

Obesity, Type 2 Diabetes, and the Metabolic Syndrome



Pathophysiologic Relationships and Guidelines for Surgical Intervention

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KEYWORDS

- Obesity • Metabolic syndrome • Diabetes • Bariatric metabolic surgery
- Insulin resistance • Gut • Microbiota

KEY POINTS

- Visceral obesity is associated with systemic low-grade inflammation leading to insulin resistance, β -cell dysfunction, and cardiometabolic diseases.
- The gastrointestinal tract is a key organ in metabolic regulation; hence, it is a biologically rational target for interventions aimed at treating metabolic syndrome, obesity, and type 2 diabetes (ie, metabolic surgery).
- Recent randomized clinical trials show that bariatric/metabolic surgery causes greater improvement of type 2 diabetes and reduction of cardiovascular risk compared with life-style modification and medical therapies.
- Based on such clinical and mechanistic evidence, several international professional organizations and government agencies have recently suggested expanding the indications for bariatric/metabolic surgery to include patients with inadequately controlled type 2 diabetes and a body mass index as low as 30 kg/m² and 27.5 kg/m² for Asians.

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INTRODUCTION

Obesity represents one of the primary causes of preventable deaths. In 2014, an estimated 1.9 billion adults were considered overweight and more than 600 million were obese, translating to 13% of the worldwide adult population.^{1,2} Also, the prevalence of morbid obesity (defined by a body mass index [BMI] >40 kg/m²) has almost doubled since 1980.¹ Such increase in the prevalence of obesity and morbid obesity has been related to a variety of factors including sedentary lifestyle, disproportionate caloric intake, stress, socioeconomic status, in addition to ethnicity and genetic susceptibility. Obese men and women are at significantly higher risk of developing type 2 diabetes mellitus (T2DM).^{3,4} In fact, the prevalence of T2DM has increased in parallel with the augmented prevalence of obesity. Currently, T2DM affects about 285 million people worldwide, a number predicted to almost double by 2030.⁵

The term “metabolic syndrome” (MS) is generally used to indicate the cluster of central obesity, insulin resistance (IR), hypertension, and hyperlipidemia. Metabolic syndrome results in a greater risk of developing T2DM and cardiovascular disease, 2 of the principal causes of death worldwide.⁶

Bariatric surgery causes significant and sustained weight loss and can considerably reduce IR, with dramatic clinical improvement or remission of insulin-resistant states (ie, dyslipidemia, hypertension, hyperuricemia, sleep apnea). Experimental evidence from animals shows that the effects of bariatric surgery on insulin sensitivity and glucose homeostasis are not just the consequence of mechanical reduction of food intake or energy absorption but derive from a variety of physiologic mechanisms, including changes in gut hormones, biliary acids metabolism, nutrient sensing, and microbiota.⁷

This knowledge corroborates evidence of a critical role of the gut in glucose and energy homeostasis and supports consideration of the gastrointestinal (GI) tract as a rational biological target for interventions aimed at treating obesity, diabetes, and metabolic disorders.⁸ Recent randomized clinical trials show that bariatric surgery results in better control of T2DM and greater reduction of cardiovascular risk factors compared with a variety of lifestyle interventions and medical therapies.^{9–12} Based on such mounting mechanistic and clinical evidence, conventional bariatric procedures are now increasingly being proposed not only as mere surgical management of obesity but also as a valuable approach to intentionally treat T2DM—a new concept and practice referred to as “metabolic surgery.”^{13–15}

Obesity and the Adipose Tissue

Obesity has become a pandemic and has received increasing attention over the past decades for the implications it carries in the development of numerous chronic diseases. In the last 30 years, the average BMI has increased at a rate of 0.4 kg/m² per decade worldwide.¹⁶ Among high-income countries, the United States has the highest prevalence of obesity, with one third of the population having a BMI of 30 or greater.¹⁷ Even though the prevalence of obesity in the United States tended to stabilize after 2005, the prevalence of severe (BMI >35 kg/m²) and morbid (BMI >40 kg/m²) obesity has continued to increase. Between 1986 and 2000, the prevalence of subjects with a BMI of 40 or greater quadrupled and that of subjects with a BMI of 50 or greater quintupled.^{17,18}

Obesity is a condition characterized by an excess of body adiposity and for practical reasons is commonly measured by BMI, an expression of body weight as a nonlinear function of height. A BMI ≥ 30 kg/m² indicates the presence of obesity; when BMI exceeds 40 kg/m², the subject is regarded as morbidly obese.¹⁹

However, using BMI as a unit of measure assumes that adipose tissue has an even distribution throughout the body, because it does not take into account the diverse topographic deposition of body fat among individuals. Thus, BMI is not a measure of dysfunctional adipose tissue nor an accurate metrics of metabolic disease. In fact, an excessive and preferential accumulation of fat in visceral depots may not be necessarily associated with a high BMI; nonetheless, it strongly correlates with those metabolic disturbances that increase the risk of developing cardiovascular disease.²⁰ A significant number of individuals present hyperglycemia, hyperinsulinemia, IR, hyperlipidemia, and hypertension despite a lean body type and a normal BMI, a phenotype often referred to as “metabolically obese but normal weight subjects.”^{21,22} Conversely, many persons categorized as obese by BMI lack all the components of MS and display average risk of developing cardiovascular disease compared with the general population; this group of subjects is referred to as “metabolically healthy obese.”²³

It has been shown that subcutaneous adipose tissue (SAT) distribution, common in women, is related to metabolic protection, conversely to central or intra-abdominal obesity, typical of men, which frequently accompanies MS.^{24,25} In addition, ectopic fat accumulation in organs such as liver, skeletal muscles, heart, kidneys, pancreas is associated with metabolic comorbidities.²⁶ In consideration of the importance of fat distribution in metabolic disease, waist circumference (WC) is widely considered a more reliable predictor of cardiometabolic risk than BMI. A WC ≥ 88 cm in women and WC ≥ 102 cm in men is considered an independent risk factor for developing cardiovascular disease and atherogenic dyslipidemia, and a rough measure of the degree of IR.¹⁹

The exact reasons behind the differential deposition of adipose tissue in the various regions of the body are unclear; both modifiable factors (eg, physical activity, nutritional status, growth hormone, glucocorticoids, sex steroids) and nonmodifiable factors (such as gender, age, ethnicity, and genetic susceptibility) seem to play a role.¹⁹

The adipose tissue exerts metabolic and endocrine functions and is characterized by great pliability and expandability. Whereas adipocytes in the subcutaneous tissue can become both hyperplastic and hypertrophic, visceral adipose tissue (VAT) appears to have a limited capacity of recruitment and differentiation of new adipose cells and is more prone to develop hypertrophic cells with impaired adipocyte function.²⁷ Such dysfunctional adipocytes cause altered secretion of adipocytokines (ie, adipokines) and an elevation of free fatty acids (FFAs) release into the circulation that ultimately leads to the onset of obesity-related IR, the common denominator of MS and other metabolic disorders.^{19,28,29}

Metabolic Syndrome: Definitions and Pathophysiologic Aspects

In the late 1970s, the term “metabolic syndrome” was proposed to identify a cluster of interrelated factors, comprising visceral obesity, IR, hypertension, and dyslipidemia, that were associated with an augmented risk of developing T2DM and cardiovascular disease.³⁰ In the 1980s, Reaven³¹ proposed that IR could be the primary defect of the syndrome, arguing that insulin-resistant subjects could develop MS even though they were not obese. The World Health Organization (WHO)¹ and the American Heart Association subsequently recognized MS³² as a distinct clinical entity with its own code (277.7) in the WHO’s ICD-9 classification. However, in the following years, other scientists and clinicians have challenged the idea of MS as a separate clinical entity. In 2012, a joint statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes was particularly critical of the idea of MS as a distinct clinical entity.³³ In particular, this statement argued that existing definitions

of MS are based on ambiguous or unclear criteria and that the cutoff points used to define abnormal levels of the individual components ignore the continuum in risk associated with glucose, blood pressure, and lipids levels. This statement also questioned the evidence that the syndrome as a whole adds to cardiovascular disease prediction beyond the contribution of the individual component risk factors.

Despite this, MS continues to be considered a distinct entity by many researchers that investigate the link between IR and metabolic disease, whereas clinical cardiologists rely on MS for their assessment of cardiometabolic morbidity and mortality in individual patients. One of the most commonly used definitions of MS was proposed in 2001 by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)³⁴ and includes criteria such as WC, triglycerides, high-density lipoprotein (HDL)-cholesterol, blood pressure, and fasting glycemia. The presence of abnormal levels of 3 of these 5 variables, listed in **Table 1**, is used for a diagnosis of MS.

The definition of MS by the International Diabetes Federation (IDF) slightly differs from the one reported because it recommends considering a different cutoff for WC in relation to the ethnicity of the individual; this is based on knowledge that persons of Asian descent can have abdominal obesity and an elevated risk for cardiovascular disease at lower BMI levels compared with individuals of other ethnicities.³⁵ Using the NCEP-ATP III definition, the prevalence of MS among US adults was estimated to range from 22%³⁶ to 34% and up to 39% when using the IDF criteria.³⁷

Prospective population studies showed that the relative risk for the development of atherosclerotic cardiovascular disease in patients with MS is twice as high as that of the general population; the risk of developing T2DM is 5-fold greater.^{38–44}

A diet rich in lipids and carbohydrates contributes to the emergence of 2 of the essential factors for the diagnosis of MS: visceral obesity and IR. The increased VAT contains hypertrophic, dysfunctional adipocytes at increased lipolytic activity; this can cause high release of FFAs in the splanchnic circulation, thus directly reaching the liver.⁴⁵ It is also thought that when peripheral adipocytes have surpassed their capacity and are no longer capable of storing triglycerides, these will be deposited in other tissues (mainly liver and skeletal muscle), favoring the establishment of peripheral and hepatic IR.

Table 1 Criteria for diagnosis of metabolic syndrome according to National Cholesterol Education Program–Third Adult Treatment Panel, International Diabetes Federation, World Health Organization			
	NCEP: ATP III	IDF Central Obesity (as WC Gender/Ethnicity- Specific) + 2 of the	WHO
Criteria	Three of the Following:	Following:	Hyperinsulinemia + 2 of the Following:
waist circumference (cm/inches)	>102/40 in men >88/35 in women	>94/37 in men >80/31.5 in women	>94/37 in men and/or BMI >30 kg/m ²
Triglycerides	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
Cholesterol-HDL	<40 mg/dL men <50 mg/dL women	<40 mg/dL men <50 mg/dL women	<35 mg/dL men <39 mg/dL women
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg	≥140/90 mm Hg
Fasting plasma glucose	≥110 mg/dL	FPG ≥5.6 mmol/L or T2DM	—
Microalbuminuria	—	—	>30 mg/g

The augmented flow of FFAs to the liver causes an increase in hepatic neoglucogenesis contributing to the development of hyperglycemia.^{46,47} In addition, in the presence of IR, high circulating levels of FFAs induce hepatic triglyceride synthesis leading to hypertriglyceridemia and overproduction of very low-density lipoproteins (LDL), rich in Apo B and triglycerides.⁴⁸ In the setting of hypertriglyceridemia, LDL and HDL undergo alterations of their composition. LDL triglyceride content increases at the expense of phospholipids, and esterified and nonesterified cholesterol. As a result, LDL particles become smaller in size and denser, possibly becoming more atherogenic. Similarly, the cholesterol portion of the HDL lipoprotein core is reduced with an inconstant increase in triglycerides, resulting once again in small, dense particles that undergo a higher rate of clearance from the circulation.^{49–51} In fact, reduced serum levels of HDL, elevated triglycerides, and small, dense LDL represent the typical lipidic profile present in MS-related dyslipidemia.

Hypertension is one of the components of MS with the latest onset. Adipocytes are capable of producing several biologically active peptides, including angiotensinogen, angiotensin converting enzyme, and cathepsins. An expanded adipose tissue could result in increased production of angiotensinogen, which in turn may lead to the onset of obesity-associated hypertension. Moreover, IR might also contribute to the development of hypertension because of reduced stimulation of nitric oxide, causing a decreased vasodilation.^{52,53}

LINKING OBESITY TYPE 2 DIABETES MELLITUS AND METABOLIC SYNDROME: PATHOPHYSIOLOGIC EVIDENCE

Obesity, T2DM, and cardiometabolic disorders are associated with IR.³¹ Nevertheless, most obese subjects with IR do not develop hyperglycemia. Physiologically, the pancreatic islet β cells present adaptative features allowing an increased insulin release to overcome IR and maintain normal glucose tolerance. However in patients with T2DM, IR is not completely compensated by β cells.^{54,55} Herein, the principal pathophysiologic mechanisms associated with obesity, T2DM, and other metabolic disorders are presented.

Insulin Resistance

IR is considered the most important pathophysiologic aspect linking obesity and cardiometabolic diseases.^{31,56} IR is an impairment of insulin action on insulin-sensitive tissues characterized by a decreased glucose access in muscles and an increased neoglucogenesis in the liver, resulting in fasting as well as postprandial hyperglycemia. IR has systemic impact causing arterial endothelial dysfunction, atherosclerosis, increased lipolysis, sarcopenia, decreased bone mass, and β -cell mass.^{27,57}

Pancreatic β -Cell Dysfunction and Defective Insulin Secretion

Studies have shown that the basal insulin secretion rate and the insulin output in response to an oral glucose tolerance test grow in a linear fashion as BMI increases.⁵⁸ A hyperbolic correlation instead has been found between β -cell function and insulin sensitivity.⁵⁹ Hence, on a background of IR, the β cell must enhance its insulin release in order to compensate and maintain a state of euglycemia.⁶⁰

β -Cell failure is a requisite for the development of T2DM, whereas skeletal muscle IR is evident decades before β -cell failure and overt hyperglycemia occur.^{61,62} High-risk individuals with IR who are prone to develop diabetes show a progressively reduced β -cell function over time, whereas “nonprogressors” can maintain increased insulin secretion that compensates for the worsening insulin sensitivity.⁶²

This capacity of β cells to adjust their secretive function to the grade of insulin sensitivity is known as disposition index (DI). DI is calculated as the product of β -cell sensitivity multiplied by the insulin sensitivity. The disposition curve typically follows a hyperbolic function⁵⁹; this implies that the product of insulin sensitivity and secretion should yield a constant for a given degree of glucose tolerance and thereby provide a measure of β -cell function.

Progression from normal glucose tolerance to impaired fasting glycemia, impaired glucose tolerance, and finally, T2DM, is likely the result of various contributing factors, including high-caloric diet, lack of physical activity, and genetic predisposition. In a first compensatory phase, the insulin-resistant state causes an increase in total insulin secretion rate, determining hyperinsulinemia.⁶³ In this stage, greater insulin secretion is mainly due to β -cell hyperplasia and to a lesser extent hypertrophy, globally contributing to an increased islet mass, as found in human autopsies.^{63–65} Subsequently, as a consequence of increasing glucose levels (ie, glucotoxicity hypothesis), a loss of acute glucose-stimulated insulin secretion develops, resulting in the inability to promptly respond to glycemic increments. The prolonged exposure to hyperglycemia and increased circulating FFAs favor a constant, low-grade inflammation, leading to stress of endoplasmic reticulum, altered function of mitochondria, increased release of reactive oxygen species, and ultimately, oxidative stress in the β cell. Oxidative stress in the β cell in turn is responsible for changes observed in β -cell phenotype, differentiation, and gene expression, which might be responsible for such loss of acute secretory action.^{66–69} Moreover, a higher insulin request, caused by a state of IR, conduces to increase cosecretion of insulin and islet amyloid polypeptide. The presence of amyloid in high concentrations is toxic and contributes to inducing β -cell apoptosis.^{70,71} Chronic hyperglycemia and worsening of IR cause a critical decline in β -cell mass, ultimately leading to overt diabetes.⁷¹

Inside the β cells, insulin granules ready for the secretion are docked to the cell membrane; when glucose binds to the glucose transporter isoform GLUT2, they fuse with the membrane and secrete packages of insulin. Diabetic subjects lose the capacity to promptly secrete such already synthesized insulin granules and therefore characteristically lack the first phase of insulin secretion in response to a glucose load; they also usually show an exaggerated second phase of insulin secretion. Although loss of first-phase insulin secretion was thought to be an irreversible defect, bariatric metabolic surgery (BMS) has been shown to promptly restore the first phase of insulin secretion within 1 month of the operation, suggesting that such defect is instead a reversible phenomenon rather than a structural defect of the β cell.^{72,73}

The Adipose Tissue in Metabolic Diseases

Adipose tissue affects metabolism by releasing FFAs and adipocytokines. The over-secretion of some of these cytokines may act as a potential mediator of inflammation leading to IR.

Factors with deleterious effects on metabolism

Free fatty acids Increased FFAs levels are observed in human obesity and T2DM and are strongly correlated with the level of IR.^{54,74} FFAs have anti-insulin action and are produced during the metabolism of lipids. When reaching insulin-sensitive tissues, increased FFAs levels lead to increased liver glucose production and muscular lipid storage, leading to IR state in T2DM patients.^{74,75} In obesity, which is considered a low-grade inflammatory state, increased circulating levels of FFAs appear to be positively correlated with plasma levels of pro-inflammatory cytokines, which are known to be associated with IR and T2DM.⁷⁴

Proinflammatory adipocytokines

Obesity and T2DM are associated with the overproduction of proinflammatory cytokines such as Tumor necrosis factor- α (TNF- α) Interleukin-6 (IL-6).⁷⁶ These cytokines are produced by the adipocytes among many other cell types and inhibit insuling signaling which in turn promote IR. TNF- α may also have direct deleterious effect on Beta-cells by inhibiting insulin secretion and promoting B-cell apoptosis as observed in-vitro.^{76,77} An associaton has been demonstrated between IL-6 signaling pathway in the adipose tissue and IR, with a positive correlation between IL-6 serum levels and IR levels.^{77,78} Other cytokines such as IL-1 beta, Resistin, Retinol binding Protein-4, Visfatin, Plasminogen Activator-1 (PAI-1), Monocyte Chemoattractant Protein-1, fibrinogen and angiotensin are increasingly produced by the adipose tissue in obesity and T2DM. These cytokines contribute to inflammation, lipid accumulation and participate to the development of endothelial dysfunctions and therefore myocardial infarction, stroke and cardiomyopathy.⁷⁶

Protective adipocyte-derived factors

Leptin is an adipocytokine that reduces appetite and IR along with improvement of metabolic disturbances associated with T2DM. Increase in tissue sensitivity of insulin by leptin may be due to its action on oxidation of FFAs, leading to decreased FFAs in the circulation.⁷⁸ Unlike other adipocytokines, serum levels of adiponectin are decreased in obesity and T2DM. This cytokine has insulin-sensitizing and antiatherogenic actions. In human obesity and T2DM, this adipocytokine has been shown to stimulate FFAs oxidation, and therefore decrease plasma FFAs oxidation, reduce lipid accumulation and increase insulin sensitivity. Adiponectin reduces endothelial dysfunction by increasing nitric-oxide synthesis and decreasing the expression of adhesion molecules and also prevents atherosclerosis by inhibiting LDL oxidation.^{79,80} Other adipocytokines, such as Apelin, appear to have antiobesity and antidiabetic actions, because of its possible positive role in energy metabolism and insulin sensitivity.⁷⁸

Body fat distribution

Another critical factor involved in IR and metabolic diseases is body fat distribution. All definitions of MS include a measure of WC (**Table 1**). Obesity is often associated with IR; however, insulin sensitivity varies markedly in lean individuals and in obese subjects because of differences in body fat distribution.¹⁹ Lean individuals with a more peripheral type of fat distribution (ie, SAT) are more insulin sensitive than obese subjects who have predominantly central fat distribution (ie, VAT).⁵⁴ VAT is more resistant to the antilipolytic action of insulin than SAT, which may explain the association between VAT, IR, and T2DM.^{81,82}

Tissular and Systemic Inflammation

Obesity, T2DM, and MS are associated with low-grade systemic^{83,84} and tissular inflammation in the adipose tissue, the liver, the pancreas, and the intestine.^{85–87} Infiltration of immune cells, including macrophages, mast cells, and lymphocytes, was found in these tissues with a modification in cell population into a proinflammatory profile. These cells produce proinflammatory cytokines that interfere with insulin signaling in insulin-sensitive tissues, cause β -cell dysfunction, and consequently, insulin deficiency. Obese and T2DM patients show increased white blood cell counts, plasma levels of coagulation factors (fibrinogen and PAI-1), C-reactive protein (CRP), serum amyloid A, and proinflammatory cytokines (TNF- α , IL-1 β , and IL-6).⁷⁸ The overexpression of these cytokines, and especially CRP, contribute to systemic inflammation and lipid accumulation, which in turn have deleterious effects on blood vessels, leading to

endothelial dysfunction, myocardial infarction, cardiomyopathy, and death in the general population as well as in patients presenting with MS.⁷⁹ These markers are strongly associated with central adiposity,⁸⁸ IR, and MS.⁸⁷

Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea (OSA) is linked to obesity and affects 15% of men and 6% of women.⁸⁹ OSA is characterized by airway obstruction during sleep, responsible for chronic hypoxia; this leads to the activation of the hypothalamic-pituitary-adrenal axis, causing oxidative stress, systemic and tissular inflammation (adipose tissue and liver), and increased secretion of proinflammatory adipocytokines (Resistin, TNF- α , IL-6, plasminogen activator-1). These disturbances result in decreased insulin sensitivity and pancreatic β -cell dysfunction. OSA is known as a critical independent risk factor of cardiovascular disease, hypertension, MS, and T2DM.^{90,91}

Sympathetic Nervous System Overdrive

Recent evidence from experimental and human studies has linked obesity, T2DM, and other metabolic comorbidities to a chronic activation of sympathetic nervous system (SNS), possibly caused by different types of stimuli (ie, food intake, hyperinsulinemia, glucose consumption, increased adiposity, and hyperleptinemia; hypothalamic-pituitary-adrenal axis activation).⁹² Chronic activation of SNS results in increased adrenergic outflow with high levels of circulating catecholamines and glucocorticoids, leading to IR. SNS activation increases glucose release from the liver, reduces insulin, increases glucagon release by the pancreas, and increases lipolysis in the adipose tissue.⁹² These effects are associated with vasoconstriction in peripheral arteries, which also results in impaired glucose uptake in skeletal muscle.⁹² The effects of chronic SNS activation can therefore predispose to IR, hypertension, renal disease, and cardiac dysfunctions (ie, diastolic dysfunction, left ventricular hypertrophy).⁹³

THE GUT AS A BIOLOGICALLY RATIONAL TARGET FOR THE TREATMENT OF CARDIOMETABOLIC DISEASES

Mechanisms Linking the Gut to Cardiometabolic Diseases

A growing body of evidence has accumulated, especially in the last decade, supporting a role of the gut in the physiology of metabolic regulation and in the pathophysiology of cardiometabolic disorders. This evidence comes from physiologic studies as well as from investigations regarding the mechanisms of weight loss and glycemic improvement after bariatric/metabolic surgery. Here the role of various aspects of intestinal physiology in metabolic regulation and metabolic disease is briefly reviewed.

Gut microbiota

The human gut microbiota (GM) is a complex entity composed of more than 1000 species of comensal microorganisms.⁹⁴ GM is present across the GI tract with greater concentrations in the ileum and colon. In physiologic conditions, the GM contributes to intestinal system maturation, host defense against pathogens, degradation of non-digestible polysaccharides and plays an important role in body fat distribution and control of energy homeostasis.⁹⁵ The GM is influenced by diet, lifestyle, physical exercise, antibiotics, and genetic background.⁹⁶ GM modulates energy harvesting from dietary fibers, fat storage, lipopolysaccharides (LPS) content, and the production of short-chain fatty acids which in turn regulate host food intake, insulin signaling and

generate low-grade inflammation.^{88,97–99} Interestingly, germ-free mice appear to be protected from high-fat diet (HFD)-induced obesity and metabolic alterations.¹⁰⁰ In addition, mice transplanted with GM isolated from obese donors develop increased body fat content and IR.^{101,102} Metformin administration in mice is associated with an increase of *Akkermansia muciniphila*, a mucin-degrading bacteria known to positively impact obesity and diabetes,¹⁰³ resulting in improved weight loss, glycemic control, and reduced systemic inflammation.^{104,105} In humans, obesity and T2DM have been associated with altered GM composition, reduced diversity, and gene richness.^{106,107} Recently, metabolomics studies of human plasma samples allowed the identification of GM products, such as trimethylamine-*N*-oxide, involved in atherogenesis and therefore linked to cardiovascular risk.¹⁰⁸

Alterations of intestinal permeability and metabolic endotoxemia

Intestinal permeability, a feature of the intestinal barrier, regulates the passage of molecules from the lumen into the interstitium. This function is finely regulated by GM and other local factors.¹⁰⁹ In rodent models of diet-induced obesity (ie, HFD), modifications of GM are associated with altered intestinal permeability characterized by a reduced expression of tight junction proteins (ie, zonula occludens-1, occludin, claudins) in the intestinal epithelial cells and an increase in the passage of nutrients and/or bacterial antigens/components (ie, LPS) responsible for systemic inflammation (ie, endotoxemia) and IR.¹¹⁰ Consistent with this model, GM composition modulation induced by antibiotics or prebiotics/probiotics in rodents improves gut permeability and reduces metabolic endotoxemia and glucose intolerance.¹⁰³ However, despite encouraging results¹¹¹ intestinal permeability alterations and its role in the crosstalk between GM and inflammation at systemic and tissular levels are still poorly characterized in human obesity and metabolic diseases.¹¹¹

Gut Adaptation to Bariatric/Metabolic Surgery

BMS is currently the most effective treatment for severe obesity and T2DM, providing sustained weight loss as well as reduction and prevention of obesity-related cardio-metabolic comorbidities.^{9,15} Given its dramatic clinical effectiveness, BMS provides an opportunity to better understand the role of the gut in physiology and disease. In addition to weight loss, BMS can cause changes in various mechanisms of GI physiology, including changes in satiety-promoting gut hormones (ie, glucose-dependent insulinotropic peptide, glucagon-like peptide 1 [GLP-1], peptide YY, and Oxyntomodulin) and increased gastric emptying. Certain bariatric/metabolic procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) cause a shift in bile acids (BAs) metabolism composition, bile flow, and increased BAs signaling through the BAs nuclear receptor Farnesoid X (FXR). GI modifications imposed by certain procedures, particularly those involving a re-routing of the small intestine (ie, RYGB, duodenal-jejunal bypass, DJB), can cause changes in microbiota composition and nutrient sensing; all of these effects appear to be involved in the metabolic benefits of BMS.^{112–114}

Gastrointestinal hormones

RYGB and SG are characterized by an excessive postprandial response of the enteroendocrine intestinal L cells responsible for a rapid increase in postprandial GI hormones.¹¹⁵ The increase in GLP-1 causes a rapid postprandial “incretin effect,” increasing insulin secretion. This mechanism is thought to be at least in part responsible for the improvement of glucose tolerance observed after these procedures.¹¹⁶ However, the underlying mechanisms supporting this phenomenon remain unclear

and debated. Specifically, it is unclear whether the increased secretion and/or release of hormones from intestinal L cells after GI surgery is due to changes in the characteristics (ie, number, functions) of the enteroendocrine cell population,¹¹⁷ due to stimulation of cells located in the distal small bowel by relatively undigested nutrients (due to a shortcut or expedited gastric emptying and intestinal transit), or if it is secondary to the lack of physiologic gastric modulation on L-cell activity.¹¹⁸ The role of GLP-1 in the antidiabetic effects of RYGB and SG also has been recently called into question by experiments showing that the improvement of glucose metabolism after surgery is substantially preserved in humans after treatment with GLP-1 receptor (GLP-1-R) agonist¹¹⁹ as well as in GLP-1R knockout mice models.¹²⁰ Ghrelin, a hunger-promoting hormone, is mostly produced in the stomach. Although no specific pattern was observed regarding Ghrelin serum level changes following gastric banding, RYGB, and biliopancreatic diversion, serum levels appeared consistently reduced after SG.¹¹⁶

Bile acids

Beyond their role in the absorption of fat-soluble vitamins and dietary lipids, BAs are key regulators of glucose and lipid metabolism as well as energy expenditure thanks to the interaction with GM.⁷ The BAs are produced from cholesterol in the liver (primary BA). Primary BAs are transformed into secondary BAs by GM in the intestine; these are absorbed in the terminal ileum, returned to the liver, and are then secreted again into the bile (enterohepatic cycle). Through FXR, BAs stimulate postprandial ileal production of fibroblast growth factor 19, which inhibits hepatic expression of cholesterol 7 alpha hydroxylase 1 (CYP7A1), thus regulating the conversion of cholesterol into BAs.¹²¹ BAs exert positive effects on metabolism by interaction with FXR and the membrane BA receptor TGR5, which inhibits neoglucogenesis and promotes insulin signaling thus controlling glucose of glucose metabolism in the liver¹²² and stimulating the intestinal secretion of GLP-1.¹²³ Increased BA serum levels are observed after RYGB and SG, but not following gastric banding, suggesting that elevated serum BAs levels in procedures that modify GI anatomy could improve insulin sensitivity, incretin secretion, and postprandial glycemia. However, changes in BAs may only partly explain metabolic improvements after RYGB.^{7,122,124}

Gut microbiota

BMS induces modifications of microbiome ecology,¹²⁵ which could mediate the metabolic effects of surgery and contribute to modulation of fat mass deposition.¹¹⁴ Recent studies in mice revealed that transfer of the GM from RYGB-treated mice to germ-free mice was associated with significant weight loss, when compared with similar recipients receiving the GM from sham operated mice.¹²⁶ These findings support the notion that changes in the GM following RYGB could contribute to weight loss.

Intestinal remodeling

Jejunioleal bypass as well as RYGB are known to induce adaptive intestinal hyperplasia and hypertrophy of intestinal villi in humans.^{127–129} In rodents undergoing RYGB, the intestinal remodeling of the alimentary (Roux) limb was associated with a modification of the intestinal glucose metabolism characterized by an upregulation of the intestinal glucose transporter GLUT-1 and increased glucose disposal toward metabolic pathways involved in tissue growth.¹³⁰ Moreover, an increase in enteroendocrine cell morphology and number (L cells) has been recently characterized in rodent models of RYGB.^{131,132} These observations could contribute to the improvement in glucose

homeostasis observed after RYGB; however, the relevance of this mechanism for the clinical effects of RYGB in humans remains unclear.

Intestinal nutrient sensing

Recent studies have shown that nutrients activate sensing mechanisms in the duodenum, triggering a gut-brain-liver negative feedback mechanism that inhibits hepatic glucose production and food intake to maintain homeostasis.¹³³ Such nutrient sensing mechanism appears to be dysfunctional in diabetes and obesity, failing to lower food intake and glucose production. Interestingly, the jejunum appears to be able to recover nutrient sensing after DJB, with resulting inhibition of glucose production,¹³⁴ suggesting that enhancement of nutrient sensing might contribute to the glucose-lowering effects of GI bypass procedures.

Changes in food preference: the gut-brain axis

Bariatric procedures reduce food intake and change food choices and preferences. In a randomized trial comparing RYGB to vertical gastropasty, Olbers and colleagues¹³⁵ reported a significantly decreased consumption of sweeteners after RYGB, but also of fatty foods with increased fibers and vegetable consumption. Some patients experience after-ingestive disabling symptoms with sweets (ie, dumping syndrome) and fatty food and in turn adapt their eating behaviors, suggesting a beneficial switch in food preferences and choices after RYGB.¹³⁶ However even if encouraging functional brain imaging studies demonstrated an involvement of different cerebral pathways in the modification of food preferences observed after RYGB.^{136,137} However, the key players responsible for these modifications are unknown.

GUIDELINES FOR SURGICAL TREATMENT OF OBESITY AND DIABETES

The role of the GI tract in the digestion and absorption of nutrients supported the idea that modifications of gastric or intestinal anatomy could be used to reduce energy intake/absorption and, therefore, produce weight loss. In the 1950s, such a concept provided a biological rationale for the use of GI surgery as a weight loss therapy for patients with morbid obesity ("bariatric surgery"). Despite ample documentation of additional metabolic benefits, obesity remained the only indication for bariatric surgery for more than 5 decades. Coherently, clinical guidelines for bariatric surgery have been merely based on weight-centric criteria.

Over the last decade, however, the use of bariatric surgery as an intentional treatment of T2DM¹³⁸ has become increasingly popular in academic circles and in the media. This idea is based on consistent clinical observations of the dramatic improvement of hyperglycemia in patients with T2DM and on the experimental evidence that rearrangements of GI anatomy similar to those in some bariatric procedures directly and weight-independently affect glucose homeostasis.¹³⁹

Numerous recent randomized controlled trials (level 1 evidence) have shown superior glycemic control after bariatric/metabolic surgery than with conventional medical and lifestyle approaches for the treatment of obese patients with T2DM.^{10,12,140,141}

Further research on mechanisms of action of these procedures and the increasing recognition of the complex and crucial role of the gut in metabolism, as described above, provide a biological rationale for the use of GI-based interventions to treat T2DM.¹⁴² Such conceptual evolution is reflected in most recent guidelines by professional organizations and government agencies that recognize the role of surgery as a treatment of T2DM and advocate the use of disease-based criteria beyond just BMI. These guidelines are contributing to transforming a weight loss intervention (bariatric surgery) into a surgical practice shaped around the goal to improve metabolism and

reduce cardiometabolic risk. Such concept and practice is referred to as “metabolic surgery.”¹³

A summary of available guidelines for surgical treatment of obesity and T2DM is presented in **Table 2**.

A National Institutes of Health (NIH) Consensus conference in 1991 produced the first guidelines published in bariatric surgery. These BMI-based recommendations state that patients with BMI of 40 kg/m² or greater or BMI 35 kg/m² or greater with concomitant high-risk morbidities (eg, T2DM, OSA, obesity-related cardiomyopathy) may be considered candidates for bariatric surgery.⁸ In 2007, delegates from the first Diabetes Surgery Summit (DSS-I), an international consensus conference, recommended expanding the use and study of GI surgery to treat diabetes, including among only mildly obese persons. Specifically, the DSS-I recommended that “diabetes surgery” should be considered in diabetic, obese patients with BMI 35 kg/m² or greater and also in carefully selected candidates with BMI 30 to 35 kg/m² and poorly controlled T2DM by lifestyle and medical interventions. Importantly, the DSS-I encouraged

Table 2 According to all committees, bariatric surgery should be considered only after failure to lose weight through lifestyle modifications and weight loss programs			
Bariatric Surgery Guidelines	Eligible	Conditional Eligibility	Ethnicity
NIH (1991)	• BMI >40 kg/m ²	• BMI ≥35 kg/m ² + • Concomitant high-risk morbidities (eg, T2DM, severe OSA)	—
DSS-I (2007)	• BMI >35 kg/m ²	• BMI 30–35 kg/m ²	—
IDF (2011)	• BMI >40 kg/m ² or • BMI >35 kg/m ² and T2DM (HbA1c <7% of 53 mmol/mol) unresponsive to medical therapy	• BMI 30–35 kg/m ² + • Inadequately controlled T2DM by full conventional therapy (HbA1c <7.5% or 58 mmol/mol) or • Other weight-related comorbidities (eg, dyslipidemia, hypertension) possibly responsive to surgical treatment	• BMI lowered by 2.5 kg/m ² in Asian subjects
ADA (2014)	• BMI >40 kg/m ²	• BMI >35 kg/m ² if inadequate control of T2DM or other comorbidities difficult to control with lifestyle and pharmacologic therapy • Insufficient data are available to recommend surgery for BMI <35 kg/m ²	—
NICE (2014)	• BMI >35 kg/m ² and Tier 3 services ^a (or equivalent)	• BMI 30–35 kg/m ² + • Recent onset of T2DM and Tier 3 services (or equivalent)	• BMI lowered by according to ethnicity

^a Tier 3 service: a community/primary care–based multidisciplinary team to provide an intensive level of input to patients.

further studies on the role of surgery in diabetes care as an important research priority.¹⁴³ In the ensuing years, several randomized controlled trials have been launched in this area, and most major worldwide bariatric surgery societies have changed their names to include the word “metabolic.”

In 2009, the ADA for the first time introduced bariatric surgery in its Standards of Care for the treatment of T2DM, limiting its use, however, to patients with BMI > 35 kg/m², because of the lack of sufficient evidence in lower BMI patients.^{144,145} In 2011, a position statement by the IDF suggested expanding the indications for bariatric/metabolic surgery to include patients with inadequately controlled T2DM and a BMI as low as 30 kg/m², or down to 27.5 kg/m² for Asians.¹⁴⁶ More recently, in November 2014, the National Institute for Health and Care Excellence in the United Kingdom (NICE), amended its 2006 guidelines on obesity management, advising assessment for bariatric/metabolic surgery in patients with BMI as low as 30 kg/m² and recent onset of T2DM.¹⁴⁷

On the 28th to 30th of September 2015, the 2nd Diabetes Surgery Summit (DSS-II) was organized in partnership with leading international diabetes organizations and held in London, United Kingdom, in conjunction with the 3rd World Congress on Interventional Therapies for Type 2 Diabetes. The aim of the DSS-II was to review available evidence and develop global recommendations that introduce surgical therapies in a rational treatment algorithm for T2DM. The DSS-II expert committee included a large group of 47 international scholars, representing various medical specialties such as endocrinology/dialectology, internal medicine, cardiology, gastroenterology, primary care, nutrition, and surgery, including official representatives of partner diabetes organizations. A report with the recommendations and guidelines developed through the DSS-II is expected to be published in the spring of 2016.

SUMMARY

Cardiometabolic disorders are characterized by a complex pathophysiology and increased risk of mortality. Experimental evidence shows that some rearrangements of GI anatomy can directly affect glucose homeostasis, insulin sensitivity, and inflammation, supporting the idea that the GI tract is a biologically rational target for interventions aimed at correcting pathophysiologic aspects of obesity and T2DM. Recent randomized controlled trials show that GI surgery results in superior glycemic control compared with conventional medical and lifestyle approaches in patients with T2DM. Such mechanistic and clinical evidence is transforming traditional bariatric surgery, focused on weight reduction, into a new surgical discipline aimed at the improvement of metabolic regulation and reduction of cardiometabolic risk (“metabolic surgery”). Future studies designed to further elucidate the mechanisms of action of metabolic surgery can inform decisions regarding the choice of procedures for individual patients, may help optimize surgical design, and could also identify targets for novel device-based and/or pharmaceutical approaches to obesity and T2DM.

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