptiometry), provide correlations close to underwater weighting. DXA, measuring bone density, lean mass, and fat mass, introduces the fat mass index as an alternative to BMI, focusing solely on fat mass. The WHO

proposes body fat percentage cutoffs of 25% and 35% for men and women, respectively.

Table 1.3 Methods for quantifying adipose tissue mass

Feature measured	Advantages	Method	Limitations
Total body water Extracellular and intracellular fluid spaces	Ease of use Low cost Speed (fast)	Bioelectrical impedance analysis (BIA)	Population specific Poor accuracy in individuals
Total and regional body fat Total and regional lean mass	Ease of use Low radiation exposure Accurate	Dual-energy X-ray absorptiometry (DXA)	Biased for body size, sex, and fatness High equipment cost Specially trained personnel
Total body water Extracellular fluid	Ease of use OK for all ages	Dilution techniques	Inaccurate in disease High equipment cost Labor-intensive analysis
Total body volume Total body fat	Relatively good accuracy Speed (fast)	Air displacement plethysmography	Less accurate in disease High equipment cost
Total and regional body volume	OK for very obese Ease of use	3D photonic scanning	Limited availability
Total body water Total body fat	Ease of use Safety Speed (fast)	Quantitative magnetic resonance imaging	High equipment cost Limited availability
Total and regional adipose tissue Skeletal muscle	Highly accurate and reproducible	Magnetic resonance imaging (MRI)	Costly

In 2017, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) introduced a new term for obesity – adiposity-based chronic disease (ABCD), focusing on the quantity, distribution, and function of adiposity [7].

Obesity complications arise from two key pathological processes: physical forces (fat mass disease) and endocrine and immune responses (sick fat disease). Adipose tissue, a dynamic and metabolically active organ, plays a crucial role in various biological processes. Dysregulated secretion of factors like cytokines and hormones can impact multiple organ systems, contributing to adiposity-based complications.

Decades of epidemiological, clinical, and translational studies highlight a robust link between visceral fat and the development of dyslipidemia, insulin resistance, hypertension, atherosclerosis, and adverse cardiac remodeling. A disease state emerges when abnormal adiposity severity translates into physiological processes and symptom burdens through identifiable mechanisms.

In order to provide a staging system able to help clinicians in phenotyping patients with obesity beyond BMI, Sharma and Kushner developed the so-called EOSS (Edmonton Obesity Staging System)[8].

It is composed of the following five stages:

0. No apparent obesity-related risk factors; normal blood pressure, serum lipids, fasting glucose, etc.; absence of physical symptoms, psychopathology, functional limitations, or impairment of well-being.

1. Presence of obesity-related subclinical risk factors; borderline hypertension, impaired fasting glucose, etc.; mild physical symptoms, psychopathology, functional limitations, or impairment of well-being.

2. Presence of established obesity-related chronic diseases; hypertension, type 2 diabetes, etc.; moderate limitations in activities of daily living or well-being.

3. Established end-organ damage; myocardial infarction, heart failure, diabetic complications, etc.; significant psychopathology, functional limitations, or impairment of well-being.

4. Severe disabilities from obesity-related chronic diseases; severe psychopathology, functional limitations, or impairment of well-being, indicating potentially end-stage consequences.

The Edmonton Obesity Staging System (EOSS) has been validated as a tool capable of identifying patients at an elevated risk of mortality. Consequently,

individuals categorized by the EOSS as having higher stages merit increased clinical and therapeutic attention.

1.1.2 Epidemiology of obesity

Obesity affects every country, with lower-income nations experiencing significant increases in the past decade. The World Health Organization refers to the global rise in obesity as an epidemic, transforming it from an individual health issue to a socioeconomic problem for communities. Projections indicate that, by 2035, overweight and obesity will cost the global economy over US$4 trillion, nearly 3% of the current global gross domestic product.[9]

The period from 2020 to 2022, marked by extensive lockdowns in many countries, appears to have heightened the risk of weight gain by limiting outdoor activities, exacerbating sedentary behavior, and disrupting access to care. National surveys and measurement programs monitoring weight and gain were also halted.

Estimates for global overweight and obesity levels (BMI ≥25kg/m²) suggest that over 4 billion people may be affected by 2035, up from over 2.6 billion in 2020. This reflects an increase from 38% of the world's population in 2020 to over 50% by 2035. The prevalence of obesity (BMI ≥30kg/m²) alone is expected to rise from 14% to 24% of the population over the same period, affecting nearly 2 billion adults, children, and adolescents by 2035 (Table 1.4).

Table 1.4 Global overweight and obesity 2020–2035

Numbers of people (aged over 5 years) and percentage of the population with overweight or obesity

	2020	2025	2030	2035
Number with overweight or obesity (BMI≥25kg/m²) (millions)	2,603	3,041	3,507	4,005
Number with obesity (BMI ≥30kg/m²) (millions)	988	1,249	1,556	1,914
Proportion of the population with overweight or obesity (BMI ≥25kg/m²)	38%	42%	46%	51%
Proportion of the population with obesity (BMI ≥30kg/m²)	14%	17%	20%	24%

1.1.3 Etiology and pathophysiology of obesity

Obesity develops when an individual's energy intake consistently surpasses energy expenditure, leading to the storage of excess energy as triglycerides, primarily in adipose tissue. Control pathways for food intake and energy expenditure involve short-term mechanisms from the gastrointestinal tract to the central nervous system and long-term signals, regulated by leptin, an adipocyte-derived hormone that influences the body weight 'set point.' These pathways converge in the hypothalamus, a crucial regulator of food intake, energy expenditure, and metabolic processes.

Genetic and environmental factors can influence these energy homeostasis mechanisms. Highly rewarding foods, rich in sugars and fats, can stimulate eating even when there's no absolute energy requirement, contributing to the obesity epidemic, especially in societies with abundant food availability. While rare genetic disorders like leptin deficiency or mutations in the pro-opiomelanocortin gene highlight the biological importance of these systems, the recent surge in obesity prevalence is primarily attributed to adverse environmental factors.

Factors such as the widespread availability of high-energy foods, combined with a substantial decline in physical activity levels, override the body's regulatory systems and contribute significantly to the rise in obesity. When the energy intake from food and drink surpasses that expended by the body through metabolism and physical activity, the excess is stored as fat, potentially leading to obesity if the imbalance persists. The onset and severity of obesity result from a complex interplay of genetic and environmental factors. Understanding the regulation of energy balance is crucial in comprehending the pathogenesis of obesity.

1.1.3.1 Regulation of energy balance

Humans exhibit tight regulation of energy balance; however, there's a tendency to gain about 1 kg per year throughout adult life. This reflects the evolutionary mechanism of energy balance, which evolved to protect against weight loss rather than preventing weight gain. The central nervous system governs food intake and

energy expenditure. Afferent signals from the gastrointestinal tract, liver, and adipose tissue regulate energy intake, while efferent neurohormonal signals influence the digestion and metabolism of food. Long-term regulation is also influenced by signals from adipose tissue, particularly the hormone leptin.
The central nervous system (CNS) regulates energy balance by interpreting metabolic signals through various neurohumoral pathways, controlling energy intake. However, factors like sight, smell, texture, and food-related memories, along with social situations, also influence these systems. The CNS responds to circulating nutritional and neurohormonal signals through approximately 50 different neurotransmitters, influencing feelings of hunger, satiety, and metabolic rate. Generally, signals that increase food intake tend to lower metabolic rate, and vice versa.

1.1.3.2 Regulation of food intake

Food intake is subject to both short-term and long-term control, involving nutrients, hormones, and neurotransmitters. Hunger arises partly due to decreasing concentrations of nutrients like glucose, fatty acids, and amino acids, along with changes in hormone levels. Ghrelin, mainly secreted by the stomach between meals, stimulates food intake and is a crucial hunger signal[10].

After a meal, nutrient concentrations and specific satiety hormones like cholecystokinin, glucagon-like peptide-1, pancreatic polypeptide, oxyntomodulin, and peptide YY increase. This leads to a decrease in hunger signals, promoting a feeling of fullness by acting directly or indirectly on the brain, often through the vagus nerve. These endocrine signals from the gut form the gut-brain axis, contributing to appetite regulation.

Long-term mechanisms in energy balance are primarily mediated by leptin, an adipocyte-derived hormone, with circulating concentrations reflecting adipose tissue stores. Leptin acts in the hypothalamus through downstream signaling pathways, particularly in the arcuate nucleus. When adipose tissue mass is low and leptin decreases, neuropeptide Y secretion increases, stimulating food intake, and reducing thermogenesis.[11] Although the body switches off some hunger signals

and increases dietary thermogenesis in response to energy excess, these mechanisms are relatively weak, promoting biased energy homeostasis that favors weight gain.

Leptin also influences neural circuits in the human brain, enhancing responses to satiety signals while reducing the perception of food reward. Insulin and glucocorticoids may act as modulating factors in this process, with glucocorticoid administration stimulating appetite and deficiency reducing appetite.

Incretin hormones like glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) play roles in appetite regulation. While the physiological impact of GLP-1 on food intake is not fully investigated [12], its analogues used in type 2 diabetes treatment result in significant weight loss. Peptide YY (PYY) belongs to the pancreatic polypeptide family and circulates as PYY1–36 and PYY3–36. It is secreted in response to a meal and stimulates gastrointestinal absorption of fluids and electrolytes and delays gastric emptying.

Neurotransmitter systems, including dopaminergic, serotoninergic, and endocannabinoid systems (CB1 and CB2 receptors), also contribute to appetite regulation. CB1 receptor blockade suppresses appetite, inducing a feeling of satiety.

1.1.3.3 Regulation of metabolism

The regulation of metabolism involves three components of total energy expenditure (TEE): basal metabolic rate (BMR), diet-induced thermogenesis (DIT), and physical activity (PA).

Basal metabolic rate (BMR) represents the foundational energy costs required for vital bodily functions such as respiration, cardiac pumping, and protein turnover. Contrary to the notion of reduced BMR contributing to obesity, individuals with obesity exhibit higher BMRs than lean counterparts, both at rest and during physical activity. This discrepancy is primarily due to the greater lean body mass in people with obesity, where lean body mass significantly influences BMR.

In sedentary individuals, BMR constitutes 65–70% of total energy expenditure (TEE). Dietary thermogenesis, accounting for 5–10% of TEE, reflects the energy used in the digestion, absorption, transport, and storage of energy within a meal. It is highest for protein-rich meals, moderate for carbohydrate-rich meals, and least for fat-rich meals.

1.1.3.4 Etiology of obesity

Regarding the etiology of obesity, the interplay between individual factors, determined by genetics, and environmental factors, such as how an individual relates to and responds to food, especially when widely available, plays a vital role in obesity development.

1.1.3.4.1 Inherited causes

Genetic factors may influence obesity in two ways: through single gene defects or susceptibility genes. Single gene defects causing obesity are rare, but significant progress has been made in identifying them. Congenital leptin deficiency, the monogenic obesity syndrome, leads to marked hyperphagia and severe obesity, with a therapeutic response to recombinant leptin. Other disorders include defects in the POMC (pro-opiomelanocortin) gene and melanocortin-4 receptor deficiency. These inherited causes are extremely rare and not associated with common forms of obesity or body fat distribution in the general population. However, melanocortin-4 receptor mutations may occur up to 1 in 20 cases of severe early-onset obesity in children [13].

The second mechanism involves susceptibility genes, where environmental factors act in conjunction to cause obesity. Genetic epidemiology studies have discovered variants in the FTO gene (fat mass and obesity-associated gene), strongly linked to obesity-related traits in different populations. Variant alleles of the FTO gene are relatively common and present in about 16% of the population [14].

Severe obesity is a sign of various inherited syndromes, with Prader-Willi syndrome being the most common. Children with this syndrome have uncontrolled appetite leading to severe obesity and related complications, such as type 2 diabetes and obstructive sleep apnea. They also may have learning difficulties, short stature, almond-shaped eyes, small hands and feet. Other rare genetic disorders associated with obesity include Albright hereditary dystrophy, Alstrom-Hallgren syndrome, Cohen syndrome, Carpenter syndrome, Grebe syndrome, Beckwith-Wiedemann syndrome, Adiposogenital dystrophy syndrome, Kleine-Levin-Critchley syndrome, Young-Hughes syndrome, Laron dwarfism, X-linked mental retardation-hypotonic facies syndrome, Borjeson-Forssman-Lehmann syndrome, and pseudohypoparathyroidism type 1a.

1.1.3.4.2 Environmental causes

Adverse environmental conditions play a significant role in the development of obesity, particularly in individuals at risk. The widespread availability and palatability of cheap, energy-dense food, coupled with decreased physical activity levels, contribute significantly to this obesity epidemic.

1.1.3.4.2.1 Dietary factors

There has been a notable shift in dietary patterns in many western countries, marked by an increase in the supply and consumption of energy-dense foods, as well as fat and sugar-rich soft drinks. Epidemiological data associates a high-fat diet with obesity[15]. The rise in fast food consumption and changes in eating patterns, such as irregular meals and increased snacking, are additional contributing factors.

1.1.3.4.2.2 Physical activity

Over the past 50 years, there has been a substantial decline in physical activity. Improved transportation facilities and sedentary leisure-time pursuits like watching television and playing computer games have all contributed to reduced physical activity levels in both adults and children [16].

1.1.3.4.2.3 Other lifestyle factors

Sleep deprivation can contribute to uncontrolled hunger and appetite, decreasing leptin and increasing ghrelin levels [17]. Smoking cessation is associated with an average weight gain of 4–5 kg, emphasizing the importance of offering appropriate dietary and exercise advice to those quitting smoking. Obesity is more prevalent in lower socioeconomic groups, and ethnicity also influences obesity incidence. South Asians, especially individuals from the Indian subcontinent, often exhibit high prevalence of abdominal obesity, contributing to insulin resistance.

1.1.3.4.3 Endocrine causes

Previously undiagnosed endocrine diseases may be the primary cause of obesity. However, while hypothyroidism can cause modest weight gain, its treatment is not associated with weight loss. Cushing's syndrome, a rare cause of obesity, is characterized by progressive centripetal obesity. Growth hormone deficiency in adults is linked to increased body fat and reduced lean body mass, correctable with growth hormone replacement. Obesity may occur due to polycystic ovarian syndrome (PCOS), affecting about 50% of females with PCOS [18]. Undoubtedly, ruling out these endocrine causes is essential in assessing individuals with obesity.

1.1.3.4.4 Hypothalamic obesity

Hypothalamic obesity is a rare syndrome resulting from injury to the ventromedial or paraventricular regions of the hypothalamus, where metabolic information about nutrient stores is integrated. Trauma, tumors (such as craniopharyngiomas and pituitary macroadenomas with suprasellar extension), inflammation, surgery, or increased intracranial pressure can damage these regions, leading to hyperphagia and subsequent obesity. Autonomic imbalance and hyperinsulinemia exacerbate weight gain by promoting fat deposition. Physical activity reduction and endocrine abnormalities like growth hormone deficiency and hypogonadism may contribute to an unfavorable distribution of body fat, increasing metabolic risk in affected individuals [19].

1.1.3.4.5 Drugs

Certain drugs can promote weight gain, including psychoactive drugs, antiepileptics, oral hypoglycemic agents, and hormones (Table 1.5).

Table 1.5 Drugs associated with weight gain

Class of drugs	Examples
Anticonvulsants	Sodium valproate, carbamazepine, gabapentin
Antidepressants	Citalopram, mirtazepine, amitriptyline, clomipramine, doxepin, imipramine
Antipsychotics	Clozapine, olanzapine, risperidone, lithium, chlorpromazine
Beta blockers	Atenolol
Corticosteroids	Prednisolone, dexamethasone
Insulin	All formulations
Migraine relieving drugs	Pizotifen
Oral hypoglycemic agents	Glibenclamide, Gliclazide, Repaglinide, Pioglitazone
Protease inhibitors	Indinavir, ritonavir
Sex steroids	Medroxyprogesterone acetate, combined oral contraceptives

These effects may be due to central impacts on appetite (e.g., psychoactive drugs and antiepileptics) or peripheral metabolic effects (e.g., oral hypoglycemic agents and insulin). Patients taking such drugs should be aware of potential side effects, enabling them to implement appropriate dietary and physical activity measures when possible, and consider alternative agents.

1.1.3.4.6 Pregnancy and menopause

Pregnant women often experience weight gain, with postpartum weight retention compared to nulliparous women. Menopause, marked by a decline in female sex hormones, can also lead to subsequent weight gain. Females may have a higher predisposition to obesity than males due to these factors, along with gender differences in the brain's response to hunger [20].

1.1.3.4.7 Eating disorders and psychological causes

Bulimia nervosa, characterized by episodes of binge eating, can be associated with obesity. Psychological factors, especially stress, are linked to increased food consumption, particularly high-energy foods, possibly due to elevated glucocorticoid

levels [21]. Improper eating habits within families and parental conflicts can lead to childhood overeating due to unsatisfactory personal relations, lack of confidence, and low self-esteem, which may persist into adulthood.

1.1.3.5 Pathophysiology of obesity and associated comorbidities

Adipose tissue can undergo pathological changes in size, distribution, or function, defined as adiposopathy (disorders of function and structure). It's crucial to distinguish between fat mass accumulation (adiposity) and adiposopathy, often coexisting [22].

1.1.3.5.1 Anatomical changes in adiposopathy

Healthy adipocytes have lipid droplets constituting the main part of cell volume, while supportive structures (collagen matrix, vasculature, immune cells) collectively equal 50% of total mass. Excess nutrient intake recruits preadipocytes through PPAR-γ (peroxisome proliferator-activated receptor gamma), facilitating storage of excess energy. Dysfunctional PPAR-γ activation hinders this process, leading to hypertrophy of adipocytes. Intra-abdominal or visceral fat accumulation has systemic effects, influencing vascular tone, increasing peripheral resistance, and raising intra-abdominal pressure. This pressure elevation can result in mechanical issues and affect the function of organs in the abdominal and retroperitoneal spaces.

1.1.3.5.2. Adipose tissue Inflammation and hypoxia

Hypertrophied adipose tissue triggers hypoxia-inducible factor 1 (HIF1), leading to cell death. This initiates inflammation and recruits proinflammatory macrophages, suppressing adipogenesis and hindering nutrient uptake. The hypoxic inflammatory environment inhibits the production of the insulin-sensitizing hormone adiponectin, while increasing proinflammatory cytokines like TNF-α and IL-6. Adipocytes under oxidative stress produce plasminogen-activator inhibitor (PAI)-1, associated with hyperinsulinemia, obesity, and dysmetabolic syndrome. PAI-1 contributes to coagulation and fibrosis, exacerbating the hypoxic burden [23].

1.1.4 Health Complications of Overweight and Obesity

Obesity, as measured by BMI, significantly correlates with increased total mortality across age groups and genders.

Table 1.6 Health conditions associated with overweight and obesity

System	Obesity-related disorder
Neurological	Pseudo-tumour cerebri (benign intracranial hypertension) Alzheimer disease Transient ischaemic attack/stroke
Cardiovascular	Hypertension Ischaemic heart disease Premature (sudden) death Reduced exercise intolerance Deep vein thrombosis Chronic venous insufficiency Lymphoedema
Pulmonary	Obstructive sleep apnoea Asthma
Gastrointestinal	Gallstone disease Gastro-oesophageal reflux disease Non-alcoholic fatty liver disease GI cancers, mainly colorectal and oesophageal cancer
Renal	Glomerulosclerosis
Endocrine	Increased insulin resistance Impaired glucose tolerance Type 2 diabetes Dyslipidaemia Polycystic ovary syndrome in females Infertility Decreased libido Certain cancers (prostate, endometrial, ovarian and breast cancer)
Musculoskeletal	Osteoarthritis Chronic back pain
Psychosocial	Eating disorders Poor self-esteem Anxiety Depression Social isolation and stigma

A prospective cohort study showed that non-smokers aged 40 with obesity lived significantly fewer years than their counterparts without obesity [24]. The increased mortality is mainly attributed to specific causes such as ischemic heart disease, stroke, diabetes, and liver disease (Table 1.6).

The impact of obesity on life expectancy is substantial, with total years lost ranging from 5 to 20 years, dependent on the BMI class and associated co-morbid conditions. Identifying weight-related complications and assessing their severity holds significance for two crucial reasons in individuals dealing with overweight or obesity. Firstly, understanding the presence and severity of weight-related complications guides the need for more assertive therapeutic interventions to enhance individual health. Secondly, as these complications can be mitigated or reversed through weight loss therapy, the evaluation establishes specific targets for weight loss, integrating these goals as desired outcomes in the therapeutic plan.

For instance, if a patient is diagnosed with prediabetes, aiming for a 10% body weight loss is rational, representing a threshold for maximal diabetes prevention. Conversely, in patients with T2DM (type 2 diabetes mellitus), where the goal is to improve glycemia, dyslipidemia, and hypertension, there isn't a clear threshold of weight loss for optimal clinical benefit. Studies, such as Look AHEAD, indicate progressive improvements in metabolic parameters with increasing weight loss, emphasizing the individualized approach to obesity management [25].

This perspective underscores the goals of weight loss therapy – to enhance the health of individuals with overweight or obesity by addressing and preventing weight-related complications. It aligns with the "complications-centric" approach recommended by the American Association of Clinical Endocrinologists (AACE) [26]. In this paradigm, the focus shifts from baseline BMI to the presence and severity of weight-related complications when determining the modality and intensity of weight loss therapy. This approach signifies a medical model for obesity care, where weight loss interventions are directed towards treating or preventing weight-related complications as the primary endpoint of therapy.

1.2 Treatment of Obesity

The primary goal of obesity treatment is to mitigate morbidity and mortality while enhancing psychological well-being and social function. Beyond weight reduction, effective risk reduction include interventions such as lipid-lowering, blood pressure management, and diabetes medication. Psychological therapies are also valuable, addressing both weight loss and the enhancement of well-being and social function. Consequently, a collaborative approach involving various healthcare professionals becomes crucial to achieve these objectives.

To attain success in treating obesity, the focus should switch from providing recommendations and education to actively targeting behavioral changes in patients. Ideally, healthcare workers involved in obesity care should be trained in behavioral techniques, known to significantly improve outcomes. In cases where specialized training is unavailable, minimal intervention strategies like the 5As (ask, assess, advise, agree, and assist) can serve as a guide for effectively counseling patients on behavioral changes [27].

5As Overview:

Ask: Seek permission to discuss weight.

Assess: Nonjudgmentally explore drivers of obesity and the patient's readiness for change.

Advise: Evaluate body mass index, waist circumference, obesity stage, and complications.

Agree: Discuss health risks, benefits of modest weight loss, long-term strategy, and treatment options.

Assist: Collaboratively identify and address barriers, providing necessary resources.

In summary, treating obesity requires a comprehensive and collaborative approach, addressing not only weight but also psychological and social aspects. Focusing on changing behaviors, especially with trained care workers, enhances the chances of successful outcomes

The management algorithm by the Italian Society for Obesity (2016) offers a tailored approach for patients with overweight or obesity [28]. It considers both BMI and the

stage of obesity using the Edmonton Obesity Staging System (EOSS). This refined strategy aids clinicians in phenotyping patients with obesity, guiding the selection of appropriate treatment strategies based on individualized assessments (Table 1.7).

Table 1.7 Treatment Algorithm of Patients with Overweight and Obesity

EOSS	BMI < 30	BMI 30-35	BMI 35-40	BMI >40	Age (years)
STAGE 0					> 60
					< 60
STAGE 1				S	> 60
					< 60
STAGE 2				S	> 60
					< 60
STAGE 3			S	S	> 60
					< 60
STAGE 4					> 60
		S	S	S	< 60

lifestyle intervention

pharmacological therapy (In patients with T2DM, is indicated the use of antidiabetic medications that have additional actions to promote weight loss, such as GLP-1 analogs).

bariatric surgery

rehabilitation (physical, neurological, cardiopulmonary, psychiatric)

S surgery to be considered in selected cases with favorable risk/benefit profile

1.2.1 Behavioral interventions

Behavioral interventions are basic components of a comprehensive approach to managing obesity, addressing multifaceted aspects such as sleep patterns, dietary habits, physical activity, medication use, and potential surgical interventions [29]. Traditionally, physicians rely upon giving “information, education, and advice”, which often encounters low success rates, primarily due to lack of motivation and confidence [30].

Emphasizing the "how to" of change, behavioral counseling becomes a cornerstone in the intricate landscape of obesity management plans. This counseling not only

encompasses effective communication skills but also embodies a supportive spirit, marked by values such as autonomy, empathy, and nonjudgmental guidance. Furthermore, it integrates a repertoire of behavioral strategies, self-monitoring, goal setting, and thorough planning.

These specialized skills empower healthcare professionals, enabling them to collaboratively engage with patients in the pursuit of adopting and sustaining recommended health behaviors [31]. By fostering a partnership between healthcare providers and individuals living with obesity, this approach seeks to create an environment conducive to the long-term adherence to healthier lifestyles.

1.2.2 Nutritional Interventions

Dietary interventions for addressing obesity encompass a spectrum of approaches, ranging from low-fat and low-carbohydrate diets to high-protein regimens, very low-calorie diets incorporating meal replacements, Mediterranean dietary patterns, and intermittent energy restriction strategies. Despite extensive evaluation through randomized clinical trials, reviews, and meta-analyses, determining the optimal dietary weight loss strategy remains challenging. The key to successful weight management, however, lies in the reasonable combination of these diverse dietary methodologies within the context of a healthful and balanced diet. This approach prioritizes safety, efficacy, nutritional adequacy, cultural acceptability, economic viability, and, crucially, long-term compliance and maintenance of weight loss [32].

Establishing realistic weight loss goals emerges as a cornerstone [33]. A pragmatic approach involves aiming to shed 5–10% of initial body weight within the first six months, correlating not only with achievable outcomes but also a substantial improvement in cardiometabolic risk factors. Beyond the initial weight loss phase, the focus pivots to the more critical goal of weight loss maintenance and prevention of regaining lost weight.

The physiological response to weight loss entails a resistance to further reductions, driven by compensatory biological adaptations involving shifts in hormone balance

related to appetite regulation, declines in resting energy expenditure, and reductions in diet-induced thermogenesis [34]. Diet-induced weight loss triggers alterations in orexigenic and anorexigenic hormones, with a 10% weight loss associated with a notable reduction in total energy expenditure [35]. The heightened drive to eat post-weight loss outstrips corresponding adaptations in energy expenditure, emerging as a primary driver of recurrent weight gain. This phenomenon persists for up to a year after initial weight loss, contributing to relapses and the challenges faced by around 20% of patients with obesity in preserving long-term weight loss [36].

The ideal diet for weight loss maintenance should include continuity, ease of compliance, and a low energy density [37]. Predictors of sustained success in maintaining weight loss include self-monitoring of body weight, medical supervision for psychological support and positive feedback, consistent food intake, regular breakfast consumption, low-fat dietary choices, limited intake of unhealthy snacks, and elevated levels of regular physical activity. Preliminary evidence even suggests that the pace of meal consumption (fast vs. slow) may impact body weight control and maintenance, with slower consumption leading to a more pronounced rise in anorexigenic hormones and an enhanced feeling of fullness [38]. This holistic understanding underscores the multifaceted considerations integral to formulating effective dietary strategies for obesity management.

1.2.2.1 Conventional hypocaloric diets

Conventional hypocaloric diets typically focus on reducing daily energy intake by 500–750 kcal. This is often achieved through diet plans ranging from 1200–1500 kcal/d for females to 1500–1800 kcal/d for males. These diets are commonly characterized by a macronutrient composition of 30% fat, 50% carbohydrates, and 20% protein, with a specific emphasis on limiting saturated (animal-derived) fat and increasing the consumption of fiber-rich foods like fruits and vegetables. The latter not only promotes satiety but also offers a diverse array of beneficial micronutrients.

A targeted reduction of daily energy intake by 500–600 kcal can result in a modest weight loss of around 0.5 kg per week or approximately 2 kg per month. Individualization of conventional diets is crucial based on each patient's weight loss

trajectory, considering their unique food preferences. These diets are typically followed over extended periods to achieve clinically meaningful weight loss.

While energy-restricted diets demonstrate modest effectiveness for short-term weight loss, it's essential to recognize the heterogeneity in individual responses to hypocaloric diets. Long-term adherence to these diets remains challenging for many individuals . The common nature of these dietary approaches underscores the importance of tailoring interventions to the specific needs and responses of each participant for sustainable outcomes [39].

1.2.2.2 Low-fat diets

Low-fat diets have been historically recommended as safe and effective weight loss strategies based on various observations. These include the idea that a high fat/carbohydrate ratio can lead to overconsumption and weight gain [40]. Additionally, fat is absorbed more readily than carbohydrates, and a diet with a high fat/carbohydrate ratio may result in lower fecal energy loss. Moreover, carbohydrate is more thermogenic than fat, contributing to higher energy expenditure during a diet with a low fat/carbohydrate ratio [41]. There's also concern that a high-fat diet might harm the intestinal barrier and cause intestinal dysbiosis, impacting body weight and metabolic variables [42].

Meta-analyses comparing popular weight loss diets indicate that low-fat diets are equally effective as other diets in terms of weight loss, with no significant differences in qualitative aspects, compliance rates, and adverse events [43]. Studies also suggest that the effects on weight loss, total and visceral fat loss, and lean body mass preservation are similar for both low-fat and higher-fat diets, especially when both adhere to high-quality diet standards [44].

In systematic reviews and meta-analyses comparing low-fat diets with other dietary interventions, the long-term impact on body weight depends on the intensity of the diet intervention in the comparison group. While low-fat diets are more effective in weight reduction compared to usual diets, their effectiveness becomes comparable or less significant when compared to other higher-fat dietary interventions [45].

1.2.2.3 Low-carbohydrate diets

Low-carbohydrate diets, originated from the ketogenic Atkins diet with its severe carbohydrate restriction (<30 g/d) [46], have evolved to include less stringent carbohydrate limits, accompanied by increased fiber intake. While these diets have demonstrated short-term efficacy in weight loss and metabolic improvements for patients with diabetes, their long-term compliance poses challenges and potential risks.

The current versions of low-carbohydrate diets maintain substantial carbohydrate restrictions, and despite adjustments compared to the original Atkins diet, compliance remains difficult. High fat intake in conjunction with significantly reduced carbohydrate intake may lead to elevated low-density lipoprotein (LDL) cholesterol levels and increased mortality risk [47]. Meta-analyses have indicated that very low carbohydrate ketogenic diets show short-term effectiveness compared to other dietary strategies for weight loss and metabolic improvement in diabetes patients [48].

However, when assessing low-carbohydrate diets in broader contexts, conflicting evidence arises from meta-analyses of randomized clinical trials. Some suggest that low-carbohydrate diets yield better weight loss outcomes than low-fat diets, acknowledging potential risks associated with increased LDL-cholesterol [49]. Others propose that low-carbohydrate diets achieve comparable weight loss to balanced or low-fat diets in the short term [50]. Certain meta-analyses even indicate that low-carbohydrate diets without energy restriction can be as effective as energy-restricted low-fat diets for weight loss, emphasizing potential benefits on triglycerides and high-density-lipoprotein (HDL) cholesterol levels [51]. However, the available data on the long-term safety and efficacy of these diets beyond one year are limited, necessitating caution and further research before endorsing their prolonged use.

1.2.2.4 High-protein diets

High-protein diets, where protein constitutes 20–30% of the total daily energy intake, have been suggested to enhance weight loss compared to lower-protein diets (15–20%). These diets promote satiety, preserve lean body mass, and elevate diet-induced thermogenesis, contributing to a weight loss of approximately 3.8 kg in a six-month program for overweight individuals [52]. Studies demonstrate that energy-restricted, high-protein diets may yield equal or greater weight loss and metabolic benefits than high-carbohydrate diets in women with obesity, affecting body composition, blood lipid profile, and glucose homeostasis [53].

The advantages of higher-protein diets extend to preventing the loss of lean body mass and enhancing insulin sensitivity, particularly in overweight individuals with insulin resistance or type 2 diabetes. While short-term data (up to 6 months) support the efficacy of higher-protein diets for weight loss, longer-term data remain limited and inconsistent [54].

However, concerns have been raised regarding the impact of high-protein diets, especially those rich in animal-derived proteins, on serum lipids and cardiovascular disease risk. Additionally, these diets may pose risks such as nephrolithiasis, diabetes mellitus, atherosclerosis, and progressive kidney damage in susceptible individuals. As a prudent dietary recommendation, partially replacing refined carbohydrates with low-saturated fat protein sources is advised.

Formula diets, characterized by high protein content, represent an example of such dietary approaches.

1.2.2.5 Formula diets

Formula diets, categorized as very-low-calorie diets (VLCD, <800 kcal/d) or low-calorie diets (LCD, 800–1200 kcal/d), are a potent intervention in weight management. Comprising nutrient-enriched meal replacements like bars, soups, and drinks, they offer a greater energy deficit than conventional hypocaloric diets. With drastic energy restriction, formula diets induce significant weight loss of 10–20 kg within 8–12 weeks [55]. To maintain weight loss and prevent regain, strategies

like high-protein diets, anti-obesity drugs, partial meal replacements, and increased physical activity are implemented.

After the initial rapid weight loss phase, strategies ensure weight loss maintenance. Gradual reintroduction of food occurs, transitioning patients back to a healthy and balanced dietary plan. The reduced caloric and carbohydrate content of formula diets increases circulating blood ketones, potentially reducing hyperinsulinemia in patients with obesity, sustaining hunger suppression, and enhancing compliance. Profound initial weight loss may motivate severely patients with obesity, fostering adherence to the diet.

It's crucial to emphasize that formula diets are intended for short-term use, up to a maximum of 12 weeks. They should be applied in carefully selected patients under continuous medical supervision, accompanied by sufficient education and psychological support. When these requirements are met, formula diets can lead to significant weight loss and maintenance, offering health benefits in terms of improved metabolic profiles and symptomatic relief in various patient subgroups, including those with diabetes, osteoarthritis, obstructive sleep apnea, psoriasis, and pre-operative morbidly patients with obesity planning bariatric surgery [56].

1.2.2.6 Intermittent energy restriction

Intermittent energy restriction (IER) involves alternating between periods of reduced energy intake and unrestricted feeding. Despite its popularity, reviews highlight a lack of high-quality evidence supporting the long-term superiority or equality of intermittent diets compared to continuous energy restriction [57]. Limited randomized studies comparing intermittent and continuous hypocaloric diets report equal efficacy in weight loss for up to 6 months in overweight and patients with obesity [58].

Data on the impact of intermittent diets on various factors, including ectopic fat stores, adipocyte size, adipose tissue function, fat-free mass, insulin resistance, and metabolic flexibility, are currently scarce and heterogeneous. The optimal pattern and severity of energy restriction (e.g., 5:2, alternate days, five consecutive days

per month, energy restriction by 60–70%, or complete fasting) remain controversial. Additionally, the ideal macronutrient composition for such intermittent diets is unclear. An individualized critical appraisal is necessary to determine which patients might benefit from intermittent diets based on their social and personal contexts and coexisting clinical conditions.

The well-established rule that weight loss requires a negative energy balance, with energy intake lower than expenditure, is widely accepted. The ideal diet for treating overweight or obesity is described as safe, efficacious, healthy, nutritionally adequate, culturally acceptable, economically affordable, and supportive of long-term compliance and weight loss maintenance. While various dietary plans show promise in promoting weight loss in adults, the optimal diet remains debated, emphasizing the need for individualization.

Conventional hypocaloric diets are safe, healthy, and modestly effective. There's insufficient evidence favoring low-fat diets over other higher-fat interventions for long-term weight loss. Low-carbohydrate diets are effective in the short term, but adherence and potential health risks require consideration. High-protein diets may prevent muscle loss but pose challenges for long-term adherence and specific health conditions. Formula diets offer rapid weight loss for specific groups in the short term.

Regarding the debate on diet quality versus quantity, both play a role. Shifting to a healthy dietary pattern, tailored to individual preferences and lifestyle, proves effective for long-term weight loss and cardiometabolic health. This pattern should limit added sugars, refined grains, and highly processed foods while emphasizing fruits, vegetables, whole grains, and low-fat dairy. Combining this with education, motivation, and behavior modification supports slow, steady weight loss and overall health benefits. Setting realistic goals and prioritizing weight loss maintenance are crucial, promoting continuous adherence to a balanced diet rich in high-quality fats and carbohydrates for optimal health outcomes.

In essence, scientific evidence consistently supports a healthy diet characterized by variety and rich in fruits, vegetables, whole grains, and high-quality proteins, while minimizing added sugar, refined grains, and highly processed foods. Those making

such dietary choices may find it easier to manage body weight without daily calorie counting or strict portion control.

Crucially, the best diet is one that individuals can sustain over the long term, minimizing recurrent weight gain. Therefore, flexibility and personalization to align with values and preferences are key considerations. Nutrition interventions should prioritize health outcomes beyond just weight, emphasizing food quality and fostering a positive, enduring relationship with food.

In conclusion, adults dealing with obesity can explore diverse, flexible nutrition approaches tailored to their preferences and values, with an emphasis on health. Collaborative care involving a registered dietitian experienced in medical nutrition therapy for obesity management is recommended for comprehensive support [59].

1.2.3 Physical exercise

Physical exercise plays a crucial role in weight reduction by increasing energy consumption, but its weight-reducing effect is most significant when combined with caloric intake reduction. For effective weight loss, it is recommended to engage in physical exercise for more than 150 minutes per week, aiming for an energy expenditure of 1200–1800 kcal per week [60].

Before initiating physical exercise, it's essential to rule out contraindications for additional physical activity. Rather than solely focusing on its impact on body weight, physical activity should be considered within the broader context of its influence on overall health outcomes. It contributes to the preservation of physical function, social participation, and quality of life.

Both aerobic and resistance activities offer various benefits, including improvements in cardiorespiratory fitness, mobility, strength, muscle mass, health-related quality of life, mood, as well as supporting weight and fat loss. Moreover, regular physical activity aids in maintaining weight after weight loss across the lifespan [61].

The American College of Sports Medicine (ACSM) provides clear exercise prescription guidelines based on the FITT Principle: Frequency, Intensity, Time, and Type [62]. While there are specific guidelines for various populations, customization is often necessary to accommodate individual physical abilities and preferences.

Regardless of the population, prioritizing enjoyment in exercise is crucial for better adherence [62]. Tailoring exercise routines to align with personal preferences can enhance motivation and sustained engagement in physical activity.

1.2.4 Psychological interventions

Psychological interventions play a crucial role in addressing the psychosocial causes and consequences of obesity. These interventions may involve tasks to address stigmatization, self-esteem issues, stress management, sustainable social support, and coping with triggers for unfavorable eating behavior. The goal is to establish structured yet flexible eating behavior, recognizing that permanent caloric restriction may not be feasible.

Group therapies, despite limitations in individualization, leverage group dynamics and interpersonal aspects significant in treating patients with obesity. Specific psychotherapy for mental disorders like depression, anxiety, or eating disorders, often more prevalent in patients with obesity, should be integrated into obesity treatment.

Evidence supports psychotherapeutic treatments, particularly cognitive-behavioral therapy and interpersonal psychotherapy, for binge-eating disorder, a relevant consideration in obesity treatment. These interventions may extend over a longer course, maintaining effectiveness. Various psychological approaches, including cognitive-behavioral therapy, acceptance and commitment therapies, and compassion-focused therapies, can be employed.

Integration with mental health services is crucial, especially for conditions like severe mental illness, depression, anxiety, eating disorders, attention deficit hyperactivity disorder, and trauma [63].

1.2.5 Pharmacotherapy

Pharmacotherapy is recommended for weight loss and maintenance in adults with a BMI ≥30 kg/m² or BMI ≥27 kg/m² with related complications. European options include liraglutide, semaglutide, naltrexone-bupropion combination, and orlistat. Healthcare professionals should consider mechanisms of action, safety, side effects, contraindications, drug interactions, administration, and cost when selecting the most appropriate pharmacotherapy [64]

1.2.5.1 Orlistat

Orlistat serves as a lipase inhibitor designed for weight loss and maintenance. Its mechanism involves inhibiting enzymes crucial in the digestion of fats, thereby preventing the absorption of around 30% of dietary fat in the gastrointestinal tract. Rigorous clinical trials have illustrated that Orlistat users experience a weight loss ranging from 2.7 to 3.19 kg more than those on a placebo regimen over a span of one to two years. Notably, about 34% of individuals using Orlistat achieve a weight loss exceeding 10%, a notably higher percentage compared to a placebo [65].

Despite its efficacy, Orlistat's tolerability poses significant considerations. While the drug's minimal absorption (<1%) from the gastrointestinal tract eliminates systemic side effects, it introduces a set of gastrointestinal challenges. Users may encounter unpleasant side effects such as flatus with discharge, fecal urgency, and oily stool, affecting at least 10% of patients and sometimes leading to discontinuation due to intolerability.

An intriguing aspect influencing the tolerability of Orlistat is the dietary fat intake of users. It has been observed that a reduction in dietary fat intake often correlates with an improvement in the tolerability of Orlistat. Therefore, understanding and managing these nuances are crucial for healthcare professionals and patients navigating the landscape of weight loss interventions with Orlistat [66].

1.2.5.2 Naltrexone SR/Bupropion

Naltrexone SR/Bupropion (NB) presents a combination therapy approved by the FDA for addressing obesity. This combination comprises an opioid antagonist (Naltrexone) and a mild reuptake inhibitor of dopamine and norepinephrine (Bupropion). The therapeutic effects of NB in reducing appetite are achieved through complementary actions that increase α-melanocyte-stimulating hormone (MSH) levels in the hypothalamus.

Bupropion stimulates the release of MSH from pro-opiomelanocortin (POMC), while Naltrexone, acting as an opioid receptor blocker, removes the feedback inhibitory effects of β-endorphin. This synergy enhances the appetite suppressant effects of Bupropion by modulating hypothalamic responses to MSH. Notably, NB has undergone evaluation through randomized placebo-controlled studies demonstrating a placebo-subtracted weight loss ranging from 4.2% to 5.1% over one year [67].

Despite its efficacy, NB comes with some common side effects, including nausea, headache, insomnia, dry mouth, constipation, diarrhea, vomiting, and dizziness. Additionally, while NB has shown improvements in weight-related metabolic indices, its effects on blood pressure appear to be less favorable compared to a placebo.

1.2.5.3 Liraglutide

Liraglutide, initially licensed for treating type 2 diabetes mellitus (T2D), is a glucagon-like peptide 1 (GLP1) analogue. Boasting 97% homology with human GLP1, Liraglutide stimulates glucose-induced insulin secretion, suppresses glucagon secretion, inhibits gastric emptying, and decreases appetite by acting within the arcuate nucleus of the hypothalamus. Under the name Victoza, Liraglutide is licensed for glycemic management in T2D, with subcutaneous injections up to a dose of 1.8 mg daily.

The SCALE studies have demonstrated the efficacy and safety of Liraglutide at 3 mg daily subcutaneous injections (Saxenda) for weight management [68]. These studies include assessments of Liraglutide in patients both with and without T2D, as well as for weight maintenance following initial loss (SCALE Maintenance). Over one year, the SCALE studies revealed a placebo-subtracted weight loss ranging from 4% to 6.1%. Even after three years of Liraglutide 3 mg daily subcutaneous injections, weight loss is maintained, accompanied by a reduced risk of T2D in individuals with obesity and pre-diabetes.

Gastrointestinal symptoms, such as nausea, vomiting, constipation, and diarrhea, are among the primary side effects of Liraglutide. It's important to note that individuals with a personal or family history of multiple endocrine neoplasia or medullary thyroid cancer should not be prescribed a GLP1 agonist.

1.2.5.4 Semaglutide

Semaglutide, initially authorized for treating type 2 diabetes as a supplementary measure to diet and exercise, has gained approval for managing obesity and overweight conditions with at least one weight-related comorbidity. In randomized controlled trials, semaglutide demonstrated a notable body weight loss of nearly 12% over 68 weeks and 15.2% over 104 weeks [69]. However, gastrointestinal adverse events are common, and reports of pancreatitis, diabetic retinopathy, and severe allergic reactions have surfaced.

The heightened media attention has resulted in increased demand for semaglutide, causing supply challenges across its various licensed products, including those used for diabetes treatment. The National Institute for Health and Care Excellence (UK) recommends semaglutide as a weight management option for a maximum treatment duration of 2 years. Ongoing studies aim to assess semaglutide's impact on longer-term health benefits.

Pharmacotherapy plays a crucial role in managing obesity, often complementing lifestyle measures. However, in Europe, the pharmacological management of obesity faces challenges such as limited therapy options, issues of tolerability, costs

(including self-funding), and mode of administration. A common concern with all obesity pharmacotherapies is their limited durability, as the positive weight-loss effects are typically confined to the duration of the therapy, and there is a tendency for recurrent weight gain after discontinuation.

1.2.5.5 Tirzepatide

Tirzepatide stands out as an innovative pharmacotherapeutic approach, representing a single molecule that demonstrates dual agonism by activating both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. These incretin hormones play crucial roles in regulating insulin and glucagon secretion, with additional impacts on nutrient and energy metabolism, gastric emptying, appetite suppression, and enhancement of satiety. Initially developed for addressing type 2 diabetes mellitus (T2DM), tirzepatide's versatility extends to potential applications in obesity, cardiovascular disorders associated with T2DM, heart failure, non-alcoholic steatohepatitis, obstructive sleep apnea, and even the reduction of mortality/morbidity in obesity [70]. In May 2022, tirzepatide received its first approval in the USA to improve glycaemic control in adults with T2DM, as an adjunct to diet and exercise. Tirzepatide is in phase III development for heart failure, obesity and cardiovascular disorders in T2DM, and in phase II development for non-alcoholic steatohepatitis.

1.2.5.6 The future of obesity pharmacotherapy

Exciting advancements in obesity pharmacotherapy are on the horizon with the emergence of novel drugs, orforglipron and retatrutide, poised to revolutionize current treatment paradigms. Unveiled at a recent American Diabetes Association meeting and featured in the New England Journal of Medicine, these drugs, having demonstrated remarkable efficacy in phase II clinical trials, present a significant leap forward.

1.2.5.6.1 Orforglipron

Unlike other GLP-1agonists, orforglipron is a nonpeptide molecule and it can be conveniently administered as an oral formulation, simplifying both its usage and manufacturing. The anticipated cost-effectiveness of orforglipron positions it as a more accessible option for a broader demographic. In a clinical trial (NCT05051579) involving 272 participants, at week 26, orforglipron resulted in a mean change in body weight ranging from −8.6 % to −12.6 %, compared to −2.0 % in the placebo group. By week 36, the mean change with orforglipron ranged from −9.4 % to −14.7 %, while the placebo group showed a mean change of −2.3 %. Notably, 46–75 % of participants achieved a weight reduction of at least 10 % with orforglipron [71].

1.2.5.6.2 Retatrutide

Retatrutide takes a unique approach, acting as an agonist of multiple receptors—glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon. This distinctive mechanism contributes to its unparalleled potential for treating obesity, with a phase 2 clinical trial (NCT04811760) demonstrating impressive results. By 48 weeks, a significant percentage of participants achieved weight reductions of 5 % or more (92–100 %), 10% or more (75–93 %), and 15 % or more (60–83 %) in the retatrutide groups, while the placebo group showed lower percentages (27, 9, and 2 % respectively). Participants receiving the highest dose of retatrutide experienced an average weight loss of 24.2 % over 11months, surpassing the typical 15–20 % weight loss observed with current approved drugs [72].

While the promise of orforglipron and retatrutide is undeniable, it's essential to address potential side effects, particularly gastrointestinal events like nausea and vomiting, reminiscent of current GLP-1 receptor agonists. However, careful dosage management can alleviate these concerns. Additionally, recognizing that discontinuation might lead to recurrent weight gain underscores the need for comprehensive research into long-lasting weight-loss solutions, potentially reshaping the landscape of obesity pharmacotherapy.

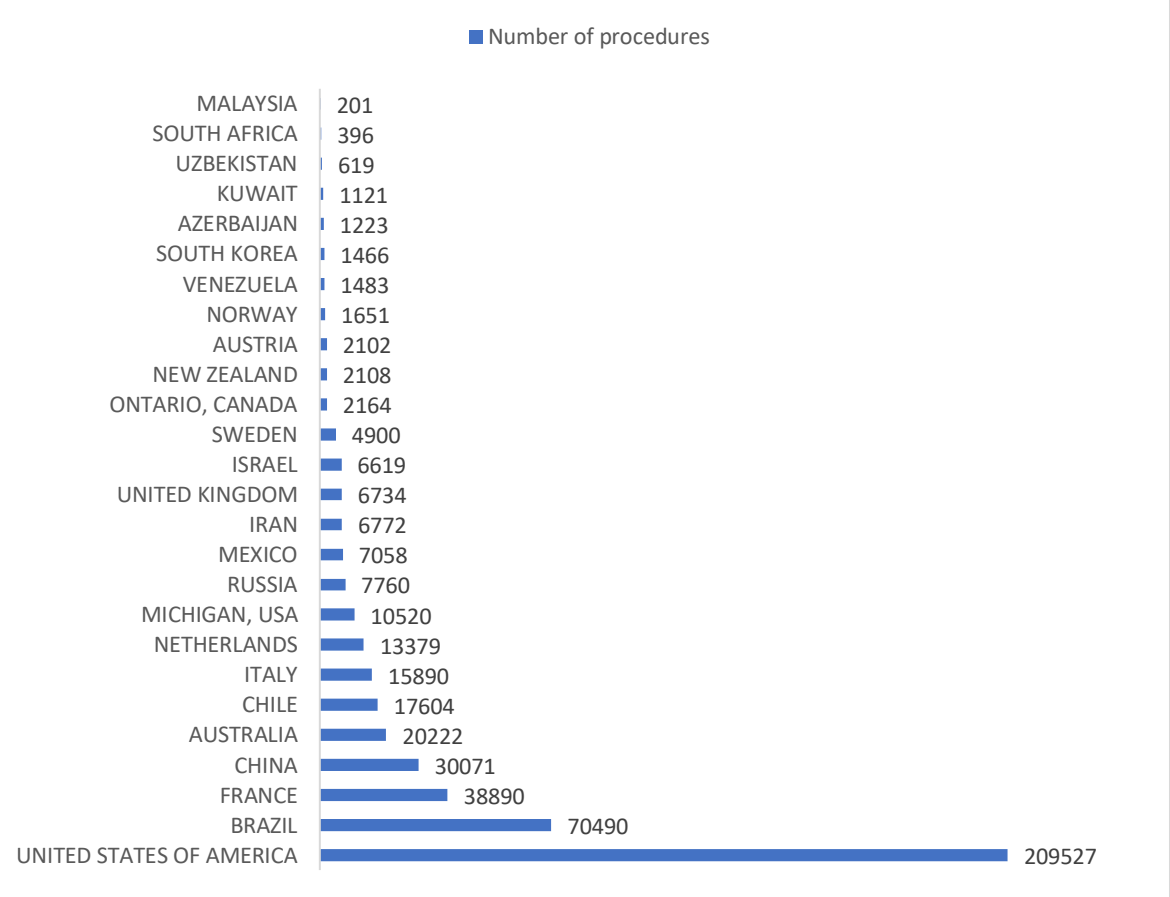
Pharmacotherapies play a crucial role in the management of obesity, often complementing lifestyle measures. While pharmacotherapy can be a valuable complement to obesity management, considering it as a sole solution would oversimplify the multifaceted nature of obesity. Nonetheless, exploring novel pharmacotherapies holds potential, especially in the realm of maintaining body weight following initial loss.

1.2.6 Bariatric surgery

While dietary management, consistent physical activity, and drug interventions have traditionally served as primary therapeutic measures, current trends indicate that bariatric surgery stands out as the most effective option for patients with elevated body mass index (BMI) and/or concurrent comorbidities. Research comparing medical and surgical interventions for individuals with clinically severe obesity consistently demonstrates superior outcomes in the short, medium, and long term, favoring the surgical approach. These benefits include sustained weight loss, effective comorbidity control, diminished occurrence of major macrovascular events, and reduced mortality rates [73].

1.2.6.1 IFSO 8th Global Registry Report

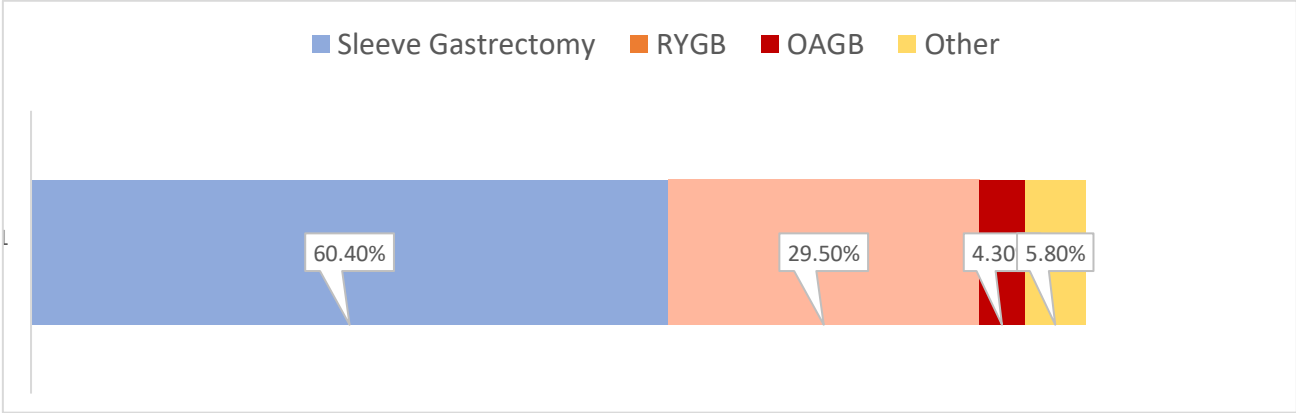
Fig 1.1 Number of metabolic bariatric surgical procedures per country or region, primary and revisional



In the 2022 according to IFSO (International Federation for the Surgery of Obesity and Metabolic Disorders) 8th Global Registry Report, 480,970 operations were conducted across 24 countries, encompassing 81.4% of known registries (Fig 1.1) [74].

Sleeve gastrectomy (SG) emerged as the predominant procedure worldwide, trailed by Roux-en-Y Gastric Bypass (RYGB) and One Anastomosis Gastric Bypass (OAGB). "Other" procedures, including SADI-S (Single Anastomosis Duodenal-Ileal Bypass With Sleeve), BPD (Biliopancreatic Diversion), AGB (One Anastomosis Gastric Bypass), and endoscopic methods, are on the rise (Fig.1.2).

Fig.1.2 Proportion of different types of bariatric surgeries worldwide



Females constitute the majority of individuals undergoing metabolic bariatric procedures for obesity. Median starting BMI ranged from 36.1 kg/m² in South Korean females to 47.65 kg/m² in South African males. Asian populations displayed lower BMIs, correlating with a higher likelihood of obesity-related diseases.

Median surgery day age ranged from 34 years in Kuwait to 45 years in Italy and the Netherlands. Type II diabetes was the most prevalent preoperative co-morbidity, with varying rates across countries.

Males undergoing metabolic bariatric procedures are disproportionately affected by OSA (Obstructive sleep apnea), Hypertension, Diabetes, and Dyslipidemia. Sleeve gastrectomy dominates primary operations, while Roux-en-Y gastric bypass leads in revisional procedures.

Laparoscopic surgeries prevail, but robotic surgery, especially in revisional cases, is on the rise. Metabolic bariatric surgery exhibits high safety, with reported mortality rates below 1% in most registries.

1.2.6.2 Indications for metabolic bariatric surgery (MBS)

The criteria for metabolic bariatric surgery (MBS) were established in 1991 by National Institutes of Health (NIH) consensus panel, universally applying a threshold of a body mass index (BMI) 40 kg/m² or BMI 35 kg/m² with co-morbidities [75]. Conditions potentially improved by sustained long-term weight loss through MBS include:

1. Type 2 diabetes (remission, improved blood glucose control).
2. Type 1 diabetes (reduction in insulin requirements).
3. Poorly controlled hypertension (remission or reduced medication).
4. Ischemic heart disease (lowered risk of heart attack and stroke).
5. Fatty liver disease (reduced progression to cirrhosis).
6. Large joint arthritis (pain reduction, potential delay to joint replacement).
7. PCOS-related infertility (improved fertility).
8. Kidney failure (improved kidney function or transplant opportunity).
9. Liver cirrhosis (improved liver function or transplant opportunity).
10. Obstructive sleep apnea (remission or reduced CPAP pressures).
11. Severe asthma (improved control, reduced shortness of breath).
12. Gastro-esophageal reflux disease (remission or reduced symptoms).
13. Severe urinary incontinence (symptom improvement or resolution).
14. Facilitate weight loss for cancer surgery in high BMI candidates with increased perioperative risks.

While there are no absolute contraindications to metabolic bariatric surgery (MBS), relative contraindications may include:

1. Severe heart failure.
2. Unstable coronary artery disease.
3. End-stage lung disease.
4. Active cancer treatment.
5. Pregnancy.
6. Portal hypertension (Child's B or C cirrhosis or portal pressures greater than 12 mmHg).
7. Drug or alcohol dependency.
8. Deliberate self-harm or suicide attempt in the preceding 12 months.

9. Severe, active, and ongoing eating disorders (patients should be referred for psychiatric consultation).
10. Active psychiatric disorder (severe depression and/or personality disorder).
11. Patients unwilling to adhere to postoperative supplements, follow-up, or blood monitoring.
12. Impaired intellectual capacity or inability to care for oneself.
13. Unfit for general anesthesia.

Since the publication of the Consensus Statement, numerous studies worldwide have enriched understanding of the obesity epidemic and metabolic and bariatric surgery (MBS), demonstrating its efficacy and durability in treating severe obesity and associated co-morbidities. Extensive research on the safety of bariatric surgery has reported very low perioperative mortality rates ranging between 0.03% and 0.2% [76].

Given these advances, MBS has become a commonly performed operation in general surgery, preferably using minimally invasive approaches. The American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) jointly advocated for MBS based on BMI thresholds, age, and comorbidities [77]:

1. MBS is recommended for individuals with BMI 35 kg/m², regardless of comorbidity presence or severity.
2. MBS is recommended for patients with Type 2 Diabetes (T2D) and BMI 30 kg/m².
3. Consider MBS for individuals with BMI 30–34.9 kg/m² who don't achieve substantial weight loss or co-morbidity improvement with nonsurgical methods.
4. BMI thresholds for obesity may differ among populations; access to MBS should not be denied based solely on traditional BMI risk zones.
5. Children and adolescents with BMI above 120% of the 95th percentile and major co-morbidity, or BMI above 140% of the 95th percentile, should be considered for MBS after evaluation by a specialized multidisciplinary team.
6. No upper age limit for MBS; older individuals benefiting from MBS should be considered after assessing co-morbidities and frailty.

7. Carefully selected higher-risk individuals for general surgery may benefit from MBS.
8. MBS is an effective treatment for clinically severe obesity in patients requiring other surgery, such as joint arthroplasty, abdominal wall hernia repair, or organ transplantation.

Since the 1950s, diverse surgical procedures, broadly classified as restrictive, malabsorptive, or mixed, have been proposed for weight loss and comorbidity control. However, it's now recognized that the traditional classification lacks precision, as the success of bariatric procedures is attributed to substantial changes in neural and endocrine signaling pathways [78]. Anatomically, procedures are better classified into those with or without small bowel diversion.

In the first group (without intestinal bypass), procedures like Laparoscopic Adjustable Gastric Band (LAGB), Vertical Banded Gastroplasty (VBG), and Laparoscopic Sleeve Gastrectomy (LSG) are prominent. The second group (with intestinal bypass) includes Roux-en-Y Gastric Bypass (RYGB), One-Anastomosis Gastric Bypass (OAGB), and others. Some techniques, like VBG and JIB, are no longer used, but there's a range of operative techniques with distinct technical designs and mechanisms of action.

Bariatric procedures, with or without small bowel diversion, modify digestive system anatomy and impact overall gastrointestinal physiology. They alter food intake, digestive processes, hormones, motility, microbiota balance, neural signaling, and more, collectively known as the BRAVE effect. While these changes are therapeutic, they can lead to adverse effects, necessitating a thorough understanding of anatomical and physiological changes for optimal patient outcomes.

Recognizing that there is no ideal bariatric procedure, clinicians worldwide engage in debates not only on superiority but also on tailoring procedures to individual patients. Developing an understanding of the "ideal" operation is crucial for personalized decision-making in bariatric surgery

1.2.6.3 Types of bariatric procedures

1.2.6.3.1 The Laparoscopic Adjustable Gastric Band

The Laparoscopic Adjustable Gastric Band (LAGB) is a restrictive procedure involving the placement of a silicone band around the upper stomach, near the cardia (Fig. 1.3). This creates a smaller, superior pouch (10–20 mL) and luminal narrowing, slowing food emptying. Adjustments to the band's internal diameter, managed through a subcutaneous access port, regulate restriction and emptying speed. LAGB is reversible, with potential restoring the original gastrointestinal anatomy after device removal.

Food passing through the band stimulates afferent vagal nerve fibers, triggering early satiety. Optimal results occur with textured foods, promoting prolonged satiety. While reduced portion size, slowed eating, and early satiety contribute to gradual weight loss, the absorption of energy-rich liquids can pose challenges, limiting the effectiveness of weight reduction efforts.

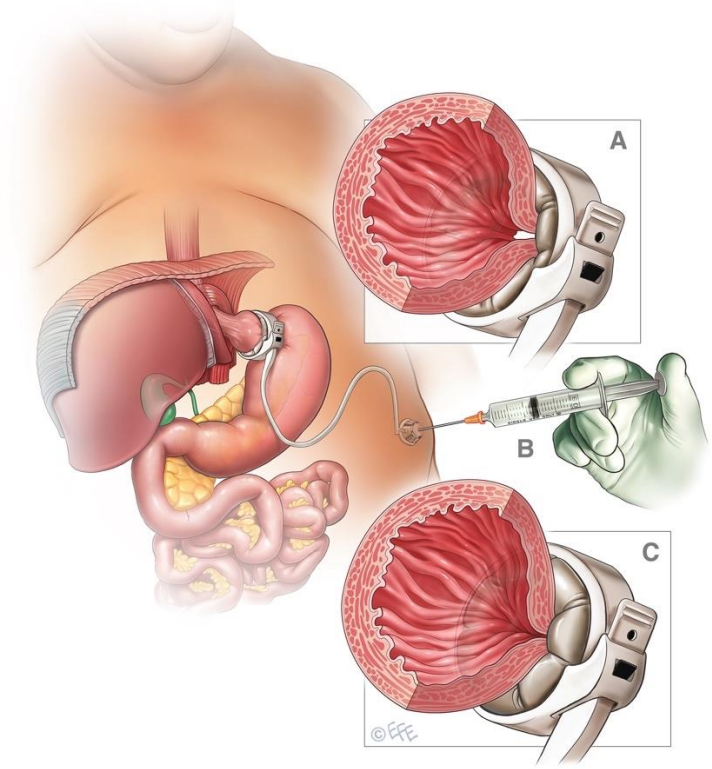


Fig. 1.3 Laparoscopic Adjustable Gastric Band

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1.2.6.3.2 Laparoscopic Sleeve Gastrectomy

Laparoscopic Sleeve Gastrectomy (LSG) has become the rapidly growing choice among both surgeons and patients, attributed to its excellent outcomes in weight loss, control of obesity-related comorbidities, and improved quality of life. Its popularity may be explained a faster and technically less demanding surgical procedure compared to some alternatives [79].

In LSG, about 70–80% of the stomach is removed through stapled vertical gastrectomy, including a portion of the antrum, most of the body, and the entire gastric fundus (Fig. 1.4). The pylorus is preserved, maintaining the gastric emptying mechanism. Notably, there is no intestinal bypass, keeping the original absorptive surface and reducing adverse events related to nutrient malabsorption commonly associated with bypass procedures.

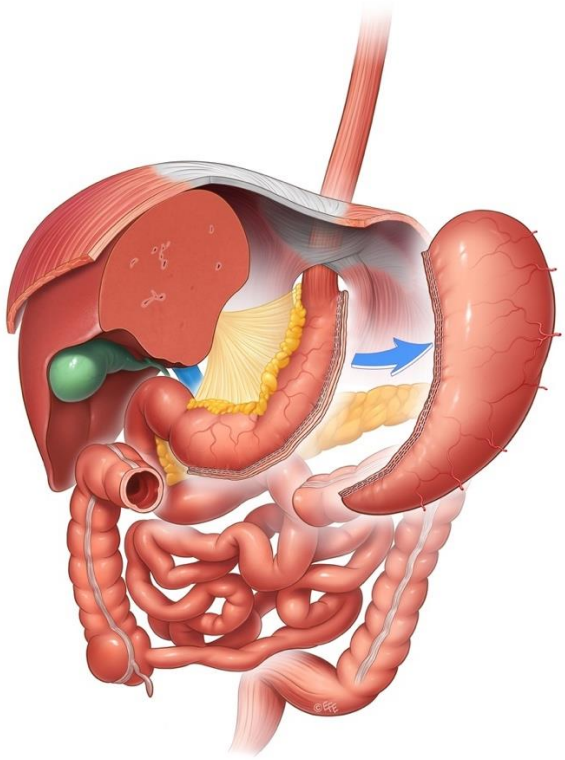

Fig. 1.4 Laparoscopic Sleeve Gastrectomy

The anatomical change involves a reduction in the size of the gastric reservoir to approximately 100–150 mL capacity. While this "simple" alteration is irreversible, it induces profound modifications in the functioning of the entire digestive system.

1.2.6.3.3 Roux-en-Y Gastric Bypass

In Roux-en-Y Gastric Bypass (RYGB), a small pouch based on the lesser gastric curvature is created in the upper stomach using linear staplers, excluding approximately 95% of the stomach. The alimentary pathway is reconstructed connecting alimentary and biliopancreatic limbs through distal enteroenterostomy (Fig. 1.5).

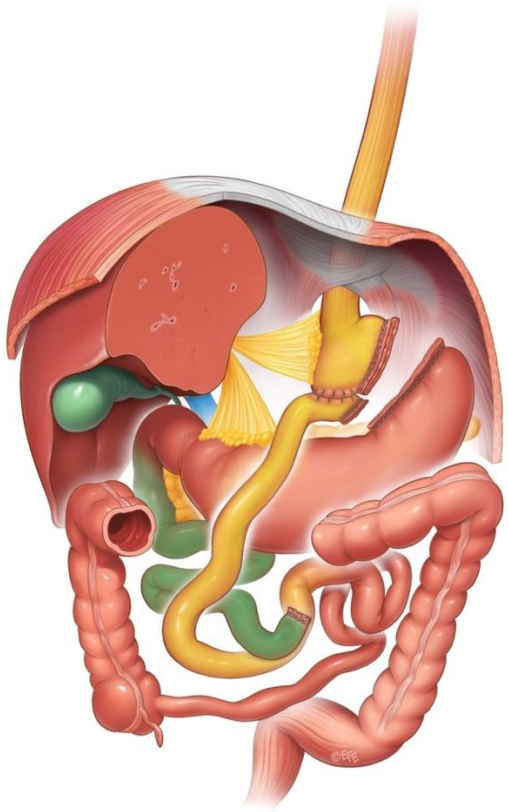

Fig. 1.5 Roux-en-Y Gastric Bypass
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The alimentary limb, usually 100–120 cm long, allows the flow of food mixed with saliva and minimal gastric juices. In contrast, the biliopancreatic limb (50–150 cm) permits the flow of gastric and biliopancreatic secretions without food. The ingested food meets these secretions after enteroenterostomy in the common channel. The length of the common channel varies based on the total length of the small bowel. RYGB results in reduced gastric capacity (20–30 mL) and excludes a significant portion of the stomach, duodenum, and a variable length of the jejunum (usually 50–150 cm). This configuration imposes restriction and substantially alters neurohormonal signaling, impacting digestion and absorption processes. Although

RYGB may induce some nutrient deficiencies (primarily due to duodenal bypass), the malabsorptive component is considered generally mild [80].

1.2.6.3.4 The One-Anastomosis Gastric Bypass

The One-Anastomosis Gastric Bypass (OAGB), introduced in the early 2000s, shares principles with Roux-en-Y Gastric Bypass (RYGB) but is technically simpler and faster. In this procedure, a long and narrow "Sleeve-like" pouch is created based on the lesser curvature of the stomach, followed by an end-to-side anastomosis between the gastric pouch and the small bowel approximately 150–200 cm distal to the duodenojejunal flexure (angle of Treitz) (Fig. 1.6). Unlike RYGB, there is no alimentary limb; instead, there are afferent and efferent loops. The gastric reservoir capacity is reduced (more than Laparoscopic Sleeve Gastrectomy but less than RYGB), and the entire duodenum and the first 150 to 200 cm of the small bowel (jejunum) are bypassed.

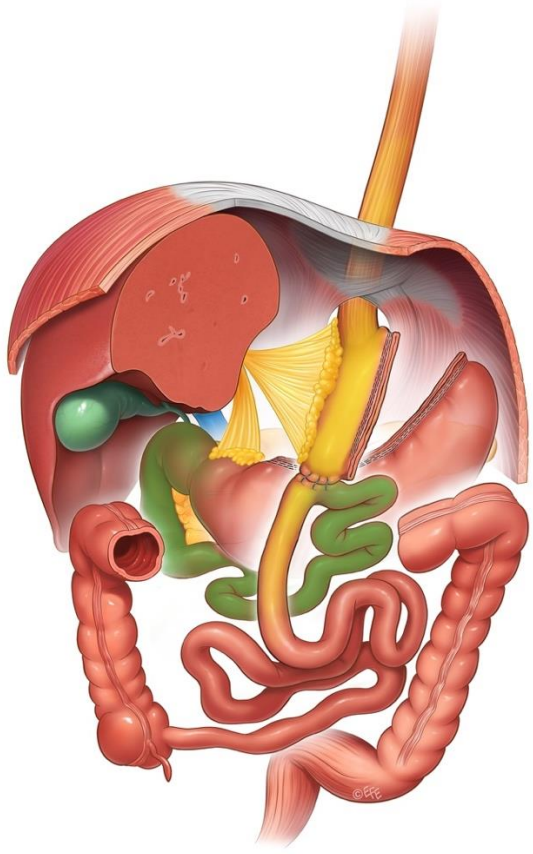

Fig. 1.6 The One-Anastomosis Gastric Bypass

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The One-Anastomosis Gastric Bypass (OAGB) is commonly described as a malabsorptive procedure, showing a higher incidence of diarrhea, steatorrhea, deteriorated liver parameters, and nutritional adverse events [81].

1.2.6.3.5 Biliopancreatic Diversion with Duodenal Switch

Biliopancreatic Diversion with Duodenal Switch (BPD-DS), though infrequently performed today, is primarily a malabsorptive procedure. A recent innovation, known as Single-Anastomosis Duodenoileal Bypass with Sleeve Gastrectomy (SADI-S), represents a contemporary effort to reduce side effects and simplify the technical aspects [82].

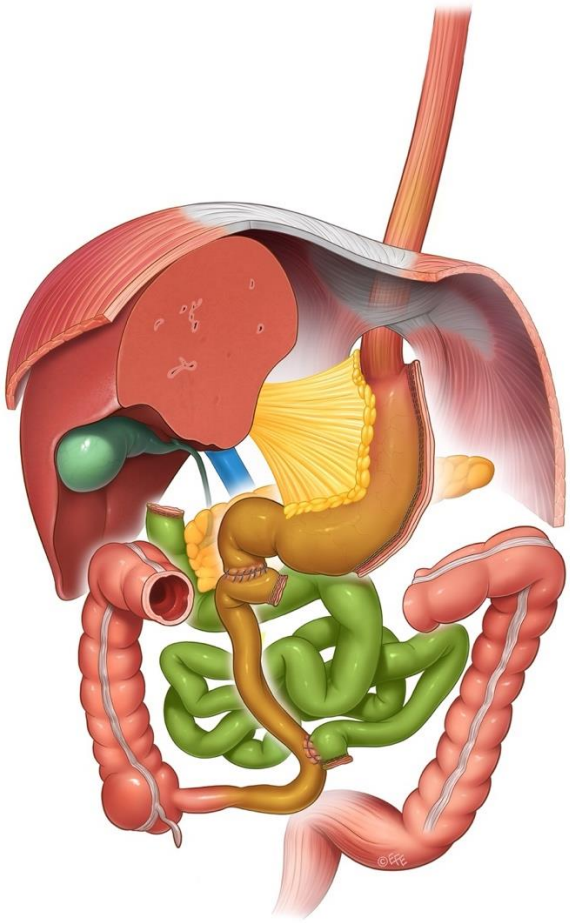


Fig. 1.6 Biliopancreatic Diversion with Duodenal Switch

Described typically as a "malabsorptive" procedure, BPD-DS incorporates both restrictive and malabsorptive elements. Restriction results from Sleeve

gastrectomy, involving linear stapled transection of the duodenum immediately after the pylorus. The reconstruction of food transit is achieved through an end-to-side, hand-sewn Roux-en-Y duodenoileostomy. Enteroenterostomy is then performed at a distance of 50–120 cm from the ileocecal valve. The final configuration of the small bowel diversion in BPD-DS (similar to classic BPD and SADI-S) involves longer alimentary and biliopancreatic limbs and shorter common channels. The length of the common channel (remaining short) predominantly determines the degree of malabsorption and can be a contributing factor to severe, sometimes uncontrollable adverse effects.

1.2.6.4 Mechanism of Action of Bariatric procedures

Over the past three decades, the understanding of bariatric surgery's mechanism of action has evolved. Initially it was classified as restrictive or malabsorptive, focusing on reducing food intake or absorption. Recent studies revealed that bariatric surgery brings about changes in gastrointestinal system by means of bile flow alteration, altered flow of nutrients, vagal manipulation, enteric and adipose hormones modulation, changes in microbiota composition and in the functioning of the brain-gut axis [83].

1.2.6.4.1 Gut Hormones

The evolving understanding of postoperative enterohormone behavior represents a significant breakthrough in the field of bariatric surgery. This knowledge, often associated with the principles of metabolic surgery, has not only transformed the comprehension of physiological mechanisms but has also paved the way for the development of new pharmacological treatments.

Bariatric surgery, by nature, induces notable changes in the fasting and postprandial levels of various enterohormones. This hormonal shift profoundly influences hunger and satiety regulation, as well as overall metabolic control.

The concept of the incretin effect, where insulin secretion is amplified after oral glucose intake compared to parenteral infusion, serves as a foundational aspect in understanding the metabolic impact of bariatric surgery. Enterohormones such as

glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), originating from enteroendocrine K- and L-cells, respectively, take center stage as key players in this physiological orchestra. Their increased post-bariatric surgery levels not only signal the presence of nutrients in the bloodstream but also contribute significantly to the metabolic changes observed.

GIP, originally known for its role in gastric inhibition, has been subject to investigation, but its relevance after specific bariatric procedures remains unclear. In contrast, GLP-1 emerges as a powerful incretin associated with bariatric surgery, showcasing heightened postprandial levels that exert substantial influence on both weight loss and glycemic control. The stimulation of ileal L-cells, especially after procedures like Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD-DS), results in markedly elevated postprandial GLP-1 levels [84].

Beyond GIP and GLP-1, other enterohormones, including glucagon-like peptide 2 (GLP-2), oxyntomodulin (OXM), and peptide YY (PYY), undergo significant transformations post-bariatric surgery [85]. GLP-2 demonstrates heightened postprandial levels after RYGB, correlating with enhanced satiety regulation. OXM, recognized for its anorexigenic effects, increases after RYGB. As for PYY(3-36), the active form of PYY, its postprandial growth following various bariatric procedures prompts further exploration to unravel its impact on weight loss and metabolic control.

In essence, the interplay and altered release of enterohormones after bariatric surgery signify a pivotal mechanism in achieving weight loss and addressing or even resolving obesity-related comorbidities. Deep research of this physiological landscape may give the potential for more targeted and effective interventions in obesity management.

1.2.6.4.2 Bile acids

Bile acids, pivotal in the enterohepatic circulation, undergo substantial alterations following bariatric surgery, contributing to the metabolic transformations observed. Acting as ligands for farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5), bile acids play important role in weight loss, glycemic control, and lipid regulation. FXR, distributed in liver, intestine, pancreas, and brain, promotes weight

loss by decreasing lipogenesis, improving insulin sensitivity, and ameliorating lipid profiles, thus impacting hepatic steatosis and non-alcoholic fatty liver [86].

Stimulation of FXR, particularly in intestinal enterocytes, triggers the downstream mediator fibroblast growth factor 19 (FGF19), initiating a cascade that reduces bile acid synthesis in the liver through FGF receptor 4 (FGFR4). FGF19 further promotes hepatic protein and glycogen synthesis, diminishes gluconeogenesis, and regulates lipid levels, also contributing to reduced food intake and glucose homeostasis.

Peroxisome proliferator-activated receptor α (PPARα), another hepatocyte nuclear receptor, collaborates with FXR in mitigating non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH). PPARα stimulates mitochondrial fatty acid uptake and β-oxidation, subsequently reducing triglyceride levels and elevating high-density lipoprotein (HDL). The synergistic interplay between PPARα and FXR appears in positive metabolic effects.

Research by Mazzini et al. showcased increased FXR and PPARα gene expression in liver biopsies post-RYGB, resulting in the remarkable remission of NASH/NAFLD [87]. Notably, these metabolic benefits persisted independently of weight loss or the presence of NASH disease. Huang et al. reported elevated FGF19 levels post-sleeve gastrectomy (SG), correlating with substantial remission rates of diabetes mellitus (DM) and NAFLD.

Despite these promising findings, the mechanisms underlying these changes need further exploration.

1.2.6.4.3 Gut microbiota

Obesity, characterized as a chronic inflammatory state, involves mechanisms such as endotoxemia from the release of lipopolysaccharide (LPS) by Gram-negative bacteria in the gut. Elevated levels of LPS binding protein (LBP) in obesity and diabetes patients decrease after bariatric surgery, with LBP showing correlation with greater weight loss. This reduction is attributed to changes in gut flora post-bariatric surgery, linked to resolving inflammation, insulin resistance, and diabetes remission. The gut microbiota, functioning as a symbiotic ecosystem, comprises major constituents like Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria.

The evolving science of inducing floral symbiosis without surgery has explored fecal oral transplantation for obesity or non-alcoholic fatty liver disease (NAFLD) [88].

Continued research aims to unravel the intricate interplay between gut microbiota, bariatric procedures, and metabolic outcomes, offering potential targets for therapeutic interventions beyond surgery.

In unraveling the physiological transformations following bariatric surgery, a clearer comprehension of obesity as a chronic condition appears. While the complete mechanisms of surgical efficacy remain elusive, the ongoing exploration promises a brighter and more promising future in understanding and addressing obesity.

2 Sleeve Gastrectomy with Transit Bipartition and SASI (Single Anastomosis Sleeve Ileal) bypass

Bariatric surgery evolved from the principles of mechanical restriction and malabsorption, offering substantial weight loss and improvements in comorbidities but posing various complications. Some procedures impede food ingestion, leading to issues like dysphagia, vomiting, and esophagitis, while others hinder nutrient absorption, potentially causing hypoproteinemia [89]. Certain surgeries involve partial exclusion of digestive system segments, complicating endoscopic access.

Challenges in traditional approaches are prompting bariatric surgeons to explore less risky alternatives. The goal is procedures that are easy to perform, avoid segment exclusion, eliminate endoscopic blind areas, and ensure predictable weight loss and metabolic outcomes without excessive malabsorption [90]. The ideal bariatric procedure should alter neuroendocrine control of hunger and satiety without compromising digestive functions such as gastrointestinal motility, peristalsis, and enzyme secretion.

2.1 Sleeve gastrectomy with transit bipartition

In 2012, S. Santoro presented the 5-year results of sleeve gastrectomy with transit bipartition (SG + TB) as an innovative metabolic intervention for obesity (Fig.2.1) [91].

The SG + TB procedure was initially designed for functional restrictiveness, aiming for a metabolically driven reduction in the rate of gastric emptying and intestinal transit, rather than a physical restriction. This concept aligns with the idea of primarily focusing on metabolic aspects in surgery [92]. The SG + TB combines moderate restriction with early nutritive stimulation of the distal gut while diminishing the exposure of the proximal bowel to nutrients without excluding the duodenum.
The SG + TB operates on the bipartition principle, diverting a significant portion of the ingested meal early into the ileum, while the remaining part follows the normal duodenal pathway. This principle addresses the notion that individuals with severe obesity might excessively absorb nutrients in the proximal bowel, aiming to counterbalance digestive tract signaling abnormalities. The SG + TB treatment

introduces a new equilibrium: the gastroileal anastomosis promotes distal gut activity, quickly delivering food to the ileum. Concurrently, it reduces proximal gut activity by diverting food away from this region.

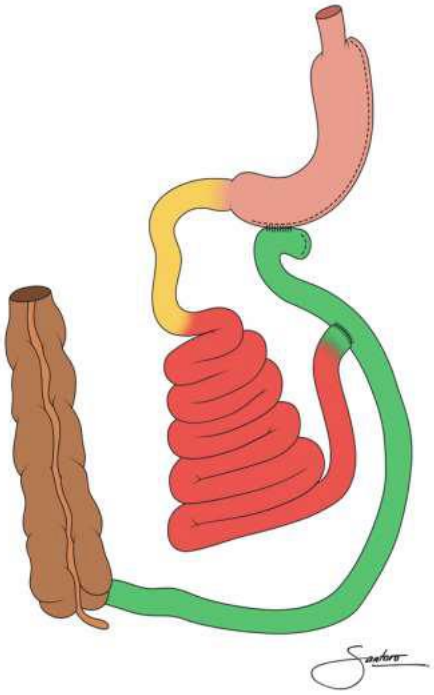


Fig.2.1 Sleeve gastrectomy with transit bipartition
(used with kind permission of the author Dr S. Santoro)

It was shown, that SG + TB treatment leads to early and substantial increase in GLP1 levels, coupled with a reduction in post-prandial GIP, potentially contributing to metabolic improvement without causing undernutrition, hypoproteinemia, or anemia [93]. Notably, the study revealed growth of serum FGF19 concentrations three months post-surgery, suggesting improvements in lipid metabolism through increased fatty acid oxidation and a reduction in the production of Lipoprotein(a), a highly atherogenic particle.

2.2 SASI (Single Anastomosis Sleeve Ileal) bypass

In 2016, Mahdy et al. introduced a modification of the original Santoro procedure. Instead of a Roux-en-Y anastomosis, they selected a simpler and safer approach,

performing a single loop anastomosis between the gastric antrum and the ileum (Fig. 2.2) [94]. This modification reduced the number of anastomoses to one (loop), maintaining the therapeutic effect of the original procedure on weight loss and improvement in diabetes mellitus.

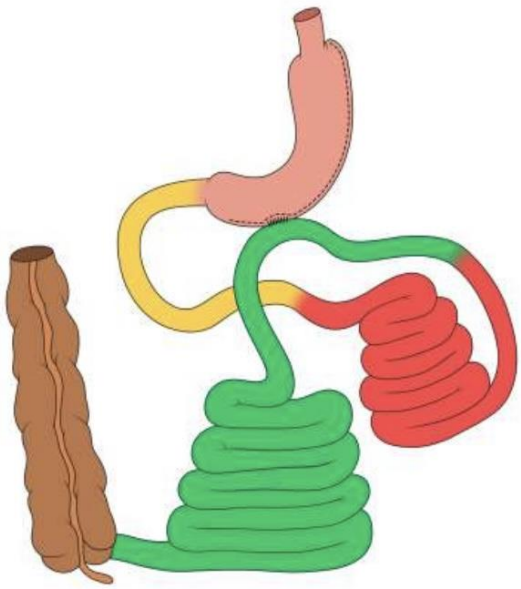


Fig. 2.2 Single Anastomosis Sleeve Ileal bypass
(used with kind permission of the author Dr S. Santoro)

A possible explanation of the mechanism of action of the SASI bypass was devised by Mahdi et al. that patients who undergo the SASI bypass eat less food because they experience early satiety due to a hypothalamic-generated satiety sensation which is caused by the perception of nutrients in the distal bowel. The intense distal gut stimulation reduces proximal bowel activity. The distal gut hormones such as GLP-1 have central satietogenic effects, and they also reduce gastric emptying which is known as the ileal break mechanism.

The bipartition advantages include weight loss similar to duodenal switch but simpler and safer, high resolution of type 2 diabetes (T2DM), no excluded segments, functional restriction instead of mechanical, immediate ileal nutritive stimulus, full endoscopic access, and low intra-gastric pressure [95] .

Bariatricians have recently conducted a thorough investigation into the effects of the SASI procedure, presenting promising conclusions on its efficacy in obesity treatment.

In 2021, Emile et al. [96] conducted a systematic review of ten studies (published between 2016 and 2020) on the SASI bypass, involving 941 patients. At 12 months, there was a significant decrease in median preoperative body weight (121.6–84.05 kg, $p = 0.003$) and BMI (45.6–29.1 kg/m², $p = 0.0002$), with a median %EWL of 90.1%.

For patients with type II DM (481), 98.1% showed complete or partial improvement. Improvement rates for hypertension, hyperlipidemia, and GERD were 51%, 76.6%, and 92%, respectively.

Complications were recorded in 12.3% of patients, with 10.4% being minor and 1.9% major. Complications included bilious vomiting, diarrhea, hypoalbuminemia, marginal ulcer, bleeding, obstruction, dumping, leak, hypocalcemia, GERD, excessive weight loss requiring conversion to sleeve gastrectomy, and trocar site hernia.

Subgroup analysis based on common limb length and anastomosis size revealed that a longer common limb (300–350 cm) was associated with lower %EWL at 6 months, greater improvement in hypertension, and fewer complications. Using a 4-cm anastomosis was linked to significantly higher %EWL at 6 and 12 months, greater improvement in hypertension, and fewer complications.

3 Goal of the study

Since the introduction of the SASI bypass in 2016, only a limited number of studies have examined its efficacy and safety. Given the relatively recent emergence of the SASI bypass, a comprehensive analysis is needed to provide insights into the current state and outcomes of this procedure. With a mere seven years since its inception, analyzing the accumulated data becomes crucial for informed decision-making when selecting an appropriate surgical intervention for patients with morbid obesity.

As the popularity of the SASI bypass grows, particularly in regions like South America and the Near East, a deeper understanding of its outcomes becomes essential. This not only contributes to the developing of common surgical approaches but also aids in standardizing factors such as efferent limb length and anastomosis size. The evolving knowledge base surrounding SASI bypass is pivotal for surgeons, guiding them in navigating the complexities of this procedure.

Furthermore, the lack of information concerning the postoperative management of patients after SASI bypass underscores the need for dedicated research in this area. This study aims to fill these knowledge gaps, at least, partially, by assessing the outcomes of SASI bypass conducted at our medical center. The focus lies on evaluating weight loss, improvements in comorbidities, and the occurrence of complications. The goal of this research is not only to contribute to the existing body of evidence but also to provide valuable insights that can inform clinical practices and enhance patient care in the context of SASI bypass.

4 Methods of the study

We conducted a retrospective study involving patients with obesity who underwent SASI bypass at a single institution (Medical Center “Medeor,” Chelyabinsk, Russia) between February 2017 and March 2022. The study included patients who completed at least one-year follow-up. Informed consent was obtained from all patients, providing details on the operative and postoperative aspects, including potential complications.

4.1 Preparation for Surgery

Prior to surgery, all patients underwent a comprehensive preoperative assessment, which included a detailed medical history, clinical examination, and laboratory investigations such as blood glucose, lipid profile, and thyroid and suprarenal hormonal evaluation. Additionally, routine gastroscopy and abdominal ultrasound were conducted. Psychological evaluations were also performed to identify any binge eating habits or psychiatric disorders that could contraindicate surgery or necessitate specialized pre- and postoperative care.

4.2 Operative Technique

Our operative technique aligns with the method reported by Mahdy [94], with some technical nuances. The laparoscopic sleeve gastrectomy (SG) involves stapling alongside a 39 Fr. bougie on the lesser curvature. The staple line initiates approximately 5-6 cm from the pylorus. Identification of the ileocecal junction is followed by measuring 250 cm or 350 cm upwards. A side-to-side, stapled anastomosis is created between the gastric wall and the ileal loop, positioned 2-3 cm away from the pylorus, utilizing a 45-mm staple suture. The defect of the gastroileal anastomosis is closed with a continuous running suture, and the anastomosis is tested for water tightness with a dye test.

4.3 Follow-up

All patients adhere to the same postoperative protocol, encompassing a liquid diet for two weeks, followed by a soft diet for the subsequent two weeks. Low-molecular-weight heparins are prescribed for two weeks, and esomeprazole is used for 1-3

months to prevent marginal ulcers. Additionally, all patients receive diet recommendations, vitamin and mineral supplementation, and adhere to a follow-up schedule. A multidisciplinary team (MDT) manages patients at 1, 3, 6, and 12 months postoperatively. Continuous registration of data includes information on weight loss, metabolic status, postoperative changes, and complications.

4.4 Data Collection and Analysis

Postoperative BMI changes, the percentage of excess weight loss (% EWL), the percentage of total weight loss (%TWL), remission of comorbidities and complications were comprehensively analyzed. Pre- and post-surgery assessments of glucose, cholesterol, protein levels were conducted. Changes in nutritional status were also evaluated. Additionally, the study estimated the impact of the efferent limb length on weight loss results and protein levels as well as the influence of the efferent limb length on remission of comorbidities and nutritional status.

Study outcome measures were estimated according to recommendations indicated in Standardized Outcomes Reporting in Metabolic and Bariatric Surgery [97]

1. The percentage of total weight loss (%TWL), calculated as
[(initial weight –postop weight)/ initial weight] × 100.
2. The percentage of excess weight loss (%EWL): calculated as
[(initial weight –postop weight)/ [(initial weight –ideal weight)] × 100, where ideal weight is defined by the weight corresponding to a BMI of 25 kg/m2
3. Complete remission of T2DM was defined as a fasting plasma glucose level < 5,5 mmol/L or HbA1C level < 6% without the use of hypoglycemic medication at 1 year after surgery.
4.Remission of hypertension. It was considered if the patient was normotensive (BP < 120/80) without antihypertensive medication.
5. Remission of hyperlipidemia. It was defined as normal lipid panel off medications (cholesterol < 6,2 mmol/L, TG < 2,3 mmol/L, LDL-C < 4,1 mmol/L)

6. Postoperative complications, which were defined as “an undesirable and unintended result of the operation affecting the patient that occurs as a direct result of the operation.”

4.5 Statistical analysis

The recorded data were analyzed using the Jamovi statistical program, version 2.3.28.0. Quantitative data were expressed as mean ± standard deviation (SD), while qualitative data were presented as frequency and percentage.

The paired sample t-test of significance was used when comparing related samples. Categorical variables were compared for independent samples using the chi-square test. The confidence interval was set at 95%, and the accepted margin of error was 5%. A P-value < 0.05 was considered statistically significant.

5 Results

5.1 Patients' characteristics

During the study period, 66 patients underwent laparoscopic SASI bypass, and 59 patients (89.4%) with completed follow-up (12 months) were included in the study. The mean age was 44.8 ± 9.53 years and the mean BMI was 47.62 ± 8.9 kg/m2; 27 of them (45.8%) had Type 2 Diabetes Mellitus. Patient demographics and preoperative data are summarized in table 5.1.

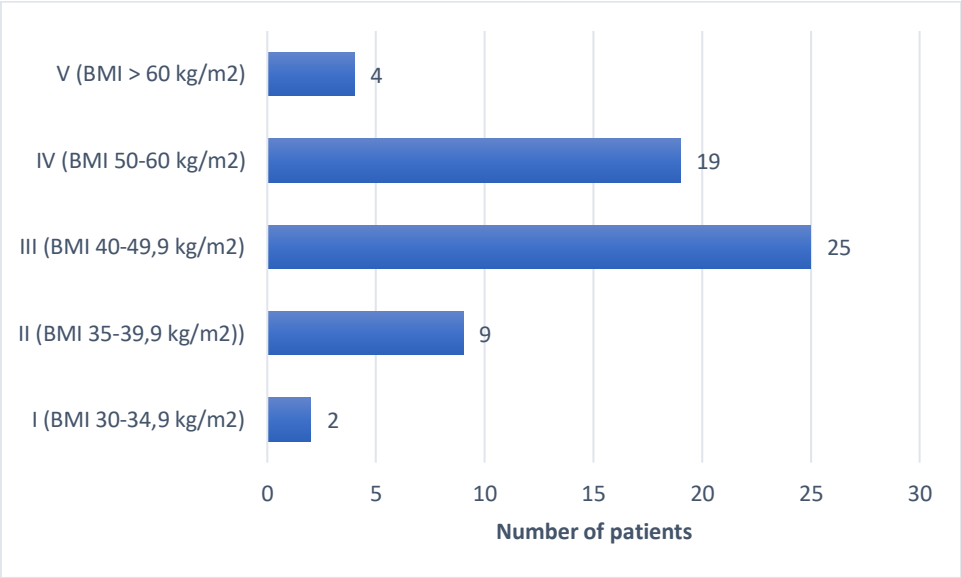
Table 5.1. Preoperative data (n=59)

Gender	
Female	44 (74.6%)
Male	15 (25.4%)
Age (years)	
Range	24-67
Mean ± SD	44.8±9.53
Weight (kg)	
Range	89-207
Mean ± SD	132.95±26.7
BMI (kg/m2)	
Range	33.4-65.3
Mean ± SD	47.62±8.9
FBG	8.39±3.78
HbA1c	7.12±2.03
Pre-diabetes	7(11.9)
T2DM	27(45.8)
Hypertention	54(91.5)
Dyslipidemia	39(66.1%)

BMI body mass index; T2DM type 2 diabetes mellitus;
FBG fasting blood glucose; HBA1C hemoglobin A1C

Mean preopertative BMI was 47.62±8.9 kg/m2, ranging from 33.4 kg/m2 to 65.3 kg/m2. Based on BMI classification, 2 patients had class I obesity, 9 patients had class II obesity, 25 patients had class III obesity, 19 patients had class IV obesity and 4 patients had class V obesity (figure 5.1).

Fig. 5.1 Class of obesity: BMI distribution before the surgery



The length of the common channel, counted from the ileocecal valve, was 250 cm in 30 patients and 350 cm in 29 patients.

5.2 Weight loss

1 year after SASI bypass a significant reduction in BMI was observed (from 47.60±8.09 to 30.08±5.42; $p < 0.001$).

Table 5.2 Weight loss 1 year after SASI bypass

	Preoperative	Postoperative	p-value
Mean body mass index (kg/m2)	47.60±8.09	30.08±5.42	<0.001
Mean body weight (kg)	132.95±26.72	84.05±17.18	<0.001
Total weight loss. %		36.00±10.3	
Excess weight loss. %		79.80±21.8	

The %TWL was 36.00±10.3 (range, 20-59) and the %EWL was 79.80±21.8 (range, 41.13-141.50). Similarly, preoperative body weight was also significantly decreased at 1 year of follow-up (from 132.95±26.72 kg to 84.05±17.18 kg) (Table 5.2).

5.3 Improvement in Comorbidities

All patients with Type 2 Diabetes Mellitus and prediabetes achieved remission within a year. Additionally, 24 (85.7%) of 28 patients with hyperlipidemia 46 (85.2%) of 54 patients with hypertension, achieved remission following the SASI bypass. Improvements in obesity-related comorbidities were all statistically significant as shown in Table 5.3

Table 5.3 Improvement in obesity related comorbidities 1 year after SASI bypass

Comorbidities	Preoperative (n)	Postoperative (n)	Remission (n, %)	p-value
Prediabetes	7	0	7(100%)	<0.001
Type 2 diabetes mellitus	27	0	27(100%)	<0.001
Dyslipidemia	28	4	24(85.7%)	<0.001
Hypertension	54	8	46(85.2%)	<0.001

5.4 Changes in laboratory parameters

The observed significant decrease in FBG, HbA1c, Cholesterol, LDL, TG levels confirmed positive metabolic changes following SASI bypass. (Table 5.4)

Changes in laboratory parameters reflecting the nutritional status at 1 year after SASI bypass included a significant decrease in serum protein levels from 74.57±4.95 g/L to 68.04±6.76 g/L ($p < 0.001$), a significant decrease in serum albumin levels from 44.85±4.39 g/L to 42.94±4.74 g/L ($p = 0.009$), a significant decrease in hemoglobin levels from 143.71±14.86 g/L to 135.63±13.58 g/L ($p < 0.001$). Significant increase in calcium level (p 0.019) may be explained by postoperative vitamin and mineral supplementation. (Table 5.4)

Table 5.4 Changes in laboratory parameters 1 year after SASI bypass

Parameter	Preoperative	Postoperative	p-value
FBG, mmol/L	8.39±3.78	5.14±0.62	<0.001
HbA1c, %	7.12±2.03	5.09±0.58	<0.001
Cholesterol, mmol/L	5.54±1.05	4.19±0.93	<0.001
LDL, mmol/L	3.57±1.03	2.60±0.84	<0.001
HDL, mmol/L	1.20±0.26	1.18±0.33	0.743
TG, mmol/L	2.27±1.57	1.16±0.48	<0.001
Protein, g/L	74.57±4.95	68.04±6.76	<0.001
Albumin, g/L	44.85±4.39	42.94±4.74	0.009
Hemoglobin, g/L	143.71±14.86	135.63±13.58	<0.001
Iron, µmol/L	15.33±5.68	16.09±5.12	0.424
Calcium mmol/L	1.19±0.51	1.31±0.49	0.019

FBG fasting blood glucose; HBA1C hemoglobin A1C, LDL low-density lipoprotein, HDL high-density lipoprotein, TG triglycerides

5.5 Complications

There were 3 early postoperative complications (5.08%), two cases of postoperative bleeding and one case of rhabdomyolysis. One patient died eight months after the surgery, with postmortem diagnosis revealing alcoholic cirrhosis.

Regarding late complications, hypoproteinemia manifested in six cases (10.16%), exclusively in patients with a 250 cm efferent limb. Revisional surgery was undertaken in three cases, involving modification of the common limb length from 250 cm to 350 cm in two patients. In one case with persistent refractory hypoproteinemia, the bypass was restored to normal anatomy.

5.6 Subgroup analysis according to the efferent limb length

To estimate the role of efferent limb length on SASI bypass outcomes, results of surgery with different length of efferent limb were compared.

Table 5.5 Impact of various efferent limb length on SASI bypass outcomes

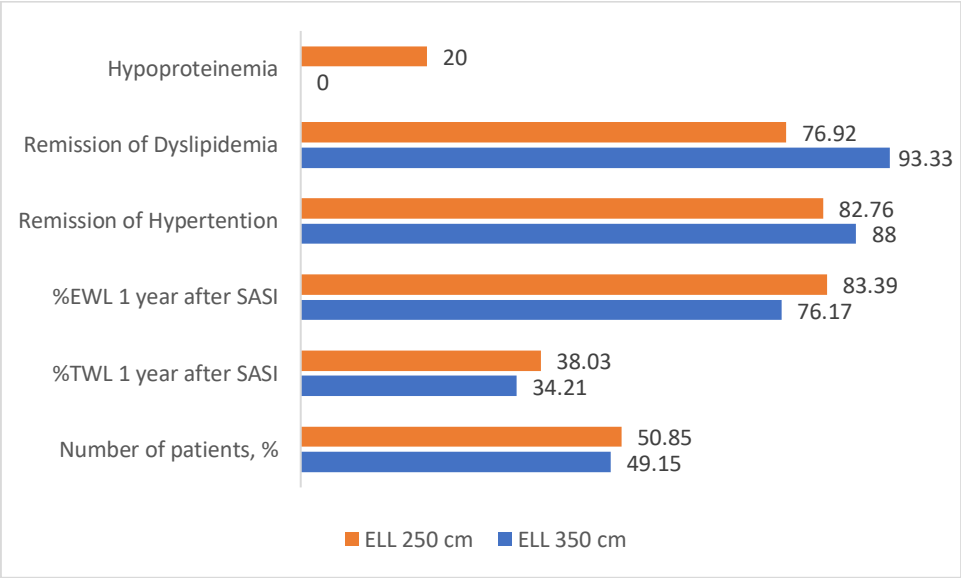
Parameter	ELL 250 cm	ELL 350 cm	P
Number of patients	30	29	
BMI 1 year after SASI, kg/m2	29.4±5.3	30.8±5.52	0.317
%TWL 1 year after SASI	38.03±11.85	34.21±8.29	0.157
%EWL 1 year after SASI	83.39±24.24	76.17±18.57	0.206
Remission of Hypertention	24/29 (82.76%)	22/25 (88%)	0.589
Remission of Dyslipidemia	10/13 (76.92%)	14/15 (93.33%)	0.216
Hypoproteinemia	6/30(20%)	0/29(0%)	0.012
FBG 1 year after SASI, mmol/L	5.11±0.7	5.17±0.52	0.711
HbA1c 1 year after SASI, %	5.05±0.64	5.1±0.29	0.807
Hemoglobin 1 year after SASI, g/L	134.31±15.5	137.18±11	0.471
Iron 1 year after SASI, µmol/L	16.74±5.48	15.56±5.52	0.479
Calcium 1 year after SASI, mmol/L	1.33±0.51	1.28±0.42	0.571

ELL - efferent limb length,
BMI body mass index, %TWL% of total weight loss, %EWL % of excess weight loss, FBG fasting blood glucose; HBA1C hemoglobin A1C.

The common limb length was 250 cm in 30 patients and 350 cm in 29 patients.

A longer common limb was associated with a significantly lower number of cases of hypoproteinemia (p = 0.012). However, there was no significant association between efferent limb length and other parameters, including BMI, %TWL, %EWL, % remission in comorbidities, and nutritional status (Table 5.5, Fig. 5.2).

Fig. 5.2 Outcomes of SASI bypass with efferent limb 250 cm versus 350 cm.



6 Discussion:

6.1 Main findings

Certainly, with the diverse array of bariatric surgery procedures available, selecting the most suitable one can be a challenging decision. Each procedure comes with its own advantages and considerations, making it crucial for healthcare professionals to carefully evaluate and choose the approach that aligns best with individual health needs.

SASI bypass is a novel bariatric procedure that is based on bipartition principle.
The reason for modifying SG with TB into SASI bypass was to simplify the procedure and to decrease the potential complication rate. Reducing the number of intestinal anastomoses is associated with less probability of postoperative leaks, anastomotic strictures and operative time.
After this operation duodenum and biliary tree keep their availability for endoscopic inspection. Moreover, if it is necessary, bypass may be reversed to the normal anatomy.

Ideally, this operation is designed to avoid excessive restriction or malabsorption, considering its anatomical features. The bipartition principle specifically influences alterations in the levels of intestinal hormones. This approach aims to achieve metabolic effects without compromising essential digestive functions. After the sleeve gastrectomy distension signals during meal are released earlier. At the period of fasting, less ghrelin is secreted because this orexigenic hormone is mostly produced by cells located in the gastric fundus, which is surgically removed. The gastro-ileal bypass provides rapid entrance of undigested chyme into the distal intestine, causing a more effective secretion of GLP-1 and PYY. These hormones reduce the rate of gastric emptying (making the stomach functionally even smaller), improve insulin secretion, and promote central satiety.

Our study confirmed that SASI bypass is highly effective in treating both obesity and its complications, The %EWL reached 79.8%, and the remarkable impact of

the SASI bypass on the glycemic control in diabetic patients was approved in our study, with remission rates 100%.

At the same time, the double-outlet for the gastric content is not a guarantee for the absence of severe malnutrition; in our study 6 patients with 250 cm efferent limb length experienced this complication.
Moreover, the presence of a double-outlet for the gastric content may be a factor affecting the reproducibility of the SASI bypass result. The variability of the percentage of gastric content passing through the gastro-ileal anastomosis may pose challenges in standardizing postoperative care. Food distribution may be unpredictable, influenced by multiple factors, such as outlet spacing, diameter ratio, pressure, content velocity, density, frictional forces, and the added impact of hormonal, behavioral, and neurological factors.

The final result of SASI bypass, including weight loss and metabolic effect, as well as developing of complications, may depend on technical aspects of this type of surgery, i.e., the efferent limb length and the diameter of gastro-ileal anastomosis.
Therefore, it is crucial to find the best decision and develop a unified approach to count on stable reproducible results.
Besides, preoperative patient counseling regarding the need for long-term follow-up, vitamin supplementation, and frequent laboratory assessment is important in order to avoid late presentation with severe malnutrition.

6.2 Limitations of the study

Limitations of the present study include its retrospective nature, small sample size, gender imbalance (74,6% were females) and the lack of a control group.
Another limitation of this study was the short follow-up of 12 months. Longer follow-up is needed to ascertain the absence of significant weight regain, relapse of the comorbid conditions, or significant nutritional deficiencies.
Lastly, other comorbidities, i.e. GERD (Gastroesophageal reflux disease), OSA (obstructive sleep apnea), as well as nutritional parameters (vitamin D, zinc, vitamin B1, B6, and B12) were not assessed.

6.3 Conclusion

SASI bypass is a novel operation with promising bariatric and metabolic effects. It is based on digestive adaptation principles and combines moderate restriction with early nutritive stimulation of the distal gut, modulating the neuroendocrine control of hunger and satiety.

According to our study, the lengthening of efferent limb up to 350 cm can prevent hypoproteinemia without compromising weight loss.

Further research, standardization, and long-term assessments to ascertain the role of SASI bypass in comparison to other bariatric procedures are needed.

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