Joel Faintuch · Salomão Faintuch
Editors

Obesity and Diabetes

New Surgical and Nonsurgical Approaches

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Dedication

Prof. Mervyn Deitel: A Gentleman and a Scholar

Some surgeons are brilliant scientists with analytical minds. They pioneer techniques and procedures, in multiple domains and specialties, and their insightful articles and books are read and cited for many years.

Others are innate leaders. They model services, launch publications, found societies, and implement new therapeutic paradigms, not only as commanders but predominantly as friends, mobilizing teams as well as generating partnership and consensus.

One should not forget those who create a following because of their accomplishments. Ethical, decent, and generous professionals, who have mentored generations, or served as role models for countless students, and still help colleagues around the world, are not plentiful anywhere.

Prof. Mervyn Deitel is unique in combining all those virtues. And he does it not to be complimented and not to win applause, but because it is his nature. Of course, as a founding member of the American Society of Parenteral and Enteral Nutrition, of the American Society of Bariatric and Metabolic Surgery, and of the International Society for the Surgery of Obesity, he was granted many stellar awards and resounding titles. However, he does not mention them. One would need to search his resumé or conduct an investigation to discover them.

Those who were fortunate to visit him, over the years, at St. Joseph's Health Centre in Toronto, where he created the Bariatric Service in 1971, were astonished to see how he juggled multiple tasks—surgical, academic, editorial, and professional. He was always busy, permanently in a hurry, as professor of Nutrition as well as of Surgery, however, with a warm and encouraging word to everyone, staff and patients alike.

He did not stop after retirement, and we should all be glad for it. He can still be encountered in major bariatric meetings, enriching sessions, and discussions with his vast knowledge and unsurpassed experience. Young attendees certainly miss the fact that he parented the journal *Obesity Surgery*, and served as editor-in-chief for

many years, rapidly converting the initially small and quaint publication into one of the most respected and prestigious surgical journals worldwide.

Indeed, Prof. Deitel has remarkable offspring to be proud of—not only intellectual but also two real children, the spine surgeon Dr. Kevin and the radiologist Dr. Wayne, who will certainly keep high and prominent the family standard. And during all his initiatives, he relied on the enthusiasm and unfailing support of his lifelong wife and companion, Frances.

This manuscript is a modest tribute to someone who wrote magnificent books and articles, full of wisdom and solid evidence. Live long and healthy, Prof. Deitel, and continue to be an inspiration to all of us who admire you.

Foreword

Obesity and diabetes continue to be significant healthcare crises the world over. These sister conditions strike humans of all races, ethnic groups, and geographic locations. Ironically, as societies around the globe become more prosperous and healthy in other regards, they also become more exposed to obesity and diabetes. At their current rates of growth, and the expense of caring for the patients afflicted with these conditions, in the not so distant future, "diabesity" may bankrupt healthcare systems around the world.

Despite the billions of dollars spent annually to treat these conditions, the prevalence and cost continue to rise. One can only conclude that conventional treatments are totally inadequate. The hundreds of popular diets, numerous medications, and thousands of weight loss clinics have not stemmed the spread of obesity. Additionally, we still do not have nonsurgical remedies for diabetes that can do more than just lower elevated blood sugars. Bariatric surgery, which has shown promise for reversing obesity and treating diabetes, has limited application as most potential candidates are not interested in undergoing these procedures, due to the operative risk or long-term sequelae.

It is obvious that mankind is in dire need for new and innovated solutions, and the answers may be found in the biology and physiology of these diseases. This is the theme behind the book entitled, "*Obesity and Diabetes: New Surgical and Nonsurgical Approaches*." Professors Joel and Salomão Faintuch have assembled a talented team of authors to explore cutting-edge concepts in the physiology of these conditions.

Prior books on bariatric surgery have traditionally discussed the mechanisms of action of the conventional operative procedures, in terms of nutrient intake restriction or nutrient malabsorption. Faintuch and colleagues go beyond the old theories. Their book includes chapters on novel surgical procedures, including the use of the surgical robot, endoscopic procedures, and controversial treatments such as left gastric artery embolization. Furthermore, they explore cellular therapy for diabetes.

The Diabesity epidemic races on. It is becoming increasingly clear that control of it will not be possible with our current treatments. New, innovative treatments with novel mechanisms of action will likely be our future. This book by Faintuch and colleagues may represent a start on that pathway.

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Contents

Chapter 1
The Dual Burden of Obesity and Diabetes: Old Problems Die Hard

Joel Faintuch and Salomão Faintuch

Abstract The array of efforts to control obesity is as wide and diversified as the mechanisms of the disease. From jaw wiring to fecal transfer, there have been virtually no limits for surgical and medical ingenuity. Initial results are always encouraging, if not for other reasons, because some placebo effect is always operative. The patient wants to lose weight, trusts the doctor, and is psychologically motivated, which can be a winning association, at least for a while.

That's why all the tenets of scientific investigation, including not only sound pathophysiological basis but also adequate controls and long-term follow-up, are indispensable. In the present chapter some creative and promising techniques will be reviewed, even though not all of them have been sufficiently tested in the bariatric population, or are ready for application.

1.1 Introduction

Obesity is the major nutritional challenge worldwide. Its companion is type 2 diabetes, the number one international endocrine and metabolic disease. Together they represent the diabesity epidemic, which is draining resources, overwhelming healthcare facilities, and impairing life expectancy and quality everywhere. Of course prevention is the best medicine, and lifestyle shifts are being recommended everywhere. Nevertheless ingrained sedentarism, deleterious dietary patterns, and unbound hedonism are not only troublesome to antagonize. They may require expensive, and legally challenging, remodeling of the very premises of modern consumer-based, car-moved, screen-gazing, and daylong-snacking civilization.

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Overeating or preference for calorie-dense foods is not equaled to antisocial behavior, or susceptible to punishment. Indeed the obese population, particularly children, is to a large extent victim of the obesogenic environment, as sometimes discussed in lawsuits (Mello et al. 2003). Yet exclusively relying on the society to solve the epidemic may not be sufficient. Personal engagement and alertness, along with well-taught and drilled healthy habits, are of fundamental importance.

1.2 History of Obesity Treatment

Avicenna (980–1037), in the famous treatise Cannon of Medicine, already reports many of the features and complications of obesity such as shortness of breath, sudden death, stroke, infertility, and reduced libido. In more recent times Charles Dickens (1812–1870), in The Posthumous Papers of the Pickwick Club (London, 1836), writes about Fat Boy Joe, a puffy adolescent who is constantly hungry, is very red in the face, and is always falling asleep. William Osler, in 1918, anticipated on such basis the Pickwickian syndrome, encompassing obesity and somnolence.

Early publications notwithstanding, obesity has not always been considered a pathologic aberration, requiring prompt and effective management, except for extreme cases. During centuries, exuberant or deviant somatic proportions were perceived as a mere variant of normal. Anatomical compendia highlighted "habitus brevilineus," in contrast to "habitus longilineus," as morphological entities, not as illnesses.

Bariatric pioneers in the 1960s and 1970s faced difficulties with health plans and reimbursing agencies, as these tended to classify weight loss interventions as merely cosmetic, not as essential metabolic therapy, and refused to provide coverage. Scott, one of the introductors of the intestinal bypass, is credited with the coining of the expression "morbid obesity," in order to differentiate conditions with major health implications and life-shortening hazards, from lesser accumulations of body fat (Scott et al. 1970).

Yet, multiple empirical classifications of severe obesity were employed by surgeons along the years, such as two or three times the ideal weight (Scott et al. 1970), 50 pounds above it, ponderal index, and Broca's index (Organ et al. 1984), until modern BMI (body mass index) driven indications, and EWL (excess weight loss) postoperative monitoring routines, eventually crystallized.

1.3 Type 2 Diabetes Treatment

The association of diabetes with obesity, or diabesity, is not peacefully enshrined in medical texts either. Of course exaggerated body fat, primarily in the visceral compartment, triggers insulin resistance and glucose intolerance. Also, during

diabetes onset, hyperinsulinemia may be prominent, exaggerating protein and lipid anabolism. Yet in early times overweight people were not so plentiful, lean diabetics predominating. Moreover, before long-acting insulin modalities (NPH) became available, and particularly before oral antidiabetics started to be manufactured, in the 1940s and 1950s, diabetic ketoacidosis in type 2 diabetes was frequent, rather than an exception during disease decompensations.

This is a phenomenon associated with anorexia, catabolism, and undernutrition. Indeed, classically diabetes featured polydipsia, polyphagia, polyuria, and weight loss, and many patients died with cachexia.

Pharmacological assistance for diabetes, nominally regular insulin, has been available for nearly one century; nevertheless prolonged remission or cure is still an elusive target for sedimented disease. In parallel, a diversified lifestyle and therapeutic arsenal can now be prescribed for obesity. Long-term results are sometimes comparable to bariatric intervention in moderate stages of the disease, including obesity-triggered diabetes when just prediabetes is present (Perreault et al. 2012).

Such progress notwithstanding, only surgery has consistently been followed by major weight loss in all categories of severe obesity, sustained for over two decades, along with significant remission rates of established type 2 diabetes. This additional bonus naturally gave rise to specific metabolic or antidiabetic operations.

1.4 Ongoing Controversies

After thousands of scientific studies and millions of bariatric interventions, the debate is not exhausted. There are voices suggesting that optimal multidisciplinary clinical management, or perhaps polytherapeutic prescription strategies, could still come close if not fully mimic surgery, for long-term amelioration or cure of obesity and diabetes (Scott et al. 1970; Organ et al. 1984; Perreault et al. 2012).

New possibilities aiming at manipulation of the hormonal milieu, beta-cell reserve, basal energy expenditure, satiety and appetite, and of course new drugs and therapeutic regimens might pave the way for more comprehensive nonsurgical protocols. Parasurgical approaches including endoscopic procedures, and even selective arterial embolization, are also the focus of interest.

1.5 Nonbariatric Nonmetabolic Gastrointestinal Operations

Of course basic pathophysiologic questions remain which have not been answered, or not even asked. What happens when gastrointestinal anatomy in diabetic patients is rearranged, in shapes somehow mimicking bariatric or metabolic interventions,

however the patient is not obese and was operated for another reason, nominally cancer?

In the case of cancer gastrectomy the doubts have been around for some time. A few reports appeared in the literature, however, with widely divergent results, ranging from 90 % remission to virtually no advantage at all. In a prospective series including retrospective findings, with a control population and a very long follow-up period, we documented remission of diabetes however in somewhat lower proportions than after Roux-en-Y procedures for morbidly obese candidates. After 7–9 years, attenuation of diabetes occurred in 32.4 % of the nonobese patients submitted to cancer gastrectomy, contrasting with 68.6 % after Roux-en-Y bypass for morbid obesity (Hayashi et al. 2013).

Such disagreement was actually expected, because lean diabetics usually suffer from more adverse genetic backgrounds and more severe pancreatic exhaustion. The cancer population was older as well. Still, the investigation starkly demonstrated that it's the reshaping of the gut architecture that improves glucose homeostasis, not necessarily weight loss.

And after colorectal resections? Here the conflict should be even more serious, because few if any roles in glucose homeostasis have been attributed to the distal gut. In the large bowel digestion is over, nutrient absorption is essentially nil, and few hormones are expressed. Yet moderate but significant amelioration of diabetes was recorded after cancer operations. As many as 42.4 % of the population exhibited improvement in the diabetic profile, compared to 7.1 and 7.7 % in two control groups (Faintuch et al. 2014). The hypothesis was linked to changes in gut microbioma, even though some hormonal changes are possible, and will require further studies.

1.6 Electrical Stimulation of the Gastrointestinal Tract and Vagus Nerve

Gastric and vagus nerve electrical stimulation have a long and scientifically rich, however somewhat convoluted history. Appetite regulation and obesity treatment are relatively recent goals, related aims being control of gastrointestinal physiology including gastric emptying. Retrograde modulation via vagi of certain brain centers, including the hypothalamic–pituitary–adrenal axis, as well as of selected psychiatric as well as immunoinflammatory phenomenons have been experimentally reported, and therapeutic indications in epilepsy and severe depression can be encountered.

Almost one century ago (McCrea and McSwiney 1926), the abdominal vagi were already experimentally submitted to faradic shocks, with changes in pyloric contractions. Along the subsequent decades, multiple mechanisms were hypothesized for the wide spectrum of visceral effects, and sometimes for the lack thereof, after different stimulation patterns.

The most tested bariatric procedure is not vagal manipulation, but direct gastric pacing. This is usually laparoscopically achieved, by means of seromuscular placing of bipolar electrodes along the lesser curvature. An implantable battery-operated unit is positioned beneath the abdominal skin.

It is accepted that such procedure, according to duration, frequency, voltage, and anatomical location, may be associated with early satiety. Changes of gastric entrainment, peristaltic waves (eventually antiperistaltic), gastric tone, pyloric and antral contractions, acid-peptic secretory activity (which is considered a side effect and thus avoided), and even stimulation of mechano-receptors, thus resulting in a space-occupying or bezoar effect, could occur. Secondary impacts on gastro-intestinal hormones, brain–gut axis, appetite, and glucose homeostasis are also postulated for these systems, often designated as gastric pacemakers, analogously to the heart-controlling apparatus (McCrea and McSwiney 1926; Mintchev 2013).

In recent years, a handful of devices were tested in different settings, among them the Transcend Implantable Gastric Stimulator (Transneuronix and Enterra, Medtronic, Minneapolis, MN, USA), the Intrapace Abiliti Gastric Stimulator (Menlo Park, CA, USA), and the Diamond/Tantalus system (Metacure, Kfar-Saba, Israel, and Dusseldorf, Germany). All of these were followed by encouraging clinical results, however, few breakthroughs; thus none is currently approved for routine weight loss treatment. Yet a few ongoing protocols exist, some targeting diabetics, and occasionally including stimulation of the small bowel, and even of the colon (Mintchev 2013). Direct vagus stimulation (vagal pacing) has also been scrutinized, with the help of the VBLOC device (EnteroMedics, St. Paul, MN, USA).

There are powerful reasons to insist with these approaches, and equally sensible motivation not to be overenthusiastic. The most positive feature is the ability of achieving bariatric-mimicking and diabetes-alleviating responses, without infringing on the anatomical integrity of the gastrointestinal tract, and with low risk and easy reversibility. On the other hand, long-term success has been much more elusive than in the case of the cardiac pacemaker. Such could be due to the complexity of gastrointestinal and food-ingestion physiology, and nominally to such factors as exhaustion of local neurotransmitters, regional tissue inflammation with fibrosis, or central mechanisms of resistance and escape, when the same electrodes are repeatedly activated.

1.7 Manipulation of the Gut Microbioma

It has been known since Metchnikoff, Nobel Prize winner of 1908, that the gastrointestinal system is colonized by germs, and these are not innocent bystanders only. Depending on the composition of the flora, the immune system, inflammation, and other phenomenons might be both positively and negatively influenced. More recently a link with obesity and diabetes has emerged.

The gastrointestinal tract contains over 100 trillion bacteria, which represent ten times more cells than the entire human organism. Nevertheless their total weight is in the range of 700–1,500 g, not 70 or 700 kg, because germ cells are considerably smaller, and there is no extracellular compartment. Yet, they all contain genetic material, and cross talk with the human genoma is now reported, with potential consequences for multiple organs and systems (Collins et al. 2013; Latulippe et al. 2013).

Much of the knowledge concerning metabolic disease stems from germ-free animals. Such artificially reared creatures are diabetes and obesity resistant; however such traits are lost when they are removed from the sterile laboratory environment, and colonization of the gastrointestinal system ensues. Direct transfer of fecal flora, between obese and lean rodents, and even between humans and rodents, provides even more striking evidence of this correlation.

How could the microbioma influence body weight of the host? Chronologically, the first hypothesis addressed fermentation of dietary fibers, and production of short chain fatty acids. This is a physiological process, mainly occurring in the large gut, which generates extra daily energy, for humans as well as for many animals. Certain microbiomas might be more efficient than others in such conversion, thus generating a surplus of calories which, after many years, would be translated into obesity.

Though not refuted, this possibility does not explain all experimental and clinical observations, and multiple other alternatives have centered around interfaces with gut hormones, gut–brain axis including cerebral regulation of appetite and satiety, and systemic inflammation (Collins et al. 2013; Latulippe et al. 2013; Duca et al. 2014; Zhang et al. 2012).

Is adoptive transfer of fecal phenotype from healthy donors an option for obese and diabetic patients? In Chinese medicine this has been practiced since the fourth century, in the form of fecal "soup," however, in the management of severe diarrhea only (Zhang et al. 2012). In recent times, a Dutch team conducted fecal exchange via nasogastric tube, in subjects suffering from metabolic syndrome. Reduced triglyceride concentration and improved peripheral and hepatic insulin sensitivity followed (Vrieze et al. 2012), although these are certainly temporary effects, which would require repeat procedures. Identification of the responsible fecal strains, and oral supplementation in the form of selective probiotics, would be not only more practical but safer. Whole fecal material is a potential source of dangerous viruses, bacteria, fungi, and parasites. In this sense, further studies will be needed.

1.8 Shades of Fat

All fat is not born equal, and brown fat has been known in newborn mammals and hibernating animals, since at least the nineteenth century. Hatai, in 1902, confirmed that dorsal and cervical embryonal fat of the human neonate is similar to the "hibernating gland" interscapular fat of cold weather mammals (Hatai 1902).

As well known, this specialized adipose tissue is responsible for non-shivering thermogenesis, during low environmental temperatures. At the same time, it may act as a regulator of body weight, antagonizing the obesogenic accumulation of lipid typical of white fat. However is it important in humans, beyond the neonatal period?

PET-CT scans, employing F-desoxyglucose, are able to track brown fat in adult individuals, especially in the interscapular area (neck and shoulders). There is some evidence that such tissue could be overactive in undernourished subjects. At the same time, interest in enhancing its metabolic function during old age, and particularly in obesity, is growing, because of functional decline during such conditions. In the laboratory, certain drugs are able to sustain or improve brown adipose tissue activity. Conversion of certain white precursor cells into novel brown, or beige/brite cells ("browning" of fat), may also be experimentally induced. However, only an adjuvant therapeutic role is envisaged for such transdifferentiation, not a mainstream approach to severe obesity, because of anatomical constraints. In human adults, its total mass is estimated as up to 100 times less than in small rodents (Heeren and Muzberg 2013).

1.9 Basic Knowledge of Obesity Pathophysiology

What is the natural history of obesity in individual organs and tissues? And to what extent could general pathophysiology, therapy, and prognosis be impacted by such knowledge? It has been known for a long time that although fat accumulation during positive energy balance predominantly occurs in subcutaneous and visceral adipose tissue, liver, heart, pancreas, peripheral muscle, and other structures tend to be affected as well.

1.10 Ectopic Adipose Tissue

Goose or duck overfeeding, for the production of liver "paté", was already popular in Europe during medieval times, and the practice may stem from the period of the Pharaohs in Egypt (2500 BCE). That's the earliest experimental model of ectopic fat accumulation, during chronic energy surplus. Originally in Japan, and subsequently in other countries, the "wagyu" cattle is also offered a high calorie diet, eventually including alcohol (beer) in the menu, for production of "Kobe beef," another classic example of muscle with high concentration of ectopic fat.

What is the importance of such nonanatomical accumulations, beyond culinary applications in the case of certain animals? The accepted canon is that excess circulating triglycerides, stemming from overfeeding or underexercising, are stored in subcutaneous and visceral adipose tissue depots. Any other destination would configurate a dysfunction, potentially generating pathological consequences.

Some evidence about the nature of such consequences is already emerging. Liver steatosis is a strong predictor of insulin resistance, and the same seems to be true for muscle and pancreas fat. Incretin-based antidiabetic drugs, nominally thiazolidinediones, at the same time retrieve ectopic fat from these sites, and improve glucose homeostasis, further reinforcing such hypothesis (Sam and Mazzone 2014). True cardiac steatosis, and not just epicardial and pericardial fat, is being recognized in obese subjects, possibly with additional metabolic associations (Granér et al. 2013).

1.11 Topographical Mapping of Body Adiposity

Regional imbalances of conventional fat deposits are also the focus of much interest. Nobody questions the deleterious role of excessive visceral adipose tissue, whereas thigh adiposity has long been recognized as a protective feature against diabetes (Eastwood et al. 2014), and possibly against cardiometabolic risk as well. Epicardial and pericardial fat may have ominous implications for coronary risk. Yet, they might be endowed with some beneficial features as well (Gaborit et al. 2013). With the exception of certain antidiabetic drugs, already alluded to with regard to ectopic fat, no therapies are available for reshaping body lipid depots, or for selectively reducing certain compartments, beyond the fact that visceral fat is the first to accumulate during overeating, and the first to melt during starvation. Still, several regional aberrations are acquiring prognostic importance.

1.12 Genome-Based Diagnosis and Prognosis

In clinical practice, each obesity and diabetes case seems somewhat different, depending on time of onset, precipitating factors, family history, metabolic complications, and other phenotypical contexts. It is tempting to think about personalized therapeutic alternatives, driven by the genetic burden. Genome-wide screening has identified patterns responsible for a small proportion of obesity heritability, and somewhat more for type 2 diabetes. Assessment of monogenic variants might become more useful for clinical or surgical management (Xia and Grant 2013). Nonetheless, in the case of diabetes risk prediction, recent methods may already be practical (Tam et al. 2013).

1.13 Final Words

This book was not devised as a comprehensive treatise of obesity and diabetes treatment. In this sense, it will not focus on all possible therapeutic avenues, which should require many more publications. Its aim is to address the most practical

emerging proposals which have been clinically utilized, or are expected to be tested in the near future. They might lead to clinical advances, to more efficient handling of this population, and even to paradigm shifts in the diabesity problem. Having been structured by experienced investigators and recognized laboratories, they represent qualified and authoritative texts in each field.

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Chapter 2
Cost of Obesity Recurrence

Caroline E. Sheppard, Erica L.W. Lester, Kevin A. Whitlock, Shahzeer Karmali, Daniel W. Birch, and Christopher J. de Gara

Abstract Bariatric surgery allows patients to lose a substantial proportion of their excess body weight; however, over time this weight may slowly return. This chapter will discuss the financial impact of obesity and its management through surgical intervention, as well as the rate of weight recurrence after bariatric surgery. The mechanistic and patient behavioural causes of this weight regain will be discussed. Revisional procedures are the current approach to modifying obesity recurrence, and various management options will be reviewed. Additionally, the costs of this endeavour, as well as the tools for evaluating costs and the economic impact of bariatric surgical revision, will be explored.

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2.1 Introduction

Obesity is an epidemic, and the associated comorbidities are well known. Deducing the costs of this major enterprise remains a significant challenge.

While the problems are plentiful, resources are scarce in public healthcare systems. Choices regarding allocation of restrictive healthcare resources are a necessary obstacle to treating this spectrum of disease. In Canada's public healthcare system, obesity treatment extends beyond managing current finite resources, and involves protecting future coffers, from the expensive results of lifetimes of obesity.

One of the realities of bariatric surgery is a subset of postoperative patients who will regain weight (Courcoulas et al. 2013). This is considered to be a failure of the original bariatric procedure. When obesity recurs, patients are faced with new challenges, and often seek advice from a bariatric surgery team for further management. There are multiple options for a patient experiencing obesity recurrence, ranging from doing nothing to performing another bariatric surgery, commonly referred to as revision surgery. Understanding where the expenses lie, not only in obesity but also in the treatment of it (including behavior recidivism, weight regain, and surgical complications), allow healthcare decision makers to optimize resource use.

The cost of obesity has been tracked globally over the past two decades. However, updated information is difficult to find. While the cost-effectiveness of bariatric surgery has been studied in length, few studies look at the long-term or lifetime financial impacts of surgery and weight regain. Information on the cost of revision procedures or comorbidity recurrence is incomplete and a challenge to locate. Inconsistencies exist between countries and institutions, while other data points are not readily available or published.

2.2 Cost of Obesity

2.2.1 Identifying Types of Cost Analysis Within Bariatric Literature

Cost analyses exist in a spectrum, from simple calculations to multifactorial summative evaluations. While the complexities are generally formulated by a health economist, certain key terms and concepts are important for understanding obesity costs, including those for revisional care and surgery.

In the case where a cost is determined without comparing alternatives to the program/service being addressed, the study is a *cost description*. While arguably the simplest form of evaluation, a cost description can provide valuable information, or impact to a bariatric program regarding a service. Sheppard et al. conducted

a cost description study, which to date is the only publication that includes the cost of revision surgery and weight regain (Sheppard et al. 2013).

To advance the breadth of the evaluation, multiple alternative actions with the same intended outcome, for instance, bariatric surgery and nonsurgical weight loss programs, can be compared. The analysis can be conducted from a variety of angles. If the evaluation contrasts the intended outcomes of the alternatives, i.e., weight loss, the study is an *efficacy evaluation*. If the cost of both programs is differentiated, without comparing clinical outcomes, the study is a *cost-analysis*.

All of these methods are considered partial healthcare evaluations. A full economic evaluation combines aspects of all aforementioned: it evaluates multiple alternatives, both with regard to outcomes and cost. A full evaluation can be further categorized as a *cost-effectiveness analysis*, *cost-utility analysis*, or a *cost–benefit analysis*. In a broad sense, analyses for guiding resource allocation decisions include cost-effectiveness analysis and cost-utility analysis. Studies that aid in determining appropriate budget expansion to adopt or include a program, or to illustrate the benefit of a program, are often cost–benefit analyses (Drummond et al. 2005).

A cost-effectiveness analysis deals with an individual consequence, that each of the alternative programs has in common: in our example, weight loss. This common outcome has an associated cost, and the programs can be compared on the basis of the cost of this outcome: for example, cost per kilogram excess weight loss.

While often a single outcome and its associated costs are adequate for a study, it can be useful to measure the preferences that the study population/participants have regarding the outcome of alternative programs. For instance, two patients, one a mail carrier and another an office administrator, each lose 40 kg of excess weight. While the outcome is the same for both, one may consider the weight loss beneficial, to earning a living and reducing the risk of injury at work: the other may not see these same rewards. Thus, the utility of the same outcome differs. A cost utility analysis expresses the cost for each unit of quality of life gained. Usually, these units are expressed as *quality-adjusted life years*, i.e., QALYs (McCabe 2007).

Cost–benefit analysis measures the outcomes and costs of programs/actions and expresses both as a summative monetary value. By providing a net cost, either positive or negative, for a program, this evaluation can aid decision makers, in adopting or rejecting programs based on their overall benefit and impact.

A well-conducted economic evaluation provides relevant alternatives and illustrates the effectiveness. Moreover, all relevant costs and benefits are expressed in an appropriately adjusted monetary value, or discount rate, to allow for variation in currency value, or inflation over the time frame of the study.

2.2.2 The Cost of Obesity

The terms direct versus indirect costs are helpful, in the conceptualization of obesity surgery and its costs. Some experts state these terms foster confusion, as

there are no clear inclusion criteria for direct cost. What one writer may include in the catchall term "indirect cost," another may have completely omitted. Caution is required when utilizing these terms, as part of a toolkit for conceptualizing the cost of obesity, revision surgery, etc., and care should be taken when interpreting studies that calculate "indirect costs" (Jacobs and Fassbender 1998).

When conducting or reviewing a study, our team considers in-hospital, out-patient clinic, pharmacologic costs, and costs of major comorbidities to be direct costs. We include diabetes, hypertension, sleep apnea, and dyslipidemia as major comorbidities. Indirect costs include but are not restricted to disability, loss of productivity/worktime/employment, and private out-of-pocket expenses such as travel, family/caretaker time, private insurance, and non-publically funded healthcare expenses.

Several countries have calculated the annual cost of obesity on their healthcare system, with varying methodologies and inclusion criteria for indirect and direct costs (Colagiuri et al. 2010; Lancy and Gruen 2013; Bahia et al. 2012; Anis et al. 2010; Corscadden et al. 2011; Scottish Government 2010; Tigbe et al. 2013; Finkelstein 2001; Cawley and Meyerhoefer 2012) (Table 2.1).

The United States remains the most expensive country to receive medical care, and has the highest expenditures for obesity management. As of 2012, the United States draws on 21 % of their healthcare costs to manage obesity (Cawley and Meyerhoefer 2012). In 2006, obesity expenditures were estimated to be 4.1 % of Canadian health expenses (Anis et al. 2010). Obese Americans were said to cost

Table 2.1 Annual cost of obesity to the healthcare system

Country	Currency	Year	Annual cost (billion)	Notes
Australia[a]	AUD ($)	2005	56.6	$2,788 per individual
Australia[b]	AUD ($)	2010	88.9	
Brazil[c]	USD ($)	2010	2.1	Including overweight costs
Canada[d]	CAD ($)	2006	11.0	Including indirect costs
Canada[e]	CAD ($)	2008	7.1	Including comorbid disease
Canada[e]	CAD ($)	2008	4.6	Without comorbid disease
Scotland[f]	GBP (£)	2008	457	Including indirect costs
United Kingdom[g]	GBP (£)	2002	0.991–1.124	Additional 2.4–2.7 billion indirect costs
United States[h]	USD ($)	2008	147	
United States[i]	USD ($)	2012	190.2	

[a]Colagiuri et al. (2010)
[b]Lancy and Gruen (2013)
[c]Bahia et al. (2012)
[d]Anis et al. (2010)
[e]Corscadden et al. (2011)
[f]Scottish Government (2010)
[g]Tigbe et al. (2013)
[h]Finkelstein (2001)
[i]Cawley and Meyerhoefer (2012)

$1,429 USD more for healthcare than normal weight individuals (Cawley and Meyerhoefer 2012). Additionally, a United States report determined that by 2018, $344 billion would be spent on healthcare costs to manage obesity (Thorpe 2009).

2.2.3 Cost-Effectiveness of Bariatric Surgery

Globally, more than 340,000 bariatric procedures are performed annually, with one-third of those procedures performed in the United States. In Canada alone, an estimated 6,000 bariatric surgeries were performed in 2012, representing a 280 % increase in 6 years (Canadian Institute of Health Information 2014). These surgeries cost the Canadian healthcare system approximately $48 million in 2012. In the Canadian province of Alberta, the cost of laparoscopic adjustable gastric band (LAGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic Roux-en-Y gastric bypass (LRYGB) is $10,500, $12,000, and $18,000 CAD, respectively. The total rate for early and late complications is 12.4 %. Across Canada, early to intermediate complication rates are 5.3 % (Canadian Institute of Health Information 2014). An average of $475 CAD per patient is spent managing postoperative complications, including band removal, ulceration, hemorrhage, staple line leak, anastomotic stricture, and internal hernia. These patients also attend a multidisciplinary clinic, in preparation for surgery, attributing an additional $500 CAD cost. In total, Canadian bariatric surgery can cost $11,475–$18,975 CAD per patient (Sheppard et al. 2013, 2014a, b). The average cost of bariatric surgery within the United States is significantly more expensive at $24,000 USD (Mehrotra et al. 2005; Cremieux et al. 2008).

Regardless of a front-loaded cost of $10,000–$25,000, bariatric surgery has been established as a cost-effective strategy for treating obesity. Bariatric surgery reduces comorbidity management costs by more than half, and monthly savings of $900 USD per patient between 13 and 24 months (Cremieux et al. 2008; Sussenbach et al. 2012). Postoperative pharmaceutical savings of $180 USD/month can be expected (Monk et al. 2004). In Scotland, a noticeable decrease of 40 % in total pharmaceutical costs was seen, 24 months after bariatric surgery. The pharmaceutical cost for managing diabetes alone decreased by 78 % (£4,500–£1,000). Both hospitalization and medical services significantly decreased in cost after surgery (Karim et al. 2013).

Cost-effectiveness is measured by calculating the *incremental cost effectiveness ratio* (ICER), which contrasts incremental costs with incremental health benefits (increased years of life). When comparing health interventions (e.g., surgery vs. nonsurgical management of obesity), a lower ICER indicates the same unit of outcome can be achieved at a lower cost (Institute of Health Economics 2012). *Incremental cost–utility ratio* (ICUR) involves incorporating QALY into the cost-effectiveness calculation. The Canadian Agency for Drugs and Technologies in Health (CADTH) determined that all primary bariatric procedures, compared to

nonsurgical treatment over a life span, corresponded with an ICUR ranging from $6,500–$12,000 per QALY (Klarenbach et al. 2010).

Bariatric surgery has been determined to be cost-effective on a global level. A study from the United Kingdom found that the ICUR for LRYGB and LAGB, compared to standard care, was £1,500 and £1,900, respectively. The ICER over 20 years was £3,500–£12,800 for LRYGB and LAGB; however, over 2 years LAGB had an ICER of £60,800 (Klarenbach et al. 2010). A study in Portugal observed an increase of 1.9 QALY compared to medical intervention and a savings of €13,000 per patient (Faria and Preto 2013).

In the United States, an ICUR of $5,400 USD–$16,000 USD for women, and $10,700 USD–$35,600 USD for men, was calculated after gastric bypass (Klarenbach et al. 2010), and an ICER over a lifetime of $6,600 USD and $6,200 USD per QALY gained, for LRYGB and LAGB, respectively (Wang and Furnback 2013). Another American study determined that the ICUR after 10 years, would be $21,600–$38,000 per QALY, or $9,400–$12,000 per QALY over a lifetime, for LRYGB and LAGB (Klarenbach et al. 2010). The United States remains one of the most expensive healthcare systems in the world, yet the cost-effectiveness of bariatric surgery, compared to standard care, is equivalent across countries.

The bypass dominates as the most cost-effective weight loss option for obese type II diabetics. Hypertension and diabetes are by far the more expensive and prevalent comorbidities, together totaling an annual cost of nearly $2,300 USD per patient in pharmaceuticals. Cost savings after bariatric surgery account for a reduction in two-thirds, of medical expenses associated with obesity (Maggard et al. 2005).

2.3 Recurrence Rate

Weight regain occurs in 10–20 % of patients after approximately 36 months post-bariatric surgery (Sheppard et al. 2013). Different philosophies exist, as to whether weight recidivism is due to a lack of behavioral lifestyle change or simply a mechanical failure of the procedure (de Gara and Karmali 2014). Several methods exist for managing such patients. These include revisional surgery, endoscopic interventions, and medical management. The frequency of undergoing revisional surgery ranges from 2.5 to 18.4 % (Sheppard et al. 2013). Inevitably, these surgeries have higher complication rates than primary surgery (Worni et al. 2013). As such, revisional surgery due to weight regain comprises a long-term direct cost to the healthcare system that has yet to be quantified.

2.4 Causes of Revision Surgery

There are several major causal factors for patients to seek or require revisional surgery. Weight regain is one of the more common long-term reasons for requesting revisional surgery.

2.4.1 Weight Recidivism

Weight recidivism has become a major concern after bariatric surgery. Long-term studies show that over time, patients slowly regain weight, and upwards of nearly 15 % will fail to lose an excess weight loss of 50 % or more, after 5 years (Magro et al. 2008). In fact 20 % of patients will incur weight regain or insufficient weight loss. This subset of patients will gain back on average 22 kg of weight and after 36 months require revisional surgery (Sheppard et al. 2013).

2.4.2 Management Type

Management of this group of patients is complex, and considerable variance of opinion exists as to best practice. Schools of thought range from a highly mechanistic management strategy through to a solely nonsurgical approach. Mechanical/technical problems may be anastomotic/stomal pouch dilatation, fistulae, ulceration, reflux and dysphagia, or lack of restriction. Multiple solutions for these have been advocated. However, given that a multidisciplinary team is beneficial in the success of primary bariatric surgery, some proponents feel it also plays a role in the success of these revisional procedures.

It has been argued that only in a multidisciplinary environment can many of these complex issues be effectively addressed. For example, failure to address important lifestyle, behavioral and psychosocial issues, almost guarantees continued or repeat failure (de Gara and Karmali 2014). In addition, long-term dietary follow-up, outside a specialty clinic, can be costly in either a public or private healthcare system, and may be a contributing factor, to those unable to afford or have these services insured. A unifying factor that draws these issues together is appropriate patient selection. The need for appropriate follow-up, with the multidisciplinary team, is critical to ensure that patients are equipped with the tools, necessary to cope and control their weight when stresses, dietary needs, or socioeconomic situations arise. Many bariatric surgeons tend to focus solely on procedural approaches; for example, the importance of original bougie size or pouch dimensions, while failing to address the behaviors that led to sleeve or pouch dilatation.

2.4.3 *Medical Tourism*

A bariatric medical tourist is an individual intentionally seeking bariatric surgery outside of the province or country, and having an unsatisfactory outcome. This has become an important component of revisional surgery, and a factor in the substantial costs, associated with managing complex bariatric revision patients. Many travel to avoid the long wait times common within a public system, or personal costs, should they either have minimal or no insurance within the private healthcare system. Many patients receive negligible education on behavioral modification pre- or postop. In addition, some institutions do not follow the NIH criteria for bariatric surgery, and patients may not be psychosocially or medically optimal to succeed after surgery. Personal choice, both of procedure and institution, is an important factor.

The burgeoning LAGB failure rate has become a dominant patient group in the revision clinic. A variety of procedural failures are seen, from weight regain to band erosion or slip. While some centers (Ardestani et al. 2011) advocate for repeat laparoscopic band readjustments, so as to avoid removal, most centers find that explantation, and subsequent conversion to a definitive restrictive and/or malabsorptive procedure, is preferred (Deylgat et al. 2012). These endeavors are costly to the healthcare system.

Laparoscopic sleeve gastrectomy patients form the next important group of patients, who may require revisional surgery. Most of these are related to acute complications. Emergent complications such as leakage, bleeding, and thromboembolic episodes can represent a huge range of costly bariatric failure (Sheppard et al. 2014a, b). Later consequences of primary surgery failure, such as weight recidivism, may present demands both for the multidisciplinary team and for formal revisional surgery.

On average the revisional surgery, and care necessary to treat weight regain and complications, is 74 times more expensive than treatment of complications performed in the appropriate healthcare system ($450 vs. $37,000) (Sheppard et al. 2014a, b). It can be expected that as the number of obese individuals increase, so will the number of bariatric medical tourists, along with other inadequately selected or followed bariatric candidates, and thus the number of patients with weight recidivism.

2.5 Management Options

There are several options for revising patients due to weight regain. The proportion of these revisional procedures within a Canadian clinic is outlined in Fig. 2.1.

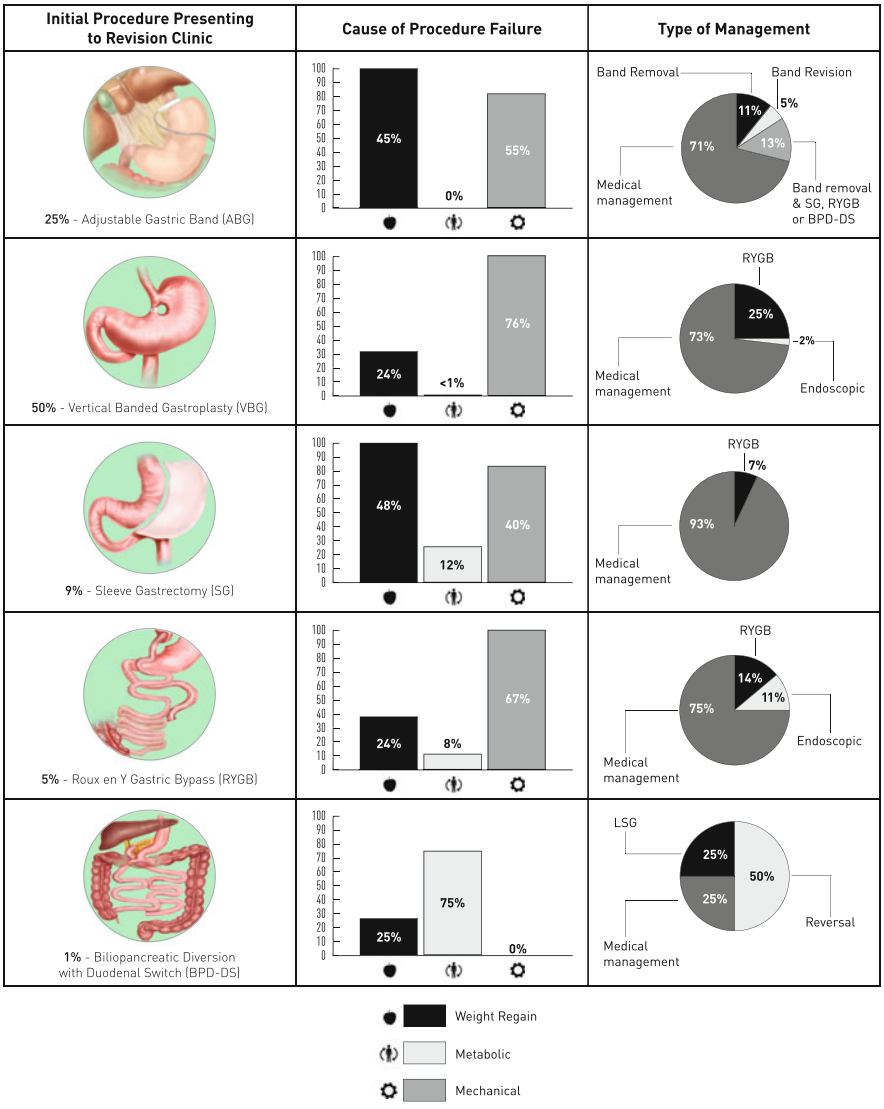

Fig. 2.1 Canadian Bariatric Revision clinic characteristics of failed primary bariatric surgery and revision surgery rates (Illustrations of bariatric procedures provided by the Centre for the Advancement of Minimally Invasive Surgery. Figure created by Maxwell Hurd, University of Alberta)

2.5.1 Revision Surgery

RYGB surgery achieves its maximal weight loss at approximately 1 year (Whitlock et al. 2013). The majority of patients then enter a maintenance phase where their weight is relatively stable. However, an average of 21 % of patients begin to regain weight at this point (Sheppard et al. 2013). The RYGB can be modified to a distal gastric bypass with revision surgery. This involves lengthening the Roux limb and effectively bypassing more small intestine. Rawlings et al. published retrospective evidence that this revision surgery is able to achieve improved weight loss (Rawlins et al. 2011). Unfortunately, there is still a paucity of evidence supporting the effectiveness of this revision strategy. For RYGB patients, converting to a duodenal switch procedure has been advocated. This is a technically challenging endeavor (Keshishian et al. 2004).

LAGB is unlike other bariatric operations, in that it does not alter the native anatomy of the gastrointestinal system. Consequently, there are multiple revision options available. LAGB can be converted to a LSG, RYGB, or a duodenal switch. Essentially the band is removed, and the subsequent operation is identical to a primary bariatric surgery. LSG has been shown to achieve significant weight loss in patients with a prior LAGB (Berende et al. 2012). However, there were 8.6 % staple-line leaks and bleeds with the LSG. This resulted in increased costs, due to reinvestigation and reoperation. This emphasizes the importance of complication rates, when considering the economic impact of a revision surgery.

Revisional surgery is inevitably more costly and complication prone than primary procedures. A recent systematic review summarized the studies of LAGB, revised to either RYGB or LSG (Coblijn et al. 2013). LSG was found to have a 5.6 % leak rate after conversion from LAGB. RYGB had a leak rate of 0.9 %. This would imply that converting LAGB to LSG is overall more costly. However, there was a wide variation in overall complication rates, for conversion to RYGB among the studies; ranging from 3.0 to 29.3 %. Ranges of this order of magnitude make it difficult for interpretation.

There is some evidence for converting LAGB to a duodenal switch procedure. A retrospective study by Topart et al. reported on 21 patients who underwent duodenal switch after LAGB surgery. However, the duodenal switch resulted in significantly more staple line leaks and bleeds, relative to the RYGB (Topart et al. 2007). Consequently, to save on the costs of reinvestigations and reoperations, LAGB is not commonly converted to the duodenal switch.

Revision surgery for a primary LSG involves conversion to either RYGB or BPD/DS. In fact LSG was originally used in a staged approach, to the RYGB and the BPD/DS, in complicated patients (Brethauer et al. 2009). LSG is now commonly done as a stand-alone bariatric procedure. There is evidence that revision to a RYGB is as effective and safe as a primary RYGB surgery (Morales et al. 2010). However, the LSG patients will incur costs needed to undergo the RYGB or the BPD/DS.

Re-sleeve, or performing a second LSG, has been described in the literature. The idea of this revision procedure is to further decrease the size of the stomach. An initial case study described this surgical approach in 2003, when a patient with a BPD/DS underwent an additional LSG (Gagner and Rogula 2003). More recently, a feasibility study reported no complications, with the re-sleeve operation for 13 patients (Iannelli et al. 2011). Unfortunately there is limited evidence for the re-sleeve procedure. Yet the possibility of a surgical procedure with less complications would result in a more cost-effective approach to revising LSG patients.

Vertical banded gastroplasty (VBG) is not commonly performed, but patients who had this procedure are now presenting for revision surgery. In fact, a recent study reports the revision rate to be 21 % (Marsk et al. 2009). VBG can be converted into a RYGB (Gonzalez et al. 2005). There is some evidence that conversion to a RYGB is a better option than simply revising the VBG (Marsk et al. 2009). Unfortunately, there were 4.8 % leaks and 1.9 % bleeds, within the first month after revision RYGB (Gagne et al. 2011). This would make RYGB a less favorable option, if the alternatives were not significantly more costly. In contrast, revision of VBG to LSG has resulted in leak rates as high as 14 % (Berende et al. 2012). Additionally, revision of VBG to BPD/DS has reported leak rates of 22 % (Greenbaum et al. 2011). There is suggestion that VBG conversion to either LSG or BPD/DS can be performed safely and will achieve further weight loss (Jain-Spangler et al. 2013). However, the evidence is primarily based on case series, and revision to RYGB is the more accepted approach.

The cost-effectiveness of revision surgery has yet to be determined. While certain economic studies have included revisional surgery for complications (Klarenbach et al. 2010), no long-term studies to date have assessed the impact of revisional surgery on the healthcare system.

2.5.2 Endoscopic Revision

Novel and innovative endoscopic strategies are advocated for primary bariatric surgery failures (Schweitzer 2004). However, the costs of these interventions have not been well documented. Endoscopic revision of RYGB procedure is becoming more established. An endoscopic transoral reduction method was recently investigated in the literature (Thompson et al. 2013). The participants had undergone RYGB surgery and were deemed to have inadequate weight loss. It is known that a larger percentage of patients with weight regain have dilated gastrojejunal junction diameter (Heneghan et al. 2012). The endoscopic approach used a suturing system to decrease the diameter of the GJ junction to 5–8 mm (Thompson et al. 2013). Experimental subjects lost a statistically significant average of 3.5 % of their preoperative weight, compared to 0.4 % in the sham-treated controls. Importantly, none of the 50 experimental patients were reported to have serious adverse events that would require future workup and gastrointestinal intervention. This is one

argument for the endoscopic approach: less risk of adverse events, because of the less invasive method.

The incisionless operating platform™ (IOP) is designed to place placating sutures, within the gastric pouch. A "TransPort" device, with four channels, allows stability of the endoscopic instruments. A full-thickness fold is created and fastened with anchors connected with a suture. The overall goal of the IOP is to reduce the size of the stoma and pouch, after they are found to be dilated. This anchor system was used in a larger prospective trial, with encouraging results in the revision of 116 RYGB patients (Horgan et al. 2010). There were no significant complications associated with the procedure, and the authors reported an 18 % excess weight loss at 6 months post-IOP. Additionally, the authors provided endoscopic evidence of the anchor durability at 12 months post-procedure. Consequently, this endoscopic revision method may have better long-term weight loss.

Another device called StomaphyX™ is designed for the revision of the gastric pouch after failure of RYGB. During endoscopy the device uses polypropylene H-fasteners to create a gastric fold. After repeated folds are created in a circumferential pattern, the pouch size is reduced. A recent retrospective review by Goyal et al., reported on 53 patients who were undergoing StomaphyX™ after RYGB surgery (Goyal et al. 2013). There were no reported complications, and at 2–4 years the excess body weight loss was 4.3 %. The StomaphyX™ has also been used for revision of VBG patients. A retrospective study of 14 VBG patients undergoing revision found an average BMI decrease of 3.6 kg/m^2 1 year post-StomaphyX™ (Manouchehri et al. 2011). There were no major complications with the procedure. Based on the limited evidence available, StomaphyX™ appeared to be a safe revision procedure with reasonable short-term weight loss. However, recent evidence suggests that StomaphyX™ may have poor weight loss outcome and increased morbidity compared to other available options (Eid et al. 2014).

Another method is called the over the scope clip (OTSC)™ (Ovesco, Tubingen, Germany). This method uses a Nitinol clip that is applied by an endoscope, in order to reduce the diameter of the gastrojejunal outlet. The idea is that this operation is best performed in patients with dilated GJ junctions, as identified by gastroscopy. In a recent study, 94 patients who initially had a transected vertical gastric bypass presented for treatment with the OTSC endoscopic method (Heylen et al. 2011). After OTSC, 2.1 % of the patients had persistent dysphagia, but there were no major complications. At 12 months post-OTSC, the average BMI had dropped 5.4 kg/m^2.

Sclerotherapy has also been described in the treatment of weight recidivism in RYGB patients. This method involves injecting a sclerosant into the dilated gastrojejunal stomal tissue. The sclerosant elicits an inflammatory response and edema, which restricts the stomal diameter (Abu Dayyeh et al. 2012). A recent retrospective study reported 231 patients who underwent sclerotherapy after RYGB. They reported that 76 % of their cohort stabilized their weight. They also reported an average of 4.4 % of total body weight loss. However, many of their patients required more than one sclerotherapy session. As well, complications included 1 % ulceration and 2.4 % bleeds, with 1.4 % requiring endoscopic clips.

A paucity of data exists on the costs of these procedures. Dakin et al. are the first to describe the costs of endoscopic revision. IOP and Stomaphyx are said to cost equivalent to an adjustable gastric band ($18,000 USD 2012), an OTSC clip to an endoscopic retrograde cholangiopancreatography ($2,600 USD 2012), and sclerotherapy to a colonoscopy ($1,200 USD 2012) (Dakin et al. 2013). However, no literature exists on the short- or long-term cost-effectiveness of these endoscopic procedures.

2.5.3 Medical Management

For bariatric surgery to be truly effective, long-term medical, dietary, and psychosocial interventions are necessary. Weight regain after bariatric surgery is equally multifaceted (Sheppard et al. 2013).

Adherence to postoperative follow-up is important for weight outcomes in bariatric surgery patients. Weight regain is more prevalent for patients who do not receive postoperative nutritional follow-up (Magro et al. 2008; Warde-Kamar et al. 2004). At these visits, proper eating behavior and practice of physical exercise are evaluated and reinforced (Bond et al. 2004). However, failure of diet and exercise programs is well known, and the costs are almost impossible to assess.

Pharmacologic options are available for weight loss and potentially for weight regain. The medications available have been shown to achieve modest weight loss, in comparison to bariatric surgery (Yanovski and Yanovski 2014). One of the most studied is Orlistat, which is designed to inhibit lipase and prevent the absorption of fats from a meal (Heck et al. 2000). A recent meta-analysis reported that Orlistat achieves 5–10 kg of weight loss, when combined with behavioral intervention (Leblanc et al. 2011). Importantly, the weight loss was maintained for up to 24 months.

Another commonly used agent is Lorcaserin. This medication is designed as a selective agonist of the serotonin 2C receptor (Smith et al. 2009). The idea is that it reduces appetite, which subsequently reduces weight. The efficacy of Lorcaserin is similar to Orlistat, in terms of weight loss. A large randomized trial of 3,182 obese patients compared Lorcaserin to placebo (Smith et al. 2010). After 1 year, half of the Lorcaserin-treated patients achieved 5 % weight loss or more.

Solely a medical management program is not a cost-effective method for long-term weight loss. No significant difference exists in the QALY, between primary care physician follow-up and lifestyle behavior modification programs. Short-term ICER is $115,397 USD per QALY, compared to a willing-to-pay cost of $50,000 USD per QALY. Lifestyle counseling programs were only cost-effective, if the payee were to invest $400 USD per kg-year, for a loss of 10.87 kg-year (Tsai et al. 2013). Furthermore, the cost of Orlistat is €66 or $138 USD per month, resulting in an ICER of €17,000 per QALY (Lacey et al. 2005). Both Orlistat and Locaserin are not cost-effective therapies for weight loss, and only 10 % of simulations were cost-effective at $100,000 USD per QALY. To date, targeted

medical interventions have not been successful and far outweigh the cost of primary bariatric surgery.

Limited data is available on the cost analysis of these revisional options for weight regain. Data exists in reviews and only as cost ranges. These novel technologies and therapies tend to fail, are temporary fixes, have a large "halo effect," and adhere to the sin wave of technology. The ultimate goal of revisional procedures is to decrease the comorbidities of patients, and long-term data is needed in order to determine their efficacy.

2.6 Costs Associated with Obesity Recurrence

While information increases on weight regain in long-term studies around the world, very little research has been done to look at the revision rates, within the postoperative bariatric population, due to either weight regain or comorbidity recurrence. It would be safe to say that not only do these patients begin to accumulate costs in surgical needs but also in recurrent pharmaceutical costs, to manage their comorbidities. Characterizing the costs and cost-effectiveness of revisional surgery will be a necessary component to analyzing the overall benefit of bariatric surgery, for patients and the healthcare system.

2.6.1 Revisional Surgery Costs: Public Healthcare Versus Private

Bariatric revision surgery is a growing enterprise and is a major healthcare cost, so much so that weight loss programs have begun to implement revisional surgery into their practice, throughout Canada and the USA. In Canada, these costs are significant enough to our healthcare system, that separate clinics from the primary surgical clinics are being funded. These clinics specialize in revising bariatric procedures and reconnecting patients with a multidisciplinary team. The understanding of these clinics is as stated in the literature, that postop primary bariatric surgery is successful with a team approach and lifestyle modification, and it should also be so after revisional surgery, not just a technical surgical issue.

These clinics are funded through the healthcare system and generally comprise approximately 50 revisional procedures each year per institution. The provincial government funds all of these costs for patient care. Depending on the province, certain revisional procedures are covered (LAGB only covered in Alberta, Québec, and Newfoundland and Labrador, whereas the Maritimes only cover LSG). While other provinces do not have the facilities, surgical expertise, or resources to perform revision bariatric surgery, patients are referred, and their original province is billed.

Table 2.2 Public healthcare costs for revisional surgery in CAD

Procedure	Surgeon billing ($)	Anesthesiologist billing ($)	OR costs ($)	Hospital stay ($)	Total ($)
LAGB removal	900	400	1,100	1,500	3,900
LAGB removal and revision	2,500	1,400	8,900	10,500	23,300
Revision LRYGB/ LSG	2,900	1,100	5,600	9,000	18,600
VBG revision	2,700	1,100	5,600	9,000	18,400
Reversal of BPD-DS	2,900	1,100	5,600	9,000	18,600

Abbreviations: *CAD* Canadian dollars, *OR* Operation room, *LAGB* Laparoscopic adjustable gastric band, *LRYGB* Laparoscopic Roux-en-Y gastric bypass, *LSG* Laparoscopic sleeve gastrectomy, *VBG* Vertical banded gastroplasty, *BPD-DS* Biliopancreatic diversion–Duodenal switch

Revisional costs are billed similarly to a primary bariatric procedure, and each procedural cost is tabulated as shown in Table 2.2.

These costs were based on the single payor healthcare provider, in the province of Alberta, Canada. The majority of expenditures are from VBG revision, comprising 85 % of surgeries. However, depending on which Canadian province, costs may vary. In major bariatric centers in provinces, such as British Columbia and Ontario, surgical billing for these bariatric procedures varies from $1,100 CAD to $1,400 CAD, respectively. Additional billing modifiers for patient BMI exist, in some provinces equivalent to an increase in 25 % (Ministry of Health and Long Term Care 2014).

Other public healthcare systems globally also have bariatric surgery coverage, through their national healthcare system, such as most European countries and Australia. Several institutions in these countries have commented on the cost-effectiveness of primary bariatric surgery, including revision rates, however not the specific cost of a revisional procedure.

The complexity of the US multipayor system and the variability of insurer coverage, with its case-by-case approach for specific bariatric surgical, endoscopic, and non-procedural interventions across different states, make cost calculations a challenge. However, notably in the literature, primary bariatric surgery is substantially more expensive in the USA than Canada for gastric bypass ($24,000 USD vs. $18,000 CAD), respectively (Mehrotra et al. 2005). One article determined the difference in costs between primary and revisional gastric band conversion to gastric bypass in the USA. It demonstrated that revisional surgery was $13,000 USD more expensive, at approximately $50,000 USD (Worni et al. 2013). No other published literature exists to date, quantifying the cost of revisional surgery in the USA.

While the cost-effectiveness of revisional surgery due to weight regain has yet to be calculated, the cost-effectiveness of weight regain 5 years after primary bariatric surgery was ascertained for LRYGB and LAGB. The ICER was $24,100 USD and $26,700 USD for LRYGB and LAGB relative to no surgery, respectively. The willingness to pay for most bariatric procedures is $50,000 USD per QALY,

making bariatric surgery with weight regain still cost-effective but not ideal for patient health. However, with the increasing number of LAGB removals and revisions, the cost analysis could be adversely affected (Wang et al. 2014).

2.7 Complication Rates and Costs of Revision Surgery

The average cost of an operative revisional procedure is $5,600 CAD in Alberta, Canada. The complication rate of revision surgery ranges from 5.5 to 19.4 % (Worni et al. 2013; Ardestani et al. 2011; Biertho et al. 2005; Mognol et al. 2005; Nguyen et al. 2012; Tucker et al. 2008; Yazbek et al. 2013; Hedberg et al. 2012). Because of the complexity of revision surgery, complication rates have been noted to increase, some significantly higher than after primary surgery. They are particularly high after biliopancreatic diversion and duodenal switch (21–25 %) (Klarenbach et al. 2010).

Complication costs can vary from $200–$400 for an investigative procedure to $800–$1,000 for a single surgical procedure. The average cost of complications after LSG revision surgery is $1,500 CAD, $9,900 CAD after RYGB, and $1,300 CAD after LRYGB. These costs do not factor in procedures necessary for ventral or incisional hernia. A second revisional surgery has been noted to occur in 20–25 % of revision surgeries, and 13–25 % of secondary revision surgeries are due to obesity recurrence (Jacobs and Fassbender 1998; Finkelstein 2001; Rawlins et al. 2011; Gagner and Rogula 2003). In addition, hospital stay has been noted to be longer than for primary surgery by several days, thereby incurring an additional cost to the system (Worni et al. 2013; Nguyen et al. 2012; Tucker et al. 2008). Each day in hospital has a cost of $1,500 CAD or $3,000 CAD for the intensive care unit (ICU). As noted in the US literature, revisional gastric banding incurs an additional $4,000 USD in hospital stay, compared to primary gastric banding, and $13,250 USD for revisional gastric bypass (Keshishian et al. 2004; Gonzalez et al. 2005).

Other expenses to factor in are the cost of a bariatric intervention team. It involves the cost of consultations with dieticians, psychologists, nurses, and surgeons. Most patients will have four to seven appointments with the team before undergoing surgery, leading to a cost of approximately $500.

2.8 Recurrence of Comorbidities and Associated Costs

Obese individuals are known for incurring twice or more healthcare expenditures than their normal weight counterparts. Several sources have reported the cost savings of bariatric surgery because of comorbidity resolution. Pharmaceutical costs are a major component of these total expenses. Diabetes is a costly comorbidity, ranging from $1,250 to $5,000 CAD in ongoing pharmaceutical costs, as well as €2,950 EU and £1,550–£4,500 GBP in annual costs (Karim et al. 2013;

Klarenbach et al. 2010; Lacey et al. 2005; Clegg et al. 2003). Other large expenses include the cost of continuous positive airway pressure (CPAP), hypertension, and hyperlipidemia treatment, along with knee replacements. These have been reported to be yearly costs of $280, $800, and $500 CAD, respectively, with knee implants in a much higher range. Hypertension has also been quoted to cost £2,000 GBP annually (Karim et al. 2013).

Obese nonoperated individuals already have significantly higher pharmaceutical expenditures than normal weight individuals (£400 vs. £15 men, £210 vs. £75 women). Additional costs are increased primary care visits (£130–£175) and hospitalization (£1,200–£1,300). However, these costs are noted to increase within the first year of surgery and reduce slightly over time. Each increase in one BMI point denotes an increase of £15 per person per year in healthcare expenditures (Tigbe et al. 2013).

Primary bariatric surgery reduces comorbidities by 40–70 %, depending on the procedure (Peterli et al. 2013; Leyba et al. 2011). Resolution and improvements in cormorbidities have been implicated in annual cost savings of pharmaceuticals of $2,200 USD per patient, after gastric bypass (Monk et al. 2004). Other countries have reported reductions of 40 % in pharmaceutical costs and a total cost savings of £30,400 GBP per year (Karim et al. 2013).

Several publications have described revisional surgery as being necessary for comorbidity resolution after weight regain. The percentage of comorbidities in revision patients ranges from 13 to 42 %, similar to rates in the primary bariatric population. One study reported that comorbidity recurrence was the primary cause of revision surgery, in 22 % of patients. A single study by Weiner et al. 2013, in the United States healthcare system demonstrated that by the fourth postop year, costs of inpatient stay, physician and outpatient visits, and pharmacy costs began to increase. No literature so far has commented on weight recurrence, in the period from band removal to revisional surgery, or the costs of weight regain during this time.

Studies reporting on follow-up of longer than 5 years have noted that weight regain has been a factor in comorbidity return. One study determined that after a period of 10 years, weight regain created an increase in all collected comorbidities, including diabetes (1–7 %), hypertension (24–41 %), and hyperlipidemia (27–30 %) (Sjöström et al. 2004). However, another long-term Swedish study noted that there was a cost savings over a 7–20 years period of $230, between the control and bariatric surgery population for comorbidities. The weight loss of the long-term data was found to be 17–18 % at 10–20 years following primary surgery (Neovius et al. 2012).

Figure 2.2 depicts an overall summary of costs, from primary bariatric surgery to revisional bariatric surgery.

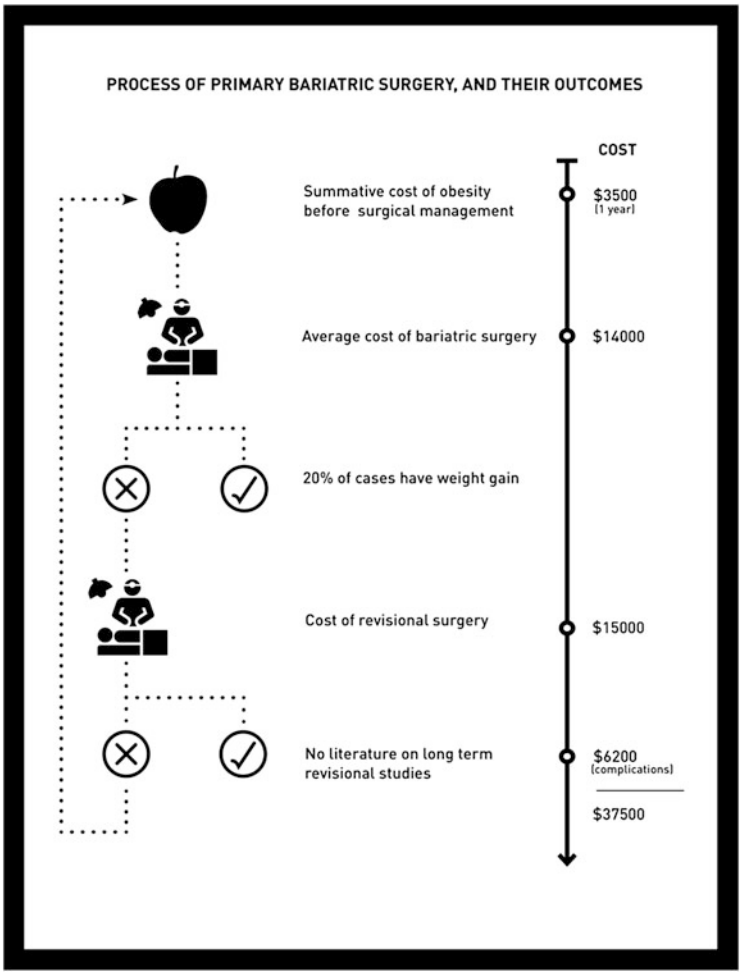

Fig. 2.2 Total cost of bariatric surgery over 5 or more **years** (Figure created by Maxwell Hurd, University of Alberta)

2.9 Summary

Obesity consumes a large amount of health resources to manage associated medical, mental health, and social issues. Billions of dollars are spent and invested in this complex chronic disease. Bariatric surgery is the only evidence-based resource for sustainable weight loss. However, weight regain has been noted in 10–20 % of patients after 36 months. Along with weight recidivism, comorbidities can also recur, costing more in clinical and pharmaceutical care. Whether more effective patient selection, and multidisciplinary revisional interventions (surgery, endoscopic treatment, and medical management), could result in cost savings has yet

to be determined. However, all contribute to the global costs of bariatric surgical failure. These cannot be overlooked, in an accurate economic analysis. These costs may range from $15,000 CAD to $24,000 USD per patient, totaling millions in revision expenditures in North America. It is essential to include them in the overall cost-effectiveness assessment of bariatric surgery.

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Chapter 3
Recent Trends in Bariatric and Metabolic Surgery

Rudolf A. Weiner, Islam A. El-Sayes, and Sylvia R. Weiner

Abstract The worldwide incidence of obesity is showing an evident increase in the number of obese population from year to year. This rise is not anymore restricted to developed countries. Surgical solutions designed to counteract the obesity epidemic are rapidly increasing, and recent approaches start to replace the already established operations. Distinguished from other procedures, sleeve gastrectomy seems to be the new leading procedure in the near future. This is attributed to many factors, including relative simplicity of the procedure, lower cost, reasonable outcome in terms of weight loss and improvement of the associated comorbidities, and the available conversion options in case of unsatisfactory outcome. Additionally, an accepted postoperative complication rate played a significant role in its widespread. Another procedure is the mini-gastric bypass which can be applied either as a primary procedure or as a secondary solution after a failed sleeve gastrectomy. Other procedures involving sleeve gastrectomy as a restrictive component include, for example, Single Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy (SADI-S) which avoids the risk of biliary reflux encountered with mini gastric bypass. Additionally, it is a simple procedure compared to the classical duodenal switch operation. Another example is the transit bipartition which saves the pyloric function and the duodeno-jejunal protein absorptive effect, and provides at the same time a distal malabsorptive component, thereby achieving the intended weight reducing and metabolic outcome. Jejuno-ileal and duodeno-ileal interposition seem also to add a significant entero-hormonal effect to the constructed sleeve. EndoBarrier is also a recent minimally invasive procedure which produces a reasonable anti-diabetic outcome. Similarly, different trials for recent endoscopic approaches are currently in the evaluation phase. Added to this, several gastric space occupying modalities have also been tried.

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3.1 Introduction

In 2005, 23.2 % (937 million) of the world's adult population was overweight, and 9.8 % (396 million) was obese. According to current projections, the number of overweight individuals will increase from 2005 to 2030 by 44 %, to reach a total of 2.16 billion, corresponding to 38 % of the world's adult population (Kelly et al. 2008). During the same interval, the number of obese individuals will increase by 45 % to reach a total of 1.12 billion (20 % of the world's adult population).

In 2005, the **prevalence of overweight** was higher in economically developed countries compared to developing countries (35.2 vs 19.6 %). Similarly, the prevalence of obesity was higher in developed countries compared to developing ones (20.3 vs 6.7 %). However, growth in population size, aging, urbanization of lifestyle all will contribute to an epidemic of overweight and obesity in developing regions in the next few decades (Kelly et al. 2008).

This overwhelming increase in the prevalence of morbid obesity with its associated comorbidities pushed institutions worldwide to search for new minimally invasive modalities to face this epidemic. Over the past years, standard procedures like biliopancreatic diversion (BPD), duodenal switch (DS), gastric banding (LAGB), and Roux-en-Y gastric bypass (RYGB) established their position in the armamentarium of bariatric procedures. More recently, new surgical as well as endoscopic bariatric procedures started to replace, or at least compete with these standard procedures. In this chapter, we will focus on the evolution of sleeve gastrectomy (SG), mini gastric bypass (MGB), as well as other bariatric procedures, which depend primarily on **sleeve gastrectomy** as a restrictive element. Recent endoscopic procedures will also be highlighted.

3.2 Surgical Procedures

3.2.1 Sleeve Gastrectomy

The worldwide map has been showing a tremendous tendency towards more performance of SG. Few years ago, it was just regarded as the newest member in the family of bariatric surgical interventions. But recent reports anticipate that SG could be the leading bariatric surgical intervention in the near future (Buchwald and Oien 2009, 2013).

In 2003, this procedure was not actually reported as a standalone surgical intervention. In 2008, more than 4,000 SG's were performed, still far below the performance rates of other standard procedures, namely RYGB (26,000, 39 %) and gastric banding (28,000, 43 %) (Buchwald and Oien 2009). This was however a clue for a tendency of growth. In 2011, more than 31,000 (27 %) SG were performed, exceeding gastric banding (20,000, 17 %) but still below RYGB (49,000, 43 %) (Buchwald and Oien 2013). This represented however a more

than fivefold growth rate of this recent procedure, compared to only 88 % growth of RYGB. In Europe, again this fivefold growth rate of SG was reported between 2008 and 2011, compared to only doubling of RYGB. In the same interval, a 40 % drop in gastric bands was documented (Buchwald and Oien 2013).

Another study analyzed the trend of bariatric surgical intervention in USA from the last quarter of 2008 through the third quarter of 2012 (Nguyen et al. 2013). Data showed a steep increase in the performance rate of SG from 0.9 to 36.3 %, with a concomitant decrease in the use of laparoscopic RYGB from 66.8 to 56.4 %, and of **laparoscopic gastric bands** from 23.8 to 4.1 %. This was associated with an increase in the number of institutions performing laparoscopic sleeve gastrectomy. The number of those performing laparoscopic RYGB and gastric bands remained stationary throughout the period (Nguyen et al. 2013). Analysis of these data leaves few doubts that SG could be the future leading procedure of bariatric intervention.

Buchwald and his colleagues proposed a possible explanation for this phenomenon (Buchwald and Oien 2013). Every procedure goes through an ascending, then stable or maturity phase, and passes to an aging phase, where new procedures start to replace it to avoid the encountered long-term complications or the unsatisfactory outcome attributed to such a traditional procedure. This applies to gastric banding in Europe, where the oldest bands were placed, and to RYGB in USA where they were first practiced. This decline contrasts with the flourishing of SG, which is currently accepted by the ASMBS as a **standalone bariatric surgical intervention** (ASMBS 2012).

Compared to RYGB, SG seems to be a relatively easier and quicker procedure. Moreover, it can be practiced in super–super obese patients, in whom RYGB would require greater technical and surgical command. SG also showed very reasonable results, in terms of its weight loss outcome. Data from the fourth international consensus summit on sleeve gastrectomy reported excess weight loss (%EWL) from 50 to 60 %, up to 6 years after SG (Gagner et al. 2013).

SG proved to have significant antidiabetic efficacy, which ranged from 60 to 90 % in recent reports (Rao and Kini 2012). This efficacy was almost comparable to that encountered after the gold standard RYGB at 1 and 2 years postoperatively (de Gordejuela et al. 2011). Proper patient selection assures better postoperative diabetes improvement or remission. Patients with a shorter history of diabetes, those with a less severe diabetic state, and those who encounter better weight loss are candidates for a better antidiabetic effect. Although long-term results are still lacking, 3 years follow-up studies showed an up to 80 % diabetes free status (Abbatini et al. 2010). A recent nationwide survey in Germany reported a 6-year antidiabetic efficacy of SG of 59 %, which was lower than the standard RYGB (83 %), but still promising (Weiner et al. 2014).

Another factor is possibly the lower cost of SG, compared to RYGB. Nguyen and his colleagues reported lower hospital costs (USD $\$13.081 \pm 4.471$ vs $\$14.401 \pm 3.851$, respectively) and shorter length of stay (2.07 ± 0.92 vs 2.26 ± 1.04 days, respectively) (Nguyen et al. 2013).

A large study from the USA reported that rates of serious **complications after SG**, although higher than those encountered after gastric banding (2.2 % versus 0.9 %), were lower than after RYGB (3.6 %). Additionally, no mortality was

encountered, versus 0.04 % after gastric banding and 0.14 % after RYGB (Birkmeyer et al. 2010). Reports from the American College of Surgeons (Hutter et al. 2011) stated that 30-day morbidity rates after SG are comparable to those after RYGB (5.61 vs. 5.91 %, respectively). Similarly, 30-day readmission rates were comparable in both procedures (5.40 vs 6.47 %, respectively).

In our opinion, another point which played a role in widespread performance of sleeve gastrectomy is the lack of standard second-step procedures in patients with non-satisfactory outcome after RYGB. The available few options after failed RYGB include for example banded RYGB (with subsequent foreign-body-attributed side effects) or distalization (with severe malabsorptive outcome, if patients are not properly monitored). On the other hand, sleeve gastrectomy can be considered as a first-step procedure. If not followed by the expected antiobesity or antidiabetic outcome, it can be converted into malabsorptive second-step procedures, which have a significant additional outcome. Those include for example single anastomotic (**mini) gastric bypass**, SADI-S (single anastomotic duodenoileal bypass sleeve) and the classical BPD-DS. Mini gastric bypass and SADI-S are expected, in our opinion, to have a leading role—either as primary or revisional procedures—in the next few years.

3.2.2 Mini Gastric Bypass

Analysis of worldwide bariatric practice in 2008 didn't mention MGB (Buchwald and Oien 2009). In 2011, more than 5,000 MGBs were performed worldwide, accounting for about 1.5 % of bariatric practice, which was almost the same as the classical BPD-DS, both coming directly after SG (Buchwald and Oien 2009). We expect flourishing of MGB in the next few years. MGB is a relatively safer and easier alternative, entailing a single anastomosis, with a shorter operative time and lower complication rate compared to the gold standard RYGB (Lee et al. 2012; Peraglie 2008). It omits also the possibility of developing postoperative internal herniation (Fig. 3.1).

Despite its relatively recent nature, this procedure achieved very satisfactory weight loss results for up to 5 years. At 1 year postoperatively, %EWL ranged from 57 % in small-sized studies up to 86 % in larger ones (Mahawar et al. 2013). Results of 80 % EWL at 18 months were reported. At 2 years postoperatively, %EWL ranged from 64 to 92 % in large series. Promising long-term results were reported 5 years postoperatively, EWL exceeding 70 % (Lee et al. 2008). Noun et al. (2007), reported more or less similar results of EWL, reaching 68 % when they followed the patients for up to 5 years.

MGB is in our opinion a promising revisional procedure after a failed sleeve. We analyzed our results in revision, due to insufficient weight loss or comorbidity improvement after sleeve gastrectomy (Weiner et al. 2011). MGB achieved a BMI loss which was significantly higher than that achieved after re-sleeve, RYGB, and banded sleeve as possible alternatives for insufficient weight loss after initial sleeve. The BMI drop experienced with MGB was lower than that encountered

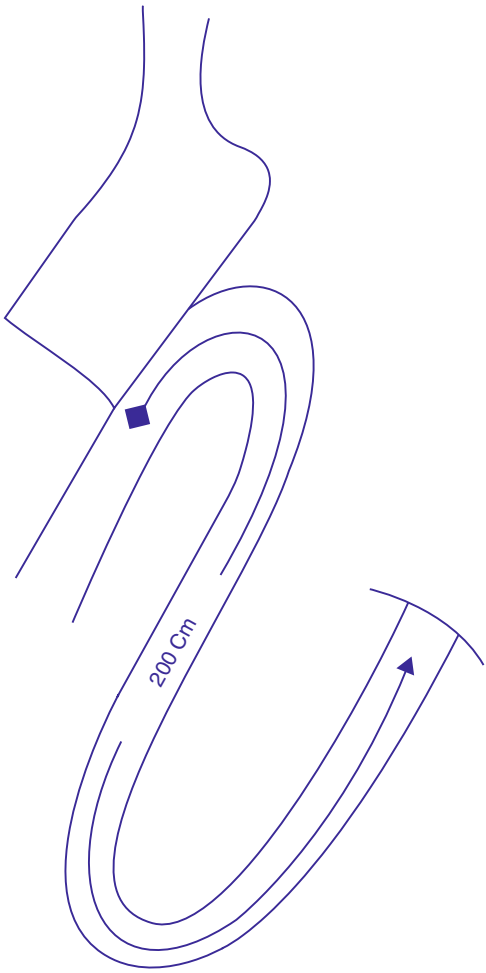

Fig. 3.1 Mini-gastric bypass

with BPD-DS as a possible revisional alternative, but the feasibility of MGB should be put in consideration. In their series of 24 patients, Chakhtoura et al. (2008) converted patients with prior LAGB and vertical gastroplasty using MGB. Rutledge (2006) reported an EWL of 79 % at 1 year follow-up after converting patients with history of LAGB in MGB. Wang et al. (2004), in a series of 29 patients, reported promising results of converting patients with vertical gastroplasty in MGB.

The reported **antidiabetic efficacy** of a relatively simple procedure like MGB is another supporting factor for its further worldwide spread in the next years. 87 % of patients in the series reported by Lee et al. (2008), experienced successful treatment of their diabetic state. His results were more promising in patients with BMI of more than 35 kg/m^2, who showed a noticeable reduction of their glycosylated hemoglobin levels within 1 year after surgery. A diabetes resolution rate of 90 % was reported by

Piazza et al. (2011). Kim and Hur (2011), reported a diabetic resolution rate of 70 % in a series of ten patients. Recent reports demonstrated a higher tendency for diabetes remission with MGB, relative to SG (Milone et al. 2013).

3.2.3 *Other Recent Bariatric Procedures Involving SG as a Restrictive Element*

Several studies discussed the combination of SG (as a restrictive element), with malabsorptive elements, to augment its metabolic and/or weight loss effects. These are all recent procedures with promising results. However, several critical questions are still in need to be thoroughly answered before accrediting these procedures as weight loss/metabolic procedures, and applying them on a large scale. For example, they still lack long-term results. Second, can these procedures be implemented as a second step, in patients who don't achieve satisfactory results with SG alone? Third, comparative studies between these procedures are currently lacking, namely with BPD/DS and with each other, regarding their metabolic/bariatric outcome.

3.2.4 *Single Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy*

In 2010, Sánchez-Pernaute et al. published the 3-year postoperative results of their innovative SADI-S technique (Fig. 3.2). This operation entails transection of the first part of the duodenum after construction of a sleeve-like stomach. The transected duodenum is then anastomosed to an ileal loop, with the anastomosis lying 200 cm proximal to the ileocecal junction.

It has the advantages of the classical BPD/DS, but avoids the risks associated with creating several anastomoses and mesenteric windows. Additionally, the operative time will be shorter. Another advantage here is that the preserved pyloric sphincter will relieve the possibility of gastric pouch cancer development associated with biliary reflux, which is encountered in MGB. This preserved pylorus will also be highly prophylactic against any dumping symptoms, associated with either classical RYGB or MGB. Compared to the classical RYGB, it will have a greater malabsorptive component, with resultant weight loss and comorbidity control. The published results showed excellent weight reduction results. Three months postoperatively, mean %EWL reached 53 %. At 6 months, it exceeded 81 % and reached 87 % at 9 months. %EWL at 1 year reached 94 % and continued to increase to reach 98 % at 18 months and 114 % at 2 years, a percentage which was maintained through the third year.

Among the 50 patients, there were 27 patients with diabetes mellitus (DM) type 2. Mean blood glucose levels dropped from a preoperative value of 174 mg/dl to

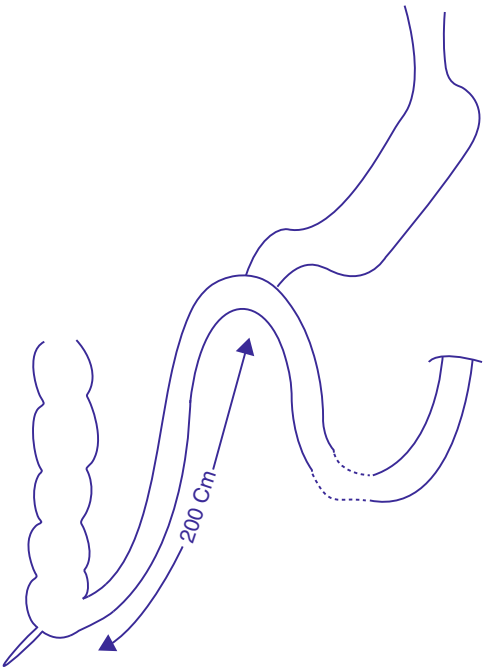

Fig. 3.2 Single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S)

97 mg/dl. All diabetic patients stopped their antidiabetic treatment within 6 months after the operation. Resolution of other comorbidities was also achieved.

In 2014, Lee et al. published results of 50 morbidly obese patients who underwent a similar procedure called **single-anastomosis duodenal–jejunal bypass** with Sleeve Gastrectomy (SADJB-SG). They referred to it also as a short or **mini-duodenal switch** (Fig. 3.3). It entails a duodeno-jenunal rather than the duodeno-ileal bypass performed by Sánchez-Pernaute et al. Sleeve gastrectomy was performed using a 45Fr bougie, starting 6 cm proximal to the pylorus. A single loop anastomosis was however performed at a distance of 150–200 cm from the ligament of Treitz, to a transected sleeve stomach, at the level of the proximal duodenum (unlike Sánchez who constructed his anastomosis 200 cm proximal to the ileocecal junction). They compared 1-year results prospectively, with classical RYGB (with a 100 cm long biliopancreatic limb and a 150 cm long alimentary limb) and with MGB (a single loop anastomosis to a longer proximal gastric pouch, 150–200 cm distal to the ligament of Treitz).

In this report, operative time and hospital stay were significantly longer than RYGB and MGB. This may be due to practicing a new procedure, compared to a much higher experience in RYGB and MGB. However, %EWL was significantly higher, compared to RYGB and MGB (80.3 %, 63.4 %, and 68.6 % respectively). Serum high-density lipoprotein level was also significantly higher after SADJB-SG, compared to RYGB and MGB (53.6 mg/dl, 38.6 mg/dl, and 47.1 mg/dl respectively). Unexpectedly, serum cholesterol level was significantly higher after SADJB-SG, compared to RYGB and MGB (188.1 mg/dl, 151.5 mg/dl, and

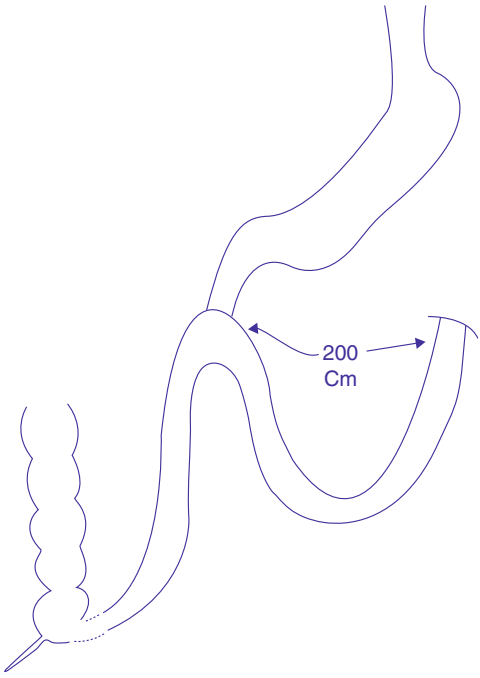

Fig. 3.3 Single-anastomosis duodenal–jejunal bypass with sleeve gastrectomy (SADJB-SG)

173.8 mg/dl respectively). Similarly, low-density lipoprotein level was significantly higher after SADJB-SG, compared to RYGB and MGB (114.7 mg/dl, 73.1 mg/dl, and 111.9 mg/dl respectively). They didn't have a reasonable explanation for this finding. On the other hand, mean glycosylated hemoglobin (HbA1c) level one year after surgery dropped from 9.2 % before surgery to 6.1 % one year after surgery, and 64 % of the diabetic patients showed complete remission.

In the same year, Mui et al. (2014) published 1-year follow-up results of a case report for a novel technique, involving a loop gastroileostomy, with the anastomosis constructed at a distance of 250 cm from the ileocecal junction (Fig. 3.4). They claim that tailoring of this anastomosis will reduce the sleeve tube pressure, which plays a central role in post sleeve gastrectomy leakage. Moreover, gastrografin imaging showed that the preferential contrast passage through the anastomosis obviates the need for duodenal transection. This patient was diabetic, with a BMI of 33 kg/m^2 and HbA1c of 10.1 %. At 1 year postoperatively, his BMI dropped to 23.3 kg/m^2 and his HbA1c dropped to 4.8 %, with complete withdrawal of antidiabetic therapy 2 months after the operation. This patient developed however mild hypoalbuminemia and anemia, compared to baseline. This might be explained by the preferential passage of food material through the anastomosis, with resultant bypass of intestinal segments.

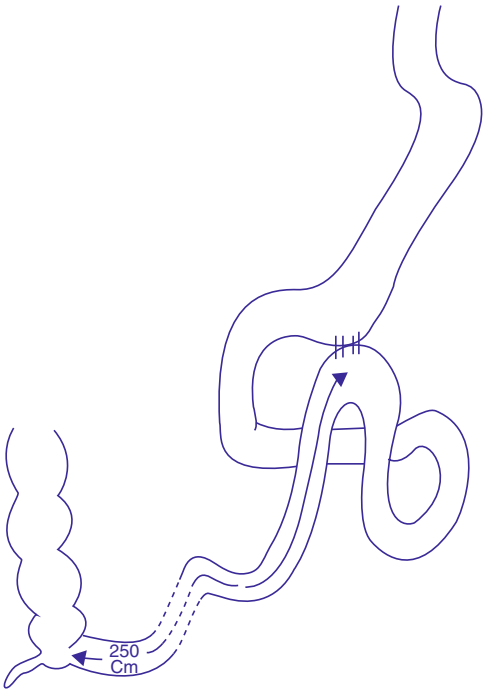

Fig. 3.4 Sleeve gastrectomy with loop bipartition

3.2.5 Sleeve Gastrectomy with Roux-en-Y Duodeno-jejunal Bypass

Several studies in the literature assessed the effect of constructing a sleeve stomach and anastomosing it in a Roux fashion to an intestinal alimentary limb, aiming at achieving a duodeno-jejunal bypass (Tables 3.1 and 3.2, Fig. 3.5). A combined mechanism of action is achieved in this way: the bypass of small intestinal segments contributes to the foregut–hindgut hypothesis formerly described by Rubino (Rubino et al. 2006; Cummings et al. 2007). The constructed sleeve adds a restrictive element together with the reduction in orixigenic ghrelin hormone levels (Langer et al. 2005; Karamanakos et al. 2008).

3.2.6 Sleeve Gastrectomy with Transit Bipartition

In 2012, Santoro et al. published results of transit bipartition in more than 1,000 patients. This large-sized series discussed the technique and outcome of a novel procedure, based on anastomosing a Roux-en-Y ileal loop to the lowest part of the

Table 3.1 Results of Roux-en-Y duodeno-jejunal/ileal bypass procedures combined with sleeve gastrectomy

	Author and year	Mean operative duration (min)	Number of patients	Bougie size (Fr)	Length of BPL (cm)	Length of alimentary limb (cm)	Length of CC (cm)	Complications: Number (%)	%EWL (follow-up duration in months)								
									3	6	9	12	18	24	36	48	60
Sleeve gastrectomy with transit bipartition	Santoro et al. (2012)	170	1,020	36	–	180	80	• Fistula: 9 (0.9) • Bleeding: 8 (0.8 %) • Reoperation: 19 (1.9 %)	46.3	72.2	91			94	85	78	74
Sleeve gastrectomy with Roux-en-Y duodeno-jejunal bypass	Raj et al. (2012)	143	38		–	–	–	Reoperation due to internal herniation in 1 patient	34	60		71	73				
	Navarrete et al. (2011)	148	10	60	50	100	–	• Transfusion due to intra-abdominal bleeding in 1 patient • Surgical wound infection in 1 patient				Average weight loss = 8.5 kg					
	Kasama et al. (2009)	217	21	45	50–100	150–200	–	Reoperation due to leak at angle of His in 1 patient	47	63	66	78	96				

BPL biliopancreatic limb, *CC* common channel

Table 3.2 Results of Roux-en-Y duodeno-jejunal/ileal bypass procedures combined with sleeve gastrectomy

	Author and year	Effect on diabetes mellitus	Effect on hyperlipidemia	Effect on hypertension	Effect on respiratory problems	Effect on orthopedic complains	Follow-up duration
Sleeve gastrectomy with transit bipartition	Santoro et al. (2012)	• 86 % complete remission • 14 % improvement	• Hypertriglyceridemia improved in 85 % of patients • Hypercholesterolemia improved in 70 % of patients	Resolution in 72 % of patients	• 91 % resolution • 9 % improvement	• 83 % resolution • 17 % improvement	5 years in 59.1 % of patients
Sleeve gastrectomy with Roux-en-Y duodeno-jejunal bypass	Raj et al. (2012)	• Remission in 19 patients (73 %) • Improvement in 5 patients (19 %) • Dropped level of HbA1c in 2 patients (8 %)	• Resolution in 19 patients (86 %) • Improvement in 3 patients (14 %)	• Resolution in 11 patients (69 %) • Improvement in 3 patients (19 %) • No effect in 2 patients (12 %)			Mean follow-up period of 17 months
	Navarrete et al. (2011)	• Remission in 4 patients (40 %) • Improvement in 3 patients (30 %) • Control in 3 patients (30 %)	Serum cholesterol and triglyceride levels are normalized in all patients				12 months
	Kasama et al. (2009)	• 93 % resolution (13 patients) • 7 % improvement (1 patient)	Resolution in 11 patients (100 %)	• Resolution in 7 patients (86 %) • Improvement in 1 patient (14 %)			18 months

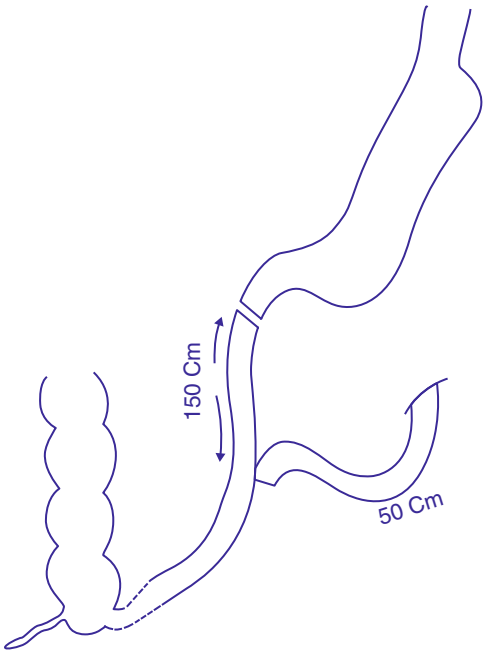

Fig. 3.5 Sleeve gastrectomy with Roux-en-Y duodeno-jejunal bypass

constructed sleeve without duodenal dissection or division (Fig. 3.6). It is a simplified modification of BPD/DS omitting the step of duodenal division. This has several advantages. First, duodeno-jejunal bypass avoids excessive absorption of fat rich diet in obese patient, which prove to be exaggerated in the first 70 cm of the small bowel. Second, ileal shift of nutrients induces enterohormonal changes with resultant stimulation of secretion of glucagon-like peptide 1 (GLP-1), which is a fasting state-inducing distal bowel hormone, with significant antidiabetic effect (Santoro et al. 2012; De Paula et al. 2010).

At the same time, maintaining the passage of nutrients through the duodeno-jejunal tract, although much lower than in normal, will avoid the undesirable malnutritional outcome encountered in BPD/DS, mainly the hypoalbuminemic state. Maintaining an endoscopic access to the duodeno-jejunal segment is another privilege of this procedure over the classical BPD/DS (Santoro et al. 2012). Tables 3.1 and 3.2 summarizes the results of some published Roux-en-Y duodeno-jejunal/ileal bypass procedures combined with sleeve gastrectomy.

3.2.7 Ileal Interposition

De Paula and other authors published several series, since the middle of the last decade till recently (DePaula et al. 2008, 2012; Kota et al. 2012; Goel et al. 2011;

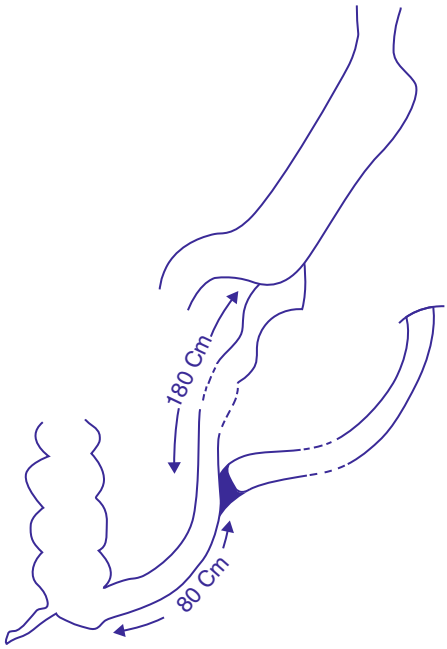

Fig. 3.6 Sleeve gastrectomy with transit bipartition

Tinoco et al. 2011; Kumar et al. 2009). They discussed the outcome of a novel technique including a combination of ileal interposisition and sleeve gastrectomy. Ileal interposition focuses on inducing a neuroendocrine brake, aiming at ameliorating the effects of metabolic syndrome, apart from its weight reduction effects. This technique included two different modalities: the duodenal ileal interposition-sleeve gastrectomy, DII-SG (Fig. 3.7), and the jejunal–ileal interposition-sleeve gastrectomy, JII-SG (Fig. 3.8, Tables 3.3, 3.4, 3.5, and 3.6) (DePaula et al. 2008, 2012).

Sleeve gastrectomy and fundal resection are followed by a considerable reduction in serum ghrelin levels, an orexigenic hormone, which is involved in inducing acute insulin resistance (Vestergaard et al. 2008). Adding an ileal interposition was proved to be followed by a considerable spike in serum levels of GLP-1, GIP, and peptide YY (DePaula et al. 2008). Early contact of nutrients with the interposed ileum, with subsequent hormonal brake, lead to restoration of the early phase of insulin secretion, which is impaired in those patients. Additionally, hypertrophy of pancreatic beta cells and inhibition of glucagon release were noticed. Interleukin-6, leptin, and resistin also decreased postoperatively. Adiponectin levels showed an increase after ileal interposition, and it is known that hypoadiponectinemia is

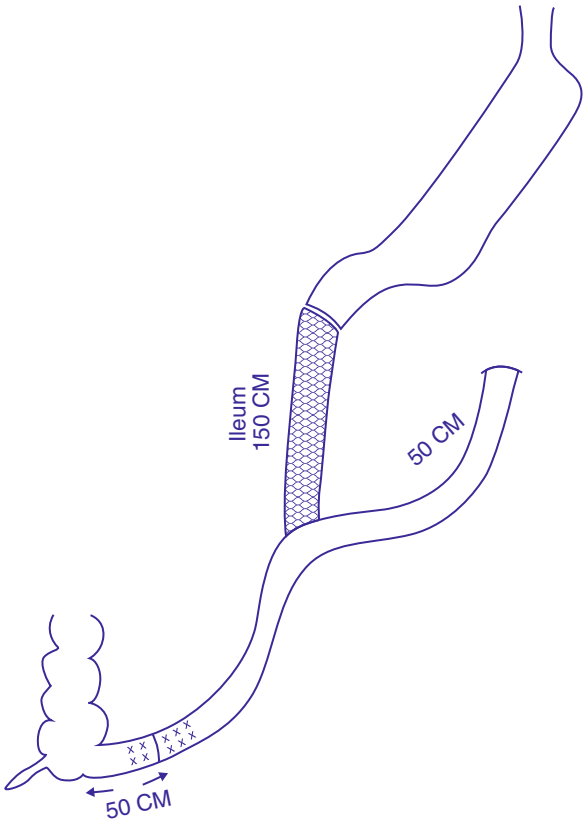

Fig. 3.7 Duodenal ileal interposition-sleeve gastrectomy, DII-SG

related to the degree of insulin resistance, and considered an indicator of metabolic syndrome (DePaula et al. 2008).

Improvement in parameters of metabolic syndrome after this procedure reached figures similar to those achieved after RYGB, SG, and even BPD-DS (Schauer 2005; Frezza et al. 2009). Surprisingly, metabolic results were not related to the initial BMI in this group of patients, and were also not related to the postoperative BMI (DePaula et al. 2012). These operations lead to significant metabolic improvements in patients with BMI less than 30 kg/m^2, in whom glucose control was not related to postoperative weight loss (DePaula et al. 2009).

A prospective randomized comparison between JII-SG and DII-SG showed the latter to show a greater decrease in postoperative HbA1c levels (De Paula et al. 2010). This could be explained by duodenal exclusion and suppression of the so-called foregut "**Rubino factor**," which is supposed to be responsible for insulin resistance in those patients (Rubino and Marescaux 2004). Another explanation is the higher shift of the interposed ileal segment in DII-SG, with subsequent

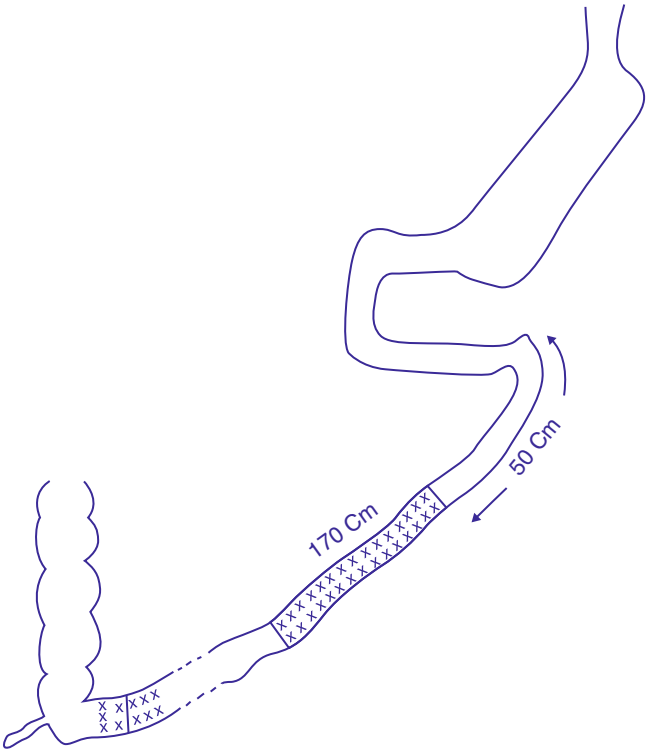

Fig. 3.8 Jejunal–ileal interposition-sleeve gastrectomy, JII-SG

earlier nutrient ileal contact and GLP-1 release. That is why we think that these procedures would be of greater effect in severely diabetic obese subjects.

DII-SG, despite its close similarity to the classical BPD/DS, excludes only the duodenum and the proximal 50 cm of the jejunum. It avoids the documented malnutritional outcome after the latter, while maintaining the intended hormonal brake (DePaula et al. 2012).

3.2.8 Sleeve Gastrectomy Plus Side-to-Side Jejunoileal Anastomosis

Melissas et al. (2012) published results of a novel procedure involving an isoperistaltic jejunoileal anastomosis. Anastomosis was done between two loops, the proximal 100 cm distal to the ligament of Treitz, and the distal 100 cm proximal to the ileocecal valve (Fig. 3.9). The procedure was performed in 32 patients, who were followed for 6–24 months. Eight diabetic patients showed complete remission, and one showed marked reduction of insulin requirements. Nine hypertensive

Table 3.3 Results of studies addressing ileal interposition

Author and Year	Number of patients	Sleeve bougie size (French)	Type of operation	Preoperative BMI (kg/m^2) mean ± SD (Range)	Age Mean ± SD (Range)	Gender m/f	Follow-up in months mean ± SD (Range)	Complications	Mortality	Mean postoperative BMI (±SD) (kg/m^2)
De Paula et al. (2010)	202	38	• JII-SG (125 patients) • DII-SG (77 patients)	29.7 ± 3.5 (21.5–34.9)	52.2 ± 7.5 (29–72)	70.8 % / 29.2 %	39 ± 9 (25–61)	1 % leak rate	• Early:1 % • Late:1 %	23.5 ± 3.1[a]
Kota et al. (2012)	17	32–60	DII-SG	29.2 ± 7.5 (22.4–37.5)	50.7 ± 8.1 (34–66)	12/5	9.1 ± 5.3 (3–21)	Ileal perforation (1 patient)	None	22.1 ± 2.9[a] after 1 year
Goel et al. (2011)	5	36	JII-SG	29.4	47.33	2/3	6	No major complications	None	Mean BMI drop was 8.4 kg/m^2
Tinoco et al. (2011)	30	32	JII-SG	30.8 ± 5.1	49.7 ± 8.9	20/10	13 ± 3.3 (6-18)	• Metabolic ketoacidosis (1 patient) • Urinary tract infection (1 patient) • Diarrhea (2 patients)	None	25.7 ± 4[a]
Kumar et al. (2009)	10	32–58	JII-SG	33.8 ± 6.5 (25.5-45.5)	48.2 ± 9 (34-62)	4/6	2-16	No major complications	None	26.2

BMI Body Mass Index, *SD* standard deviation

[a]Significant change compared with the preoperative value

Table 3.4 Results of studies addressing ileal interposition

	Mean (±SD) HbA1c level (gm/dl)		Mean (±SD) fasting blood glucose (mg/dl)		Postprandial glucose level (mg/dl)	Diabetes mellitus remission (%)	Comments
	Preoperative	Postoperative	Preoperative	Postoperative			
DePaula et al. (2012)	8.7 ± 1.7	6.1 ± 1.1[a]	202.1 ± 1.7	112.2 ± 30[a]	Mean dropped from 263.3 ± 101.5 preoperatively to 130 ± 45.7 postoperatively[a]	86.4	Mean daily insulin requirement dropped from 48.9 units to 15 units.
Kota et al. (2012)	9.8 ± 1.8	6.6 ± 0.6[a] after 1 year	236.5 ± 88.4	103.1 ± 18.2[a] after 1 year	Mean dropped from 305.1 ± 124.3 preoperatively to 138.4 ± 38.9 1 year postoperatively[a]	70	
Goel et al. (2011)	9 ± 0.7	6.2 ± 0.2	256.8 ± 40.99	158 ± 25.5	49.6 % reduction postoperatively	40	Mean daily insulin requirement reached 90.3 units preoperatively and was stopped within 5 months postoperatively.
Tinoco et al. (2011)	9.5 ± 1.7	6.2 ± 1.8[a]	201 ± 78.5	99.6 ± 19.7[a]		80	
Kumar et al. (2009)	Ranged from 8.7 to 15.8	Ranged from 5.7 to 8.5	No significant change			70	

SD standard deviation, *HbA1c* glycosylated hemoglobin

Remission was differently defined according to each author. De Paula et al. defined complete remission as: a return to "normal" measures of glucose metabolism, HA1C below 6, and fasting glucose <100 mg/dl, for at least 1 year, with no active pharmacologic therapy. Kota et al. and Tinoco et al. defined it as HbA1c <6.5 % without requiring oral or parenteral hypoglycemic agents. Goel et al. defined it as glycemic control with discontinuation of pharmacologic therapy or ongoing procedures for 6–12 months. Kumar et al. defined it as HbA1c <7 % without requiring oral or parenteral hypoglycemic agents

[a]Significant change compared with the preoperative value

Table 3.5 Results of studies addressing ileal interposition

	Effect on lipid profile							
	Effect on serum LDL level (mean ± SD) (mg/dl)		Effect on serum cholesterol level (mean ± SD) (mg/dl)		Effect on serum triglyceride level (mean ± SD) (mg/dl)		Effect on mean HDL level (mg/dl)	
	Preoperatively	Postoperatively	Preoperatively	Postoperatively	Preoperatively	Postoperatively	Preoperatively	Postoperatively
DePaula et al. (2012)	107.3 ± 37.4	90 ± 25.6[a]	204.7 ± 53.2	160.1 ± 28.3[a]	273.4 ± 222.2	110.3 ± 66.1[a]	45.5 ± 19.9	49.9 ± 13.4
Kota et al. (2012)	97.4 ± 41.7	83.1 ± 15.1[a] after 1 year	164.2 ± 52.7	135.3 ± 18.2[a] after 1 year	184.8 ± 85.8	88.5 ± 27.7[a]	Not available	
Goel et al. (2011)	Not available							
Tinoco et al. (2011)	Not available							
Kumar et al. (2009)	No significant change		No significant change		No significant change		No significant change	

LDL low-density lipoprotein, *HDL* high-density lipoprotein
[a]Significant change compared with preoperative value

Table 3.6 Results of studies addressing ileal interposition

	Cardiovascular events	Renal effects	Retinopathy
DePaula et al. (2012)	• Remission of hypertension in 87.5 % of patients • Cardiovascular events were detected preoperatively in 24.8 % of patients and postoperatively in 2.5 % of patients	• Resolution of microalbuminuria was achieved in 71.1 % of patients • Mean microalbuminuria level dropped from 99.7 ± 193.2 to 37.5 ± 91.5 μg/min postoperatively[a]	
Kota et al. (2012)	87.5 % remission	• Mean microalbuminuria level dropped from 42.5 ± 30.1 to 16 ± 7.8 mg/24 h 1 year postoperatively[a]	
Goel et al. (2011)	• Mean systolic blood pressure dropped from 141 ± 11.6 to 118 ± 3.7 mm/Hg • Mean diastolic blood pressure dropped from 83 ± 4.3 to 80 ± 4.4 mm/Hg	31.1 % reduction in serum creatinine level	
Tinoco et al. (2011)			
Kumar et al. (2009)	100 % remission	No significant changes	Was detected in one patient and improved markedly after operation.

[a]Significant change compared with preoperative value

patients and seven with dyslipidemia exhibited complete remission. No major perioperative events were encountered. Mean %EWL at 12 months was 77 %, significantly higher than among patients who underwent simple SG (Melissas et al. 2012).

3.3 Endoscopic Procedures

These modalities have promising results; however, they are still in the infancy, with lack of long-term results and large-sized studies.

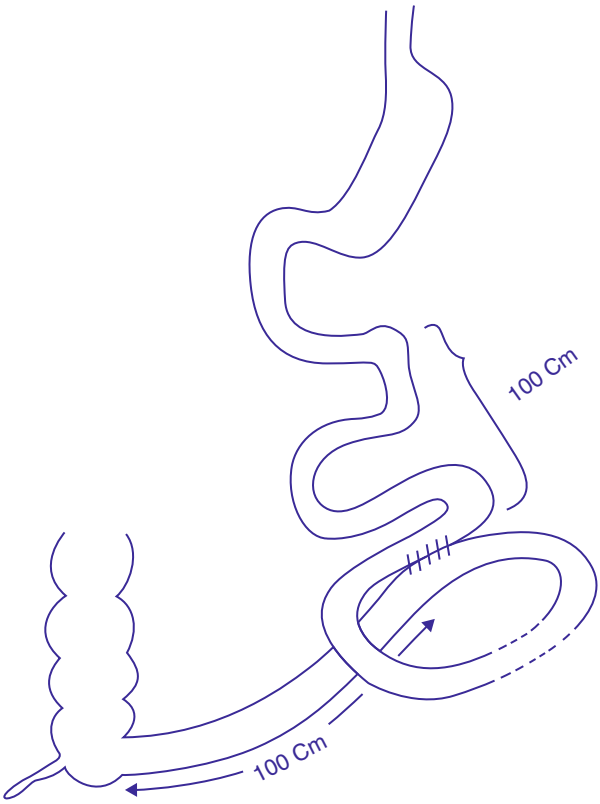

Fig. 3.9 Sleeve gastrectomy plus side-to-side jejunoileal anastomosis

3.3.1 EndoBarrier

The Duodenal–jejunal bypass sleeve (DJBS, EndoBarrier Gastrointestinal Liner; GI Dynamics Inc., Lexington, Massachusetts, USA) is a relatively recent metabolic/bariatric minimally invasive procedure. The idea was to develop new strategies which can achieve reasonable results, as stand-alone procedure, or a first step prior to definitive surgical intervention, in better general and metabolic patient state (Gersin et al. 2007, 2010; Rodriguez-Grunert et al. 2008; Tarnoff et al. 2009; Rodriguez et al. 2009; Schouten et al. 2010; de Moura et al. 2011, 2012).

It is an endoscopically and fluoroscopically inserted 60-cm impermeable fluoropolymer liner implant, usually terminating in the proximal jejunum, being open at both ends, with a nitinol anchor, which reversibly fixes the device to the wall of the duodenum. The reversibility of this procedure is a definite advantage for this procedure, compared to the technically demanding reversibility of bariatric surgical intervention.

This procedure helps in metabolic control of Type II diabetes and in weight loss (Patel et al. 2012) (Table 3.7). Its function is based on preventing the ingested food from contacting the proximal intestine (duodenum and proximal jejunum). The

Table 3.7 Effect of EndoBarrier on weight loss and metabolic control

	Duration of study	Number of patients	Mean basal BMI (kg/m^2)	Comorbidities	Weight loss	Effect on comorbidities	Complications	Preterm removal
Gersin et al. (2007)	12 weeks	1	45.2 (119.5 kg)	Dyspnea, arthritis, depression, hyperlipidemia, GERD	9.5 kg			
Rodriguez-Grunert et al. (2008)	12 weeks	12	43	Diabetes mellitus (4 patients)	%EWL = 23.6 %	Cessation of hypoglycemic medications in the entire 12 weeks	1. Pharyngeal tears in 2 patients 2. Implant site inflammation in all patients 3. Episodes of: • Abdominal pain (6) • Nausea (18) • Vomiting (16)	2 patients after 9 days (due to poor device placement)
Tarnoff et al. (2009)	12 weeks	25	42	Diabetes mellitus (3 patients)	%EWL = 12 %	• Diabetes resolution (1 patient) • Diabetes improvement (2 patients)	• Mild degree of residual duodenal inflammation was noted in 8 patients 4 weeks post-explant. • Non cardiac chest pain related to insertion procedure (1 patient) • The following events were reported in	5 patients • Sleeve obstruction (1) • Anchor migration (1) • Upper GI bleeding (3)

(continued)

Table 3.7 (continued)

	Duration of study	Number of patients	Mean basal BMI (kg/m^2)	Comorbidities	Weight loss	Effect on comorbidities	Complications	Preterm removal
							16 patients (number of attacks) – Abdominal pain (16) – Nausea (7) – Vomiting (8) – Abdominal distension (11) – GI bleeding (4) – Constipation (1) – Epigastric discomfort (1)	
Rodriguez et al. (2009)	24 weeks	12	38.9	• Diabetes mellitus (12 patients) • Hypertension (7 patients) • Hyperlipidemia (3 patients)	Mean weight loss at 20 weeks = 10.2 kg	• 40 % of patients stopped treatment with oral hypoglycemic drugs • Mean HbA1c level dropped from 9.2 % to 7.8 % • Mean FPG changes of 83 mg/dl	The following events were reported (number of attacks): • Upper abdominal pain (2) • Vomiting (7) • Nausea (5) • Hypoglycemia	2 patients
Gersin et al. (2010)	12 weeks	21	40	• Diabetes mellitus (67 %) • Heart diseases (10 %) • Hypertension (57 %)	Mean % EWL = 11.9 %		The following events were reported (number of attacks): • Upper abdominal pain (14)	8 patients: • GI bleeding (3 patients) • Abdominal pain (2 patients) • Nausea and

				• Dyslipidemia (43 %)			• Procedural nausea (10) • Nausea (6) • Procedural vomiting (6)	vomiting (2 patients) • Unrelated pre-existing illness (1 patient)
Schouten et al. (2010)	6 months	30	48.9	• Diabetes mellitus (8 patients) • Hypertension (15 patients) • Hyperlipidemia (6 patients)	• %EWL = 19 % at 12 weeks 24.3 % • %EWL = 24.3 % at 24 weeks (3 patients)	At 12 weeks: • Drop of FPG from 11.1 to 9.3 mmol/l • Drop of HbA1c from 8.8 to 7.7 %	At least one adverse event in all patients (mainly abdominal pain and nausea during the 1st week)	4 patients: • Anchor migration (1 patient) • Anchor dislocation (1 patient) • Sleeve obstruction (1 patient) • Continuous epigastric pain (1 patient)
De Moura et al. (2011)	6 months	77	43.8	• Diabetes mellitus and obesity in all patients • Hypertension in 86.1 % of patients • Hyperlipidemia in 36.7 % of patients	• Average %EWL of 12.6 % • A significant association was found between % EWL of more than 10 % of initial weight and control of TG/HDL ratio	• A significant reduction of average TG/HDL ratio from 5.75 to 4.36 in 54 patients, of those 23 patients showed a significant reduction from 5.15 to 2.85 (resolution of insulin resistance) • All patients showed a significant improvement in HbA1c levels	Minor ulcer formation in few patients	16 patients • Device migration (9 patients) • Free device anchor (4 patients) • Bleeding (1 patient) • Decision of researcher (1 patient) • Patient request (1 patient)

(continued)

Table 3.7 (continued)

	Duration of study	Number of patients	Mean basal BMI (kg/m^2)	Comorbidities	Weight loss	Effect on comorbidities	Complications	Preterm removal
De Moura et al. (2012)	52 weeks	22	44.8	• Diabetes mellitus (all patients) • Hypertension (16 patients) • Sleep apnea (4 patients) • Hyperlipidemia (4 patients)		At 52 weeks, in 13 patients: • A statistically significant decrease of mean FBG of 37.1 mg/dl • A statistically significant decrease of mean HbA1c of 2.3 % • A statistically significant decrease of serum insulin level of 10.1 microunit/ml	• Upper abdominal pain (11 patients) • Nausea (7 patients) • Vomiting (7patients) • Back pain (5 patients)	9 patients • Migration (3 patients) • GI bleeding (1 patient) • Abdominal pain (2 patients) • Investigator request (2 patients) • Unrelated malignancy (1 patient)
Sandler et al. (2011)[a]	12 weeks	22	42	• Diabetes mellitus (7 patients) • Increased HbA1c (4 patients) • Hypertension (2 patients) • Hyperlipidemia (3 patients)	Mean % EWL = 39.7 % at 12 weeks	• Normalization of blood glucose levels through the study and cessation of antidiabetic medications • Improved HbA1c level by end of the trial • Remission of hypertension and hyperlipidemia	One patient had intolerance to pureed food at 2 weeks	5 patients due to pain with swallowing which improved with device removal

Cohen et al. (2013)	52 weeks	20	30	• Type 2 diabetes mellitus (all patients)	mean body weight had decreased by 6.5 ± 4.1 kg at 52 weeks	At 52 weeks: • A significant drop in mean FPG level of 45.8 ± 63.9 mg/dL • A significant drop in mean HbA1c level of 1.16 ± 1.36 mg/dL • Low-density lipoproteins and triglycerides demonstrated substantial decrease by week 4 and remained low through the end of the study	• Gastrointestinal disorders, including abdominal pain, nausea, and vomiting (13 patients) • Metabolism and nutrition disorders, including hypoglycemia and iron deficiency (14 patients)	4 patients • Subject non-compliance with the study visits (1 patient) • Recurring abdominal pain (1 patient) • Device rotation and/or migration (2 patients)

[a]Gastro-deuodeno-jejunal bypass sleeve
GERD Gastro-esophageal reflux disease, *GI* Gastrointestinal, *FPG* Fasting plasma glucose

biliary and pancreatic juices are then expected to flow along the outer surface of the implant, to meet the ingested food distal to its outlet. Accordingly, and similar to RYGB, the rapid improvement in glycemic control has been attributed to neurohormonal regulatory factors, triggered by chyme (incompletely digested nutrients), diverted away from the proximal intestine and delivered directly to the distal intestine (Escalona et al. 2012). This neurohormonal process is also responsible for weight loss. The advantage of the EndoBarrier is however reversing type II diabetes mellitus, independently of weight loss (Patel et al. 2012). The development of such a minimally invasive modality, with reasonable antidiabetic effect, may extend the current indications for patients unfit for surgical intervention, as well as those with mild degrees of obesity (BMI ranging from 28 to 35 kg/m^2) (Koehestanie et al. 2014).

Even if long-term outcome of this procedure will not prove to be of value, it can be at least implemented for preoperative preparation, of diabetic morbidly obese patients. This has been proved to maintain long-term weight loss after operative intervention. Randomized studies comparing EndoBarrier to dietary restriction alone have proved superior results with EndoBarrier (Escalona et al. 2012).

A modification of this technique was performed by Escalona and his colleagues (2010). They combined EndoBarrier with a restrictor orifice (flow restrictor). At 12 weeks, %EWL (40 %) was superior to that encountered after EndoBarrier alone, in its best documented results reaching 23.6 % by Rodriguez-Grunert et al. (2008). However, repeated orifice dilatation sessions and delayed gastric emptying occurred.

The DJBL can be considered analogous to RYGB, without gastric restriction. In a trial to achieve additional endoscopic gastric restriction, Sandler et al. (2011), described the human experience with a gastro-duodeno-jejunal endoscopically delivered 120-cm-long fluoropolymer bypass sleeve (ValenTx, Inc. Carpinteria, CA). The device has a polyester cuff which was attached endoscopically at the gastrooesophageal junction, at the level of the Z-line. The attachment was performed using eight endoscopically delivered, full-thickness suture anchors. Laparoscopic visualization was conducted to ensure full-thickness attachment and avoid visceral injury. Laparoscopic approximation of diaphragmatic crura was performed as well. Removal of the device at the end of the study was done endoscopically. Results are also shown in Table 3.7. The procedure showed very reasonable weight loss results, in addition to its metabolic outcome.

3.3.2 TOGA®

Transoral endoscopic vertical gastroplasty (TOGa®) is a relatively recent endoscopic procedure, implementing a set of orally introduced staplers, aiming at creating a stapled gastric sleeve. Vacuum pods inside the device gather tissue, from opposing anterior and posterior gastric walls, to prepare for creating transmural stapling. Repeating this process forms a sleeve of the desired length,

which can extend from the angle of His to the antrum. Outlet restriction can then be deployed. Studies implementing this technique on 29 morbidly obese patients showed no serious early or late complications, and documented an EWL% of 43 % at 12 months and 37 % at 24 months (Nanni et al. 2012).

Visualizing the anatomy and orientation of the constructed sleeve can be done using plain abdominal radiographs or gastrografin studies, which will additionally help in excluding any leaks, as well as gaps between the deployed staple lines (Moreno et al. 2008). Another study on 11 patients showed a mean %EWL of 19.2 %, 33.7 %, and 46.0 % at 1, 3, and 6 months, respectively. In addition, quality of life scores were significantly improved. The reported side effects were not serious and included mild epigastric pain, throat pain, esophagitis, nausea, and mild dysphagia (Moreno et al. 2008).

Another larger study including 21 patients (seven diabetics, eight suffering from hypertension, and three from hyperlipidemia) reported reasonable weight loss results of 16.2 %, 22.6 %, and 24.4 % at 1, 3, and 6 months respectively. Follow-up after 6 months showed a drop of HbA1c level from 7.6 to 6.6 %. Four patients showed remission of hypertension and two of hyperlipidemia. Six out of eight scores for quality of life were significantly improved (Devière et al. 2008).

3.3.3 StomaphyX®

It is another recently implemented endoscopic gastric plicating device. In 2007, the US Food and Drug Administration approved the StomaphyX, as a procedure which enables suctioning and suturing of gastric tissue. The aim is to reduce gastric capacity, either as a primary intervention or in patients showing insufficient weight loss after primary bariatric intervention (Swidnicka-Siergiejko et al. 2011).

3.3.4 EndoCinch®

EndoCinch® (Bard, Murray Hill, NJ, USA) is a suturing device that is mounted on the tip of the gastroscope. It was originally developed for gastroesophageal reflux disease, and recently for obesity. A study including 64 morbidly obese patients demonstrated the weight reducing effect of this device, which acts by implementing seven endoscopic gastric sutures, in a continuous and cross-linked fashion, to limit gastric distensibility. The reported %EWL at 1 and 12 months after the procedure reached 21 % and 58 %, respectively. Repeated interventions are also possible (Coté and Edmundowicz 2009).

3.3.5 The Trans-oral Endoscopic Restrictive Implant System

The trans-oral endoscopic restrictive implant system (TERIS) is a gastric band-like technique, depending on creating plications, with subsequent attachment of a restrictor diaphragm in the cardia region. The resulting gastric pouch can be modified or removed. %EWL at 3 months reached 22 % (ASGE et al. 2012). However, complications like gastric perforation have been reported (de Jong et al. 2010).

Another modality involves the use of an endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, TX, USA), to implement a series of free-hand, full-thickness closely spaced interrupted sutures along the gastric wall. It forms a sleeve-like gastric lumen, which appears in postprocedural contrast swallows. Follow-up endoscopies after 3 months showed an intact gastric sleeve lumen (Abu Dayyeh et al. 2013).

3.3.6 Gastric Space-Occupying Bariatric Modalities

Apart from the thoroughly documented use of the BioEnterics **intragastric balloon** (BIB) (Allergan Inc, Irvine, CA, USA), other more recent balloons are being described. Those include for example the Heliosphere bag (Helioscopie Medical Implants, France) which is a safe and well tolerated air-filled balloon (30 g weight). It maintained a weight loss of greater than 10 % in about 30 % of the patients, up to 12 months after its removal (Mion et al. 2007). Another example of gas-filled device is the Obalon® gastric balloon (OGB, Obalon Therapeutics Inc, Carlsbad, CA, USA). It has a maximal volume of 250 ml and is fitted in a large gelatin capsule. If safe and well tolerated, a second and a third balloon is ingested after 4 and 8 weeks, respectively. The balloons are removed after 12 weeks. In a study which included 17 patients, only 10 tolerated a third balloon. The most commonly reported side effects were epigastric pain, nausea, and vomiting. Those were however controlled. %EWL at 4, 8, and 12 weeks was 12.4 %, 29.2 %, and 36.2 % (Mion et al. 2013).

Another modality is the semistationary antral balloon (SAB, JP Industria Farmaceutica, SP, Brazil). It causes intermittent pyloric occlusion, prolongation of gastric emptying, and stimulation of antral and duodenal satiety receptors, through its lodgement in the gastric antrum. This is achieved by a metallic counterweight at its caudal end. In a recent study, this type showed a median weight loss of 6.5 kg after 4 months. However, leakage and distal migration were anticipated (Lopasso et al. 2008). Another possibility is the **Silimed gastric balloon**, which is rolled up in a thin silicon sheath, to facilitate insertion and subsequent filling with saline. The insertion and removal technique was proved in a study to be simple and quick; however, early removal may be necessary (Carvalho et al. 2009). **Intragastric expansion capsules**, which can be controlled by wireless techniques,

or transcutaneous energy transmission to adjust its volume, are being tested in some centers. They would represent yet another interesting option for noninvasive antiobesity treatment (Yambe et al. 2013).

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Chapter 4
Perspectives of Robotic Bariatric Surgery

Almino Cardoso Ramos, Eduardo Lemos de Souza Bastos, and Keith Chae Kim

Abstract Robotic surgery is an emerging and promising technology in bariatric surgery. Current studies have confirmed its feasibility and safety with a relatively short learning curve. The advantages for the surgeon are already well established with better ergonomics. The potential benefits to the patient are still being studied. Robotic surgery seems to offer more advantages for complex cases, such as super obesity and revisional surgery.

4.1 Introduction

Obesity is considered a multifactorial disease, with growing incidence and high morbidity and mortality rates, mainly due to important obesity-related comorbidities that affect the quality and length of life. In the recent years, obesity has emerged as the most common noninfectious epidemic worldwide, with a global prevalence of around 12 % reaching up to 33 % in the United States of America (World Health Organization 2014).

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Changes in lifestyle with healthy habits, mainly based on nutritional changes and physical activity, are the key therapeutic recommendations for the initial treatment of obesity. These interventions achieve better results for mild obesity; however, for patients with more severe degrees of obesity, the only long-term effective treatment with significant and sustained weight loss, remission or improvement of comorbidities, and reduction in overall mortality rate is bariatric surgery (Buchwald et al. 2004; Christou et al. 2004; Sjöström et al. 2007).

Although bariatric surgery, in the initial stages, was challenged with significant perioperative morbidity and mortality, many factors have led to considerable improvement in perioperative outcomes, including a transition to a minimally invasive laparoscopic approach, which minimizes **surgical trauma**, results in more rapid recovery, and markedly reduces complications. The **laparoscopic approach** is currently considered the standard of care in bariatric surgery (Reoch et al. 2011; Banka et al. 2012; Masoomi et al. 2012). However, there are challenges to the laparoscopic approach related to available instruments, the body habitus of the patient population, and the relative complexity of the surgery. Current laparoscopic instruments lack the degree of freedom of movements and precision, that can potentially maximize surgeon dexterity and facilitate intuitive movement, and most of the procedures are performed with 2-dimensional visualization. Additionally, the **ergonomic challenges** of working with obese patient body habitus can lead to surgeon fatigue and even muscular and orthopedic injuries. Lastly, owing to the advanced skill sets needed such as for suturing, laparoscopic bariatric procedures such as the Roux-en-Y Gastric Bypass (RYGB) require a relatively long learning curve (Oliak et al. 2003; Schauer et al. 2003).

The surgical robot was developed with the intentions of enhancing dexterity and precision, in order to facilitate minimally invasive procedures, bringing the possibility to overcome some of the limitations associated with traditional laparoscopy. Some of the features include increased degrees of freedom of movement of the instruments, scaling of motion, **tremor filtration**, and an advanced high definition, **3D visualization** system. Additionally, the robotic arms and instruments are designed to mimic the human arms and hands (Fig. 4.1), so that instrument control and movements are more intuitive compared to laparoscopic instruments. Initial reports of the application of the robot in bariatric surgery seem to support some clinical translation of the advantages of the robotic system, with excellent clinical results, and similar or even lower complication rates, and a safe and shorter learning curve compared to the conventional laparoscopic approach (Markar et al. 2011; Gill et al. 2011; Ayloo et al. 2011; Park et al. 2011; Fourman and Saber 2012; Ramos et al. 2013).

Despite these advantages, bariatric surgery performed via robotic technology is still scarce, compared to regular laparoscopy. The relatively high skill set among bariatric surgeons, and the high penetration of minimally invasive surgery, seems to make the advantages of robotic system less compelling, but the growing is evident and the future is promising. Globally, the high costs associated with the purchase of a robotic system, as well as the increased per case costs, remain a key barrier to adoption of this technology. However, with the introduction of new robotic platforms, the costs of this technology will likely be reduced and further facilitate

Fig. 4.1 The similarity of the robotic grasper and the human hand (copyright Intuitive Surgical International—reproduced by courtesy of the manufacturer)

adoption, and the robotic bariatric surgery may become as common as conventional laparoscopic approach within a few years.

4.2 History and Evolution of Robotic Surgery

Since its introduction in the 1980s, several robotic systems have been developed. The first robotic device that was approved by Food and Drug Administration (FDA) for laparoscopic surgery was the AESOP (Automatic Endoscopic System for Optimal Position) by Computer Motion. This company was founded as "Dynamic Microsystems" in 1989, with support from NASA (National Aeronautics and Space Administration) and the National Science Foundation's Small Business Innovation Research Program.

The primitive AESOP consisted of an operating table-mounted articulating arm that provided seven degrees of freedom and was used to maneuver the camera during laparoscopic surgery. This device received FDA approval in 1993 shortly after the first clinical procedures were reported. Thereafter, Computer Motion acquired additional capital to develop an entire robotic system for laparoscopic surgery, and in the mid-1990, **ZEUS**, a master–slave robotic surgical system, was created. The most noteworthy project involving the ZEUS robot was a dramatic demonstration of telepresence, by the performance of a **transatlantic cholecystectomy** with the surgeon in New York, USA, and the patient in Strasbourg, France, in early September 2001 (Marescaux et al. 2001).

At the same time frame, another robotic system was developed in Northern California, resulting in the only available system for laparoscopic surgery up to now, the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA). As its origins were military, many initial efforts on tele-robotic surgery were conducted, with aims of developing a system of remotely providing surgical care to injured soldiers in the field.

Following this initial phase, Intuitive Surgical International was founded to develop this technology, for use in civilian surgical practice. With this endeavor the emphasis shifted from telepresence to delivering a system that could facilitate minimally invasive surgical procedures, by mimicking the intuitive hand-like

manipulations of open surgery, while maintaining all the benefits of the laparoscopic approach. The early prototypes were able to demonstrate the ability to develop manipulators with seven degrees of freedom that closely mimicked the movements of the human hand and wrist. This technology was developed as a master–slave system, in which there are three major components: the **surgeon console** (or the master), the **patient cart** (or the slave), and the **video cart**. The surgeon sits at a console remote from the patient (master), usually in the surgical suite, and performs the operation by manipulating the arms and instruments of the patient cart (slave), that is docked to the patient.

The first prototype was tested in April 1997, and in that same month, a cholecystectomy was performed, marking the first robotic surgical procedure. By December 1998, the first commercial version of the current da Vinci Surgical System was released, with intentions for use in cardiac surgery, and the first robot-assisted coronary bypass procedure was achieved shortly thereafter. Less than 2 years later, the first human trial with robotic-assisted surgery, involving 200 patients undergoing cholecystectomy and Nissen fundoplication was completed, and in July 2000, the da Vinci robotic system received FDA approval, for limited surgical use in abdominal surgeries. Further procedures were approved in the following years, for virtually all types of surgeries in different specialties.

Currently it has remained the only FDA approved robotic platform on the market, for minimally invasive abdominal and thoracic surgery. Over the last decade, the system has evolved through four major platform upgrades, from the Standard to the S System, to the Si System, and most recently to the Xi System.

These changes have resulted in improved visualization, an expansion of the operative field facilitating multi-quadrant surgery, improved ergonomics, and the addition of an array of specialized instruments for different surgical specialties, including an articulating vessel sealer and a robotically controlled stapler. In addition, starting with the Si system, other capabilities have been added in modular fashion, to support **single incision surgery** with the VeSPA™ surgical instruments, fluorescence imaging with the Firefly™, and data integration at the console, with a 3-dimensional surgical navigation model with TilePro™ display. Currently **fluorescence imaging** and use of 3-dimensional reconstruction of computed tomography images are already being used in limited settings, to facilitate identification of anatomical structures and to "preplan" surgical approaches. Nevertheless, the potential of the digital interface between surgeon and patient is still in its infancy (Kim et al. 2013).

4.3 The Da Vinci Surgical System

The da Vinci robot is a master–slave system, whereby the surgeon sits at the console (master) and performs the procedure by manipulating controllers that translate the movement into tissue manipulation through the surgical cart (slave),

Fig. 4.2 Da Vinci robotic systems have three major components: the surgeon console, the surgical cart, and the vision cart (copyright Intuitive Surgical International—reproduced by courtesy of the manufacturer)

that is docked to the patient. The system has three major components: the surgeon console, the surgical cart, and the vision cart (Fig. 4.2).

The shared core technology of the four versions offers the following distinguished features: physical separation of the surgeon from the patient through telepresence; a 3-dimensional stereoscopic image (HD for the S and Si model), with up to ten times magnification; wristed movements of the robotic instruments providing seven degrees of freedom (compared with five degrees of freedom for standard laparoscopic instruments); anthropomorphic design of the surgical arm and instruments for intuitive control; and software features such as tremor filtration and optional motion scaling up to 3:1.

The surgeon console allows the surgeon to control up to four robotic arms, including the videoscope, in a very ergonomically friendly manner (Figs. 4.3, 4.4, and 4.5). The system is designed to offer hand–eye alignment, which means that the endowrist instruments move in the same way with respect to the camera, as the hands of the surgeon move with respect to the surgeon's eye. The instrument tips automatically align with the controllers at the surgeon console, and their movements mimic the movements of surgeon's hand. These features establish a strong sense of **hand–eye coordination**, and natural intuitive motion, promulgating the illusion that the robotic instruments are his/her fingers. These advantages, together with the 3D vision, mimic the feel of open surgery, with the sense of actually being within the operative field.

As was intended, these key features of the robotic system significantly enhance dexterity, when compared to traditional laparoscopy, and enable minimally invasive surgery. This impact was quickly recognized in urology. Although cardiac surgery was the first intended target for introduction of the robotic system, urologic

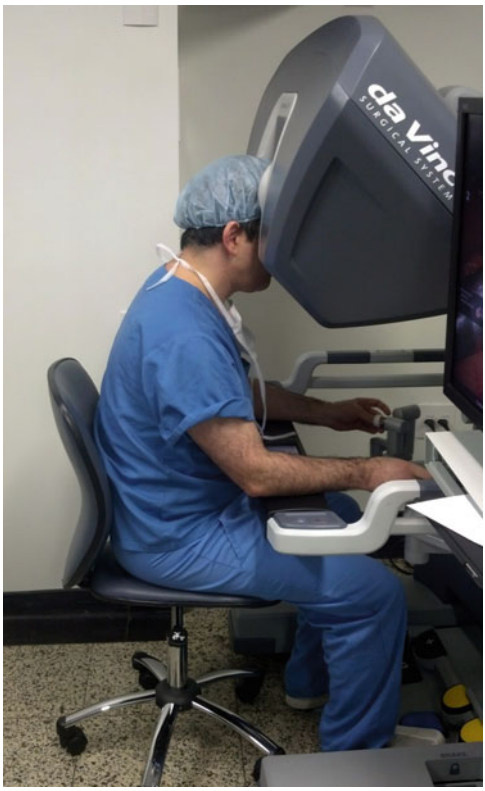

Fig. 4.3 Ergonomic advantages of robotic surgery

Fig. 4.4 The surgeon controlling the robotic arms through the surgeon console

surgery, and specifically prostatectomy, was the first area that saw widespread adoption of the robotic technology. It quickly evolved from a predominantly open procedure to a minimally invasive robotic procedure.

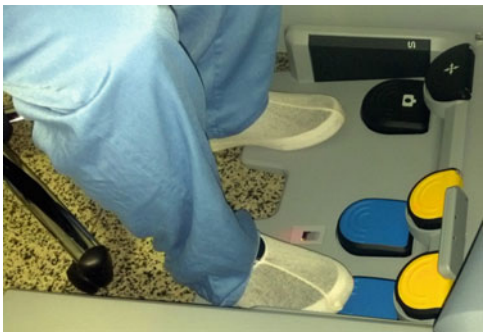

Fig. 4.5 Control by pedals at the surgeon robotic console

4.4 The Learning Curve and Training Program

Advances in surgical technology are often associated with a learning curve, before the surgeon becomes proficient, and truly learns how to use the innovation. This is certainly the case with the robotic platform, with the caveats that the learning curve also involves the surgical team, instead of just the surgeon. In many instances the surgeon is learning a new technique, concurrently with learning to use the robot.

The surgeons to be trained can be divided into three groups: those who are really novices in surgical practice; those who are surgeons, but do not master the laparoscopic approach; and finally those who already have training in laparoscopy. Each in their own way, all of these "levels" of surgeons have to go through the robotic learning curve.

The learning curve is typically defined by **stabilization of operative times**, and/or the achievement of certain clinical benchmarks. It can be described as having three components: the starting point, the slope of the curve, and the plateau of the curve. The starting point may be variable, since each physician has a previous individual experience that conducts to different initial levels of expertise. The **slope of the curve** represents how fast the surgeon learns the needed new skills, and varies by procedure, by surgeon, and by how many and how often the new procedure is performed. Finally, the plateau is when the changes in the outcomes being measured are not significant, the surgeon is usually deemed trained, and he may reach the end of the learning curve [18].

The appropriate way of analyzing the learning curve is an important topic of debate, and there has been a wide variation in the endpoints used; however, a comprehensive review of the literature indicated that the "duration of the procedure" is the most commonly used method, for establishing the learning curve in robotic surgery (Harrysson et al. 2014). Meanwhile, it seems that the most appropriate way of defining the learning curve process is the association of the operative time, number of conversions, nature of the results, and complication rate.

Based just on operative time, the initial studies suggested the learning curve of the robotic RYGB to be around 15–30 cases. Additionally, stabilization of operative time appears to occur at a lower number of cases, in centers focusing the use of

the robotic platform, with high volume and a dedicated robotic team and program (Mohr et al. 2005; Ayloo et al. 2011, 2014; Vilallonga et al. 2012). This represents a significant decrease when compared to the learning curve of laparoscopic RYGB, which is believed to be around 100 procedures (Oliak et al. 2003; Schauer et al. 2003; Zevin et al. 2012).

A prospectively randomized trial, which compared fellows naive to both robotic and laparoscopic RYGB, found significantly shorter operating times per BMI during the robotic learning curve, when compared to the laparoscopic procedure (Sanchez et al. 2005). On the other hand, when taking into account clinical variables such as conversions, postoperative morbidity, and length of hospital stay, the learning curve for a totally robotic RYGB approaches more closely that of the laparoscopic RYGB (Renaud et al. 2013).

After undertaking the required training, it would be wise to arrange any proof or certification. Currently there is no surgical society mandated or even suggested criteria, for privileging or certifying the use of the robotic platform, and most hospital systems have adopted their own criteria. In the coming years, it would be desirable to establish global **parameters for certification**, based on scientific and practical qualifications of surgeons.

4.5 MIMIC Simulator and Da Vinci Technology Training Path

Classically, the surgical training begins with theoretical knowledge, goes to dry training models in basic or electronic simulators, reaches animal models and assisted-training field, and **proctored surgeries**, with the tutor observing the first sequence of operations. Finally the surgeon could be considered able to start his/her own series, based on the good performance in the previous steps. The robotic platform training phase in animal models was replaced by simulators, allowing the creation of specific situations of surgical reality, which may accelerate the training and acquisition of surgical skills, using models quite similar to airline pilot graduation programs.

Nowadays, simulators are very requested in robotic surgery training. The Mimic® robotic simulator was created to introduce virtual surgery, as a valid tool for medical training. This organization has been working with Intuitive Surgical to integrate simulation software with the da Vinci Si surgeon console (dV-Trainer, Mimic Technologies, Seattle, WA) (Mimic Technologies 2014). The quality of surgical training is improved with the program, by the simulation of surgical reality in a progressively difficult, step-by-step planed strategy of surgical training.

The da Vinci System manufacturer provides an oriented program, the "da Vinci **Technology Training Pathway**", which intends to train, and not to substitute formal medical surgical training or certification. The goal of this team-oriented program is to help surgeons and staff to develop the knowledge and skills needed to

use the technology safely and efficiently. It focuses several steps: system knowledge/skill development and peer-to-peer education.

The "**system knowledge and skill development**" consists in understanding the da Vinci Surgical System and learning technical skills that will be used in the operating room. The "peer-to-peer education" is a surgeon-to-surgeon instruction and mentorship program that is conducted by qualified, independent medical professionals. Both are fundamental to better practice in robotic surgery.

The first phase (Introduction) is designed to give a foundational understanding of the system. The second one (Technology training) introduces surgeons to the core of the technology, where the surgical teams complete online product training modules, view full-length procedure videos, attend hands on training sessions at a local hospital, and a full day of training at a da Vinci Training Center. The third phase consists in initial case series plan (Skills application). The surgeons are assisted by experienced proctoring surgeons during their first procedures, providing direct support and help in ensuring proper technique, showing the best way for doing the different steps of the procedures, and resolving eventual difficulties in order to keep the safety for the patient. The last phase is a continuing development (also Skills application) conducted by experienced, independent surgeons, who contract with Intuitive Surgical to offer multiple specialties training through select centers. The surgeon should be supervised until he is deemed competent.

Following the initial case series, post-case debriefing is held for the entire team. The team reviews the results with an eye toward benchmarking and improving clinical performance. Surgeons are very encouraged to engage in additional skills simulator and skills drill practice, which are designed to optimize intraoperative dexterity, and to revise the videos of the surgeries, trying to understand what could be done better in the next ones (Intuitive Surgical 2014).

4.6 Robotics in Bariatric Surgery

The bariatric surgery population presents unique **anatomical challenges** that influence the complexity of the surgical procedure, including a thick abdominal wall, larger liver, and excessive intra-abdominal fat. Additionally RYGB, the most commonly performed bariatric procedure in the United States, involves two bowel anastomoses, requiring **intracorporeal suturing**.

The robotic system, with high definition, magnified, 3-dimensional vision, seven degrees of freedom, scaling of motion and tremor filtration, ergonomic advantages, and, most importantly, anthropomorphic design of the system intended to mimic those of the human hand, helps overcome the added challenges of performing these procedures in a minimally invasive fashion, and presumably facilitates a more predictable and safer outcome.

One of the most significant differences between robotic surgery and conventional laparoscopy is that with robotic surgery a computer, or digital interface, exists between the surgeon and the patient. This allows a limitless potential for data

use, particularly imaging, that can be collected both preoperatively and in real time, and manipulated and integrated with the surgical anatomy, to help identify critical anatomical structures.

Since the first robotic bariatric procedure, placement of an adjustable gastric band was performed in 1998 (Cadiere et al. 1999) by using the Mona, an early version of the current da Vinci System; almost all bariatric surgical procedures have been performed to varying degrees using the robotic system. Systematic reviews had already established the safety and feasible of the robotic approach in all of them (Gill et al. 2011; Cirocchi et al. 2013).

RYGB is considered in many countries the gold standard of surgical treatment of morbid obesity. The introduction of robotics technology in RYGB began with a **hybrid method** (Horgan and Vanuno 2001; Talamini et al. 2003), called "robotic-assisted." In this technique the operation starts as a conventional laparoscopy, and the robot is docked to the patient only to perform a specific step, usually the **handsewn gastrojejunostomy**, followed by the same conventional laparoscopy to finish the procedure.

After the initial experience, the robot was docked to the patient from beginning to end of the procedure, featuring the totally robotic bariatric surgery (Mohr et al. 2005, 2006; Sanchez et al. 2005). Although this is called "totally robotic," still today there is need for an assistant surgeon to fire the stapler by an auxiliary trocar. The recent FDA approval for the staplers coupled to robotic arms could make the procedure totally robotic soon.

In some cases, the hybrid technique could represent a preliminary step toward performing a totally robotic RYGB, a sort of "staff training" in managing the technology, especially the time when the robot is attached and unattached to the patient, called "docking and undocking time." Although these may seem responsible for greater operative time observed in robotic RYGB, they have a tendency to become shorter along with experience, not more than 5–10 min for skilled groups.

Although it is difficult to completely capture the whole financial impact of one technique versus the other, cost is perhaps the greatest barrier to the adoption of robotic technology over conventional laparoscopy. **The capital cost** of the robotic system (approximately U$ 2,000,000) has to be added to an annual maintenance fee of about 10 % of the purchase price and to the costs of disposable items. Both the procedural cost and the total cost of performing robotic RYGB have been found to be greater than for the laparoscopic technique (Hubens et al. 2008; Curet et al. 2009; Scozzari et al. 2011).

On the order hand when the **costs of supplies**, hospital stay, and complications for the robotic approach were compared to open and laparoscopic technique, the total cost could be similar or even less. Factors that contributed to increased costs for the open and even laparoscopic techniques were length of hospital stay, time in the intensive care unit, and complication rates including anastomotic leaks. In addition, the robotic RYGB was able to report significant savings with regard to instrumentation costs by avoiding the use of expensive **laparoscopic staplers** and replacing by laparoscopic suturing (Hagen et al. 2012).

Thus, it is expected that in a short period of time, the cost will be no longer a barrier to the widespread adoption of robotic technology in bariatric surgery.

4.7 The Robotic Roux-en-Y Gastric Bypass

While worldwide experience in robotic RYGB has involved short follow-up to date, results about weight loss and complication rates are similar to laparoscopic RYGB (Ayloo et al. 2011), even in a large series with over a thousand patients (Tieu et al. 2013). On the other hand, robotic RYGB has shown higher total operative time (Myers et al. 2013), and a greater overall cost of the procedure. With increasing experience of the groups, both cost and surgical time tend to decrease, and reach the laparoscopic results.

One technical aspect of the robotic RYGB is the gastrojejunal anastomosis. Typically in the laparoscopic approach, it is performed using either a circular or a linear stapler. However, with the greater ease and precision of suturing with the robotic system, this anastomosis has been more commonly performed as a two-layered, completely sutured technique, with a lower leak rate and stricture rate with respect to traditional laparoscopic approach.

The **surgical steps** of the robotic RYGB are very similar to conventional laparoscopy. The access to the peritoneal cavity is achieved with six trocars: two 12-mm disposable trocars (a long one to serve as the camera, and one of regular length to serve as the assistant trocar); one 5-mm reusable trocar for the liver retractor; and the other three 8-mm robotic trocars for the robotic arms (Figs. 4.6 and 4.7). Two Cadiere forceps, one ultrasonic scissor and one needle holder, are utilized. Once all of the trocars have been placed, the pelvis is inspected for any adhesions, and these are taken down if found, prior to docking the robot. The da Vinci Si Surgical System® is then docked, straight over the patient's head (Fig. 4.8). This requires close collaboration with the anesthesiology team, as this space is traditionally reserved for the anesthetic equipment.

The operation starts with the opening of the phrenoesophageal membrane next to the esophagogastric angle, and resection of the fat pad, to expose and visualize the left crus. The gastric lesser curvature is then opened at the level of the third vessel, with ultrasonic scissors, and dissection is performed toward the **esophagogastric transition**, to access the lesser sac. A rectangular gastric pouch is created using blue loads of the linear stapler (Echelon Endopath Flex Staplers, Ethicon Endo-Surgery, Inc.). A single transverse staple line is first created, perpendicular to the lesser curvature, followed by subsequent staple fires vertically, perpendicular to the transverse staple line, toward the **angle of His**, to create a completely divided proximal gastric pouch calibrated around a 32 Fr bougie.

The stapling is performed by a skilled assistant at the operating table, while the surgeon at the console provides the exposure and directs the assistant. The greater omentum is then divided in the midline, to the level of the transverse colon, with the ultrasonic scissors, and the ligament of Treitz is identified. The jejunum is then

Fig. 4.6 8 mm robotic trocar for docking the robot's arms

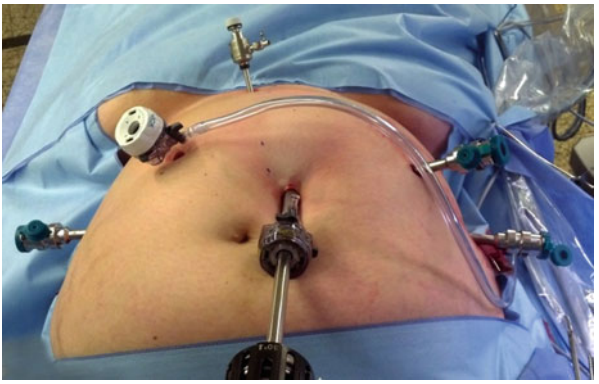

Fig. 4.7 Six port placement for the totally robotic RYGB

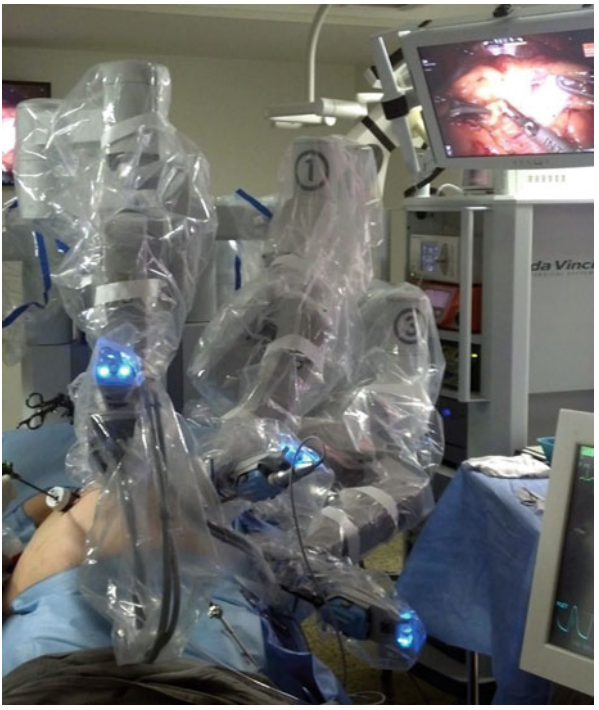

Fig. 4.8 Robotic arms docked to the patient ("blue light")

measured for a distance of 50–100 cm from the ligament of Treitz (**biliopancreatic limb**), and this segment is brought in an ante-colic, ante-gastric fashion, to the posterior face of the gastric pouch. A gastrojejunal anastomosis is then performed as a loop gastrojejunostomy, using a linear stapler with a blue cartridge, and applying only the distal 15–20 mm of the stapler to provide a more restrictive anastomosis. Again, the stapler is handled by the assistant at the tableside.

Because of the enhanced dexterity of the robotic system, more surgeons have gravitated toward a sewn two-layered **gastrojejunal anastomosis**. The jejunal loop is then divided on the biliopancreatic side of the gastrojejunostomy, and the small bowel is measured another 100 cm along the alimentary limb, distal to the gastrojejunal anastomosis. The biliopancreatic limb is then anastomosed to the 100 cm mark of the alimentary limb, in a side to side, functional end-to-end fashion, with a white cartridge of the linear stapler. The resulting enterotomy is closed with absorbable running suture. The mesenteric and Peterson's defects are closed with permanent suture. Prior to conclusion of the procedure, a leak test is conducted with methylene blue. The peritoneal cavity is not routinely drained. The aponeurosis hole in the trocar camera site is closed with absorbable suture.

4.8 The Robotic Sleeve Gastrectomy

The sleeve gastrectomy (SG) was first described as an effort to improve the results, and reduce some of the common complications of the classic biliopancreatic diversion (BPD) (Marceau et al. 1993), and some years later was performed by laparoscopy (Ren et al. 2000). The SG, as an isolated procedure, was initially intended as a first-stage of a two-stage procedure, in high-risk super obese patients (Regan et al. 2003); however more recently it has gained popularity as a stand-alone surgery (Deitel et al. 2011; Rosenthal et al. 2012; Kehagias et al. 2013). Currently, SG is recognized both as a primary bariatric procedure and as the first stage in high-risk patients, as part of a planned staged surgical strategy (ASBMS 2012). Bolstered by satisfactory short and long-term weight loss and metabolic results (Paluszkiewicz et al. 2012; Trastulli et al. 2013; Diamantis et al. 2014), the SG has gained rapid popularity among surgeons and patients and may become the most common bariatric procedure performed globally in the near future.

The laparoscopic approach may be more advantageous in SG than in RYGB, as dissection of the gastric short vessels is very difficult in open surgery with a high risk of bleeding. In addition, proximal stomach stapling near the angle of His can be performed more safely, with the direct vision provided by laparoscopy.

Although laparoscopic SG is frequently considered as a less technically demanding procedure compared to RYGB, without advanced suturing techniques, this does not necessarily mean that it is always an easier operation. The approach to the **uppermost part of the greater curvature**, where the stomach has to be detached from the spleen by dissection of the short vessels in a limited space, is often a challenge. This aspect of the procedure, as well as **oversewing the gastric staple**

line, is greatly facilitated by the wristed instruments and the improved visualization of the robotic platform.

In general the totally robotic SG follows very closely the steps of the laparoscopic SG. The most significant difference is that the stapling of the stomach is performed by a skilled assistant at the tableside. To accommodate a stapler, which requires a 12 mm trocar, as well as a robotic arm, a double cannulation technique is used. A 12 mm trocar is placed through the abdominal wall in the usual fashion, and an 8 mm robotic cannula is placed through the 12 mm trocar ("**trocar in trocar**" **technique**) (Vilallonga et al. 2012, 2013; Diamantis et al. 2011; Schraibman et al. 2014). When the robotic arm is in use, it is docked to the 8 mm cannula, and when a stapler needs to be applied through that trocar, the robotic arm is undocked and the 8 mm cannula is simply removed. This flexibility is very desirable in robotic SG, in order to allow the assistant to insert the stapler from both the right and the left side of the patient, although robotic SG can also be performed without double cannulation (Romero et al. 2013).

Albeit an FDA approved robotic stapler is already available, its use has been limited by the increased cost and the availability of a 45 mm stapler only.

Post-sleeve gastric leaks are one of the most dreaded complications, and very often are a source of major morbidity. Because of the relative infrequency of leaks, and the low numbers of robotic SG, it is difficult to speculate what impact the robotic approach has on leaks as well as other complications. Reported outcomes show no significant difference, with the exception of longer operative times with the robotic approach (Vilallonga et al. 2012; Romero et al. 2013). However, with the better training of the surgical team, the total operative time tends to be the same.

Although the early experience in robotic SG published to date suggests that it is safe and feasible, and gives the same benefits of the laparoscopic SG with the known additional advantages of robotic features, its exact role remains poorly defined, and will need to be more clearly shown in the future.

4.9 Other Bariatric Procedures

Experience with other bariatric procedures beyond RYGB and SG is still scarce, but there are reports of the use of the robotic platform for performing **biliopancreatic diversion** (BPD) (Sudan et al. 2007; Sudan and Desai 2011), **gastric plication** (Calcaterra et al. 2012), **adjustable gastric band** (Alqahtani 2011), and **revisional surgery** (Buchs et al. 2014).

Although robotic surgery can be used as a routine for doing all kinds of bariatric cases, it is a consensus between experts about the superiority in relation to laparoscopy mainly in technically more difficult patients, such as superobesity and revisional cases.

Revisional bariatric procedures remain a true surgical challenge, carrying a high risk of postoperative complications. As demand for bariatric surgery has increased in the last decades, so too has the need for revisional surgeries. Common reasons for

performing revisional surgery include failure to lose weight, loss of quality of life, weight regain, or complications of the previous procedure (Lim et al. 2009). The technical difficulties and the risk of postoperative complications inherent in open or laparoscopic revisional surgery can be in part be overcome by using the robotic technology.

The superior visualization and enhanced dexterity allow a safer dissection within tissue planes, and facilitate the identification of critical structures. In addition, the ability to perform precise intracorporeal suturing is critical in reconstructing the anatomy, which often involves reconstruction of the gastrojejunal anastomosis in settings that compromise the ability to use a stapler. It is most likely that the robotic platform will differentiate itself from laparoscopy in revisional surgery, facilitating the safe performance and minimizing the need to convert to an open procedure (Alqahtani 2011).

4.10 Perspectives

The two most significant differences between robotic surgery and laparoscopy are telepresence, with a master–slave station, and a digital interface between the surgeon and the patient. Both aspects will profoundly dictate the future of gastrointestinal surgery.

NOTES (Natural Orifice **Transluminal Endoscopic Surgery**) and single incision approaches are now viewed without great enthusiasm, and the challenges to making these approaches available are formidable. Barriers exist in instrumentation, visualization, as well as ergonomics.

Recently, Intuitive Surgical received FDA approval for limited use of their single incision platform. This device, unlike any before it, is truly a single incision platform, whereby a single shaft enters the abdominal cavity and separates into four arms. These provide one videoscope and three working arms, which can perform complex dissection and suturing, and access all quadrants of the abdomen. This device is also controlled by the surgeon in the comfort of a console, with the same high definition 3D visualization, and the dexterity and precision of the standard multi-port robot.

The Intuitive single incision platform could represent a giant step for NOTES. This relationship of a maneuverable instrument that is controlled from a console could soon also separate the endoscopist from the patient side, and NOTES would be realized with console-controlled, multi-channel maneuverable endoscopes with functional arms.

The digital interface represents an important relation between the surgeon and the patient, similar to software in a personal home computer. This allows a limitless potential for data, particularly imaging, that can be collected both preoperatively and in real time, and manipulated and integrated with the surgical anatomy, to help identify critical anatomical structures.

The experience with the interposition of stereoscopic images in the da Vinci console will offer to the surgeon switching between the traditional endoscopic view and a combined virtual view during the procedure, an important step toward computer-aided surgery that will progress rapidly over the next years.

Recently, **near-infrared light** (NIR) technique was cleared by the FDA, to visualize blood flow and related tissue perfusion using **indocyanine green** (ICG) as the fluorescent agent, with the da Vinci Surgical System. When desired, the da Vinci visualization mode can be switched to fluorescent during which a laser, which is integrated into the camera system, excites the ICG particle, which can be visually captured by the green fluorescent color. This system has mainly been used clinically during partial nephrectomies and colorectal procedures, to help identify vessels and to assess perfusion of tissue. Moreover, assessment and modification of the margin of resection for colorectal procedures can be undertaken. This promising method is currently under thorough assessment for abdominal and pelvic malignancies.

With the rapid evolution of robotics, the overall interest in computer-aided surgery has increased, and reports can now be found describing the first steps toward augmented reality for robotic surgery. Computer-aided surgery will advance in many, probably not yet fully foreseeable ways, to improve the clinical outcomes for our patients.

The robotic technology has already established a foothold into surgical practice, and in the bariatric field it seems to offer advantages mainly in the most challenging patients, the super obese and during revisional surgery. The actual value of commercial systems is undergoing scientific evaluation by randomized clinical trials. Although with long operative time, until now the bariatric trails point to results similar to the laparoscopic traditional approach, but with less leaks and a quicker learning curve. While these initial reports are promising, they need to be certified by long-term, evidence-based outcomes to prove their real efficacy. More importantly, it will be necessary to demonstrate the cost effectiveness.

In addition, non-technical issues of equipping the operating rooms, training surgeons and its staff, and gaining widespread acceptance of this new technology are significant. The future is promising, because of the great potential of these systems to extend the capabilities of surgical performance, beyond human limitations.

Robotic technology is in the beginning, and current robotic platforms are only the first steps. Next generation systems will extend even further the capabilities. This emerging technology will provide rewarding research for years to come, with the possibility of greatly improving the quality of surgical care to patients.

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Chapter 5
Sleeve Gastrectomy and Transit Bipartition

Sérgio Santoro, Sidney Klajner, and Renato Sampaio

Abstract The modern techniques of food processing led to an increased consumption of high-glycemic index food. This leads to a hormonally hyperactive proximal gut and a hypoactive distal gut, which are linked to obesity and metabolic syndrome. Transit bipartition (TB) was designed to counterbalance these effects, by creating a gastroileal anastomosis in the antrum after the sleeve gastrectomy (SG). Unlike the previously designed malabsorptive surgical techniques, nutrient transit is maintained in the duodenum, avoiding blind loops and minimizing malabsorption. The stomach retains two outflow pathways. A lateral enteroanastomosis connects both segments at 80 t 120 cm proximal to the cecum. Distal gut hormone secretion is enhanced. SG + TB is a simple procedure that results in early satiety and rapid and maintained weight loss, with a low complication rate and rare signals of malabsorption. This strategy led to remission or major improvement of comorbidities, including diabetes, without duodenal exclusion. TB is an excellent complement to a SG.

5.1 Introduction

Quoting Prof. Stephen Palumbi, from Stanford University, modern human interventions became "the planet's most potent evolutionary force" (Palumbi 2002). Human interventions like antibiotics, seed selection for agriculture, and pesticides change the characteristics of many kinds of living populations. We artificially select species by changing the environment and we are doing it fast, sometimes too fast to obtain adaptation. Lack of adaptation induces "malfunction," in other words, disease, sometimes, extinction.

The fast environmental changes that we caused do not spare us, humans. We have modified our environment so much and so fast that now in some aspects we became unfit for the world we generated. Our gastrointestinal (GI) tract is probably unfit for the amount and the quality of the "artificial" modern diet. The

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understanding of the relations between the diet and the anatomophysiology of primate digestive tract gives a different view of obesity and associated diseases. It also provides support for the development of new strategies to treat obesity. One of these, sleeve gastrectomy and transit bipartition, is the subject of this chapter.

The epidemiology of obesity and metabolic syndrome (MS) points that there is at least one external cause: the diet. Indeed, most of the obese become healthy if they have access just to small amounts of a primitive diet. How can a sudden modification in the amount and quality of the human diet produce such a steep rise in the incidence of obesity and metabolic syndrome (MS)? Some innovative concepts arise after trying to answer this question.

5.1.1 The Cautious Gut and the Reliable Gut

To trigger a strong insulinic response including the interruption of endogenous glucose is very risky. Severe hypoglycemia is a fast killer. It is very reasonable that animals check carefully the amount and the quality of ingested food before triggering such a dangerous response.

Proximal gut hormones, like GIP (Glucose-dependent insulinotropic polypeptide), produce insulinic responses but instead of diminishing secretion of glucagon, they enhance it (Meier et al. 2003). And it is quite logical. In the proximal gut food is not well quantified, and it is still early to stop endogenous glucose production, early to cause strong satiety, and too soon to block gastric emptying (unless there is an acute hyperglycemia). The proximal gut is cautious.

It would even be very reasonable from a evolutionary point of view that duodenal–jejunal products (but not ileal products) could induce some insulinic resistance, as early suggested by Rubino (Rubino and Marescaux 2004; Rubino et al. 2006) and recently demonstrated by Salinari et al. 2013. GIP itself may be this substance, as GIP induces insulin resistance in human adipocytes (Timper et al. 2013).

Food in distal gut means much more; means you are quite well fed. It is safe to trigger an intense response that aims at reducing glycemia and at inducing satiety. Distal gut signals strongly potentiate insulinic responses (Holst and Gromada 2004), but, differently from the proximal gut, it has the authority to block glucagon secretion (Hare et al. 2009), to interrupt endogenous glucose production and the supply of fat to the circulation (clearance of triglycerides) (Meier et al. 2006); it has the ability to cause strong satiety (Batterham et al. 2003; Verdich et al. 2001) and a break in gastric emptying (Savage et al. 1987; Nauck et al. 1997). The distal gut is reliable.

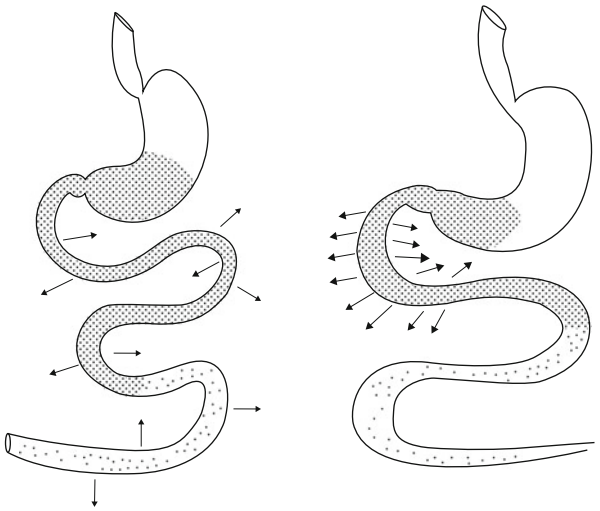

Fig. 5.1 *Left*: Pattern of absorption of a primitive diet; *Right*: The effect of a highly absorbable modern diet (Personal file)

5.1.2 The Gut Imbalance Theory

In face of "unnatural" high-glycemic index food that is easily and rapidly absorbed, this "excessive" permeability allows a fast invasion of nutrients in the blood, indeed faster than what is natural (Fig. 5.1).

Obviously, the proximal gut would be over-stimulated in this scenario, while the distal gut under-stimulated, as nutritive absorption occurs more proximally than what is "naturally" expected: an imbalance. Indeed, in obese and diabetic patients present high GIP (Vilsboll et al. 2003) (mainly a proximal gut product). If they loose weight on a diet, GIP falls (Deschamps et al. 1980). GIP is obesogenic and insulinotropic (contributing to hyperinsulinemia) (Miyawaki et al. 2002), and the therapeutic blockage of GIP has been shown to be beneficial in MS patients (Irwin and Flatt 2009; Montgomery et al. 2010).

The opposite is also very clear. The therapeutic addition of the distal **gut products or agonists** (GLP-1, PYY, oxyntomodulin) (Bhavsar et al. 2013; Batterham et al. 2002, 2003; Neary et al. 2005; Pocai 2012) is beneficial in MS patients.

Drugs and hormones that interfere in this balance, by enhancing the distal or blocking the proximal gut activity, help MS patients. Surgeries reproduce this observation. The more you shift food from proximal to distal, better the results in both, obesity and MS.

There is an imbalance in gut activity, and the introduction of easily absorbed food can completely justify that. Epidemiology, physiology, drugs, and surgeries point at the same direction.

5.1.3 A Contribution from Biology and Anthropology

Nature, through the means of evolution, adjusts permeability and extension of GI tracts of mammals, according to the quality of diet, utilizing natural selection.

Mammals do not digest fiber directly, but uses **bacterial fermentation** to obtain some nutrients (mostly short chain fatty acids). Some mammals do it in the forestomach (like ruminants); some do it in the colon (like horses, apes, and humans). The characteristics of the GI tract vary among species, mostly guided by the characteristics of diet. As a general rule, high-fiber, low-protein diet implies large and long GI tracts, able to process this type of food and also get nutrients from fermentation.

Small herbivores, such as rodents, that are not big enough for containing the necessary GI tract to this diet, sometimes use **coprophagy** (stool eating) as ways to process food twice, as if they had twice as much gut (Stevens and Hume 1995).

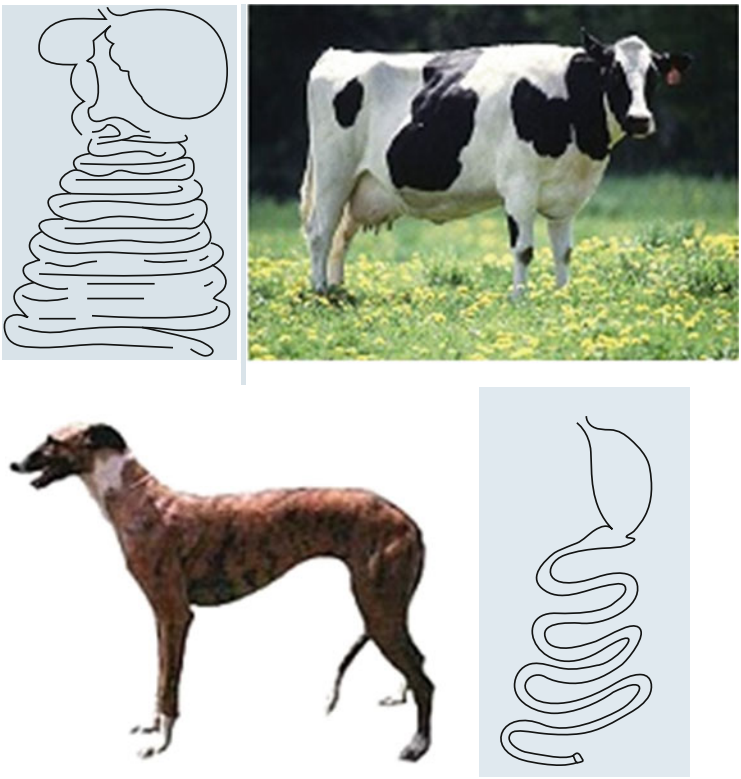

Fig. 5.2 High calorie-density diet (as in carnivores like a dog) is associated with shorter and simpler gut, and with a smaller gut/body ratio, as a rule among all mammals. Animals whose diet is fiber-rich and calorie-poor (as in herbivores like a cow) present a high gut/body ratio (Gastroenterocorporeal ratio) (Personal file)

Facing richer food, like the carnivores do, evolution has been selecting simpler and shorter GI tracts (Fig. 5.2), putting distal bowel nutrient detectors closer, since more nutrients are absorbed in shorter segments.

Primate evolution follows this rule. *Australopithecus afarensis*, an early **hominid specimen** that lived about 2.5 million years ago, was mainly an herbivore. Plant food became scarce, contributing to the extinction of the *Australopithecine*, while other groups of hominids started adding more caloric animal food, being able to eat less volume of more digestible food. It is known that in this transition from *Australopithecus* to *Homo* genus, the amount of bowel was reduced as expected (Schmid 1983; Aiello and Wheeler 1995) (Fig. 5.3).

In a quite long period of time we moved from being gatherers to **hunter-gatherers**. But, in a biological short period, agriculture came and gathering was transformed in harvesting. Hunting became slaughtering. After that, in a few centuries, even greater changes happened in human diet with refining and with industrialization. Hydration, which is obtained with water by all other animals, became a nutritive process with the development of juices and soft drinks.

Our diet became more concentrated in calories and even freer of non-digestible particles, which may lead us to think that our gastrointestinal (GI) tract is now unfit for this diet, especially if in large amounts. From this point of view, our GI tract was developed under scarcity and a poorer diet, which we don't face anymore, leading to a condition of "**proximal-distal gut imbalance**."

Evolution is doing its routine job: Selection. Some people, in face of food abundance, are becoming obese, sick, and dying earlier. So, as expected, smaller abdomens continue to be selected. Epidemiological observations confirm this rationale. Waist circumference has been pointed as a risk factor.

Sleeve gastrectomy (SG) copies natural (evolutionary) movements. It reduces gastric capacity, and smaller volumes will generate functional restriction signals earlier. The resection of the gastric fundus reduces A cell population, which produces ghrelin (a pro-appetite hormone), and parietal cell population (Langer et al. 2005; Muccioli et al. 2002).

The low gastric pH reduces the bacterial population in the food, which is low in the small bowel and becomes large again in the colon, due to the necessity of bacterial participation in the process of fiber fermentation. Simultaneously, the acid has a role in digestion, especially by activating pepsinogen and by participating in protein digestion. The less contaminated and more caloric modern diet requires a smaller amount of acid. Indeed, modern populations suffer a lot more from acid excess than from the lack of it. A **vertical gastrectomy** reduces very much the capacity of acid production, with no reports of problems related to this decrease.

A SG keeps outer stomach functions quite well. Innervation through the lesser curvature is intact. Pylorus works, providing a gradual and controlled emptying, with adjustment of osmolarity, preventing dumping and adjusting the progression of particles with different size. Bacterial population will be diminished by the action of acid, produced by the remaining parietal cells. Gastric secretions also stimulate duodenal and pancreatic secretions, while initiating protein digestion. There are no reports of lack of vitamin B_{12}, which could be a problem if the amount

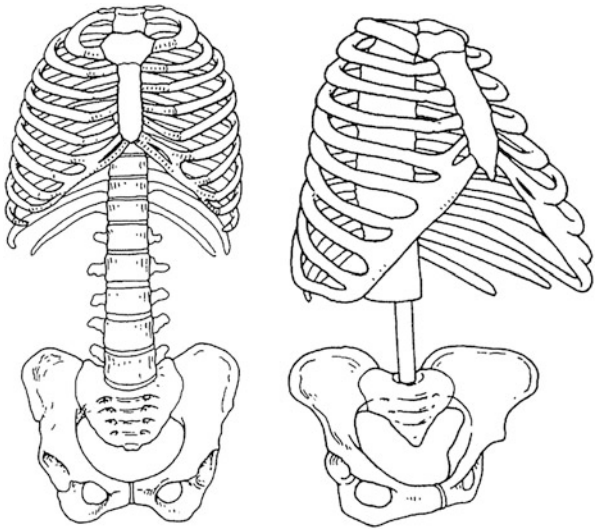

Fig. 5.3 The human abdominal cavity became smaller (*left*), when compared to primitive *Australopithecus afarensis* (*right*) (Modified from Schmid 1983)

of intrinsic factor (produced by gastric mucosa and fundamental to absorption of vitamin B_{12} in the ileum) were insufficient.

In summary, a vertical gastrectomy produces a decrease in gastric size; gastric function is quite well preserved (Gumbs et al. 2007) (Fig. 5.4).

It is an efficient procedure for weight loss (Langer et al. 2005). Differently from RYGB, in which the fall in ghrelin is controversial (Stoeckli et al. 2004; Holdstock et al. 2003; Le Roux et al. 2003), a vertical (sleeve) gastrectomy produces a significant decrease of ghrelin (Adkins and Davies 1987).

In summary, based on what is known now, it seems that a vertical gastrectomy is the maximum procedure that can be performed in the stomach for the treatment of obesity, without major disturbance in gastric functions.

5.2 The Term "Bariatric"

To move forward, we have to recognize that "bariatric" became an old and inadequate name. Bariatric refers to weight. Weight itself is not the problem, as heavy people may not be obese. Obesity and metabolic syndrome (MS) are the problem, and they may happen sometimes with not too much weight. They are metabolic problems. By calling the surgery "bariatric," it means we aim at the weight; surgical indication is guided by the weight, and the promise is a normal weight. Bariatric surgery uses mechanical restriction and malabsorption. Both are diseases, classified in the International Classification of Diseases (K.90 responds to Malabsorption) and they are not physiological at all.

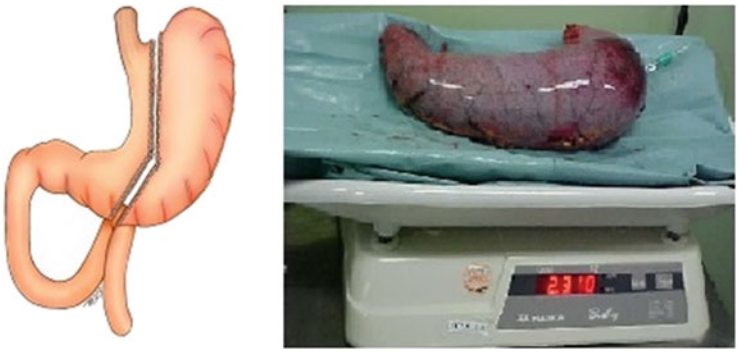

Fig. 5.4 Pattern of resection in a vertical gastrectomy (*left*). Gastric specimen (*right*), full with water (Personal file)

If we call it "metabolic," a lot changes. We aim at adjusting a metabolic response to food ingestion. The surgical indication is metabolism driven. The surgical main goal and the promise is not the weight, even because the weight does not depend on the surgery only. The goal and the promise is a metabolic change, which will help the patients in obtaining better rewards for their efforts in maintaining good health, good weight, normal glycemia, normal blood pressure, and normal blood lipids.

5.2.1 Pure Metabolic Surgery

Bariatric surgery with its tools, mechanical restriction, and malabsorption has produced unexpected beneficial metabolic results. The discovery that these results were a product of an array of different metabolic events, later created the term "bariatric and metabolic" surgery, in which the procedures are the same old ones, but with the recognition that other new mechanisms are also at work.

Between 2008 and 2011 **sleeve gastrectomy** (SG) was the only surgical procedure to treat obesity with an increase in the absolute number of procedures: it moved from 18,098 to 94,689: a +523 % difference, while all the others diminished in absolute numbers (Buchwald and Oien 2013). Probably it is because a good SG is the first recognized procedure that fits quite well in the concept of pure metabolic surgery (PMS) (a bad SG may be mechanically restrictive). Ideally, PMS does not bring new diseases on purpose to treat old ones.

5.3 Our Surgical Strategy

It is important to recognize that obesity grade I (BMI between 30 and 35 kg/m^2) has negative effects on health and quality of life and some patients, even under well conducted clinical treatments, cannot achieve weight loss. They remain in this condition in which clinicians cannot treat them and surgeons do not offer an alternative. Even a little overweight patients, but already suffering from severe comorbidities, like orthopedic incapacitating conditions or type 2 diabetes, might eventually be helped by surgeons, especially if we can adjust procedures to patients. However, up to the present day, just patients over 35 kg/m^2 of BMI are candidates to procedures aiming at weight loss.

A fast and constant change is observed in these regulatory matters and with little doubt, they will be soon modified, becoming more flexible and having not just the weight as a primary goal but also other metabolic conditions, especially diabetes.

In the opposite side are extreme obese patients. It is not easily acceptable that they might be treated the same manner as a patient with a 36 kg/m^2 BMI.

Sleeve gastrectomy has been proposed as a first step in the treatment of superobese, leaving the duodenal switch or biliopancreatic diversion (BPD) to be performed later (with lower risks) (ASBMS 2012). As the sleeve gastrectomy is a procedure with a very low potential to cause long-term problems, we think it can be used also in the other side of the line, to obese patients who are not heavy enough, nor sick enough to fulfill the traditional conditions to surgical indication. Patients that have conditions to help with exercise and are in the search for a friendly procedure may benefit from a simple sleeve gastrectomy.

These procedures may transform failing clinical treatments in successful ones, aborting progress of obesity and preventing some patients to further need more aggressive therapies.

In some patients, due to severe obesity, severe associated comorbidities, impossibility to exercise, and other conditions where the complete success of bariatric interventions is less probable, it is interesting to have a more potent procedure. We developed **transit bipartition** (TB) (Santoro et al. 2003). We developed transit bipartition (TB) as a meabolic complement to the sleeve gastrectomy

TB is a new concept that we introduced in 2003 (Santoro et al. 2003) to avoid duodenal–jejunal exclusion, because we recognize the importance of the nutritional and endocrine functions of this segment, the adverse consequences of exclusion (nutrient deficiencies, mucosal atrophy, bacterial proliferation, and lack of endoscopic access). TB is a surgical strategy to further reduce the exposition of nutrients to proximal intestinal mucosa without, however, producing exclusions. It consists in taking the proximal ileum to be anastomosed to the stomach leaving the pylorus open, as much as the duodenum, creating a division in the transit.

When compared to the traditional duodenal "switch," performed in some BPDs, bipartition is easier, avoids anastomoses with the proximal duodenum (a hard task in obese patients), and, additionally, leaves an open duodenum (Fig. 5.5).

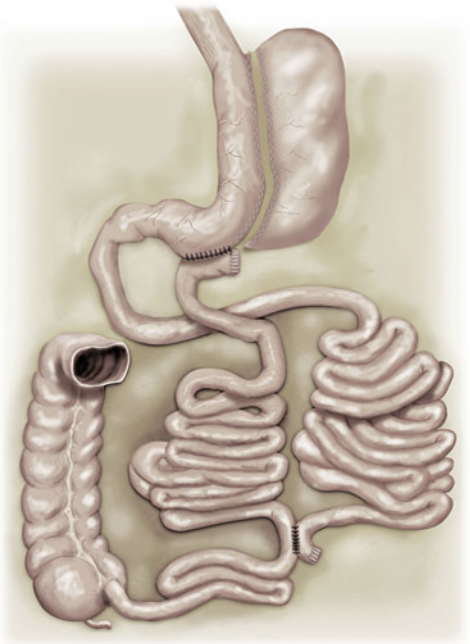

Fig. 5.5 Sleeve gastrectomy and transit bipartition (Santoro et al. 2012)

5.4 Sleeve Gastrectomy and Transit Bipartition

Evidence from several studies (Haber et al. 1977; Jenkins et al. 1980; Wisén and Johansson 1992; Ranganath et al. 1996; Lugari et al. 2002; Lam and Kieffer 2002; Bojanowska 2005) suggested that an **excessive proximal absorption** due to dietary interventions could be the cause for enterohormonal disorders. In 1997, Naslund et al. showed that the jejunoileal bypass (JIB), an old bariatric procedure that sends nutrients through a **shortcut to the ileum** (maintaining the duodenum inflow but excluding most of the jejunum and ileum), caused a long-lasting enhancement in GLP-1 secretion (Naslund et al. 1997). Consequently, it was demonstrated that GLP-1 deficient patients were indeed capable of secreting GLP-1 if distal nutritive stimuli were sufficient. Additionally, it became clear that JIB worked by promoting intentional malabsorption and through unpredicted metabolic ways. Looking back to 1980, this discovery could be explained by the observation documented by Organ et al. (1980), that JIB induced a fast remission of diabetes, before the occurrence of significant weight loss.

In 1998, the world was intrigued by an article (Hickey et al. 1998), that investigated whether type 2 diabetes mellitus (T2DM) could be a disease of the foregut. The nonrestrictive and non-malabsorptive effects of bariatric surgery became a topic of interest.

Based on these elements, we supposed that the mentioned dietetic modifications that intensify proximal absorption indeed diminish distal absorptive work, causing signaling disorders (Santoro 2003, 2008a). A surgical strategy (Santoro 2006, 2008b) was proposed to counterbalance the digestive tract signaling aiming at enterohormonal correction. It was the first strategy originally developed to maximally avoid restriction and malabsorption, instead of inducing them for therapeutic purposes.

This strategy included different procedures capable to cause metabolic interventions. Among them, we observed that sleeve gastrectomy and transit bipartition (SG + TB) were highly effective.

Patients with classic indication for bariatric surgery, that understand and accept that their surgery will basically rely on its metabolic components and not on malabsorption, are offered SG + TB. From June, 2004, until January, 2011, 1020 patients underwent SG + TB (Santoro et al. 2012).

At the time of surgery, patients had body mass indexes (BMIs) ranging from 33 to 72 kg/m^2 (average 42.2 kg/m^2). Diagnosed comorbidities included orthopedic problems, including joint pain, essential hypertension, diabetes, dyslipidemia, and respiratory problems including sleep apnea. Other frequently occurring preoperative conditions included a high prevalence of abnormally high levels of hepatic enzymes and hepatic steatosis, cholelithiasis, hyperparathyroidism, low blood thiamine, insufficient levels of 25 hydroxyvitamin D, menorrhagia in association with anemia, polycystic ovary syndrome, depression, and anxiety disorders.

5.4.1 Operative Technique

The procedure combines a typical SG with a TB; this creates a shortcut to the ileum while maintaining access to the duodenum (Fig. 5.5). The procedure may be performed in a conventional open method, laparoscopically, or, alternatively, with mixed access, where the SG is performed through laparoscopy, and a minilaparotomy is formed by the union of two trocar incisions. This approach provides adequate access for the retrieval of the gastric specimen and composes the enteric part of the surgery. Here, we describe the laparoscopic method.

Pneumoperitoneum is obtained using a Veress needle. Six trocars are positioned, including three 12-mm trocars (one in the midline 3–5 cm above the umbilicus and two others in the upper left and right quadrant) and three 5-mm trocars (one in the epigastrium for the liver retractor and two at each lateral flank).

The omental bursa is opened, and the greater omentum is sectioned with a sealer and divider device (Ultracision® or Ligasure®). The greater curvature is freed from 2 cm proximal to the pylorus up to the angle of His, including the left arm of the hiatal crura. If a hiatal hernia is present, then a hiatoplasty is performed.

A typical sleeve gastrectomy (Baltasar et al. 2005) is performed with a laparoscopic linear cutting stapler starting at the gastric greater curvature, at a point located 4–5 cm from the pylorus, up to 0.5 cm from the angle of His. A 36 French

bougie is passed to the stomach, to guarantee that the remnant gastric tube, which is positioned by the lesser curvature, has an internal lumen 3 cm wide. A seromuscular running suture is sometimes used to cover the stapling line to reduce bleeding.

After the SG, the **ileocecal transition** is located. A single stitch is used to mark the point at the ileum 80 cm from the ileocecal valve. The point at 260 cm is then located, and a perforation is made with the cautery to allow the insertion of one arm of the linear stapler into the ileal lumen. Another hole is created in the stomach antrum at the end of the stapling line, by applying the cautery against the bougie's protuberance. The other arm of the stapler is inserted in the stomach from the patient's left to the right, toward the pylorus, to create a 3- to 4-cm wide latero-lateral **gastroileal anastomosis** in an antecolic position. A 3-0 absorbable extra mucosal running suture closes the residual defect.

In the following sequence, the small bowel cranial to the gastroileal anastomosis is laterally widely anastomosed to the ileum, at 80 to 120 cm from ileocecal valve (previously marked), in a lateral–lateral mode. A laparoscopic linear stapler with a 45-mm white cartridge is used for the anastomosis. A nonabsorbable running suture closes the mesenteric borders to prevent internal hernias. Today we use a 120 cm "common channel" to avoid worsening the odor of stools. At the end of the procedure, the segment between both anastomoses is interrupted with stapling and cutting. A closed suction drain, lying along the sleeve gastrectomy staple line, is exteriorized through the lower left port incision. The other laparoscopic incisions are closed.

Patients fast in the first postoperative day (POD), and liquid fractioned meals are offered for the subsequent 12 days. Then, soft solid meals are allowed, in a slow progression toward normal food. Patients are instructed to begin meals with a portion of varied salad, enriched with protein (tuna, salmon, or chicken). Avoidance of refined sugar is advised. The patients are also advised to enroll in a physical activity program, with increasing intensity as weight loss occur. **Multivitamins** and **pantoprazol** are prescribed in the first 2 months and maintained for longer if necessary.

5.4.2 Follow-up

Patients are instructed to return after 10 days, 1 month, 3 months, 6 months, one year after the procedure and then annually, bringing blood tests, and at least one abdominal sonography performed around 1 year of surgery. Detected gallstones are surgically treated, frequently simultaneously to plastic surgery. Weight is actually measured and not self-reported. Unfortunately, around 40 % of patients return just in the early postoperative period, and not any more.

Data are collected online using an especially developed software; means, graphics, and standard deviations are immediately updated. Remission of T2DM is defined by HbA1c <6.5 % without oral hypoglycemic drugs or insulin, while improvement is defined as a reduction of at least 25 % in the fasting plasma glucose

level, and of at least 1 % in the HbA1c level, with hypoglycemic drug treatment. Systemic arterial hypertension and dyslipidemia are considered resolved when the patients do not need medication anymore, to maintain normal values for these conditions, while respiratory and orthopedic problems are considered resolved or improved based on patients perception of symptoms.

5.4.3 Early Surgical Results

The length of operative laparoscopic procedures ranged from 110 to 280 min (average 170 min). Mainly due to coverage restrictions, only 361 were laparoscopic procedures, and 659 procedures were performed with open or mixed access. In general, patients were discharged in the third POD. Early significant 30-day post-operative complications occurred in 60 patients (6 % Table 5.1). Nineteen patients required reoperation (1.9 %). There were 2 deaths (0.2 %).

5.4.4 Late Surgical Results

Late complications included 132 patients with cholelithiasis (21.9 %), 19 (3.1 %) with **incisional hernias**, and 15 (2.4 %) with internal hernias or intestinal subocclusion related to adherences. Most of these patients did not present the typical signs of obstruction, vomiting, or interruption of evacuation because of the TB. Pain was the predominant presenting symptom, along with some mostly left-sided abdominal distension. Postoperatively, three cases (0.5 %) had a hiatal

Table 5.1 Significant 30-day postoperative complications (Santoro et al. 2012)

Fistula—9[a] cases (0.9 %) Bleeding (requiring reoperation or blood transfusion)—8 (0.8 %)
Intestinal subocclusion—8 cases (0.8 %)
Non-obstructive prolonged ileus—7 cases (0.7 %)
Symptomatic atelectasis or pneumonia—5[a] cases (0.5 %)
Symptomatic partial portal thrombosis—5 cases (0.5 %)
Acute crises of urolithiasis—5 cases (0.5 %)
Early incisional dehiscence, in open cases—4 cases (0.4 %; 0.6 % of open cases)
Intraperitoneal infection or abscess of unknown origin—3 cases (0.3 %)
Cardiac complications—2 cases (0.2 %)
Compression neuroplegia—2 cases (0.2 %)
Clinically significant rhabdomyolysis—1 case (0.1 %)
Pulmonary thromboembolism—1 case (0.1 %)

[a]Refers to one case of fatality

hernia, corrected by a hiatoplasty due to gastroesophageal reflux. Approximately 35 % of patients were taking a daily or occasional **proton-pump inhibitor** (PPI) for heartburn. In relation to the frequency of bowel movements, mild constipation was rarely observed; most patients presented more frequent bowel movements, or maintained the same frequency observed before surgery. Typically, patients reported softened stools, and many reported a worsened odor in flatus and feces. However, the severity of these symptoms was rarely reported to be a problem, especially if the 120 cm common channel were used.

Radiographic gastrointestinal (GI) series routinely showed preferential flow through the wide gastroileal anastomosis (Fig. 5.6). GI ulcers were very rare (only one case, a patient with a prior history of a duodenal ulcer, who was easily cured with PPI treatment). Stenosis at the gastroileal anastomosis was rare, but this occurred in three patients, all of whom were successfully treated with endoscopic dilation. Typical dumping was not observed, but in rare circumstances, some hypoglycemia caused mild symptoms. No patients required treatment for this reason. Changes in food preferences were frequently reported, including an aversion to fatty foods.

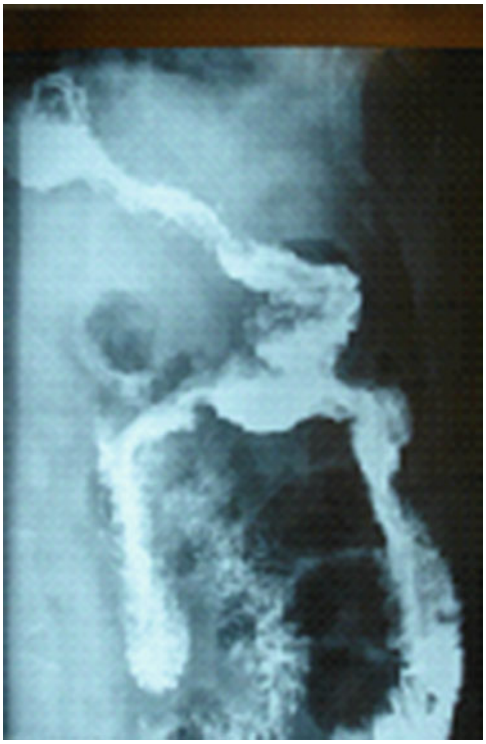

Fig. 5.6 Late radiographic aspect of a SG + TB. Observe that part of the contrast media empties through the duodenum. The gastroileal anastomosis is very well shown (Personal file)

5.4.5 *Clinical Outcome: Weight Loss and Nutritional Status*

Weight was monitored in the form of BMI and percentage of excess of BMI loss (EBMIL% = preoperative BMI—current BMI × 100/preoperative BMI—25). SG + TB presented an average EBMIL% of 74 ± 22.5 % in the fifth year (Fig. 5.7).

From a nutritional perspective, SG + TB has excellent results. Protein malnutrition, a severe adverse effect of BPDs, did not occur. Some patients temporarily presented low albumin levels, during some complication. Fortunately, there are no cases of chronic hypoalbuminemia. High levels of parathyroid hormone (PTH) and low levels of vitamin D and B_1 (thiamine) were frequently observed preoperatively (around 60 % and 40 %, respectively). **Nutritional supplementation** was started prior to surgery for many patients. These conditions frequently required continued supplementation of calcium, cholecalciferol, and thiamine postoperatively (the latter, in common multivitamin tablets). Anemia was rarely a problem and usually temporary. Around 7 % maintain hemoglobin below 12 g/dL, and this occurs especially when menstrual losses are excessive. No one developed chronic anemia below 10 g/dL (including the rare minor thalassemic patients of the group). Low plasmatic zinc was also eventually observed, but no supplementation was needed beyond the multivitamin tables. In general, the nutritional status was excellent.

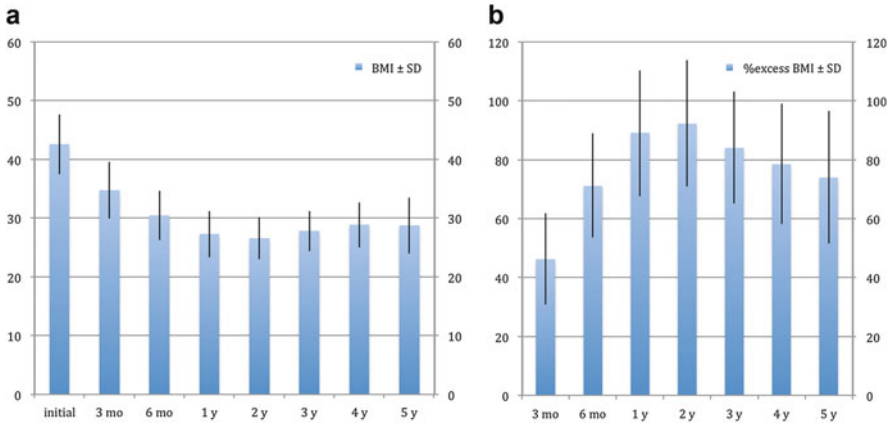

Fig. 5.7 (**a**, **b**) Graph on the *left* (**a**) shows the evolution in BMI (kg/m^2) ± standard deviation (SD) (*black bars* over the *columns*). *Graph* on the *right* (**b**) shows EBMIL% ± SD over time in months (mo) and years (y) after the procedure. Note that these columns refer to 603 patients at the initial column and at 3 months; then the numbers of patients related to columns are 450 at 6 mo, 366 at 1 y, 289 at 2 y, 183 at 3 y, 80 at 4 y, and 36 at 5 y (Santoro et al. 2012)

5.4.5.1 Clinical Outcome: Resolution of Comorbidities

Diabetes Type 2

From 333 diabetic patients, 281 had adequate follow-up (84.3 %, better than the nondiabetic group). From this group, 86 % went into complete remission; 14 % were much improved but still required some oral diabetes medication. Among these 14 % without full remission, 4 % had to restart medication very soon (usually with reduced dosages, and mostly in the worse cases) and 10 % had to do it just later, usually between 18 and 36 months, after some weight regain. Those who had to restart medication temporarily, but rapidly went into remission without medication, are counted among the 86 % of complete remission.

Diabetic patients are discharged without any medication for diabetes, but they are kept under rigid **glycemic control**, using their portable devices. If necessary, some of the previous medication could be restarted temporarily, until endogenous control improved. Usually, good glycemic control was already observed when solid food was reintroduced. It is worth mentioning that two patients did not present the expected rapid improvement, and a **stenosis of the gastroileal anastomosis** was observed. A notable fall in glycemic levels occurred immediately after endoscopic dilation. After a period of rapid improvement, a period of slow further improvement was continuously observed, for the first 6–12 months.

Other Comorbidities

Respiratory problems, including sleep apnea, were also very much improved within a few weeks. Respiratory problems were resolved in 91 % of patients, and improvements were noted in the others. The pain associated with orthopedic problems was resolved in 83 % of the patients, and was improved in the remaining patients. Hypertriglyceridemia was improved by the surgery (85 %) to a greater extent than hypercholesterolemia (70 %). Essential hypertension no longer required medication in 72 % of patients (Table 5.2).

Resolution was defined as the disappearance of the problem or withdrawal of medication. Improvement was defined as a reduction in medication required, or an improvement in objective laboratorial results or symptoms.

Table 5.2 Clinical resolution and improvement of comorbidities after SG + TB (Santoro et al. 2012)

Condition	Resolved	Improved
Orthopedic problems	83 %	17 %
Arterial hypertension	72 %	28 %
Type 2 diabetes	86 %	14 %
Hypertriglyceridemia	85 %	15 %
Hypercholesterolemia	70 %	30 %
Respiratory problems	91 %	9 %

5.5 Discussion

Due to evolutionary changes, the humans had developed different processes that affect the digestibility of food. In the 1980s, the concept of glycemic index was developed (Jenkins et al. 1980; Brand et al. 1985). An abundant high-glycemic index diet provokes fast, intense and early absorption, forcing proximal segments of the small bowel to overwork, while distal parts are exposed to fewer nutrients.

GIP is mainly a proximal bowel hormone, and it is overproduced in patients with obesity and T2DM (Vilsboll et al. 2003), while the production of GLP-1 (Lam and Kieffer 2002; Bojanowska 2005; Vilsbøll et al. 2001) and PYY (Le Roux et al. 2006), which are mainly distal bowel hormones, is deficient, as expected. A direct relationship between increased GIP and overeating was demonstrated long ago. Eating less for a few months can reduce both basal and postprandial levels of GIP (Deschamps et al. 1980).

A voluminous nutritive primitive meal would stimulate both the proximal and distal gut, in a proportional and decreasing manner. Many studies have suggested that combined GLP-1 and GIP agonism might be beneficial in T2DM (Asmar and Holst 2010). Lack of the distal stimuli would indicate that only a minor meal was consumed, or that an episode of vomiting occurred. Therefore, a strong insulinic response and an interruption in hepatic glucose production would be problematic, potentially causing hypoglycemia. It is expected that distal bowel hormones, which signal the completion of a significant meal, are preponderant. High GIP does not suppress glucagon, but GLP-1 does (Lund et al. 2011). A defect in **postprandial glucagon suppression** is a hallmark of T2DM. It has also been shown that adding exogenous GIP does not improve the treatment in T2DM, but rather makes it worse by preventing glucagon inactivation (Mentis et al. 2011). The addition of exogenous GLP-1 is very effective in suppressing glucagon and improves insulinic response and the overall control of T2DM.

GLP-1 is a more potent incretin than GIP in the diabetic, in the obese and in healthy people as well. GLP-1 is more efficient in blocking glucagon (Lund et al. 2011) and in sustaining a strong late phase of insulin secretion. Not surprisingly, **GLP-1 and PYY secretion**, as indicators of the ingestion of a significant amount of food, cause satiety, diminish gastric emptying, and contribute to the decision to terminate a meal.

The modern diet is absorbed mostly through the proximal bowel; the lack of a distal response and the excessive proximal stimulation might be detrimental. Resistance to the **incretinic effect of GIP** (Nauck et al. 1993) (which is protective if a major meal was not indicated by the distal gut) develops, but unfortunately, no resistance to its obesogenic effect seems to occur (Miyawaki et al. 2002; Marks 1988).

Enhanced secretion of GIP directly links overnutrition to obesity in general (Miyawaki et al. 2002), and to visceral obesity in particular (Oben et al. 1991). Through this link, GIP leads to detrimental effects. Indeed, anti-GIP antibodies and GIP-receptor blockers appear to help in treating obesity (Irwin and Flatt 2009).

Conversely, GLP-1 analogues, but not blockers, can help in the treatment of both obesity and diabetes.

Large meta-analyses showed that the bariatric procedures that work best (in terms of weight loss and metabolic improvement) are those that reduce the amount of food that is presented to the foregut and that enhance transportation of food to the hindgut (Buchwald et al. 2004). If a small segment of the proximal bowel is excluded, then good results still depend on some restriction, as in the Roux-en-Y Gastric Bypass (RYGB). However, if a very long proximal segment is excluded, as in the biliopancreatic bypass (BPD), then restriction is no longer needed for good metabolic results and weight loss, but malabsorption becomes a burden.

Progressively, it became clear that restriction and malabsorption were not the main cause for the good results of current bariatric procedures, and the **enterohormonal changes** that these procedures induce have been found to play a role in the success of bariatric procedures. We designed SG + TB to work primarily through metabolic ways, avoiding restriction and malabsorption, which have formed the cornerstones of bariatric surgery until recently.

It resembles very much a BPD. But, just part of the food will be submitted to a BPD. The food that goes through the gastroileal anastomosis will follow through around 2 m of ileum with no access to biliopancreatic juice (or little access, by duodenogastric reflux). There is no way to control the transit division. Studies (in publication) show a preferential transit through the gastroileal anastomosis in most patients (what also depends on the anastomosis size). Anyway, no nutrient particle will be exposed to the whole bowel, and terminal ileum will be flooded by nutrients in postprandial period (with consequent enhancement in "**meal termination**" **gut hormones**), as already demonstrated (Wisén and Johansson 1992), and this ileal nutritive charge is independent of which is the preferential way.

In all patients some food goes both ways (Wisén and Johansson 1992). Even if all food went through the gastroenteroanastomosis, we would obtain something very similar to Scopinaro's BPD, but we still would have endoscopic access to the duodenum, and also an extended access that includes the proximal ileum (Fig. 5.4), which has been helpful in the follow-up of two patients, where neuroendocrine tumors and GISTs were found.

This proposal causes intense weight loss, similar to traditional BPDs (Wisén and Johansson 1992), however, with a simpler gastroenteroanastomosis and a still functional (and endoscopically accessible) duodenum (Fig. 5.8). An open duodenum is probably responsible for the lack of nutritional problems (commonly observed in traditional BPDs that aim at malabsorption).

A duodenal–jejunal exclusion in any of its forms, including RYGB, might not be sufficiently potent if the exclusion is too short; if the exclusion is too long, it may be similar to a BPD in terms of adverse effects. Mason (1999) imagined that an ileal transposition (IT), an old experimental procedure (Koopmans et al. 1982), could be used as a metabolic intervention. IT is a complex procedure; it brings up only a portion of the ileum and still presents 100 % of the meal for duodenal absorption

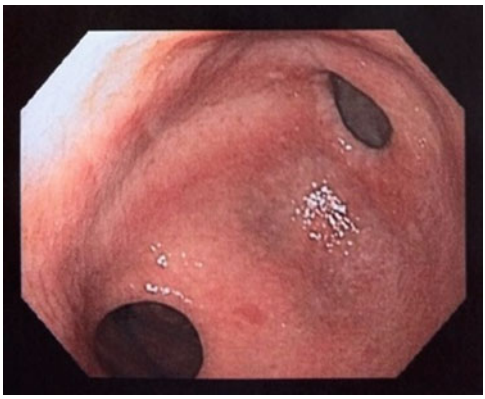

Fig. 5.8 Endoscopic view of SG + TB. Observe the pylorus at the *right side* and the gastroileal anastomosis at the lower *left corner* (Personal file)

(which allows the almost complete absorption of high-glycemic index food). These observations of the shortcomings of IT led to the creation of TB.

Another mechanism that is possibly involved in the observed metabolic improvement following SG + TB is a more intense stimulus from bile acids to the endocrine cells of the distal gut, because bile acids are known to stimulate GLP-1 and PYY secretion (Plaisancié et al. 1995; Roberts et al. 2011). The anatomic modifications that enhance bile acid distal stimulus might be responsible for the previous observations of augmented fasting levels of PYY and GLP-1, after either jejunectomies (Tang-Christensen et al. 2001) or bipartitions (Santoro et al. 2006a, b), when the nutrient stimulus cannot be the cause.

Most patients, after the procedure, do not have an altered frequency of stools evacuation or signals of malabsorption. They present an early sensation of satisfaction, and in some cases, especially with fatty meals, some degree of food aversion. All of them refer an evident change in their relation to food, especially in taste, which we attribute to enterohormonal changes.

Because distal gut hormones are satietogenic and they reduce gastric emptying, SG + TB strongly reduces meal size and overeating and leads to an important reduction in animal fat consumption by changing taste preferences. Sleeve gastrectomy is associated with high pressure in the gastric remnant, and diabetic patients might present with gastroparesis. Because TB is a gastric drainage, both issues may be improved, but this requires further investigation.

Another important issue related to bipartition is that type 2 diabetes remission occurred in 86 % of patients, without duodenal exclusion, reinforcing that this feature is not fundamental in diabetes remission. It creates the possibility of using bipartition with long common channel for those in whom the goal is not weight loss, but the enhancement of the incretin effect.

5.5.1 Conclusion

A new concept was presented: a lack of complete adaptation of the human gastrointestinal tract to the refined diet and its neuroendocrine and metabolic consequences. The original design of SG + TB aims at adaptive and neuroendocrine goals, and not at restriction or malabsorption. Absence of prostheses or excluded segments, full endoscopic access and easy feasibility, associated with a metabolic corrective intervention in the context of adverse dietetic environments, bring benefits to patients. SG + TB may be a better procedure for the treatment of morbid obesity, and an attractive alternative for the treatment of mildly obese patients with metabolic syndrome.

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Chapter 6
Surgical Options in Type 2 Diabetes

Denis Pajecki, Daniel Riccioppo, Flavio Kawamoto, and Marco Aurelio Santo

Abstract The onset of type 2 diabetes is characterized by a nonreversible complex cycle that includes severe deleterious effects on glucose metabolism. Obesity, but mainly visceral adipose tissue accumulation, is an important factor in this process. The goals of diabetes management in clinical practice, despite the improvement over the years, are often not met. In the last 20 years, based on observations of bariatric surgery series that have shown great improvement of type 2 Diabetes in morbid obese patients, metabolic surgery has emerged as a therapeutic possibility. In 2011 the International Diabetes Federation released its position statement mentioning that bariatric surgery was an accepted option for T2DM patients with BMI ≥ 35 kg/m^2 and might be considered an alternative therapy for patients with BMI ≤ 35 kg/m^2 who do not respond to standard medical therapy. Metabolic/bariatric surgery includes the application of conventional bariatric procedures (Roux-en-Y gastric bypass, biliopancreatic diversion, sleeve gastrectomy) and the introduction of new procedures (ileal interposition, intestinal bipartition) designed with the specific aim of having metabolic effects, irrespective of causing massive weight loss. The reversal of T2DM occurs due to mechanisms such as the increase in insulin sensitivity associated with an improvement in beta-cell function, including recovering the first phase of insulin secretion. This recovery is a consequence of the increase of GLP-1 production, and change in circulating bile acids. Remission of diabetes is observed on the first postoperative days after the operation.

6.1 Introduction: Pathophysiology of Type 2 Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disorder characterized by a lack of control of glucose homeostasis resulting in hyperglycemic state, high enough to significantly increase the incidence of a specific type of microangiopathy (retinopathy,

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nephropathy, and neuropathy). Type 2 diabetes (T2DM) represents 90–95 % of cases of DM. Prediabetes, also known as dysglycemia, is a condition in which blood glucose levels are higher than normal, but not high enough for the diagnosis of diabetes. People may have this condition for several years without noticing anything and before becoming diabetic (American Diabetes Association 2012).

The pathogenic mechanisms involved in the development of T2DM are: (A) peripheral insulin resistance resulting in decreased metabolic responses to insulin and (B) the progressive decline of pancreatic islet cell function resulting in reduced insulin secretion and inadequate suppression of glucagon secretion. Patients with insulin resistance require more insulin to promote glucose uptake by peripheral tissues, and the genetically predisposed ones may lack the necessary β-cell secretory capacity (Carrera Boada and Martinez-Moreno 2013).

Prediabetes can be separated into two different conditions: impaired fasting glucose (IFG), diagnosed by a fasting glucose test, and impaired glucose tolerance (IGT), diagnosed by a postprandial glucose test. The pathophysiology of IFG seems to include the following defects: reduced hepatic insulin sensitivity, stationary β-cell dysfunction and/or chronic low β-cell mass, altered GLP-1 secretion, and inappropriately elevated glucagon secretion. Conversely, the prediabetic state of isolated IGT (IGT without IFG) is mainly characterized by reduced peripheral (muscle) insulin sensitivity and a reduced second-phase insulin secretion. Individuals developing combined IFG/IGT exhibit severe defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of β-cell function (Bergman et al. 2002). In conclusion, the transition from the prediabetic states to type 2 diabetes is characterized by a nonreversible vicious cycle that includes severe deleterious effects on glucose metabolism. Obesity, but mainly visceral adipose tissue accumulation, is an important factor in this process. Many epidemiologic studies have shown that body mass index (BMI) is a powerful predictor of type 2 diabetes. Visceral fat is an important source of inflammatory cytokines such as TNF-alpha, TGF-beta, IL6, resistin, and PAI-1 that can directly affect insulin-mediated glucose uptake (insulin resistance). On the other hand, there is a reduction of secretion of other factors such as adiponectin that reduces insulin resistance (Carrera Boada and Martinez-Moreno 2013; DeFronzo 1997). This imbalance leads to a pro-inflammatory state which is related to an increased risk of cardiovascular complications. Along insulin resistance, β-cell secretory function and β-cell mass play complementary roles in the development of type 2 diabetes. This process includes islet amyloid deposits and increased β-cell apoptosis. Besides, abnormal α-cell function (glucagon secretion) is an important determinant of the magnitude of the hyperglycemia found in diabetes, and lipotoxicity characterized by an increase in circulating free fatty acids (FFAs) may contribute to progressive β-cell failure (β-cell lipotoxicity) in individuals genetically predisposed to T2DM (Carrera Boada and Martinez-Moreno 2013; Boden 1997). Another important factor in the physiopathology of the disease is related to the incretin secretion profiles. To date, only glucose-dependent insulinotropic polypeptide (GIP) and glucagon–like peptide 1 (GLP-1) fulfill the definition of an incretin hormone in humans. GIP is secreted by K cells and released from the proximal small intestine

(duodenum and jejunum) and GLP-1 is secreted by L cells located predominantly in the ileum but also in the proximal gut. Incretins bind to specific membrane receptors in β cells, enhancing the release of insulin. The profiles of these two hormones are altered in T2DM patients. While GIP concentration is normal or modestly increases in patients with T2DM, the insulinotropic actions of GIP are significantly diminished. In contrast to GIP, the secretion of GLP-1 has been shown to be deficient in patients with T2DM (Carrera Boada and Martinez-Moreno 2013).

6.2 Diagnosis and Results of Clinical Treatment of DM

The diagnosis criteria of DM, according to the American Diabetes Association (ADA), are (American Diabetes Association 2012):

Glycated Hemoglobin greater than 6.5 %
Or fasting glycemia greater than 126 mg/dL
Or glycemia greater than 200 mg/dL, 2 h after the glucose tolerance test

The test should be performed as described by the WHO (World Health Organization), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glycemia greater than 200 mg/dL (11.1 mmol/L) is considered diagnostic.

A useful method of measuring insulin resistance and β-cell function is a mathematical model that combines the measurement of fasting blood glucose and insulin. This method is called HOMA and based on it two other indices are extracted (HOMA-IR and HOMA-beta), which aim to translate insulin sensitivity and secretory capacity of β cells. The reference value of the HOMA-IR index for diagnosis of insulin resistance may be preselected, or calculated as the 95th percentile in a healthy population. In the BRAMS study (Brazilian Metabolic Syndrome Study), the cutoff point was 2.71 (Malerbi and Franco 1992).

The dosage of hemoglobin A1c became increasingly used and accepted by the scientific community after 1993, after being validated by two major clinical studies assessing the impact of glycemic control on chronic complications of diabetes: the DCCT study—Diabetes Control and Complications Trial, and UKPDS—United Kingdom Prospective Diabetes Study (Smyth-Osbourne et al. 1998; Murray et al. 2010). A1c reflects serum glucose levels 2–3 months prior to its measurement. In a nondiabetic individual, approximately 4–6 % of A1c is observed, while in the uncontrolled diabetic this percentage may reach levels two to three times above normal. A1c levels above 7 % are associated with a progressively higher risk of chronic complications. Therefore, current diabetes treatment goals set 7 % as the upper limit. If A1c is above 7 %, revision of the therapeutic regimen is indicated (Zachary and Bloomgarden 2010).

The treatment of type 2 diabetes and its complications focuses on control of glucose levels, initially based on diet, encouraging physical activities and losing weight, and oral hypoglycemic drugs (sulfonylureas, meglitinides, biguanides, pioglitazone, and DPP-4 inhibitors). GLP-1 analogues (exenatide or liraglutide) are used subcutaneously and may increase insulin secretion. Along the evolution of the disease and the impairment of insulin secretion by pancreatic β cells, patients may need insulin therapy.

The large clinical trials such as UKPDS (United Kingdom Prospective Diabetes Study), DCCT/EDIC (The Diabetes Control and Complications Trial and Follow-up Study), and ADVANCE (Action in Diabetes and Vascular Disease) (Murray et al. 2010; The ADVANCE Collaborative Group 2008) have proven the importance of the early intensive control of diabetes, to prevent complications of the disease, and to improve the quality and quantity of life of these patients, bringing the concept of "metabolic improvement."

A strategy of intensive glucose control to lower the hemoglobin A1c (HbA1c) value to 6.5 % yielded a 10 % relative reduction in major macrovascular and microvascular events (The ADVANCE Collaborative Group 2008).

On the other hand, more intensive glucose control in patients with poorly controlled T2DM had no significant effect on the rate of major CV events, microvascular complications, or death, due to complications related to hypoglycemia episodes (The VADT Investigators 2009).

In the same way, in the ACCORD study, high-risk T2DM patients submitted to intensive therapy to lower HbA1c had an increased mortality and no significant reduction in major CV events, as compared to standard medical therapy (ACCORD Study Group 2008).

The goals of diabetes management in clinical practice, despite the improvement over the years, are often not met. A Brazilian study published in 2010 showed only 27 % of control (glycated hemoglobin HbA1c—less than 7 %) in about 6,000 type 2 diabetic patients (Mendes et al. 2010); in the same way, a recent U.S. publication reported that 52.5 % of 1,343 patients with T2DM had HbA1c < 7, and only 18.8 % achieved the goal of multifactorial control (HbA1c < 7, LDL < 100 mg/dL, and less than 130×80 mmHg of blood pressure) (Starck Casagrande et al. 2013).

6.3 The Role of Surgical Treatment of Type 2 Diabetes

From the moment that the objectives of the clinical treatment of type 2 diabetes are not being achieved, despite the use of all clinical resources (medications, diet, change of lifestyle), metabolic surgery emerges as a therapeutic possibility. In the last 20 years, based on observations of bariatric surgery series, several articles have investigated whether type 2 DM (T2DM) could be a disease of the foregut (Hickey et al. 1998; Rubino and Marescaux 2004; Pories et al. 2011). The nonrestrictive and nonmalabsorptive effects of bariatric surgery became a topic of interest, and the

possibility of using bariatric surgical procedures to treat T2DM as the prime objective (metabolic surgery) became a goal among bariatric surgeons.

But the concept of metabolic surgery was defined earlier, by Buchwald and Vanco in 1978 in their book "*Metabolic Surgery*", as the operative manipulation of the normal organ or organ system, to achieve a biological result for a potential health gain (Buchwald and Varco 1978). Now, metabolic surgery is defined as any modification of the gastrointestinal (GI) tract, where rerouting the food passage seems to improve T2DM, based on mechanisms that are weight loss independent. In this way, bariatric surgery has emerged as a potentially useful treatment for T2DM (Deitel 2011). Observational studies and randomized controlled trials have shown that procedures including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), gastric banding (GB), and biliopancreatic diversion (BPD) significantly improve glycemic control, and favorably affect cardiovascular risk factors (Buchwald et al. 2009; Schauer et al. 2003; Dixon and O'Brien 2002). The remission rate of T2DM varies with the surgical procedure, and best results are seen in operations that include a bypass of the gastrointestinal tract (RYGB, BPD) when compared to those obtained with the purely restrictive operations (GB), in which remission is directly associated with weight loss (Table 6.1).

This new frontier of metabolic/bariatric surgery includes the application of conventional bariatric procedures (RYGP, BPD, SG) and the introduction of new procedures (ileal interposition, intestinal bipartition) designed with the specific aim of having metabolic effects, irrespective of causing massive weight loss.

In view of growing enthusiasm for surgical interventions to treat T2DM, the 1st Diabetes Surgery Summit was held in Rome on March 2007 to develop guidelines to use GI surgery to treat T2DM. In 2009 the American Diabetes Association first mentioned surgical therapy for treating T2DM. In 2011 the International Diabetes Federation released its position statement mentioning that bariatric surgery was an accepted option for T2DM patients with BMI $\geq$ 35 kg/m^2, and might be considered an alternative therapy for patients with BMI $\leq$ 35 kg/m^2 who do not respond to standard medical therapy (Dixon et al. 2011).

Shimizu et al. have reviewed papers about metabolic surgery for T2DM patients with BMI $<$ 35 kg/m^2, and found that most of the patients achieved normal BMI after surgery and only 2.7 % reported excessive weight loss with no evidence of malnutrition. Discontinuation of antidiabetic medication and remission of T2DM were achieved in 86.8 and 64.7 % of the patients, with FPG and HA1c at slightly above normal range. Moreover, metabolic surgery provided adequate glycemic control for 30.1 % of the patients using insulin prior to surgery (Shimizu et al. 2012).

It has been described that malabsorptive bariatric procedures have higher diabetes remission rates than restrictive ones (Buchwald et al. 2009; Scopinaro et al. 2005). Nevertheless, in the SOS study, where most surgical procedures were of the purely restrictive type, the average weight loss after 10 years was 25 % in the surgical group, compared to the control group (clinical treatment), where a weight gain of 1.6 % was observed. The risk of developing diabetes over the years has been 3$\times$ higher in the control group (Sjostrom et al. 2004). This

Table 6.1 Studies evaluating outcomes of DM control with different surgical procedures

	Studytype	Type II diabetes	BMI	Follow-p	Surgery 1	Surgery 2	Outcome	Result with 1 (%)	Result with 2 (%)
Schauer et al. (2014)	Randomized controlled trial	Yes	>35	3 years	RYGB (Koch and Finelli 2010)	Sleeve gastrectomy (Shimizu et al. 2012)	HBA1C < 6 %	38	24
Mingrone et al. (2012)	Randomized controlled trial	Yes	>35	2 years	RYGB (Deitel 2011)	BPD (Deitel 2011)	HBA1c < 6 %, normal fasting plasma glucose, and off oral hypoglycemics	75	95
Vidal et al. (2008)	Prospective	Yes	>35	1 year	RYGB (Pournaras et al. 2012)	Sleeve gastrectomy (Laferrere et al. 2008)	HBA1c < 7 % and normal fasting plasma glucose	87	87
Pinheiro et al. (2008)	Randomized controlled trial	Yes	>50	Mean 4 years	RYGB[a] (Kota et al. 2012)	RYGB[b] (Karamanakos et al. 2008)	Normal glycemia and off oral hypoglycemics	58	93
Pournaras et al. (2010)	Prospective	Yes	>35	3 years	RYGB[a] (Murray et al. 2010)	LAGB (The ADVANCE Collaborative Group 2008)	HBA1c < 6 %, normal fasting plasma glucose, and off oral hypoglycemics	72	17

[a]RYGB: a biliary limb of 50 cm and Roux limb of 150 cm
[b]RYGB with a biliary limb of 100 cm and Roux limb of 250 cm

information points to an old concept: the importance of losing weight (mainly visceral fat) as a key mechanism of T2DM control in obese patients, no matter how it is achieved (Larsson et al. 1981; Everhart et al. 1992).

6.4 Surgical Techniques

6.4.1 Current Bariatric Procedures

The technical procedure known as Roux-en-Y gastric bypass (RYGP) was endorsed as a standard in the surgical treatment of severe obesity (NIH Conference Gastrointestinal Surgery for Severe Obesity 1991). It is the mostly performed bariatric procedure in the world, and is considered the gold standard for surgical treatment of morbid obesity in the USA (Buchwald and Oien 2013).

RYGP (Fig. 6.1) is considered a combined procedure, i.e., it promotes weight loss by restricting food intake and also generates, although in small proportion, intestinal malabsorption of nutrients.

It consists in configuring a gastric pouch with a volume of about 15–30 cc, with or without the placement of a band for restriction of flow, and restoration of intestinal transit with a Roux-en-Y intestinal bypass 1.2–2.2 m long in average. About 50–100 cm is the length of the biliopancreatic limb, which leads digestive secretions to the entero-anastomosis, and 70–120 cm of the alimentary limb, which takes the bolus from the gastric pouch to the entero-anastomosis. This prevents the bypassed duodenum and first portion of jejunum to receive the alimentary bolus, which reaches more quickly the distal jejunum and the ileum, causing hormonal responses that may explain the surgical effects on glycemic control.

After RYGP, the following results can be observed, with important metabolic effects: gastric restriction, leading to early satiety, and decreasing the volume of the meals; exclusion of the fundus of the stomach from the alimentary transit, leading to a reduction in the secretion of ghrelin and subsequent anorexigenic effect; and faster arrival of nutrients to the distal intestine, in order to stimulate the release of PYY and GLP-1, which lead to decreased food intake and improve glucose tolerance (Rubino et al. 2006; Cummings et al. 2007).

The reversal of T2DM occurs due to an increase in insulin sensitivity, associated with an improvement in beta-cell function, including recovery of the first phase of insulin secretion. This recovery is due to an increase of GLP-1 production. Remission of diabetes is observed on the first postoperative days after RYGP (Laferrere et al. 2008).

This early antidiabetic effect is not observed in patients undergoing purely restrictive procedures, such as adjustable gastric banding. This finding reinforces the role of enterohormones in metabolic effects of bariatric procedures, and not just consequence of weight loss.

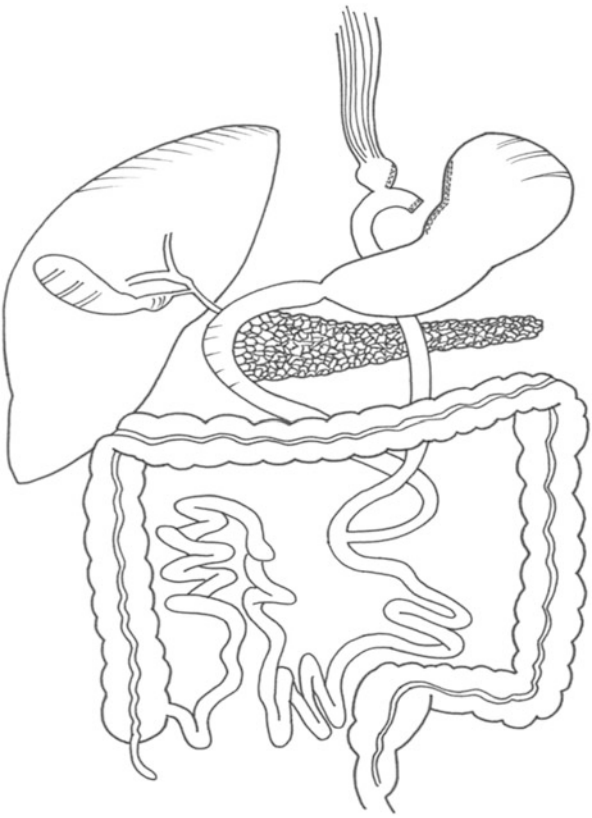

Fig. 6.1 Roux-en-Y gastric bypass (Image supplied by Dr. Daniel Riccioppo)

Thus, RYGP may be considered as a procedure with positive outcomes, resulting from the modulation of incretin hormones for the diabetic obese, and its early response goes beyond its effect on excess weight loss.

The biliopancreatic diversions are malabsorptive bariatric procedures, which promote weight loss by causing malabsorption of nutrients, without generating too much restriction on food intake. The surgical technique proposed by Scopinaro does not restrict food intake, and duodenal switch (DS) generates much less restriction if compared to RYGP. Both techniques are similar, with the DS being an evolution of Scopinaro's procedure (BPD).

In BPD (Fig. 6.2) a horizontal partial gastrectomy is performed, the gastric remnant has a volume of around 250 cc and the fundus is maintained, the duodenum is excluded, and the alimentary transit is reconstructed with a gastro-ileal anastomosis, which generates an intestinal bypass of all the jejunum, which becomes the biliopancreatic loop. This biliopancreatic channel drains the biliary and pancreatic secretion by the entero anastomosis, which is 50 cm from the ileocecal valve, to the distal ileum, called common channel. Only that portion of the ileum joins the biliopancreatic secretion and the alimentary bolus, and only in this small segment some of the food nutrients are absorbed.

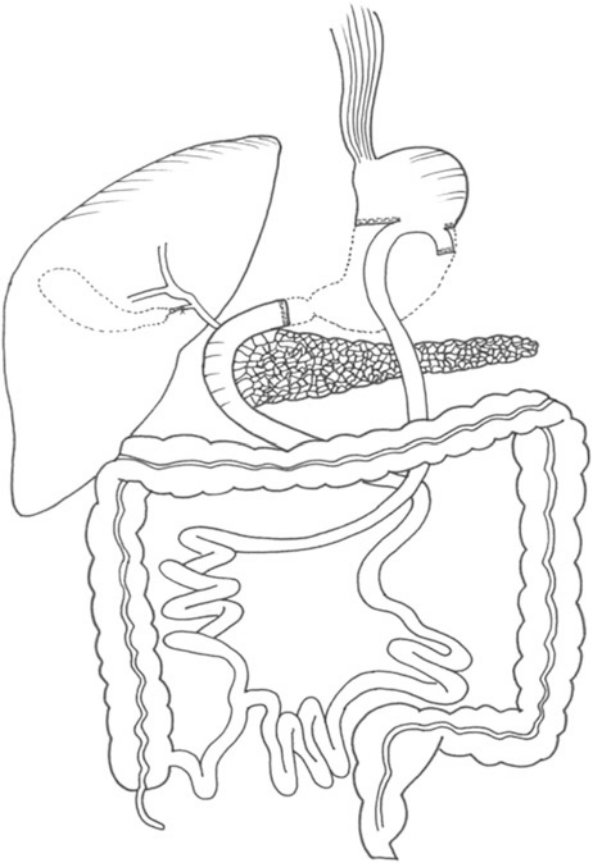

Fig. 6.2 Biliopancretic diversion (Scopinaro's procedure) (Image supplied by Dr. Daniel Riccioppo)

In DS (Fig. 6.3) the common channel is longer, with 75–100 cm, and the gastric pouch is obtained by a sleeve gastrectomy. The tubular gastric remnant is based in the lesser curvature, with a functioning pylorus and a volume around 150–200 cc. In this operation, a short segment of duodenum is preserved, with the intestinal transit reconstruction being done by a duodenolileal anastomosis. This technical modification aimed to solve a frequent complication of BPD, the stomal ulcer, and promoted improvements in the iron and calcium absorption (Dorman et al. 2012).

The effect of enterohormonal stimulation resulting from the arrival of nutrients to the distal bowel segment is evident on biliopancreatic bypass surgical procedures. The biliopancreatic diversion leads to a very effective control of lipid metabolism and DM2, promoting improved insulin sensitivity in a more intense way than RYGP (Pata et al. 2013).

More malabsorptive procedures have greater resolution capability of type 2 diabetes, arterial hypertension, hypercholesterolemia, and obesity itself. The biliopancreatic bypass with duodenal switch (DS) achieves a greater incretin effect. It might be explained by the association of the sleeve gastrectomy, which strongly

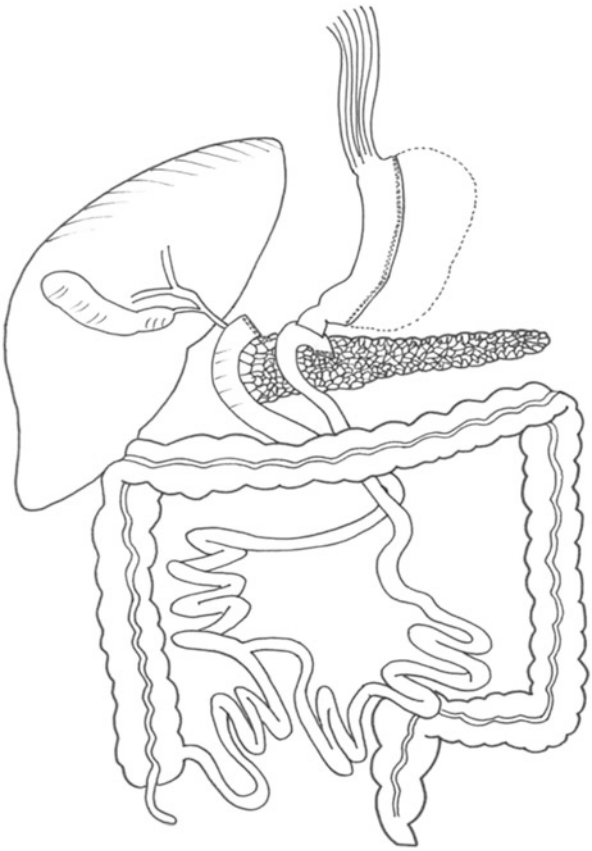

Fig. 6.3 Duodenal switch (Image supplied by Dr. Daniel Riccioppo)

decreases the secretion of ghrelin and increases the rate of gastric emptying, and duodenoileal bypass, which generates the early exposure to the nutrients at the most distal intestinal portions. The ileal mucosa contact with nutrients is known to provide more effective secretion of PYY and GLP-1, generating more satiety and optimizing the pancreatic beta-cell function (Briatore et al. 2010). In RYGP, the distal segment brought in contact with the ingested food is the jejunum, possibly explaining the results not as relevant as those found in Scopinaro's surgery and duodenal switch.

Nevertheless, T2DM typically resolves within a few days to weeks following procedures such as RYGB or BPD before significant weight loss is achieved. Although the exact mechanism is still not fully understood, growing evidence shows that procedures involving rerouting of food might improve T2DM, by enhancing insulin sensitivity and/or by improving beta-cell function, which is additive to weight loss and reduced caloric intake. Currently two hypotheses, hindgut and foregut theory, have been proposed to explain T2DM remission after metabolic surgery in addition to reduced calorie intake after surgery and surgical

induced weight loss that might contribute to improving insulin sensitivity. The first theory states that surgical rerouting of nutrients to the distal part of the small intestine results in increased secretion, and concomitant glucose-lowering effects of GLP-1, and the second emphasizes that the surgical bypass of the foregut prevents the release of a still not identified nutrient-induced diabetogenic signal ("*Rubino Factor*") in susceptible individuals (Schulman et al. 2009). Rubino et al. demonstrated that the exclusion of the duodenum promoted improvement in glycemic control, based on the foregut theory (Rubino and Marescaux 2004).

Recent studies have indicated that ghrelin gene products stimulate proliferation and prevent apoptosis of pancreatic β cells, and this could be another important mechanism, not explained by the operations. Yang et al. demonstrated a significant increase in cell survival and a decrease in cell apoptosis, after treating β cells in cultures with ghrelin (Yang et al. 2014).

The 3-year follow-up from the STAMPEDE trial (Schauer et al. 2014) has addressed questions about the durability of the benefits of bariatric surgery, as compared to intensive medical therapy for treating DM. The trial was a three-group, randomized, controlled single-center study, involving 150 obese patients, in which the efficacy of intensive medical therapy was compared with those of gastric bypass or sleeve gastrectomy. Sleeve gastrectomy (Fig. 6.4) has become a common bariatric procedure in the last decade. It was first applied as a first step of the BPD-DS in high-risk patients, but soon gained acceptance as a sole gastric procedure, with better results compared to gastric banding. It is not considered a pure restrictive procedure, as it has also enterohormonal effects, as a result of gastric fundus resection and rapid gastric emptying (Karamanakos et al. 2008). The results

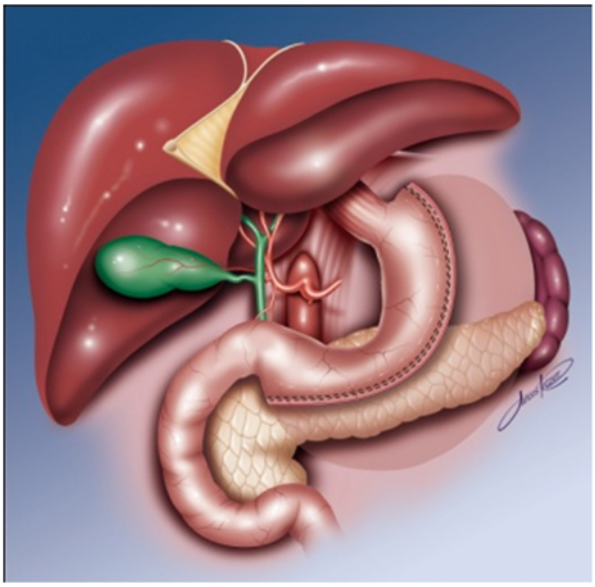

Fig. 6.4 Sleeve gastrectomy (Image supplied by Dr. Denis Pajecki)

showed that bariatric surgery was associated with superior and sustained glycemic control and weight reduction.

More than one-third of the patients in the gastric bypass group, and a fifth of those in the sleeve gastrectomy group, as compared to no patients in the medical-therapy group, had a glycated hemoglobin level of 6.0 % or less without the use of diabetes medication. Weight loss and shorter duration of diabetes were the main predictors of having a glycated hemoglobin level of 6.0 % or less after surgery. The diabetes remission rates of this study are similar to those reported by Ikramuddin et al. (2013), but are lower than those of Mingrone et al. (2012). Such discrepancies could be explained by the greater severity of diabetes in the population of the STAMPEDE study, as well as a stricter definition of remission. Metabolic and weight loss outcomes were generally similar in the two surgical groups at 1 year, although some advantages of gastric bypass over sleeve gastrectomy have emerged during longer follow-up, including a greater likelihood of reaching a glycated hemoglobin level of 7.0 % or less (a therapeutic goal of the American Diabetes Association) with no use of diabetes medication, and a greater reduction in weight and BMI. It has been demonstrated that gastric bypass was superior to sleeve gastrectomy with respect to insulin secretion, insulin sensitivity, and relative reduction in truncal fat as compared to subcutaneous fat.

The results in relation to the control of T2DM after BPD are even more impressive, ranging from 85 to 96 % (Scopinaro et al. 2011). Their wider use, however, touches on the incidence of side effects like diarrhea, excessive flatulence, and nutritional deficiencies (Koch and Finelli 2010). In a prospective randomized trial comparing medical treatment to gastric bypass and BPD, Mingrone et al. showed that, at 2 years, diabetes remission occurred in none of the patients receiving medical therapy, as compared to 75 % undergoing gastric bypass and 95 % undergoing BPD (Mingrone et al. 2012). There was no correlation between normalization of fasting glucose and weight loss, after gastric bypass and biliopancreatic diversion. Diabetes remission occurred faster after BPD, possibly because of the substantial malabsorption of fat that is characteristic of BPD, which may translate to lower levels of circulating cholesterol and triglycerides. Reductions in levels of LDL cholesterol and triglycerides after BPD helped to normalize insulin sensitivity. However, intestinal malabsorption can increase the incidence of late nutritional complications, such as hypoalbuminemia and deficiencies of vitamin D and calcium, even with vitamin and mineral supplementation, which raises concern about long-term risks of this type of procedure (Koch and Finelli 2010).

A meta-analysis of studies on various bariatric procedures involving patients with type 2 diabetes showed an overall rate of remission of hyperglycemia of 78 %, among the various procedures. Remission occurred in approximately half of patients who underwent LAGB, 80 % of those who underwent RYGP, and 95 % of those who underwent BPD (Buchwald et al. 2009).

The weight loss effect of metabolic surgery on T2DM in low BMI patients might be lower than that of bariatric surgery on T2DM in high BMI patients (Shimizu et al. 2012). Dixon and O'Brien reported that a shorter history of diabetes and

greater weight loss were positive predictive factors for remission of diabetes after gastric banding (Dixon and O'Brien 2002).

A low preoperative BMI and severe T2DM status were associated with failure of consistent durable remission of diabetes. The common causes for failure of diabetes remission after bariatric surgery are known as inadequate weight loss or regain of weight, long-standing poorly controlled or aggressive T2DM, lower preoperative BMI, and latent autoimmune diabetes in adults (LADA). LADA comprises 10 % of diabetics aged 30–55, and is more prevalent in low BMI individuals (Schernthaner et al. 2011; Geloneze and Pareja 2006).

Schauer et al. showed that a shorter history of diabetes and milder disease according to preoperative medication status were associated with an increased likelihood of remission of T2DM after RYGB (Schauer et al. 2003).

A large meta-analysis showed that the bariatric procedures that work best (in terms of weight loss and metabolic improvement) are those which reduce the amount of food that is presented to the foregut, and enhance transportation of food to the hindgut. If a small segment of the proximal bowel is excluded, then good results still depend on some restriction, such as in RYBG. However, if a very long proximal segment is excluded, as in the BPD, then restriction is no longer needed for good metabolic results and weight loss, but malabsorption becomes a burden. Progressively it became clear that restriction and malabsorption were not the main causes for the good results of current bariatric procedures, and the enterohormonal changes that these procedures induce have been found to play a role in the success of bariatric procedures. Also, the role of circulating bile acids in this complex process (in different procedures like RYGB, BPD, and SG), by binding to a nuclear (hypotalamus) receptor (FXR), that influences weight loss and metabolic control mechanisms has been recently described (Pournaras et al. 2012). This will certainly be an important issue for research in the next few years.

6.4.2 New Surgical Procedures

The existing mismatch between modern, highly processed food diet that is easily absorbed, avoiding the incretin stimulation in the distal portions of the intestine, associated with hyperalimentation and inactivity, seems to be an important triggering factor of metabolic syndrome. It seems plausible, therefore, to propose for obesity and metabolic diseases treatments that target to control the hyperalimentation.

With a better understanding of the effects of different bariatric techniques on the physiology of the neuroendocrine system, and about the various hormones and intestinal neuropeptides, new techniques have been proposed and studied as a treatment option for type 2 DM, with or without associated severe obesity. These procedures seek to stimulate L cells in distal intestinal segments, and provide favorable metabolic effects by modulating plasma enterohormones. The novel surgical procedures such as Ileal Interposition + Sleeve Gastrectomy and Intestinal Bipartition + Sleeve Gastrectomy were designed to apply hindgut and/or foregut hypothesis.

6.4.3 *Ileal Interposition + Sleeve Gastrectomy*

The ileal interposition is a procedure based on the hindgut hypothesis. In this operation, an ileal loop is placed in the intestinal transit, in a proximal position, with probable effect on the release of incretins by the early presence of chyme in this ileum segment.

Since the studies of Koopmans et al. (1982) regarding the ileal transposition regulation of appetite and weight loss effects, different authors have researched the technique. The principle that rules this procedure is the placement of distal intestinal portion, rich in L cells, in contact with the food ingested.

In a literature review conducted by Mason in 1999 (Mason 1999), the author suggests that ileal transposition may be the ideal treatment for obesity and possibly type 2 diabetes, because of the ability to promote weight loss and increase postprandial serum enteroglucagon like entero peptides (GLP-1, PYY, oxyntomodulin).

Combination of the foregut and hindgut theories explains the improvement in diabetes and weight loss after this operation. Possible mechanisms explaining the benefits of this procedure could be as follows: calorie restriction induced decreased stimulation of the duodenum, leading to attenuated secretion of the unknown culprit foregut factor (Rubino's factor); earlier exposure of food to ileum, leading to better incretin response; ileal break (food entering into ileum modulates gastric and intestinal motility to reduce food intake and absorption); and enhanced postoperative serum bile acid levels have been proposed to play a role in improved insulin sensitivity (correlated to high adiponectin levels) and increased incretin-induced insulin secretion (Kota et al. 2012).

Two different types of ileal interposition and sleeve gastrectomy have been proposed and analyzed. The jejunal–ileal interposition (JII-SG) encompasses the hindgut theory, and has the advantage of maintaining the normal food route, thus avoiding malabsorption. The duodenal–ileal interposition (DII-SG) combines both the hindgut and foregut hypotheses (Fig. 6.5). An evidence of the better performance of the DII-SG was observed in a randomized study, in which patients submitted to DII-SG achieved better glycemic control without any antidiabetic medication, than those submitted to JII-SG at 2 years follow-up, and also at 5 years for patients with BMI < 35 kg/m^2 and more severe disease (De Paula et al. 2012). The anatomical similarity of DII-SG to BPD-DS (Duodenal Switch) operation is evident. The BPD-DS has the highest rate of resolution of diabetes in morbidly obese patients; however, its long intestinal bypass results in harmful nutritional complications that can be avoided by ileal interposition. De Paula et al. did not observe protein malnutrition and fat and vitamin malabsorption, as typically seen in the BDP-DS operation, in their series (De Paula et al. 2012).

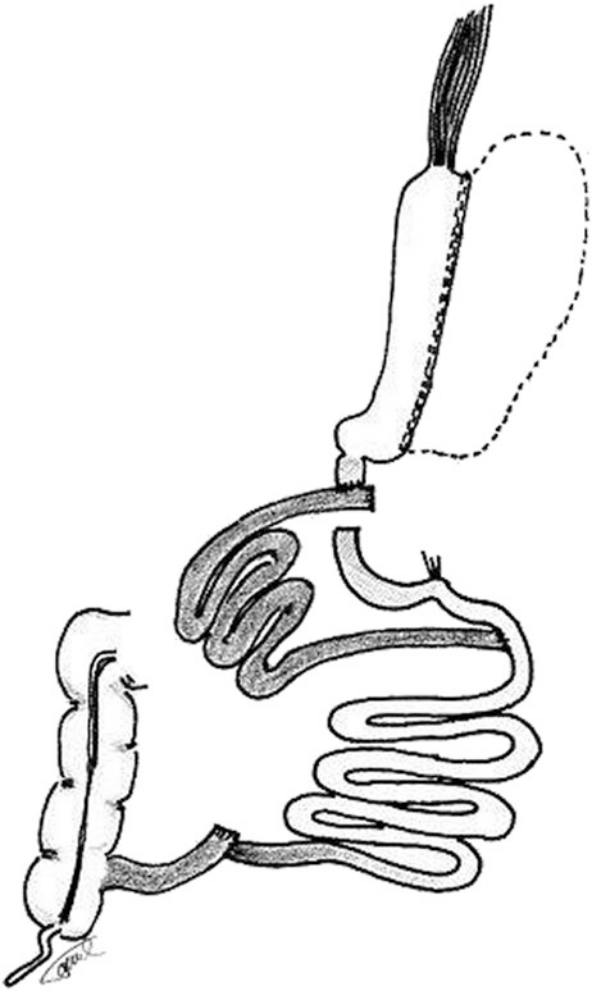

Fig. 6.5 Sleeve gastrectomy with diverted ileal interposition (Image supplied by Dr. Daniel Riccioppo)

6.4.4 Intestinal Bipartition + Sleeve Gastrectomy

This procedure can be also called partial Duodenal Switch, once it partially interrupts the flow of food through the duodenum (Fig. 6.6).

It consists of a sleeve gastrectomy, with section of the ileum 260 cm proximal to the ileocecal valve, and reconstruction of intestinal transit by a Roux-en-Y with gastro-ileal anastomosis. The food stream then occurs by dual paths, but preferably through the gastro-ileal anastomosis, for lower resistance compared to transit

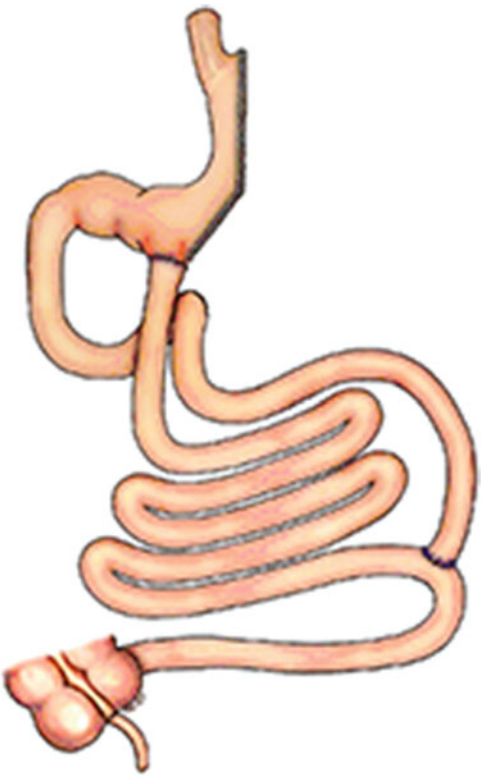

Fig. 6.6 Sleeve gastrectomy with transit bipartition, or Partial Duodenal Switch (Image supplied by Dr. Sergio Santoro)

through the pylorus and duodenum. Without completely interrupting the participation of the duodenum in nutrient absorption, this procedure would lower the risks of iron and calcium deficiencies. This procedure also generates enterohormonal stimulation by elevating production of ileal GLP-1 and PYY, decreases ghrelin due to sleeve gastrectomy, and decreases jejunal lipogenesis and cholesterogenesis, without generating exclusion of any segment of the alimentary tract (Santoro et al. 2008).

Although similar to BPD-DS it is technically simpler, because it does not require operation on the duodenum. The complementary procedure to the SG is an anastomosis, performed in the lowest and most anterior part of the stomach. It is also an "easier" operation compared to Ileal interposition, as it requires less anastomoses, and the correct positioning of the mesentery is not as challenging. Using this technique in 333 diabetic patients with a 2-year follow-up of 84.3 %, Santoro et al. showed complete remission of diabetes in 86 %, and improvement in 14 % (Santoro et al. 2012).

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Chapter 7
Endoscopic Therapeutic Options for Type 2 Diabetes

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Abstract The global obesity epidemic is expected to worsen with a concomitant increase in the comorbid conditions. Obesity is a major risk factor for type 2 diabetes, and it is not surprising that the global prevalence of this disease continues to increase. Given the emerging role of endoscopic procedures in the treatment of obesity and rapid changes in endoscopic technologies and techniques, this review considers the current state of endoscopic management of obesity and type 2 diabetes. Endoluminal interventions performed entirely through the gastrointestinal tract by using endoscopic devices offer the potential for an outpatient weight loss procedure that may be safer, less invasive, and more cost-effective, compared to current surgical approaches. Endoscopic techniques attempt to mimic some of the anatomic features of bariatric surgery and rely on gastric restriction and/or duodenal exclusion. In this chapter we will describe the two endoscopic methods that have much endorsement of the literature in relation to type 2 diabetes and are in current clinical use—the intragastric balloon and the duodenojejunal bypass liner.

7.1 Introduction

The prevalence of obesity, defined as a body mass index (BMI) of 30 kg/m^2 or more, has been increasing in developed and developing countries. It is already known that obesity is a major risk factor for cardiovascular disease, which is the main cause of death in developed countries (Lee et al. 2008). Every increase of 5 kg/m^2 in BMI raises the risk of cardiac complications by 29 %. This risk is compounded by the coexistence of other factors associated with obesity such as hypertension, dyslipidemia, and glucose metabolism abnormalities (Bogers et al. 2007).

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The change in lifestyle that occurred in the last decades, characterized by inactivity and a high calorie diet, led to an alarming increase in obesity and type 2 diabetes (Cerezo et al. 2013). Abdominal obesity leads to a cluster of metabolic abnormalities including hypertension, dyslipidemia (low HDL and increased triglycerides), and glucose intolerance with insulin resistance. This group of abnormalities is defined as Metabolic Syndrome (Cerezo et al. 2013).

Insulin resistance and lipid abnormalities, which are commonly found in obese patients with type 2 diabetes mellitus (T2DM), are strongly related to the development of heart disease. Several studies show that the presence of insulin resistance and compensatory hyperinsulinemia significantly increases the risk of death from cardiovascular diseases (McLaughlin et al. 2003, 2005; Shishehbor et al. 2004).

In the treatment of obesity and insulin resistance, the initial steps are changes in lifestyle, focusing on a balanced diet and increased physical activity, with the goal of losing weight. Associated with these measures, medications for weight control, oral hypoglycemic agents, and insulin to the treatment regimen can be added. However, diet and drug therapy offer limited potential for a sustained weight loss, being effective in less than 5 % of the cases (Kumar and Thompson 2011).

In contrast, bariatric surgery has a more prolonged response in the weight loss. Moreover, some of these surgical procedures have an excellent control of comorbidities associated with obesity, such as diabetes, insulin resistance, and hypertension (Lee et al. 2008; Kumar and Thompson 2011).

Although bariatric surgery has excellent results in weight reduction and control of comorbidities associated with obesity, it has a very specific indication and is not riskless. This kind of surgery is associated with clinical complications such as pneumonia, venous thrombosis, and thromboembolism, in addition to surgical complications such as ulcers and anastomotic leaks, with a mortality rate that can vary from 0.1 to 2 % (Flum and Dellinger 2004). However, even taking into account the risks, surgery for weight loss has a lower incidence of mortality than obesity and diabetes untreated over time (Blackburn 1995).

The use of endoscopic therapies for obesity control can provide some of the benefits achieved with bariatric surgery. Endoscopic procedures have the advantages of being reversible, present a lower risk profile, and can be used in patients who do not fit the indications for surgery. These procedures can also help in reducing preoperative weight and control comorbidities like type 2 diabetes, dyslipidemia, and hepatic steatosis (Herve et al. 2005; Mathus-Vliegen and Tytgat 2005; Schauer et al. 2007; Gersin et al. 2007; Tarnoff et al. 2008, 2009; Forlano et al. 2010; Moura et al. 2012).

Endoluminal technologies, that attempt to mimic the anatomical features and clinical efficacy of different surgical techniques, are under development and review. Among them we find endoluminal suturing or stapling devices, implantable polymers, devices that take up space in the stomach, electrical gastric stimulation, and botulinum toxin injection.

Currently, devices that prevent the contact between ingested nutrients and the mucosa of the proximal small intestine are those with the most promising results in

controlling diabetes. In this chapter we will describe only the two endoscopic methods that have a great acceptance in the literature in relation to T2DM.

7.2 Intragastric Balloon

Intragastric balloon is the most common endoscopic technique used for the treatment of obesity. It comprises a spherical silicone balloon, resistant to gastric acid degradation, by a period of approximately 6 months. The balloon is inserted endoscopically under conscious sedation, and filled with 400–700 ml of saline solution and methylene blue, which changes the color of the urine in case of rupture (Fig. 7.1). The removal of the balloon is also performed endoscopically, at the end of 6 months (Kumar and Thompson 2011). In addition to the balloon having a direct effect on diabetes, weight loss achieved with the device has a great impact on improving this comorbidity.

A meta-analysis by Imaz et al. evaluating 15 studies including 3,698 patients with intragastric balloon showed an average weight loss of 14.7 kg, 32.1 % reduction in the excess weight, and decrease of 5.7 kg/m^2 in the BMI after 6 months (Imaz et al. 2008). In another review, including 22 studies with a total of 4,371 patients implanted with intragastric balloon, an average weight loss of 17.6 kg was demonstrated, with extremes of 4.9 and 28.5 kg. A greater absolute weight loss was observed in patients with higher BMI (Dumonceau 2008).

A prospective study evaluating the effect of the balloon on weight, insulin resistance, and hepatic steatosis in obese patients showed that 76 % of patients achieved a reduction of 3.5 kg/m^2 or more in BMI. The mean weight loss compared to baseline was 16.4 kg (+8.2), with a mean reduction in BMI of 6.4 kg/m^2 ($\pm$3.2). The absolute percentage of participants with blood glucose levels higher than 100 mg/dl decreased from 50 to 12 %, and the percentage of patients with hypertriglyceridemia greater than 150 mg/dl decreased from 58 to 19 %. Patients presenting changes in ALT also decreased from 38 to 7 % (Forlano et al. 2010).

Regarding follow-up, two studies, one randomized and another uncontrolled, totaling 143 patients, showed that 1 year after gastric balloon removal, these patients had a mean absolute regain of the lost weight of 41 and 28 %, respectively

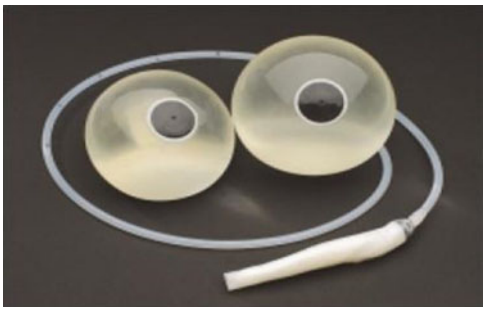

Fig. 7.1 Intragastric balloon

(Herve et al. 2005; Mathus-Vliegen and Tytgat 2005). Another study following 88 patients for a mean period of 22 months after removal observed that 50 % of patients regained some weight, 39 % maintained weight, and only 11 % continued to lose weight after withdrawal (Forlano et al. 2010).

In a European multicentric study comparing findings at baseline, at 6 months after implant (when the balloon was removed) and 3 years after balloon withdrawal, the mean BMI fell from 28.6 ± 0.4 to 25.4 ± 2.6 kg/m^2 at 6 months and to 27.0 ± 3.1 kg/m^2 at 3 years after removal. The mean percentage of excess weight loss was 55.6 % at 6 months and 29.1 % at 3 years. Patients with hypertension decreased from 29 % at baseline to 16 % at 3 years, diabetes decreased from 15 to 10 %, and dyslipidemia decreased from 20 to 18 %, showing that despite the weight regain, the balloon maintains a benefit in the reduction of the comorbidities (Genco 2013).

The intragastric balloon also has some effect on gut hormones. A prospective analysis including 22 patients with intragastric balloon, evaluating weight, glycated hemoglobin, and the effect on some gut hormones, has been reported. The mean weight loss was 18.4 kg, and it was associated with a significant decrease in glycated hemoglobin. The levels of ghrelin significantly increased after 3 months. Subsequently, the levels of ghrelin decreased but were still above baseline. Leptin significantly decreased, and the levels of adiponectin did not differ significantly (Buzga et al. 2014).

It is important to consider that not all patients have a satisfactory weight loss. Around 20–40 % fail to obtain a significant weight loss (usually defined as >10 % of the initial weight or more than 25 % excess body weight). These may be related to early withdrawal in patients with gastrointestinal or psychological intolerance to the balloon, early disappearance of the effects on hunger and early satiety, or high-calorie food intake (Dumonceau 2008).

The intragastric balloon can be a complement in the treatment of obese patients, facilitating changes in lifestyle, working as an adjunct to drug therapy, and reducing the metabolic complications. Although the balloon does not lead to a sustained long term weight reduction in obese patients, it can facilitate the control of some comorbidities such as diabetes. It can also improve the quality of life in patients with overweight and obesity, who do not want to undergo bariatric surgery.

7.3 Endoscopic Duodenojejunal Bypass Liner (DJBL): EndoBarrier™

A meta-analysis involving 136 papers with 22,094 patients who underwent different techniques of bariatric surgery showed that improvement of type 2 diabetes occurred in 86 % of patients. Analysis of the specific surgical technique reported complete remission of diabetes in 48 % of patients undergoing gastric band

placement, 84 % after RYG Bypass, and above 95 % after Bileopancreatic Diversion (BPD) (Buchwald et al. 2004).

To clarify the reason for the resolution of type 2 diabetes, Rubino et al. (2006) conducted a study comparing diabetic rats who underwent gastric bypass with and without duodenal exclusion. A significant improvement of glycemic control was observed in the group of rats who underwent the duodenal exclusion. Also, when a second operation was performed with duodenal exclusion in the rats submitted to pure gastric bypass, an improvement in glycemic control was observed. Thus, the reestablishment of the food flow through the duodenum in rats with duodenal exclusion was associated with increased levels of glucose.

The analysis of these facts demonstrates that the exclusion of the proximal segment of the small intestine appears to play an important role in improving glucose metabolism. This is the base for developing a device that permits the exclusion of the duodenum, providing a temporary endoscopic duodenojejunal bypass (DJBL) (Levine et al. 2009).

The DJBL is a sterilized, minimally invasive, single-use endoscopic device, which is employed under radioscopic control. It is composed of a nitinol anchoring, with tiny lateral barbs for fixation, and an impermeable plastic conduit made of a fluorine polymer with 62 cm in length, which impedes contact of the chyme with bile–pancreatic secretions prior to the proximal segments of the jejunum (Fig. 7.2). The device is called EndoBarrier™.

Didactically, the device has three components: the implant, the system for deployment, and the removal system.

Below the sequence for implantation and removal of the device is observed (Figs. 7.3, 7.4, 7.5, and 7.6)

To evaluate the effectiveness, safety, and tissue reaction, the DJBL was implanted in three groups of laboratory animals (Tarnoff et al. 2008). Four pigs who lived for 90 days, two for 120 days, and three in which no implant was performed, as a control group for the same period. In these series there was one migration and one partial rotation of the device. The tissue reaction caused by the device was defined as mild. There was better control of weight gain in the device group compared to the control, suggesting the effectiveness of the method.

Fig. 7.2 Impermeable plastic conduit and anchor system

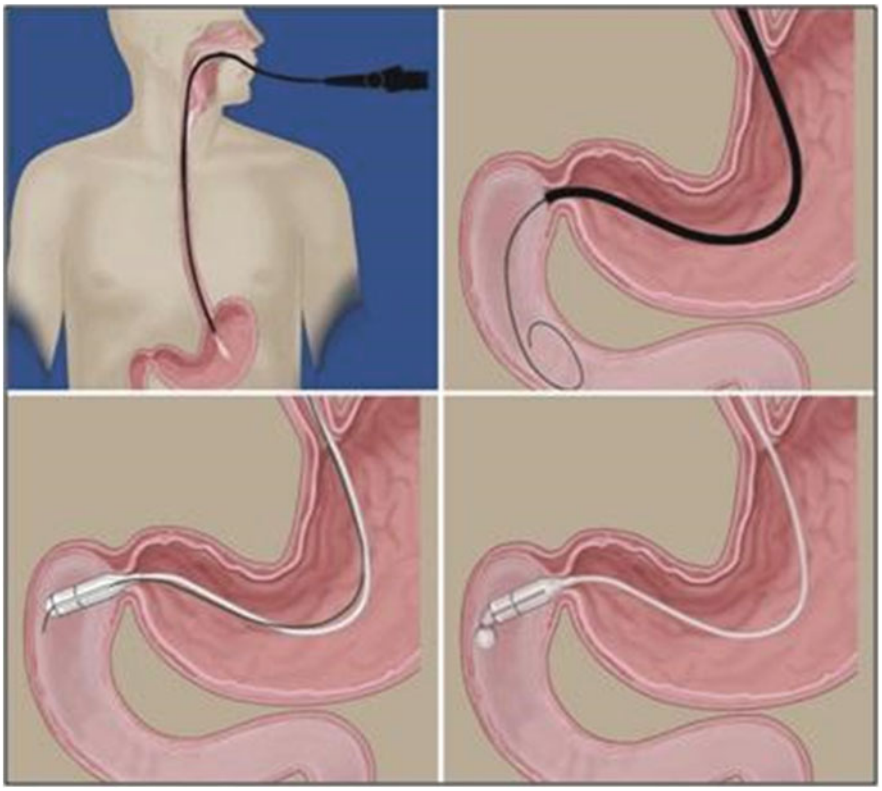

Fig. 7.3 Sequence of DJBL implant: Scope insertion. Guide wire introduction. Introduction of the device over the wire. Starting the release of the sleeve

From these studies, started the clinical trials based on the perspective that placing the "DJBL" in duodenal position could mimic some of the features of RYGB surgery, such as the exclusion of the proximal intestine to the flow of food; arrival of nutrients directly to the jejunum; segregation of the digestive secretions; and arrival of partially digested nutrients to the distal gut.

Possible mechanisms of action include malabsorption of calories, alteration of gastrointestinal motility, and modulation of gastrointestinal neurohormonal signaling.

Rodriguez-Grunert et al. (2008) conducted the first human implant and first results publication of 3 months follow-up. This study involved 12 patients (seven women and five men) aged between 28 and 54 years old (M = 41 years old) and BMI between 35 and 51 kg/m^2 (M = 42.8 kg/m^2), obtaining as result good tolerance and no serious adverse events. The average implantation time was 26.6 min. The patients reported mild abdominal pain and nausea, more concentrated in the first 2 weeks of the implant. After this period the adverse events were related to dietary transgression. All patients lost weight, with an average loss of 23.57 % of initial weight (ranging from 12.5 to 41.5 %), and obtained significant percentage

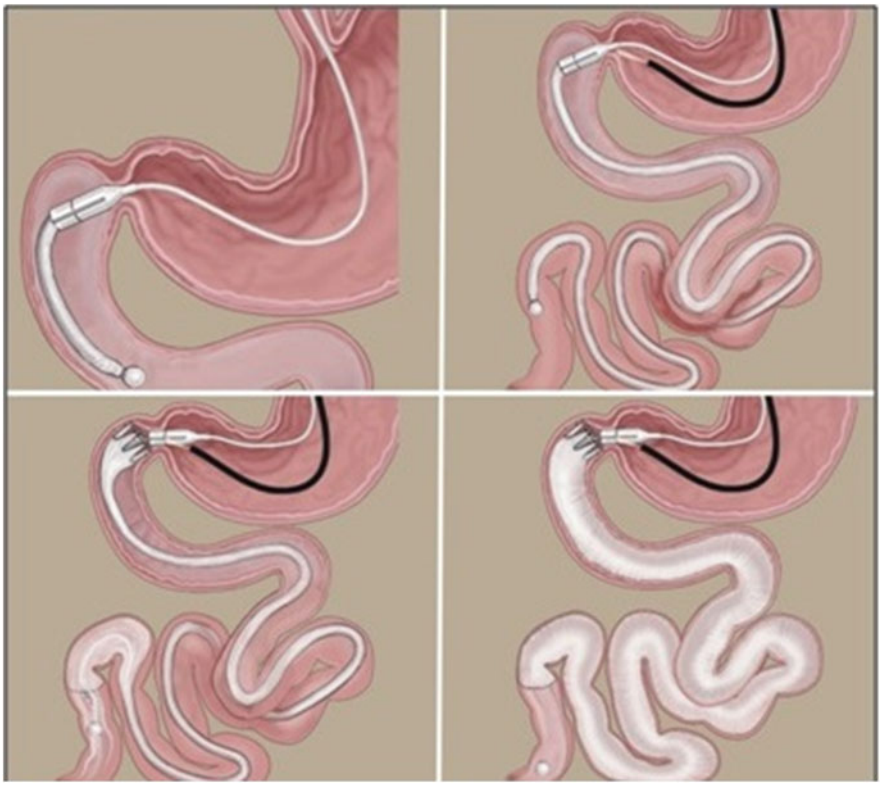

Fig. 7.4 Sequence of DJBL implant: Progression of the sleeve. Release of the anchor system. Radiologic contrast injection to expand the sleeve and verify patency

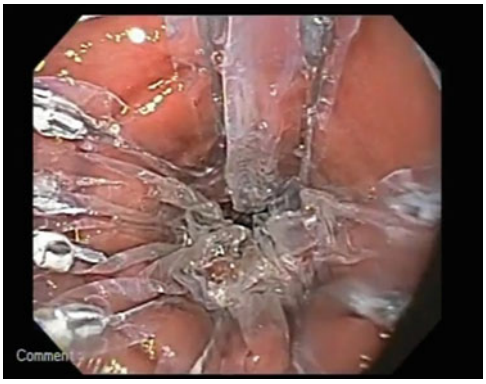

Fig. 7.5 Endoscopic view of recently implanted device

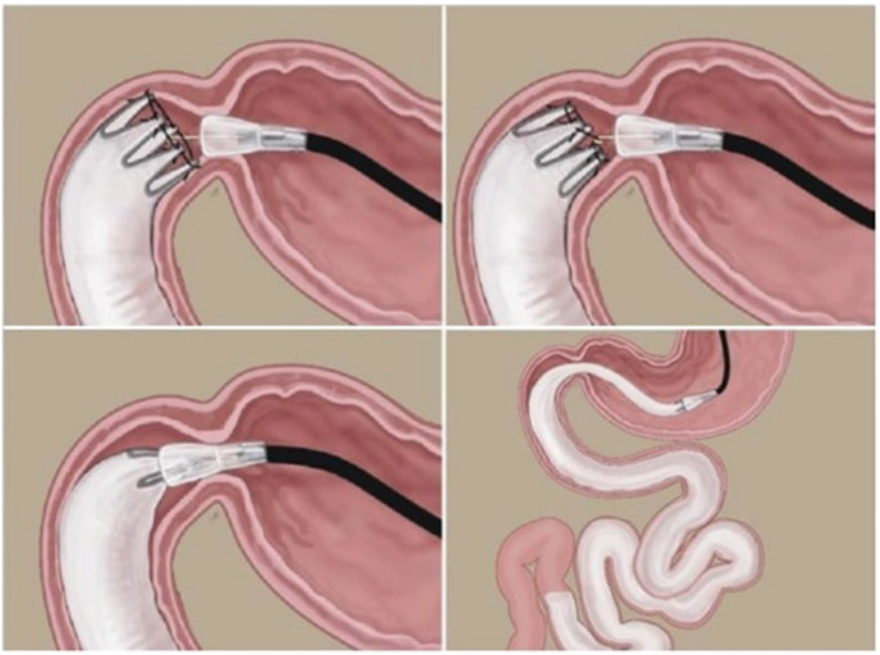

Fig. 7.6 Removal of the device

of excess weight loss. The DJBL was removed in two patients due to improper positioning.

A similar result was observed by Gersin et al. (2007), after the publication of the first procedure in the United States. The implant in a female patient, with 36 years and BMI of 45.2, was well tolerated and without complications. The total procedure time was 25 min. The device was removed endoscopically after 3 months, resulting in the total weight loss of 9.09 kg.

Based on these results, the DJBL was approved by the FDA for prospective, blinded, and randomized studies to evaluate their safety and efficacy.

Tarnoff in 2009 published the first randomized, controlled trial for weight loss, involving the implant of the device versus a control group with low calorie diet. The weight loss was higher in the DJBL group, with 22 % of excess weight loss versus 5 % in the control group ($p < 0.001$), demonstrating effectiveness in achieving short term results. However, only 80 % of the patients completed the 12 weeks implant time. The early removal of the device was performed in five patients: three with hemorrhage, one with migration, and one presenting sleeve obstruction.

In a European multicenter study, the successful implant of the DJBL occurred in 26/30 (86.7 %) patients, and before the end of the protocol the device was removed in 4/26 (15.4 %). The removals were due to migration, displacement of the fixing barbs, sleeve obstruction, and persistent epigastric pain. The average implant time of the device was 35 min (Schouten et al. 2010).

Rodriguez-Grunert et al. (2008) in a further study observed an unplanned effect of the device: the control of type 2 diabetes (T2DM) in patients who are not insulin dependent. This event sparked the interest in the use of this device in a specific protocol for type 2 diabetic patients.

The protocol including only obese diabetic patients was performed at Clinics Hospital of the University of São Paulo, Brazil. Moura et al. 2011b evaluated 22 obese and diabetic patients implanted with the DJBL for a period of 24 weeks. At the end of the study, an average weight loss of 14 kg, BMI decrease of 5.4 kg/m^2, and excess weight loss of 22.2 % were obtained. In relation to T2DM, a reduction in fasting blood glucose of 171.8 mg/dl at baseline to 141.5 mg/dl at the end was documented. The glycated hemoglobin (HbA1c) also showed a significant reduction of 8.8–7.3 % ($p < 0.001$). In this series there were four early explants. Two patients due to causes not related to the device, one with bleeding and the other for persistent abdominal pain.

Also in 2011, a second study was published (Moura et al. 2011a), including 54 obese and diabetic patients, evaluating weight loss, improvement in type 2 diabetes, and reduction of insulin resistance. This study also evaluates the cardiovascular risk using the relation triglycerides/high density lipoprotein (TG/HDL). This ratio is directly proportional to insulin resistance. A higher value corresponds to a greater amount of dense proatherogenic particles of LDL. Increased values are strongly associated with increased risk of cardiovascular events. In this study we observed a reduction in the TG/HDL ratio from 5.75 to 4.36, indicating a reduction of insulin resistance and cardiovascular risk. The patients presented an average weight loss of 12.6 %, with 70 % obtaining diabetes control, namely HbA1c below 7 % by the end of the study.

The results in 22 obese diabetic patients implanted with the DJBL for a period of 1 year was published by Moura in 2012. This group had an average loss of 39 % (+3.9) of excess weight and a reduction in HbA1c of −2.1 % (+0.3), with 73 % of patients achieving HbA1c levels lower than 7 % at end of the study.

In a study evaluating the effect of the device in 20 type 2 diabetic patients with mild obesity (average BMI 30 kg/m^2), implanted during 1 year, the fasting plasma glucose (FPG) levels dropped from 207 g/dl at baseline to 139 mg/dl in the first week, and remained low throughout the study. Mean body weight also declined, but the change was not associated with significant change in FPG at 52 weeks. HbA1c declined from 8.7 % at baseline to 7.5 % at week 52. No significant correlation between change in body weight and change in FPG or HbA1c was observed, showing that the improvement in T2DM appears to be independent of weight loss. Sixteen of the twenty subjects implanted with DJBL completed the 1 year study. Gastrointestinal disorders were reported by 13 subjects, and metabolic or nutritional disorders occurred in 14 (Cohen et al. 2013).

Another prospective study including obese patients (mean BMI 37), and evaluating the effect of the device on intestinal hormones, showed that at 24 weeks after implantation, patients had lost 12.7 kg while HbA1c had improved from 8.4 to 7.0 %. Both fasting glucose levels and the postprandial glucose response were decreased at 1 week after implantation, and remained decreased at 24 weeks. In

parallel, the glucagon response decreased (23.76 vs. 13.12 pg/ml/min), and the GLP-1 response increased (4.44 vs. 6.01 pmol/L/min). The GIP response was decreased at week 24 (baseline 115.27 vs. week 24 88.49 pg/mL/min). Insulin levels did not change significantly. Glycemic control was still improved 1 week after explantation. These results showed that the duodenal exclusion caused by the device led to a rapid improvement of glycemic control, paralleled by significant changes in gut hormones (Jonge et al. 2013).

In a recent systematic review including 10 studies, totaling 342 pacientes that were primarily investigated by the prototype of the DJBL, it was observed that in obese patients a short term excess weight loss occurred. Although studies showed a significant improvement of type 2 diabetes, there are no randomized studies comparing the response obtained with the device, with optimal drug therapy. Regarding complications (mostly minor), they occurred in 64–100 % of DJBL patients (mostly nausea and abdominal pain), compared to 0–27 % in the control groups. Gastrointestinal bleeding was observed in 4 % of patients (Zechmeister-Koss et al. 2014).

The DJBL is a new possibility of nonoperative therapy, positioned between pharmacological drugs, and the various techniques performed in bariatric surgery. This device can be used before bariatric surgery to help control T2DM, induce preoperative weight loss, reduction of visceral fat, lipid control, reduction of insulin resistance, and also reduce cardiovascular risk. These benefits can minimize the risk of perioperative clinical complications, adapt the patient to a restricted diet that will be required in the postoperative period, and even be used to replace bariatric surgery as a less invasive technique in selected cases.

The DJBL is a possible adjuvant in the management of T2DM and insulin resistance, in obese and overweight patients. In studies of morbidly obese patients with type 2 diabetes, reductions in fasting plasma glucose were seen within 1 week after implantation of the device, and were maintained through weeks 24 and 52 (Cohen et al. 2013), suggesting that it might be an effective treatment for T2DM. The DJBL is already cleared for marketing and implantation with 1 year of duration, in selected regions of Europe, as well as Australia and Chile (www.gidynamics.com/EndoBarrieroverview.php). Further studies are underway to verify the efficacy and safety for a longer period of implantation.

7.4 Conclusion

Presently, the options for treatment of type 2 diabetes and obesity are insufficient. There is a need for new options that can effectively act on the growing epidemic of these diseases. The ideal solution would address the limitations associated with medical and surgical treatment, having the following characteristics: eliminate or reduce the risks and side effects associated with drugs and surgical options, reduce patient anxiety and fear of surgery, and reduce the recovery time; act on the issue of noncooperation of the patient; produce an immediate reduction of blood glucose levels with resolution of type 2 diabetes; ability to achieve significant weight loss;

and possibility to be easily removed, or be reversible once the desired effect is achieved, and associated with changes in lifestyle.

This perfect therapy currently doesn't exist, but the endoscopic procedures are suitable options, particularly the temporary endoscopic dudenojejunal bypass liner. This technology platform probably modulates metabolic pathways involved in hormonal changes that occur after bypass operations in the gastrointestinal tract, leading to resolution or improved management of type 2 diabetes and obtaining a significant weight loss. However, the DJBL device still needs some improvements, mostly in the fixation system, aiming to reduce the rates of complications. Further confirmation of results will occur with the publication of major series, now that its commercial use was approved in some countries.

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Chapter 8
Ileal Transposition Surgery: Mechanisms of Weight Loss and Diabetes Improvements

Prasanth K. Chelikani

Abstract Bariatric surgeries produce weight loss with improvements in diabetic control through multiple mechanisms, including enhanced stimulation of the lower gut. The ileal transposition surgery was initially developed to gain insights into the lower gut mechanisms that contribute to the anorexic and weight loss effects of roux-en-Y gastric bypass, without the confounds of gastric restriction or foregut exclusion. Though ileal transposition surgery leads to hypophagia and weight loss, depending on the length of the ileum transposed, remarkably, improvements in glycemic control occur independent of changes in body weight. Some of the mechanisms that have been proposed, to explain the weight loss and glycemic benefits of ileal transposition surgery, include enhanced lower gut stimulation and consequent adaptation, increased secretion of lower gut peptides such as glucagon-like peptide-1 and peptide YY, alterations in enterohepatic bile acid metabolism, and improvements in glucose and lipid metabolism in liver, muscle, and adipose tissue. A greater understanding of the mechanisms of action of ileal transposition surgery may lead to the development of more effective and less invasive interventions that can reproduce the effects of the surgery, without attendant surgical risks and long-term complications.

Keywords Bariatric surgery • Ileal transposition • Body weight • Diabetes • Gut hormones • Glucose metabolism • Lipid metabolism

8.1 Introduction and Significance

Bariatric surgeries are one of the most effective anti-obesity interventions, often producing sustained weight loss with improvements in diabetes, hypertension, dyslipidemia, cardiovascular health, and other obesity associated comorbidities. Remarkably, resolution or improvement in some comorbidities occurs prior to

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substantial weight loss, suggesting that profound alterations in gut physiology have important roles in metabolic adaptations, following bariatric surgery. However, the mechanism(s) of action of these surgeries is poorly understood, and the surgeries are also associated with peri- and postoperative complications, poor weight loss in some patients, and long-term complications including micronutrient deficiencies (Shah et al. 2006). Therefore, elucidating the mechanisms of weight loss and metabolic improvements of bariatric surgeries is important for developing novel non-surgical approaches that could reproduce the effectiveness of surgeries without attendant surgical risks.

Bariatric surgeries involve either restrictive and/or malabsorptive procedures (Cummings et al. 2004; Kirchner et al. 2007; Kral and Naslund 2007). Roux-en-Y gastric bypass (RYGB), a reference standard for bariatric procedures, is postulated to improve energy balance through multiple mechanisms including—reducing food intake and body weight, reducing the efficiency of nutrient absorption, enhancing lower gut neuro-hormonal feedback, improving metabolic profile, reducing proinflammatory mediators and increasing anti-inflammatory markers, improving insulin sensitivity, and/or improving loading conditions by entero-cardiac modulation (Ashrafian et al. 2008). However, the relative importance of these mechanisms remains unresolved. In contrast to the complexity of RYGB, ileal transposition (**IT**) (also referred to as ileal interposition) surgery is exclusively a hind-gut procedure, that permits assessment of the direct effects of enhanced lower gut stimulation alone without gastric restriction, malabsorption or other confounding factors, that limits delineating the mechanisms of metabolic effects of RYGB surgery.

8.2 Ileal Transposition Surgery: Effects on Energy Balance

The weight loss following bariatric surgeries might be due to anorexia, malabsorption, and or increased energy expenditure; relative contribution of these factors to the regulation of energy balance is relatively unknown. Dr. Henry Koopmans pioneered the development of the ileal transposition surgical technique in a rat model (Koopmans and Sclafani 1981; Koopmans et al. 1982) to study the role of lower gut stimulation in the regulation of energy balance. The surgery essentially involves resecting a segment of the terminal ileum, and transposing (interposing) in the same direction (isoperistaltic), with an intact vascularity and innervation, distal to the duodenum (Fig. 8.1). In a seminal study, Dr. Koopmans demonstrated that transposition of 5, 10, or 20 cm of the ileum to the duodenum produced a length-dependent reduction in food intake and body weight, with the effects more robust in rats made obese with lesions in the ventromedial hypothalamus (Koopmans et al. 1982). Others studies in rats have since reported that IT surgery either produces a significant reduction in intake and weight gain (Atkinson et al. 1982; Boozer et al. 1990; Chen et al. 1990; Chelikani et al. 2010; Grueneberger et al. 2013; Koopmans et al. 1982, 1984; Ramzy et al. 2014; Strader et al. 2005; Wang et al. 2008), or no effect on these parameters (Cummings et al. 2010; Patriti

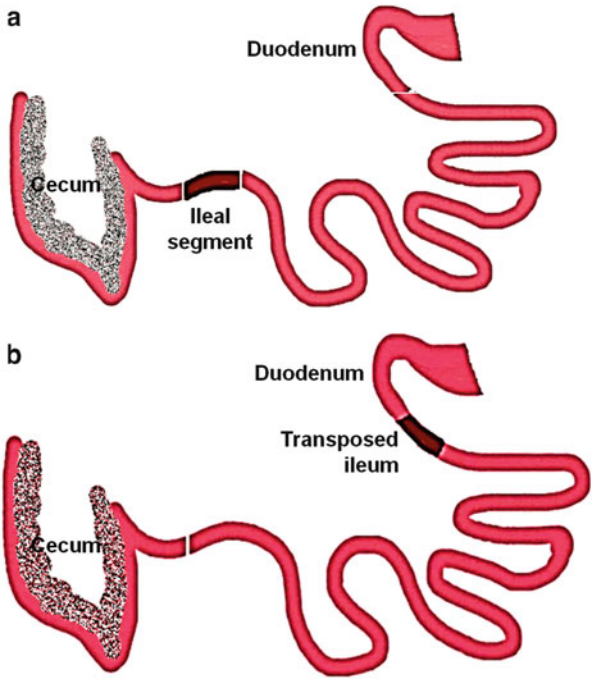

Fig. 8.1 Ileal transposition surgery. (**a**) Normal intestinal tract showing the location of transections of the ileum and duodenum. (**b**) A segment of the transected ileum is transposed in the same direction just distal to the duodenum

et al. 2007; Mencarelli et al. 2013). These inconsistencies are likely due to varying lengths of transposed ileal segments and animal models. Transposition of a 20-cm ileal segment decreased intake and weight gain (Chelikani et al. 2010; Grueneberger et al. 2013; Koopmans et al. 1984; Ramzy et al. 2014), whereas transposition of shorter 10 cm lengths of ileum either had no effect (Culnan et al. 2010; Cummings et al. 2010; Patriti et al. 2005, 2007; Strader et al. 2009), or decreased food intake and weight gain in rats (Chen et al. 1990; Koopmans et al. 1984; Ramzy et al. 2014; Strader et al. 2005). The degree of adiposity also appears to play a role, with IT producing a sustained reduction in food intake and weight gain in obese rats (Atkinson et al. 1982; Boozer et al. 1990; Chen et al. 1990; Grueneberger et al. 2013), but not in diabetic rats (Cummings et al. 2010; Patriti et al. 2005, 2007; Strader et al. 2009). Therefore, the hypophagic and weight loss effect of IT appears to be dependent on the length of the ileum that is transposed and characteristics of the animal model.

Weight loss following IT surgery is often associated with a reduction in fat mass (Kohli et al. 2010; Koopmans et al. 1982), with minimal or no malabsorption (Chen et al. 1990; Strader et al. 2005). We demonstrated that IT surgery leads to greater weight loss than pair-fed animals, suggesting that increased energy expenditure may contribute to weight loss (Chelikani et al. 2010). Others have shown that IT stimulates energy expenditure in rats (Cummings et al. 2013; Kohli et al. 2010). However, the relative contributions of reductions in food intake and increased energy expenditure to the reduction in body weight following IT surgery remain to be determined.

8.3 Ileal Transposition Surgery: Effects on Diabetes Control

In contrast to the abundance of literature on the hypophagic and weight loss effects, there is minimal information on the effects of IT surgery on diabetic control. In earlier studies with diet-induced obese rats, IT was shown to improve insulin sensitivity but not glucose tolerance (Strader et al. 2005). In Goto–kakizaki diabetic rats, improvements in glucose tolerance were observed within a month following IT surgery (Chen et al. 2011; Kindel et al. 2009; Patriti et al. 2004, 2005, 2007; Wang et al. 2008; Yan et al. 2012), but either with (Wang et al. 2008) or without accompanying improvements in insulin sensitivity or insulin secretion (Patriti et al. 2004; Patriti et al. 2005, 2007), suggesting that insulin-independent mechanisms could also play a role in the glycemic improvements. Interestingly, in streptozotocin-treated diabetic, and normal euglycemic rats (Strader et al. 2009), diet-induced obese rats (Kohli et al. 2010), overweight rats (Mencarelli et al. 2013; Nausheen et al. 2013; Ramzy et al. 2014), obese and diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats (Ikezawa et al. 2012), University of California at Davis type 2 diabetes mellitus (UCD-T2DM) rats (Cummings et al. 2010, 2013), and the fatty Zucker rats (Culnan et al. 2010), IT improved glucose tolerance and insulin sensitivity, independent of weight changes. Thus, across multiple animal models of diabetes and obesity, IT surgery often leads to profound improvements in glycemic control and insulin sensitivity that are not dependent on weight loss. The underlying mechanisms by which IT improves diabetic control are just being unraveled.

8.4 Ileal Transposition Surgery: Mechanisms of Weight Loss and Diabetic Control

8.4.1 Gut Adaptation

The weight loss and metabolic effects of IT are often ascribed to early stimulation of the translocated lower gut by ingested food. Ileal transposition produces robust structural and functional adaptations in the transposed segment. Some of these include increased villus height and width, increased mitogenic capacity, increased muscle thickness, and increased weight suggestive of hypertrophic and hyperplastic changes in the transposed segment (Koopmans et al. 1984; Kohli et al. 2010; Nausheen et al. 2013; Ramzy et al. 2014). In additional to these structural adaptations, the transposed segment also adapts functionally with increased sucrase activity (Ulshen and Herbst 1985) and glucose uptake in the ileum (Culnan et al. 2010; Menge et al. 1978).

8.4.2 *Role of Gut Peptides*

As expected from a surgical intervention that causes early stimulation of the lower gut, IT leads to increased expression of multiple gut peptides in the transposed ileum, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY) (Kohli et al. 2010; Nausheen et al. 2013; Ramzy et al. 2014; Strader et al. 2005), gastrin (Aiken et al. 1994), cholecystokinin, serotonin, and neurotensin (Hansen et al. 2014) (Fig. 8.2). A consistent finding across studies is that IT leads to increase in plasma concentrations of GLP-1 and PYY (Chelikani et al. 2010; Culnan et al. 2010; Cummings et al. 2010, 2013; Gaitonde et al. 2012; Grueneberger et al. 2013; Ikezawa et al. 2012; Kohli et al. 2010; Koopmans et al. 1984; Patriti et al. 2007; Ramzy et al. 2014; Strader et al. 2005, 2009).

Though the increased secretion of these L-cell products likely mediates the "ileal brake" phenomenon, and decreases proximal gut motility (Ohtani et al. 1999), it is unknown whether the decreased motility contributes to the hypophagic effects of IT surgery. The association of increased plasma concentrations of the incretin—GLP-1, with improvements in glucose tolerance, suggests that GLP-1 may play a role in

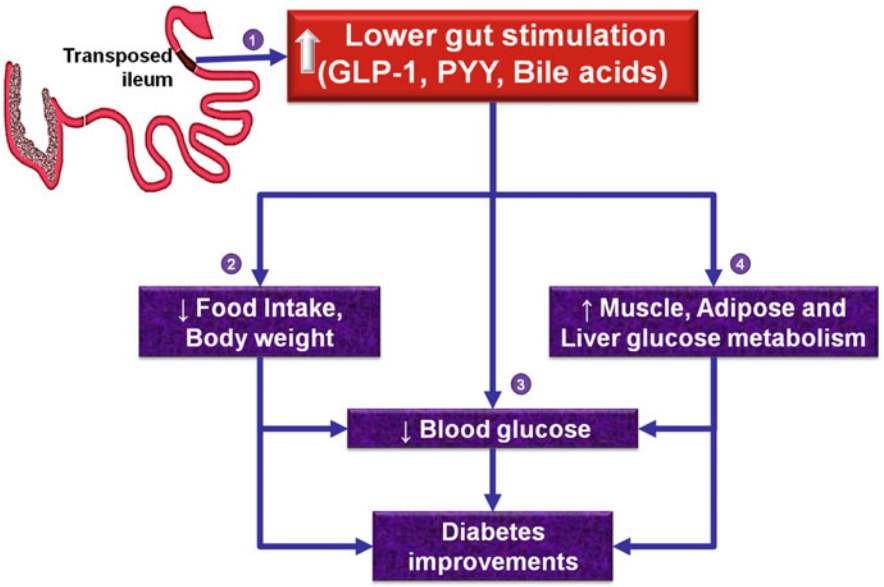

Fig. 8.2 Hypothetical mechanisms of weight loss and diabetes improvements following ileal transposition surgery. Enhanced lower gut stimulation leads to increased circulating concentrations of lower gut peptides (glucagon-like peptide-1, peptide YY) and bile acids (1) which in turn may lead to a reduction of food intake and body weight (2) with consequent indirect or direct improvements in glycemic control (3). Further, lower gut signals may improve glucose metabolism in muscle, adipose, and liver (4) with consequent diabetic improvements. However, a causative role for lower gut peptides and bile acids to the weight loss and diabetic improvements of IT surgery remains to be established

the glycemic improvements of IT (Culnan et al. 2010; Cummings et al. 2010, 2013; Gaitonde et al. 2012; Ikezawa et al. 2012; Johannessen et al. 2013; Kohli et al. 2010; Koopmans et al. 1984; Nausheen et al. 2013; Patriti et al. 2004, 2007; Ramzy et al. 2014; Strader et al. 2005, 2009; Wang et al. 2008). Systemic administration of the GLP-1 receptor antagonist exendin (9–39) has been shown to attenuate the improvements in glucose tolerance following IT, providing strong evidence for a direct role for GLP-1 receptor signaling, in the glycemic improvements of IT surgery (Gaitonde et al. 2012). However, it remains, to be determined whether GLP-1 and other gut peptides mediate the effects of IT surgery on food intake and body weight, and whether other gut peptides that are upregulated also directly mediate the effects of IT surgery on glycemic improvements. Though Dr. Koopmans noted that the weight of the pancreas is increased with IT surgery (Koopmans et al. 1984), the effects of IT surgeries on insulin concentrations were inconsistent with some studies, reporting either no change (Grueneberger et al. 2013; Ramzy et al. 2014; Strader et al. 2009), decrease in rats (Culnan et al. 2010; Cummings et al. 2010; Ikezawa et al. 2012; Koopmans et al. 1984; Nausheen et al. 2013), or increase (Cummings et al. 2013); these discrepancies could likely be due to differences in the experimental model, length of the transposed segment, frequency of sampling, and/or duration of follow-up after surgery. In general, IT surgery decreases plasma leptin concentrations, reflective of reductions in adipose reserves (Gaitonde et al. 2012; Ikezawa et al. 2012; Kohli et al. 2010; Nausheen et al. 2013; Ramzy et al. 2014). Despite changes in circulating gut hormone concentrations, it is still unknown whether these peptides act via paracrine, neurocrine, and/or endocrine routes to mediate the effects of IT surgery on energy balance and glucose homeostasis. Further, the relative importance of the enteric and central neural networks, in the metabolic effects of IT surgery, also remains to be determined (Fig. 8.2).

8.4.3 Enterohepatic Bile Acid Cycling

Apart from a role for gut peptides in the improvements in glycemic control, less is known of the downstream molecular events by which IT surgery improves glucose and lipid metabolism in peripheral tissues. Given that ileum is the major site for bile acid reabsorption, that bile acids play an important role in lipid metabolism, and that circulating bile acids and fibroblast growth factors are often increased following RYGB together with diabetic improvements in humans (Gerhard et al. 2013; Simonen et al. 2012), the mechanisms by which IT alters bile acid metabolism are just being characterized. Circulating concentrations of total, primary, conjugated, and non-conjugated bile acids have been shown to be increased in rats following IT surgery (Cummings et al. 2010, 2013; Kohli et al. 2010; Mencarelli et al. 2013). These changes are associated with an upregulation of the molecules that stimulate bile acid uptake in the intestine (e.g., ASBT, GPBAR1) and a downregulation of transcripts of key molecules involved in bile acid synthesis in the liver (e.g.,

Cyp7A1, Cyp8B1, Cyp7B1, Cyp27A1) (Cummings et al. 2013; Kohli et al. 2010). These studies are correlative and suggest that by modulating enterohepatic bile cycling, IT surgery likely contributes to improvements in glucose homeostasis (Fig. 8.2); however, it is unknown whether these alterations in bile cycling directly mediate the hypophagic and weight loss effects.

8.4.4 Glucose Metabolism in Skeletal Muscle, Adipose, and Hepatic Tissues

Skeletal muscle, liver, and adipose tissues account for about 80 %, 5 %, and 1 % of total glucose metabolized, respectively, in humans (DeFronzo et al. 1981). Excess lipid deposition in muscle and liver is a key contributing factor to impaired insulin signaling and diabetes (Samuel and Shulman 2012). We provided further insights into the role of muscle and adipose to the metabolic benefits from IT and demonstrated that the transcript and protein abundance of GLUT-4, the insulin-sensitive glucose transporter, is increased in muscle and adipose tissues following IT which is suggestive of enhanced glucose clearance by these tissues (Fig. 8.2) (Nausheen et al. 2013; Pezeshki and Chelikani 2014; Ramzy et al. 2014). Though IT did not affect expression of GLP-1 receptor in muscle, it increased the protein abundance of IRS-1 whereas IRS-1 pS636, a negative modulator of IRS-1, was decreased suggestive of enhanced insulin sensitivity (Nausheen et al. 2013; Pezeshki and Chelikani 2014; Ramzy et al. 2014). We also demonstrated that IT increased the protein abundance of muscle AMPKα (a key regulator of nutrient metabolism), increased transcript abundance of the rate-limiting glycolytic enzymes (hexokinase and phosphofructokinase) in muscle, adipose, and liver tissues suggestive of enhanced glycolytic flux, and increased mitochondrial lipid oxidative markers (CPT-1, MCAD, and COX-IV) in muscle while decreasing lipogenic transcripts (FAS) in fat and liver suggestive of decreased lipogenic and enhanced lipid oxidative capacities (Nausheen et al. 2013; Pezeshki and Chelikani 2014; Ramzy et al. 2014). However, the relative importance of gut peptides, bile acids, and neural mechanisms in mediating the observed metabolic effects of IT in peripheral tissues are still unknown (Fig. 8.2).

8.5 Conclusion

An understanding of these mechanisms may lead to the development of more effective non-surgical approaches for weight loss and diabetic control.

Acknowledgments This chapter is dedicated to the memory of Dr. Henry Koopmans—a colleague, friend, mentor, and a visionary who left a legacy on the lower gut control of energy balance. I would also like to acknowledge the contributions of my lab members—Drs. Adel Pezeshki, Saima Nausheen, and Imran Shah, and Adam Ramzy, who contributed immensely to

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Chapter 9
Left Gastric Artery Embolization to Treat Obesity: Rationale, Technique, Experimental, and Clinical Studies

Andrew J. Gunn and Rahmi Oklu

Abstract The number of overweight and obese individuals has increased dramatically in the last 20 years, suggesting that current medical and surgical therapeutic options for the bariatric patient are limited. Ghrelin, a hormone primarily produced by the epithelium of the gastric fundus, is the only known appetite-stimulating hormone. Studies in animal models have shown that catheter-directed, trans-arterial embolization of the left gastric artery, which preferentially supplies the gastric fundus, can suppress ghrelin production and modulate body weight. Investigations into left gastric artery embolization as a mechanism for weight loss in patients are nascent. This chapter will briefly outline the gastrointestinal tract's endocrine function in metabolic homeostasis, explain the rationale in targeting ghrelin to induce weight loss, describe the technical aspects of left gastric artery embolization, and review the studies evaluating the left gastric artery embolization as a means to treat obesity.

9.1 Introduction

Obesity is a public health epidemic that results in significant morbidity and mortality often from heart disease, stroke, type II diabetes, and even some cancers (Centers for Disease Control 2012). Despite advances in both medical and surgical therapeutic options, obesity rates have increased dramatically over the last 20 years (Centers for Disease Control 2012). These trends indicate that traditional methods

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to control obesity through lifestyle modifications, medications, and surgical interventions are inadequate.

Catheter-directed **trans-arterial embolization** of the left gastric artery (LGA) is a minimally invasive procedure routinely performed by interventional radiologists most commonly in the setting of gastric bleeding using a variety of embolic agents. Recent studies have shown that embolization of the LGA modulates body weight in animal models through the **suppression of ghrelin**, an appetite-stimulating hormone produced primarily by the epithelium of the gastric fundus (Arepally et al. 2007, 2008; Bawudun et al. 2012; Paxton et al. 2013). These intriguing results suggest a role for the interventional radiologist in the treatment of obesity. Here, we briefly review the endocrine system in metabolic homeostasis, the rationale in targeting ghrelin as a means to weight loss, describe the technical aspects of LGA embolization, and review the studies evaluating LGA embolization as a means to treat obesity.

9.2 Endocrine Function of the Gastrointestinal Tract in Regulating Food Intake

The neuroendocrine function of the GI tract in regulating metabolic homeostasis is well established. Secretin, a peptide synthesized by the S cells of the duodenal and jejunal mucosa, was the first GI peptide to be classified as a "hormone" in the early 1900s (Wren and Bloom 2007). The inhibitory effects of cholecystokinin (CCK) on food intake were later described as early as 1975 (Liebling et al. 1975). Although a detailed review of the complex interplay between the many GI-produced hormones involved in metabolic homeostasis and their signaling pathways is beyond the scope of this chapter, the reader is referred to several excellent reviews covering this topic (Wren and Bloom 2007; Ahima and Antwi 2008; Cummings and Overduin 2007; Dockray 2004).

9.3 Neuroendocrine Signaling Between the Gastrointestinal Tract and the Central Nervous System

The signals sent from the GI tract to the CNS that regulate metabolic homeostasis can be broadly divided into long-acting and **short-acting signals** (Wren and Bloom 2007). The **long-acting signals** generally impact an individual's energy and fat metabolism over long periods of time and play an important role in maintaining body weight. An example of a long-acting signal is that initiated by the hormone leptin, which is produced by adipose tissue in order to induce satiety and regulate body fat (Wren and Bloom 2007). The short-acting signals typically regulate the

initiation of meals via the feeling of hunger, the amount of food consumed in a meal, and the termination of meals from a feeling of "fullness." Of note, ghrelin has both short-acting effects, which trigger the initiation of feeding, as well as long-acting effects, which influence body weight and energy expenditure.

Signals arising from the GI tract can reach the CNS through two main mechanisms (Wren and Bloom 2007; Ahima and Antwi 2008). First, afferent signals from **mechanoreceptors** (detecting the stretch induced in the GI tract from a meal), **chemoreceptors** (detecting the chemical composition of the ingested meal), and **locally acting GI hormones** reach the medulla via the vagus nerve. This type of signaling is exemplified by CCK (Dockray 2004). Second, GI-produced hormones can also enter the bloodstream and directly activate the receptors in the brain. These types of receptors are most commonly found within the hypothalamus (Wren and Bloom 2007). An example of this type of signaling is affected by the hormone oxyntomodulin (Baggio et al. 2004). Interestingly, ghrelin exerts its appetite-stimulating effects both via the vagus nerve and after being released into the bloodstream by binding with the receptors in the hypothalamus (Wren and Bloom 2007; Kojima et al. 1999).

9.4 Metabolism-Regulating Hormones of the Gastrointestinal Tract

The purpose of the following section is to provide the reader with a brief introduction to some of the major GI-produced hormones in order to better understand the unique role of ghrelin in metabolic homeostasis. These are summarized in Table 9.1.

Cholecystokinin Cholecystokinin (CCK) was the first GI peptide shown to have an anoretic effect and is considered to be the prototypical satiety hormone (Wren and Bloom 2007; Liebling et al. 1975; Ahima and Antwi 2008; Cummings and Overduin 2007). Intestinal CCK is mainly produced by the I cells of the duodenal and jejunal mucosa in response to intra-luminal protein and fat (Cummings and Overduin 2007). Once released, CCK acts locally within the GI tract on vagal CCK-A receptors in order to induce satiety, delay gastric emptying, stimulate pancreatic enzyme secretion, and produce gallbladder wall contractions. The administration of CCK-A receptor antagonists to patients has been shown to increase hunger, meal size, and caloric intake (Berlinger et al. 2001); thus, CCK has been studied as a potential therapeutic target in the bariatric population. However, the very short-lived anoretic effects of CCK make its role in long-term metabolic homeostasis uncertain. In fact, trials investigating the administration of CCK and CCK-A receptor agonists for sustained weight loss have been unsuccessful to date (Cummings and Overduin 2007; West et al. 1984).

Table 9.1 Summary of major gut peptides involved in metabolic homeostasis

Hormone	Production[a]	Effect on appetite
CCK	I cells of duodenum and jejunum	↓
GLP1	L cells of distal intestine and colon	↓
Oxyntomodulin	L cells of distal intestine	↓
$PYY_{3–36}$	L cells of distal intestine	↓
Amylin	β cells of pancreas	↓
PP	Pancreatic islet cells	↓
Ghrelin	Epithelial cells of gastric fundus	↑[b]

[a]Main sites of production
[b]Only known orexigenic peptide

Glucagon-like Peptide-1 Glucagon-like peptide-1 (GLP1) is widely produced in the distal small intestine and colon by mucosal L cell in response to intra-luminal fat and carbohydrates (Cummings and Overduin 2007). The release of GLP1 results in the activation of both peripheral and central GLP1 receptors, which are found in the vagus nerve, proximal GI tract, pancreas, brainstem, and hypothalamus. Thus, the effects of GLP1 are both the result of vagal stimulation and direct activation of central GLP1 receptors after release into the bloodstream. The role of GLP1 appears to be decreasing food intake by inhibiting proximal intestinal motility, accentuating insulin release, inhibiting glucagon secretion, and stimulating the growth of pancreatic β cells (Cummings and Overduin 2007).

Oxyntomodulin Oxyntomodulin, like GLP1, is a proglucagon-derived peptide produced by mucosal L cells in the distal intestine in response to ingested nutrients (Cummings and Overduin 2007). The exact signaling mechanisms for oxyntomodulin have not been entirely elucidated. However, given its similar origin and distribution to GLP1, it is believed that GLP1 receptors are involved even though oxyntomodulin and GLP1 target different regions in the brain (Cummings and Overduin 2007). Oxyntomodulin functions to reduce food intake, increase energy expenditure, and decrease body weight (Baggio et al. 2004). Repeated subcutaneous injections of oxyntomodulin in patients over a 4-week period were shown to decrease the body weight by 0.5 kg/week and reduce food intake by 25 % (Wynne et al. 2005). Therefore, it is hoped that further study into oxyntomodulin could potentially produce therapeutic options for the bariatric patient.

Peptide YY $(PYY)_{3–36}$ $PYY_{3–36}$ is the bioactive form of PYY, which is co-secreted from L cells in the mucosa of the distal intestine with GLP1 and oxyntomodulin (Cummings and Overduin 2007). Like its co-secreted peptides, $PYY_{3–36}$ is secreted in response to nutrients in the distal small bowel. Its receptors and targets are not clearly delineated, but $PYY_{3–36}$ appears to induce satiety by delaying gastric emptying. $PYY_{3–36}$ infusion has been shown to decrease food intake by up to 30 % in obese individuals and up to 31 % in lean individuals for up to 2 h after peripheral administration (Batterham et al. 2003a, b). This same study showed that participants had a lower 24-h caloric intake after $PYY_{3–36}$

infusion in comparison to patients receiving a placebo infusion. However, other studies have shown that $PYY_{3–36}$ infusion has variable effects on animal and human subjects depending on the dose, route, and timing of infusion (Cummings and Overduin 2007). Therefore, more research is certainly needed if $PYY_{3–36}$ is to be considered as a potential therapeutic target.

Amylin **Amylin** is co-secreted with insulin from pancreatic β cells after the ingestion of nutrients. It acts to inhibit gastric emptying, gastric acid and pancreatic enzyme production, and glucagon secretion (Cummings and Overduin 2007). Currently, the amylin analogue, **pramlintide**, is available as a treatment for diabetes but has also been shown to have the added benefit of inducing mild weight loss in patients (Hollander et al. 2004).

Pancreatic Polypeptide Pancreatic polypeptide (PP) is secreted from specialized pancreatic islet cells in response to an ingested meal (Cummings and Overduin 2007). It acts both centrally and peripherally to adjust pancreatic exocrine functions, gastric acid secretion, and the motility of the GI tract. Studies have been conflicting about its role in metabolic homeostasis (Cummings and Overduin 2007), even though one study showed that the peripheral administration of PP to humans resulted in a decrease in appetite and food intake (Batterham et al. 2003a, b).

Ghrelin Kojima et al. (1999) first described the structure and function of a hormone found in high concentrations in the rat stomach, which they termed "**ghrelin**"—a highly conserved homologous form of the hormone was also found in the human stomach. Ghrelin is a 28 amino acid peptide that is cleaved from its precursor, preproghrelin. Ghrelin acts upon growth hormone secretagogue receptors (GHS-R) in the hypothalamus. The highest concentration of ghrelin is within the gastric fundus, where nearly three quarters of ghrelin is produced by fundal epithelial cells (Wren and Bloom 2007). Additional sites of ghrelin production include the mucosa of the GI tract (most prominently in the duodenum), pancreas, ovaries, adrenal cortex, and the brain; although, production in these other areas is significantly less than that seen in the gastric fundus. The signaling mechanisms for ghrelin involve both vagally mediated pathways and the direct activation of receptors in the hypothalamus after release into the bloodstream (Wren and Bloom 2007; Kojima et al. 1999).

Ghrelin plays a unique role in regard to the initiation of meals and the maintenance of metabolic homeostasis as it is the only known orexigenic, or appetite-stimulating, hormone. After release, ghrelin induces hunger, increases GI motility, and suppresses insulin production (Cummings and Overduin 2007). Ghrelin plays a significant role in the initiation of meals and mealtime hunger as plasma levels of the hormone rise significantly before meals and have been shown to decrease in response to the ingestion of nutrients, most especially carbohydrates (Cummings et al. 2002; Cummings and Overduin 2007). However, apart from these short-acting effects, there is strong evidence to suggest that ghrelin is involved in long-term metabolic homeostasis. For example, plasma ghrelin levels negatively correlate with patient's body mass index (BMI), overweight individuals have been shown to

experience an increase in circulating plasma ghrelin levels upon the completion of successful weight-loss programs, and patients with anorexia nervosa show a decrease of circulating plasma ghrelin following recovery and subsequent weight gain (Druce et al. 2004). Thus, a treatment that acts to artificially lower circulating ghrelin levels has tremendous potential as a tool to halt or even reverse the obesity epidemic as several studies have shown that the **suppression of ghrelin** or the antagonization of its receptors in the CNS has a powerful ability to promote weight loss (Hu et al. 2005).

Possible pharmaceutical interventions could target ghrelin production or receptor binding. Ghrelin is produced from a precursor called **preproghrelin,** which can be modified to form several different peptides through gene cleavage or post-translational processing. Potential pharmaceutical targets for modulating ghrelin activity include both competitive and noncompetitive inhibition of the ghrelin receptor in the hypothalamus.

9.5 Role of Ghrelin in Bariatric Surgery

Bariatric surgery is probably the best therapeutic option for obesity offering long-term benefits in weight control. There are a variety of surgical options available to the bariatric population (Baptista and Wassef 2013). The most commonly employed surgical techniques include the Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and laparoscopic adjustable gastric banding (AGB). Recent investigations have begun to evaluate the role of ghrelin after bariatric surgery (Pournaras and Le Roux 2009). Despite the exciting results of early studies which demonstrated a significant decrease in plasma ghrelin levels after RYGB surgery, follow-up investigations have had mixed results with studies showing patients having **post-procedural ghrelin levels** that are decreased, the same, or even increased when compared to preoperative values. The reasons for this **heterogeneity in plasma ghrelin** levels after RYGB are not entirely clear. It has been suggested that differences in surgical techniques, such as sparing of the vagus nerve, or the creation of vertical (rather than horizontal) gastric pouch, may be at play. Different bariatric surgical techniques have been shown to affect plasma ghrelin levels in different ways, even though they all lead to weight loss in patients (Pournaras and Le Roux 2009). For instance, patients demonstrate a significant decrease in plasma ghrelin levels after sleeve gastrectomy (which removes the gastric fundus), while no such decrease in ghrelin levels is observed in patients after AGB (which preserves the gastric fundus).

Although bariatric surgery can lead to significant weight loss, it is associated with significant morbidity and mortality. The most common complications of bariatric surgery include **anastomotic leaks** (0.1–5.6 %), intussusception (1 %), gallstones (13–36 %), and **operative revisions** (39–81 %). Anastomotic leaks can be particularly dangerous resulting in reported mortality rates of 6–50 % (Baptista

and Wassef 2013). Given these risks, a less-invasive and less-morbid therapeutic option to treat obese individuals will be more favorable in this population of patients.

9.6 Trans-arterial Embolization of the Left Gastric Artery: Technical Considerations

Percutaneous trans-arterial embolization is a minimally invasive procedure which is routinely performed by interventional radiologists on both an in-patient and out-patient basis, typically to treat a bleeding vessel or to induce ischemia within a tumor. Embolization of the upper GI arteries for bleeding is generally well tolerated given the rich collateral vascular supply to the GI tract. The LGA is a common source of upper GI bleeding and is often prophylactically embolized if no other definitive source for bleeding can be found during angiography. At current, the principles and practices governing the embolization of the LGA for bleeding are similar to those employed in the embolization of the LGA for bariatric purposes. Therefore, the purpose of the following section will be to provide an overview of the vascular supply to the stomach and review the technical aspects involved in LGA embolization.

Vascular Supply to the Stomach The **vascular supply to the stomach** is a richly collateralized network of arteries which arises from the three branches of the celiac trunk: the left gastric artery, the common hepatic artery, and the splenic artery (Fig. 9.1). The arteries of the stomach are summarized in Table 9.2.

The **left gastric artery** (Fig. 9.2) is the smallest branch of the celiac trunk although it can originate from the abdominal aorta in a small minority of individuals. The artery generally passes superiorly to give off branches to the distal esophagus before providing the major arterial supply to the gastric fundus. LGA has anastomoses with the short gastric arteries along the gastric fundus. After giving off fundal branches, the LGA passes inferiorly along the lesser curvature providing arterial supply to both the anterior and posterior walls of the stomach. The LGA is the origin of the posterior gastric arteries (PGA) in some individuals. LGA terminates at its anastomosis along the lesser curvature with the right gastric artery (RGA).

The common hepatic artery provides arterial supply to the stomach through the RGA and the **gastroduodenal artery** (GDA) (Figs. 9.3 and 9.4). The RGA is a diminutive artery that can arise either from the common hepatic artery or the proper hepatic artery. It passes from right to left along the lesser curvature of the stomach to provide arterial supply to the pylorus before terminating at its anastomosis with the LGA. The origin of the GDA is where the common hepatic artery becomes the proper hepatic artery (Fig. 9.3). The right gastroepiploic artery, one of the terminal branches of the GDA, passes from right to left along the distal portion of the greater

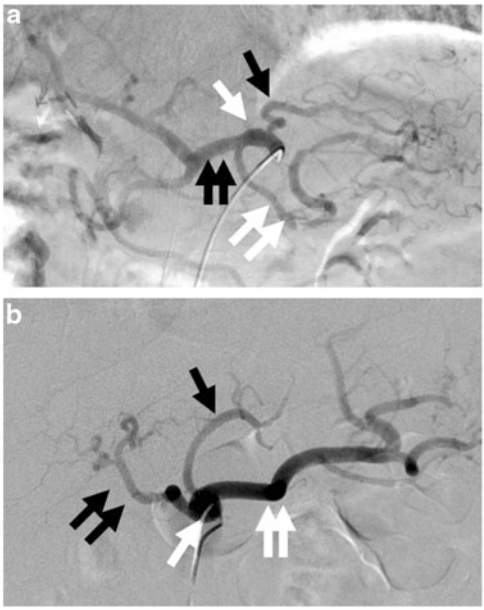

Fig. 9.1 (**a**) Digital subtraction angiogram (DSA) with a catheter located in the celiac trunk (*white arrow*) demonstrates the LGA (*black arrow*), splenic artery (*double white arrows*), and common hepatic artery (*double black arrows*). (**b**) DSA of the celiac trunk (*white arrow*) in a different patient again shows the LGA (*black arrow*), splenic artery (*double white arrows*), and common hepatic artery (*double black arrows*)

Table 9.2 Summary of the vascular supply to the stomach

Artery	Origin[a]	Vascular territory
Left gastric artery	Celiac trunk	Fundus, proximal lesser curvature
Right gastric artery	Proper hepatic artery	Pylorus, distal lesser curvature
Right gastroepiploic artery	Gastroduodenal artery	Distal greater curvature
Short gastric arteries	Splenic artery	Fundus, proximal greater curvature
Left gastroepiploic artery	Splenic artery	Proximal greater curvature
Posterior gastric artery	Variable[b]	Posterior wall of superior gastric body

[a]Most common origin
[b]May arise from the splenic artery, left gastric artery, dual origin from the left gastric and splenic arteries, or the celiac trunk

curvature of the stomach. It terminates at its anastomosis with the left gastroepiploic artery.

The splenic artery also provides arterial supply to the stomach through the **short gastric arteries** (SGAs) and left gastroepiploic artery (Fig. 9.5). The SGAs are variable in number, ranging from one to nine arteries that arise as terminal branches of the splenic artery. The SGAs are distributed along the greater curvature and fundus and have anastomoses with the LGA and **left gastroepiploic artery**.

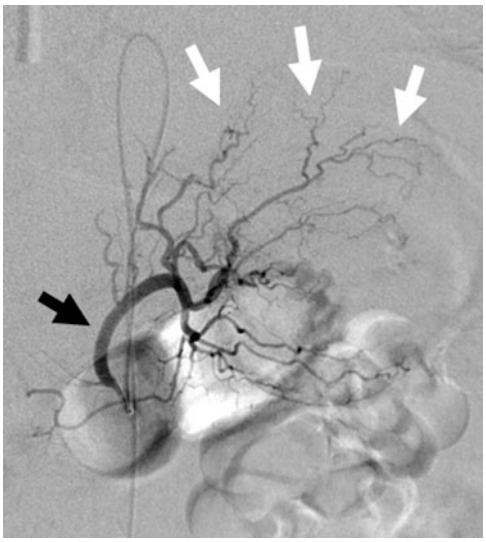

Fig. 9.2 DSA in a patient with suspected upper GI bleed shows a catheter in the LGA (*black arrow*). Notice the extensive fundal branches (*white arrows*)

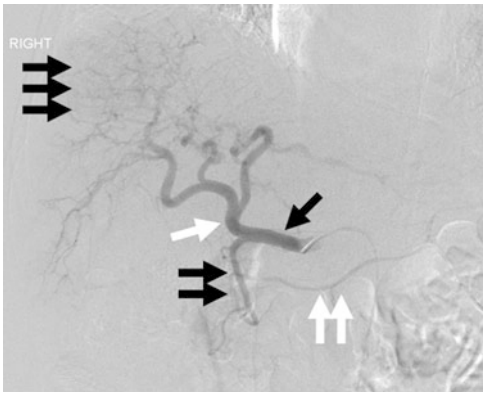

Fig. 9.3 DSA in a patient undergoing trans-arterial chemoembolization for hepatocellular carcinoma (HCC) shows a catheter in the common hepatic artery (*black arrow*) which branches off into the proper hepatic artery (*white arrow*) and GDA (*double black arrows*). The right gastroepiploic artery (*double white arrows*) is seen as a terminal branch of the GDA. A faint early tumor blush in the liver (*triple black arrows*) represents the patient's HCC

The left gastroepiploic artery is the largest branch of the splenic artery and provides arterial supply along the greater curvature of the stomach. It terminates at its anastomosis with the **right gastroepiploic artery**. The PGA provides vascular supply to the upper portion of the posterior wall of the gastric body. It can arise

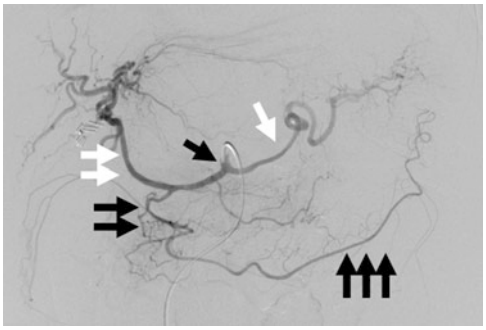

Fig. 9.4 DSA in a patient with suspected upper GI bleed shows a catheter in the celiac trunk (*black arrow*). The common hepatic artery gives rise to the GDA (*double black arrows*) and proper hepatic artery (*double white arrows*). The terminal branch of the GDA is the right gastroepiploic artery which supplies the distal aspect of the greater curvature of the stomach (*triple black arrows*). The splenic artery is also seen (*white arrow*)

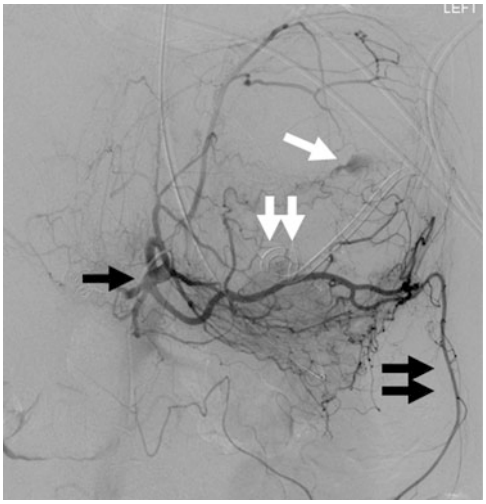

Fig. 9.5 DSA in a patient with upper GI bleeding shows the catheter in the splenic artery (*black arrow*) and a blush of contrast from the SGAs (*white arrow*) which were the source of the patient's bleeding. This was embolized with gel foam. The left gastroepiploic artery is seen along the proximal greater curvature of the stomach (*double black arrows*). The patient also has a percutaneous drainage catheter in place (*double white arrows*)

from the LGA, splenic artery, both the LGA and splenic artery, or the celiac trunk.

9.7 Therapeutic Potential of Left Gastric Artery Embolization in Weight Loss: Animal Studies

The emerging hormonal role in metabolic homeostasis, satiety, and hunger has sparked investigation into potential mechanisms that would manipulate these hormones in order to achieve sustainable weight loss in patients without the morbidity and mortality associated with invasive surgical procedures. The singular role of ghrelin as an appetite-stimulating hormone, in contrast to the abundant hormones responsible for inducing satiety, makes it a particularly attractive target. Furthermore, since the majority of ghrelin is produced in the gastric fundus, which is reliably supplied by the LGA, there is the potential to modulate serum ghrelin and patient body weight through minimally invasive, percutaneous, **catheter-directed techniques**.

Arepally et al. (2007) were the first to explore the possibility of LGA embolization as a means to treat obesity. In their pilot study, eight healthy swine underwent percutaneous angiography of the celiac axis and superior mesenteric artery (SMA) through right femoral artery access in order to identify the LGA and any other potential accessory gastric arteries. Super-selective angiography of the gastric vessels was used in order to identify all fundal vessels, including the LGA. Two of the swine underwent sham embolization of the fundal vessels with normal saline. The remaining six animals underwent **gastric artery chemoembolization** (GACE) with the sclerosing agent morrhuate sodium, which was mixed with equal parts of a nonionic contrast agent. The dose of morrhuate sodium ranged from 37.5 to 2,000 μg.

After the procedure, the swine were fed ad libitum. Body weight and serum ghrelin levels were measured prior to the procedure and at 1-week intervals after the procedure for 4 weeks in total. Histopathologic analysis of the gastric mucosa was performed after animal sacrifice at 1 month to assess for overall tissue architecture, **tissue ghrelin levels**, ulcerations, damage to the mucosa, and viability of parietal cells.

The control animals in this study showed no significant difference between pre-procedural and post-procedural serum ghrelin levels at 4 weeks. Moreover, these animals demonstrated no significant weight loss during the study period. Experimental animals which received between 37.5 and 62.5 μg of **morrhuate sodium** showed a significant increase in serum ghrelin levels after 4 weeks. This result was thought to be secondary to incomplete ablation of the fundal gastric mucosa, which may have negated the inhibitory feedback on the production of ghrelin.

The swine that underwent GACE with 125 μg of morrhuate sodium demonstrated a significant decrease in serum ghrelin levels after 4 weeks. The animal that received the highest dose (2,000 μg) during GACE died on post-procedure day #1 from a ruptured gastric ulcer. There was no significant weight loss seen in the experimental animals during the study period.

Histopathologic analysis of the gastric mucosa showed a decrease in tissue ghrelin after GACE, overall preserved tissue architecture, and microulcers at the gastro-esophageal junction in all animals. These microulcers were assumed to be secondary to non-target embolization of the distal esophageal branches of the LGA. Even though this early study was unable to demonstrate the modulation of body weight after GACE of the LGA, it was the first to prove that serum ghrelin levels could be modulated via this **minimally invasive technique**.

As a follow-up to their earlier work, Arepally et al. (2008) randomly distributed ten healthy, growing swine into two groups to evaluate the ability of GACE of the LGA to suppress serum ghrelin levels and modulate weight. The animals underwent percutaneous angiography of the celiac axis and SMA through the right femoral artery to identify the LGA and other potential accessory gastric arteries. **Super-selective angiography** of these vessels was performed to identify all fundal vessels.

Five swine underwent sham embolization with normal saline, while the other five underwent GACE using 125 μg of morrhuate sodium as the embolic agent. Of note, all animals that underwent GACE required embolization of arteries in addition to the LGA in order to achieve angiographic stasis of flow to the fundus. The swine were fed an ad libitum diet after the procedure. Body weight and serum ghrelin levels were again measured prior to the procedure and at 1 week intervals after the procedure for 4 weeks in total. No histopathologic correlation was performed in this study.

The control animals in this study had a pre-procedural serum ghrelin level of 1,078 pg/dL, which was not significantly different than the average post-procedural levels over 4 weeks (1,104 pg/dL). Conversely, animals that had undergone GACE demonstrated a significant decrease in the average serum ghrelin levels over 4 weeks (pre-procedure: 1,006.3 pg/dL; post-procedure average: 684.3 pg/dL). Serum ghrelin levels decreased each week after GACE for the first 3 weeks of the study period, but rose closer to pre-procedural levels at the fourth week (876.6 pg/dL). This finding is interesting because angiography performed 4 weeks after GACE (prior to animal sacrifice) showed that the previously embolized fundal vessels had re-obtained patency.

Thus, the increase in serum ghrelin levels at 4 weeks was thought to be secondary to either **revascularization of fundal vessels**, collateral flow to the gastric fundus, or possibly the compensatory production of ghrelin by other sites in the body. Regardless, the authors were able to demonstrate that animals gained weight at a slower pace after GACE (a 7.8 % increase in body weight over 4 weeks) than control animals (a 15 % increase in body weight over 4 weeks). Furthermore, even though intra-procedural angiography demonstrated the areas of **non-target embolization** in either branches of the hepatic, splenic, or esophageal arteries, there were no clinical sequelae in the treated animals, despite the well-recognized risks of

increased post-procedural pain and tissue necrosis in cases of non-target embolization in humans.

These findings provided more evidence that minimally invasive, trans-arterial embolization of the LGA can suppress serum ghrelin levels and modulate weight with potentially fewer complications than other, more invasive surgical techniques.

Bawudun et al. (2012) sought to assess whether the embolic agent used to embolize the LGA affected changes seen in serum ghrelin levels, body weight, and body fat composition. In this study, healthy canines underwent percutaneous angiography of the celiac trunk with super-selective angiography of the LGA. The animals were randomly divided into a control group that underwent a simulated embolization with normal saline, an experimental group that underwent LGA embolization using a **liquid sclerosing agent** (bleomycin A_5 hydrochloride (BAH) emulsed with lipiodol ultrafluid), and an additional experimental group that underwent **mechanical embolization** with 500–700 μm polyvinyl alcohol (PVA) particles. The canines were fed a fixed diet based after the procedure.

Body weight and serum ghrelin levels were measured prior to the procedure and at 1 week intervals after the procedure for 8 weeks in total. Body fat area was assessed by computed tomography (CT) prior to the procedure and 8 weeks after the procedure. Weekly barium meals during the study period, in addition to histopathologic analysis after animal sacrifice, were used to assess for gastric mucosal changes in response to LGA embolization.

The average serum ghrelin levels in both experimental groups decreased significantly over the study period in comparison to control animals. The average drop in serum ghrelin was 15.8 % with the sclerosing agent and 30.2 % after mechanical embolization, while **non-embolized animals** demonstrated a 13.6 % increase in serum ghrelin levels. Although, it should be noted that the most significant decrease in serum ghrelin was again demonstrated within the first 3 weeks after embolization of the LGA with a slow rise back toward pre-procedural levels in later weeks.

In this study, **CT angiography** performed at 8 weeks showed the LGA to be persistently occluded, suggesting that the cause for this increase in ghrelin is either collateral flow from other arteries or a compensatory increase in production from other sites in the body. Both experimental groups showed an equal decrease in the amount of both subcutaneous and overall fat area by CT, which was significantly greater than that seen in the control group. Additionally, both treatment groups demonstrated a significant amount of weight loss after LGA embolization in comparison to the control group. The weight loss seen was most pronounced within the first 3 weeks after LGA embolization with a slow rise in weights seen during later time points in the study period for both groups.

Notably, the authors were able to correlate the serum ghrelin levels with body weight. There were no clinically significant adverse events during the study period, even though non-target embolization occurred in three animals in the BAH-lipiodol group. Histopathologic analysis demonstrated no evidence of gastric mucosal ulceration or significant changes in the overall architecture of the gastric mucosa in either group. These findings demonstrated that both liquid and mechanical

embolization can safely suppress ghrelin levels, induce weight loss, and lower body fat content.

Liquid sclerosing agents show promise in suppressing ghrelin and modifying weight gain, in part, secondary to their ability to deeply penetrate into the smallest of vessels. However, these materials are known to be highly toxic and can result in clinically significant tissue necrosis. Therefore, Paxton et al. (2013) sought to evaluate the efficacy of bariatric LGA embolization using **clinically available microspheres** (40 μm), a mechanical embolization agent. These extremely small spheres can pass deeper into tissues than the much larger **PVA particles** (range from 300 to 1,000 μm) and provide long-term occlusion to the fundal vessels. These characteristics could hopefully induce a more permanent weight loss.

In this study, ten growing swine underwent percutaneous angiography of the celiac axis and SMA to delineate the gastric vascular supply. Super-selective angiography was used to identify all fundal vessels. The fundal vessels included the LGA, small branches of the splenic artery (likely SGAs), and an accessory LGA arising from the left hepatic artery. Five animals underwent embolization of the fundal vessels with normal saline. The experimental animals' vessels were embolized with 4–6 mL of 40 μm microspheres mixed with equal parts of nonionic contrast. After the procedure, the swine were fed a fixed diet. Body weight and serum ghrelin levels were measured prior to the procedure and at 1-week intervals after the procedure for 8 weeks in total. The gastric mucosa was evaluated by endoscopy, rather than by histopathology, in order to replicate the clinical conditions.

The pre-procedure serum ghrelin levels in the control and experimental groups were 1,591.6 pg/dL and 1,605.7 pg/dL, respectively, which were not significantly different. The post-procedure average serum ghrelin levels in the control and experimental groups were 1,920.5 pg/dL and 1,067.8 pg/dL, respectively. The decrease in serum ghrelin levels for the experimental group was significantly greater than that seen in the control group. Additionally, the experimental animals gained less weight over the study period (3.8 kg) than the control animals (9.4 kg).

Endoscopy performed at 3 weeks after LGA embolization demonstrated ulcers in 40 % (2/5) treated animals, but both were located along the lesser curvature rather than at the gastric fundus. All the treated animals demonstrated mild gastritis at endoscopy. These results show that LGA embolization to treat obesity is feasible with commercially available products and results in significant changes in serum ghrelin and modulation of subject weight.

9.8 Therapeutic Potential of Left Gastric Artery Embolization in Weight Loss: Preliminary Observations in Humans

Despite promising animal data, weight loss in humans after LGA embolization has not been sufficiently documented. To date, the safety profile and efficacy of bariatric LGA embolization in humans as a prospective treatment for weight loss have not been established. Kipshidze et al. described their initial prospective experience with **bariatric LGA embolization** in five patients during a recent conference proceeding (Kipshidze et al. 2013). In this preliminary report, five obese patients underwent bariatric embolization of the LGA using 300–500 μm microspheres. Esophageal and gastric mucosa were evaluated by endoscopy in each patient, 1 week after the procedure, to identify any significant structural changes.

Patient's weight loss was evaluated 6 months after the procedure. In this small group of patients, the mean patient body weight decreased by 29.1 pounds in 6 months with all patients demonstrating a decreased appetite during the first post-procedural week. Endoscopy found no significant alterations to the stomach mucosa and the most common complaint was mild epigastric discomfort in the immediate post-procedural period. While more robust data is needed, this early report is the first to provide evidence in humans that LGA embolization can be safely performed in a prospective manner in order to treat obesity with initial success.

9.9 Conclusions and Future Directions

Trans-arterial embolization of the LGA is an exciting new potential treatment for the bariatric patient, which has had good success in animal models to date. Currently, the human data is very limited and future research is needed to determine the safety profile and long-term clinical efficacy of the bariatric embolization of the LGA. This will require robust data from multi-center, randomized trials. Furthermore, the potential role of LGA embolization in the schema of bariatric therapy is yet to be investigated. Is this a primary therapy that could replace more invasive surgical techniques or an **adjunctive therapy** that could be used in combination with bariatric surgery to produce greater clinical benefit? Could LGA embolization be employed in morbidly obese patients who are too **critically ill for an invasive procedure** as a means to weight loss while awaiting clearance for bariatric surgery? Additionally, it will be interesting to see how future modifications of the technique with more sophisticated embolic materials and improved operator experience affect clinical outcomes.

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Chapter 10
Pharmacologic Approach to Type 2 Diabetes in Obese Patients

León E. Litwak, Carla Musso, and Susana Fuentes

Abstract Obesity, as a result of sedentary lifestyles and the rapid nutritional transition from healthy diets (high in fiber and low in fat and calories) to the so-called "westernized diets" (**calorie-dense meals** containing refined carbohydrates, red meats, sugary desserts, drinks, and high-fat foods), has reached epidemic proportions and is the major risk factor for developing Type 2 Diabetes Mellitus (T2DM) (Cordin et al. 2005). On the other hand, genetic and environmental factors play a concurrent role in the development of T2DM with obesity being one of the most important components. The association of obesity and T2DM leads to numerous healthcare problems including hypertension, coronary heart disease, stroke, cancer, and reproductive abnormalities (Haslam and James 2005).

10.1 Introduction

Obesity, as a result of sedentary lifestyles and the rapid nutritional transition from healthy diets (high in fiber and low in fat and calories) to the so-called "westernized diets" (**calorie-dense meals** containing refined carbohydrates, red meats, sugary desserts, drinks, and high-fat foods), has reached epidemic proportions and is the major risk factor for developing Type 2 Diabetes Mellitus (T2DM) (Cordin et al. 2005). On the other hand, genetic and environmental factors play a concurrent role in the development of T2DM with obesity being one of the most important components. The association of obesity and T2DM leads to numerous healthcare

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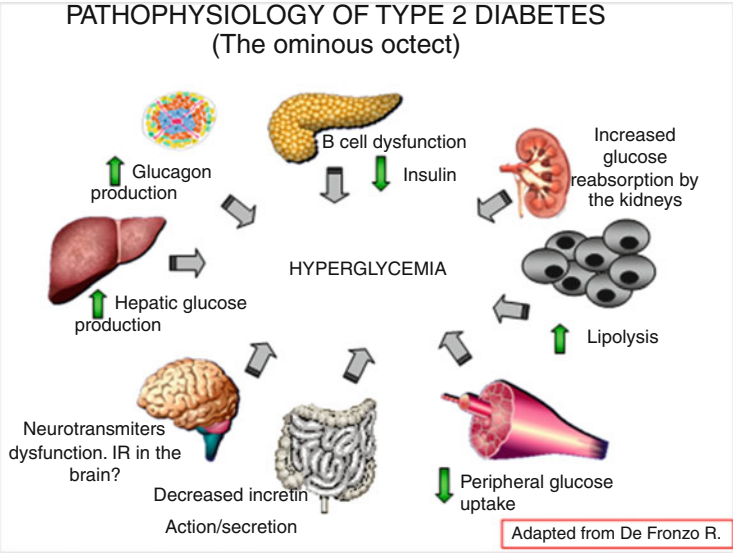

Fig. 10.1 The ominous octet. Adapted from DeFronzo R

problems including hypertension, coronary heart disease, stroke, cancer, and reproductive abnormalities (Haslam and James 2005).

Obesity affects a great proportion of the population of western countries (36 % of the USA population) (Ogden et al. 2012). T2DM also shows a fast and sustained increase in its prevalence affecting around 390 million people (International Diabetes Federation 2012). Several different overlapping mechanisms can lead to the development of T2DM. As described in Fig. 10.1, the decreased insulin sensitivity in the liver, muscle, and adipose tissue induces an increase of hepatic glucose production, a decrease in peripheral glucose uptake, and an increase in lipolysis (de Fronzo 2009).

The imbalance between alpha and beta cells is a novel mechanism implicated in the pathogenesis of Type 2 DM described in the last few years. It is due to a defective action of **incretin hormones**, mainly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). This impaired action causes the failure to suppress glucagon release after a meal ingestion, increasing glucose concentration. The decrease in GPL-1 action in the brain together with insulin resistance (IR) in the central nervous system produces the dysregulation of food-intake behavior (less satiety). GIP and GLP-1 are released predominantly from L and K cells (in the proximal and distal intestine) following nutrient ingestion promoting insulin secretion, glucagon release inhibition, delaying gastric emptying, and enhancing satiety (controlling weight) with GLP-1 being much more effective than GIP. GLP-1 and GIP have multiple actions that enhance beta-cell response in a

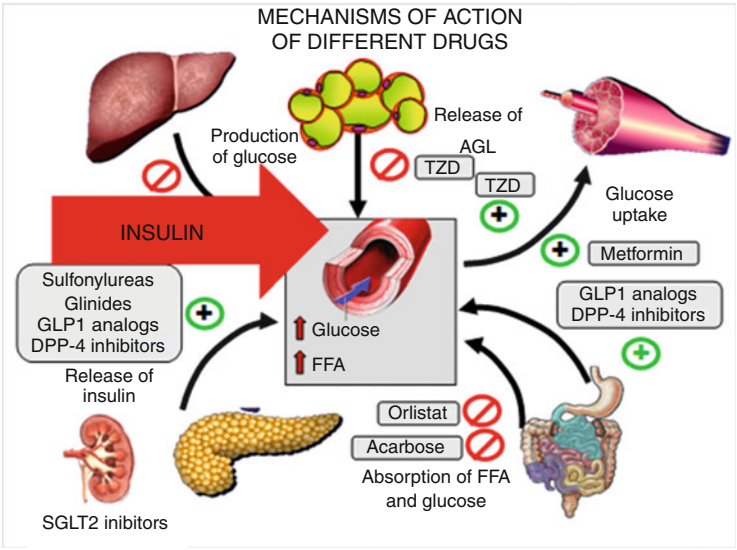

Fig. 10.2 Mechanism of action of different drugs for the treatment of type 2 diabetes

glucose-dependent fashion. In T2DM, the incretin response is diminished (Van Genugten et al. 2013).

Finally, another interesting mechanism described recently is the diminished action of the **sodium-glucose cotransporter 2** (SGLT2) in the kidney. This defect decreases glucose excretion. The kidney contributes to glucose homeostasis by filtering and reabsorbing glucose back into the circulatory system. In non-diabetics, approximately 180 g of glucose is freely filtered per day, which is all reabsorbed in the proximal convoluted tubule. Two transporter families are involved with glucose reabsorption: glucose transporters (GLUTs) as passive transporters and SLGTs as secondary active transporters. Two of the six SLGTs are well characterized: (1) SLGT-1—with low capacity, located in small intestine and in the renal proximal convoluted tubule responsible for only 10 % of glucose re-absorption and (2) SLGT-2—with a high capacity of absorption, in the early proximal convoluted tubule, responsible for the remaining 90 % of glucose reabsorption (Vasilakou et al. 2013) (Fig. 10.1).

A better knowledge of the pathophysiology of T2DM and its comorbidities has challenged the development of many new drugs to safely treat hyperglycemia (Fig. 10.2) with the aim to reduce and maintain glucose concentrations as close to normal for as long as possible after diagnosis, preventing the development of chronic complications.

10.2 From the Classical Approach to the New Drugs in the Treatment of Type 2 Diabetes

10.2.1 Metformin

According to national and international guidelines, **metformin** is the recommended first-line oral therapy for the treatment of type 2 diabetes together with lifestyle intervention at the time of diagnosis. However, it could also be combined with almost all the rest of antidiabetic agents with the progression of the disease (Nathan et al. 2009).

10.2.1.1 Mechanisms of Action

Metformin is effective only in the presence of insulin, decreasing hepatic glucose output and increasing insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver), particularly after meals. It has an antilipolytic effect lowering serum-free fatty acid concentrations reducing substrate availability for gluconeogenesis (UKPDS 1995).

Metformin ameliorates hyperglycemia by reducing insulin resistance. These effects have been linked to the expression of insulin receptors as well as **tyrosine kinase activity** along with the modulation of the incretin axis. Metformin also increases plasma GLP-1 levels and gene expression of the **islet incretin receptor** via peroxisome proliferator-activated receptor-α (PPAR-α). Whatever be the role, metformin through all these mechanisms primarily inhibits hepatic glucose output and significantly increases insulin sensitivity (Viollet et al. 2012).

The pharmacokinetics of metformin is described in Table 10.1.

10.2.1.2 Doses, Associations, and Efficacy

Metformin should be indicated as monotherapy for the treatment of hyperglycemia in patients with type 2 diabetes who do not achieve the expected levels of glycemic

Table 10.1 Pharmacokinetics of metformin

Bioavailability	50–60 % absorption in the small intestine; estimated maximum concentration 0.9–2.6 h and 4–8 h with standard formulations with delayed absorption
Plasmatic concentration	Maximum 1–2 μg/ml within 1–2 h after oral doses of 500–1,000 mg of the standard formulation; approximately 20 % less with the extended release
Half-life	6 h of removal
Metabolism	Not metabolized
Distribution	Concentration in most tissues similar to plasma; higher in the liver and kidney; the highest concentration in salivary glands and intestinal wall

Table 10.2 Effects of metformin against insulin resistance syndrome

Features of the insulin resistance syndrome	Effect of metformin on the features of the insulin resistance syndrome
Hyperinsulinemia	Reduces hyperinsulinemia during fasting periods
Abdominal obesity	Generally stabilizes weight, reduces weight gain, and facilitate weight loss
Glucose intolerance or type 2 diabetes	Counteracts insulin resistance (increases the suppressive effect of insulin on hepatic glucose production and increases its muscle uptake). Slows the progression of prediabetes to diabetes, improves glycemic control in type 2 diabetes
Dyslipidemia (↑ c-VLDL-TG, ↑ c-LDL, ↓ c-HDL)	Improves slightly the lipid profile
Hypertension	No significant effect on blood pressure in most studies
Procoagulant state	Some antithrombotic activity (e.g., Decreases PAI-1, fibrinogen, and platelet aggregation)
Atherosclerosis	Facts of antiatherogenic activity in preclinical studies

c-HDL cholesterol bound to high density lipoprotein, *c-LDL* cholesterol bound to low density lipoprotein, *c-VLDL* cholesterol bound to very low density lipoproteins, *PAI* plasminogen activator inhibitor, *TG* triglycerides

control with a non-pharmacological approach based on diet, exercise, and diabetes education.

Metformin should be combined with sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones, GLP-1 agonists/analogs (exenatide, liraglutide), dipeptidyl peptidase-4 inhibitors (DPP-4), and insulin.

Metformin lowers HbA1c by 1.5%, similar to that achieved with sulfonylurea (Hermann et al. 1994). Metformin shows potential beneficial effects associated with the decrease of insulin resistance (Table 10.2).

Initial doses (500 mg once a day) must be slowly increased at weekly intervals and administered two or three times a day before or together with meals considering a maximum dose of 2,550 mg/day.

10.2.1.3 Side Effects and Contraindications

At the start of the treatment, patients could present gastrointestinal side effects (abdominal discomfort, diarrhea, nausea, anorexia, and metallic taste). They can be minimized by titrating the dose gradually and take the tablets with meals.

Metformin reduces intestinal absorption of vitamin B12 in up to 30 % of patients, and lowers serum vitamin B12 concentrations in 5–10 %, but rarely causes megaloblastic anemia.

Metformin is weight neutral and does not produce hypoglycemia compared with other traditional oral agents (Bailey and Turner 1996).

Metformin should be used carefully in patients with impaired renal function (creatinine $\geq$1.5 mg/dl in men or $\geq$1.4 mg/dl in women and/or glomerular filtration rate $<$60 ml/m/1.73 m^2). However, the last international guideline allows its use in

Table 10.3 Clinical use of metformin

Alone or in combination with other oral antidiabetic agents and/or insulin in patients with type 2 diabetes inadequately controlled with diet and exercise
Directions for use: available presentations—500, 850, and 1,000 mg. Simple or extended release. Better to administer with meals, and increase doses in a gradual way Maximum dose 2,550 mg/day (2,000 g/day in children)
Contraindications: renal and hepatic impairment; heart or respiratory failure; hypoxemia; severe infection; alcohol abuse; history of lactic acidosis; pregnancy; temporary suspension during scans with intravenous contrasts
Gastrointestinal adverse effects relieved by reducing doses; may interfere with the absorption of vitamin B12 and folic acid
Risk: lactic acidosis in patients with contraindication; hypoglycemia in combination with other drugs or in moderate alcohol consumption

patients with a glomerular filtration rate over 30–45 ml/m if they have received it before. In elderly patients, it is contraindicated if the estimated glomerular filtration rate is less than 60 ml/min/1.73 m^2. Temporary suspension of metformin is mandatory 48 h prior to any intravascular contrast procedure.

Hypoxia and hypoperfusion states are considered a contraindication to metformin administration, in particular, acute heart failure, severe respiratory failure, and sepsis. The presence of severe liver disease and a history of lactic acidosis, alcohol abuse, or other functional disorders that could produce abnormal lactate metabolism are also considered as contraindications. At present, metformin is not recommended during pregnancy and lactation. Metformin is not effective as a primary therapy in **type 1 diabetes**.

Lactic acidosis remains as one of the main concerns because of the high case fatality rate. However, most cases occurred in patients with a shock state and/or tissue hypoxia or in the presence of several other predisposing conditions like impaired renal function and heart failure (Table 10.3).

10.2.2 Sulfonylureas

Sulfonylureas have been established in the treatment of Type 2 DM and were the first oral glucose-lowering medications to be introduced into clinical practice. Since then many different molecules had been developed (1st and 2nd generations of sulfonylureas)

10.2.2.1 Mechanisms of Action

Their main mechanism of action is the insulin release from pancreatic islet beta cells increasing insulin disposal during fasting and postprandial periods. There were described many other actions of sulfonylureas: Decrease of the exaggerated hepatic

glucose overproduction and the improvement of insulin sensitivity in muscle and adipose tissue. The main source of sulfonylurea receptors is not only located in beta cells but also distributed in many organ tissues like myocardial cells.

The sulfonylurea receptor is a component of the ATP-dependent potassium channel (Aguilar-Bryan et al. 1995).

Sulfonylurea binding to its receptors leads to the inhibition of these channels, which alters the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion in the beta cells and also to the blockade of ischemic preconditioning in myocardial cells. The net effect is an increased responsiveness of beta cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin secretion at different blood glucose concentrations. Thus, sulfonylureas are useful only in patients with some remaining beta cell function (Ashcroft 1996).

The **1st generation sulfonylureas** (tolbutamide, chorpropamide) have been stopped and there should be very few patients using them. The **2nd generation sulfonylureas**, glipizide, glyburide (glibenclamide), gliclazide, and glimepiride, have structural characteristics that allow them to be given in much lower doses than the 1st generation. Nevertheless, they are equally effective in lowering blood glucose concentrations in spite of differences in absorption and metabolism, as well as in effective dose

10.2.2.2 Doses, Associations, and Efficacy

Sulfonylureas usually lower HbA1c by 1–2 %. They are most likely to be effective in patients whose weight is normal or slightly increased (Bressler and Johnson 1997).

They can be combined with any other drugs like metformin, TZD, incretin-mimetics, DPP4I, and/or insulin. Doses and pharmacokinetics of the SU are described in Table 10.4.

10.2.2.3 Side Effects and Contraindications

Sulfonylurea is usually well tolerated. Hypoglycemia and weight gain are the most common side effects (Gangji et al. 2007).

Hypoglycemia is associated with high SU doses, alcohol abuse, impaired renal function, co-administration of salicylates, sulfonamides, fibric acid derivatives (gemfibrozil), and warfarin, or after missing meals and/or exercising.

Weight gain has been described during the UKPDS trial in the SU's cohort. A change in body weight, pooling the results of many publications of this trial, gave a mean increase in weight of 2.31 kg (95 % CI 1.31–3.32) in the sulfonylurea-treated groups compared with comparator groups. For this reason, SUs should not be the first-line drug election for obese Type 2DM patients.

Table 10.4 Dosage and administration of sulfonylureas and meglitinides

Drug	Dose (mg/day)	Maximum effect (h)	Half-life (h)	Metabolites	Excretion
Sulfonylureas					
Tolbutamide	500–3,000	3–4	4.5–6.5	Inactive	Kidney
Clorpropamide	100–500	2–4	36	Active or unmodified	Kidney
Tolazolamide	100–1,000	3–4	7	Inactive	Kidney
Glipizide	2.5–40	1–3	2–4	Inactive	Kidney 80 %, stools 20 %
Glipizide LA	5–20	Constant/ days	–	Inactive	Kidney 50 % stools 50 %
Glibenclamide	1.25–20	2–4	10	Inactive and weakly active	Kidney 60 % stools 40 %
Glibenclamide (micronized)	1.5–12	2–3	–4	Inactive and weakly active	
Glimepiride	1–8	2–3	9		
Glinides					
Repaglinide	0.5–4 each meal	1	1	Inactive	Stools
Nateglinide	60–120 each meal	1,8	1.4	Weakly active	Kidney 80 % Stools 20 %

Table 10.5 Contraindications for the use of insulin secretagogues

Diabetes type 1 or pancreatic diabetes
Pregnancy
Major surgeries
Infections or severe traumas
History of sulfonylurea or a related molecules' severe adverse reaction. e.g., sulfonamide (doesn't exclude repaglinide)
Predisposition to severe hypoglycemia (e.g., patients with significant hepatic or renal disease)

It has been described unfavorable cardiovascular effects probably related to the blockade of ischemic preconditioning mentioned before, an endogenous mechanism that protects the heart from ischemic injury associated with hypoglycemic episodes producing electrocardiographic abnormalities and arrhythmias (Marques et al. 1997). Gliclazide showed less hypoglycemia and less association with CV mortality.

The three main problems in relation to treatment with insulin secretagogues are

- Hypoglycemia
- Weight gain
- Cardiovascular risk (an open discussion to date)

Contraindications for treatment with insulin secretagogues are as follows: Type 1 diabetes, pregnancy, major surgeries, infections, severe trauma, allergy predisposition, and severe hypoglycemia risks (Table 10.5).

Table 10.6 The most frequent causes of secondary failure of sulfonylurea

Patient-related factors
Weight gain or inadequate diet
Poor adherence to treatment guides
Physical inactivity
Stress
Intercurrent diseases
Comorbidities
Disease-related factors
Functional loss of pancreatic beta cells
Increased insulin resistance
Treatment-related factors
Inadequate posology
Concomitant diabetogenic drugs

The response to sulfonylurea can decrease over time. The more common factors are listed in Table 10.6.

10.2.3 Meglitinides

10.2.3.1 Mechanism of Action

The **meglitinides** are short-acting glucose-lowering drugs. They are structurally different from sulfonylureas and exert their effects via different receptors in the beta cell surface, but activating the same insulin release pathway generating short and increased prandial insulin release because of their shorter half-life (Fuhlendorff et al. 1998).

10.2.3.2 Doses, Associations, and Efficacy

Doses have been described in Table 10.4

They can be administered alone as monotherapy or in combination with almost all the other antidiabetic drugs except sulfonylureas and rapid-acting insulin.

The clinical efficacy of meglitinide as monotherapy is almost similar to that of the sulfonylureas (Wolffenbuttel and Landgraf 1999).

10.2.3.3 Side Effects and Contraindications

Nateglinide is metabolized in the liver with renal excretion of active metabolites. In the presence of decreased renal function, the accumulation of these metabolites

increases the risk of hypoglycemia. This drug must therefore be used cautiously in people with high risks of hypoglycemia.

Repaglinide is mainly metabolized by the liver with less than 10 % renal excretion. Dose adjustments with this agent do not appear to be necessary in patients with renal impairment and should be administered in patients with a glomerular filtration rate of up to 45 mg/dl.

There are no long-term studies of meglitinides to assess cardiovascular outcomes or mortality.

The advantages of repaglinide (the most popular meglitinide) over SUs are the ability to produce less hypoglycemia and the potential use in patients with moderate impaired renal function.

The most common side effects are hypoglycemia and a very slight increase of weight, but significantly lower than SUs.

10.2.4 Thiazolidinediones

Thiazolidinediones are antihyperglycemic drugs whose main action is to increase peripheral insulin sensitivity.

The 1st thiazolidinedione drug generation, troglitazone, approved in 1997, had to be retired because of liver toxicity. Rosiglitazone (a 2nd generation thiazolidinedione) has been recently associated with cardiovascular complications, and it is being used only in a few countries with severe restrictions. The 2nd generation thiazolidinedione in use without restriction is pioglitazone.

10.2.4.1 Mechanism of Action

Thiazolidinediones increase insulin sensitivity acting mainly in peripheral tissues like adipose tissue, muscle, and less in the liver, increasing glucose utilization and decreasing glucose production. The mechanism by which the thiazolidinediones exert their effect is not fully understood. They bind to and activate one or more **peroxisome proliferator-activated receptors** (PPARs), which regulate gene expression in response to ligand binding (Vidal-Puig et al. 1997).

PPAR-gamma (one of the PPARs receptor family) was found predominantly in adipose tissue, pancreatic beta-cells, vascular endothelium, macrophages, and the central nervous system. On the other hand, PPAR-alpha is expressed mostly in liver, heart, skeletal muscle, and vascular walls. The various thiazolidinediones have differential effects on PPAR-gamma and PPAR-alpha receptors. Troglitazone and rosiglitazone are purely PPAR-gamma agonists, while pioglitazone also exerts some PPAR-alpha effects. This may account for the different effects that pioglitazone and rosiglitazone have on lipids.

Thiazolidinediones improve insulin action in skeletal muscle by facilitating glucose transport activity, thereby increasing the rates of muscle glycogen synthesis and glucose oxidation.

The insulin-sensitizing effect of thiazolidinediones may be related in part to the regulation of adipose tissue production of adipokines via PPAR-gamma activation

PPAR-gamma activation mediates weight gain by promoting increased feeding. This finding accounts, in part, for the weight gain associated with treatment (Lu et al. 2011; Ryan et al. 2011). Thiazolidinediones increase peripheral fat content (with a slight increase of weight) but reduce visceral fat. An interesting preserving pancreatic beta-cell function has been demonstrated.

Finally, new "dual" PPAR agonists (gamma and alpha) are being investigated to probe if they could effectively treat both hyperglycemia and hyperlipidemia.

10.2.4.2 Doses, Associations, and Efficacy

When used as monotherapy, they reduce hemoglobin HbA1c percentage between 0.8 and 1.5 %, showing the same potency as that of metformin

Thiazolidinediones could be administered as monotherapy or in combination with complementary antidiabetic drugs such as metformin, sulfonylureas, meglitinides, incretin mimetics, and DPP4 inhibitors. The association with insulin is not recommended and the combination with sulfonylurea has to be avoided in obese type 2 diabetic patients. The **association of thiazolidinedione and metformin** is very rational and very effective because metformin inhibits hepatic glucose production (improving insulin sensibility in the liver), whereas thiazolidinediones act by improving peripheral uptake and utilization of glucose in muscle and fat. In this way both reduce in a complementary action central and peripheral insulin resistance (Raskin et al. 2001; Kipnes et al. 2001).

10.2.4.3 Side Effects and Contraindications

The main side effects of thiazolidinediones are as follows: (1) potential liver toxicity although there are many trials showing improvement in patients with hepatosteatosis; (2) weight gain; (3) fluid retention and possible induction or worsening of heart failure in susceptible patients; and (4) bone fractures.

Weight gain: It is both dose-dependent and time-dependent and can be substantial (Fonseca et al. 2000). The most relevant clinical aspects of these drugs are summarized in Table 10.7

Contraindications of TZDs are Type 1 diabetes, liver disorders, and pregnancy, and the relative contraindications are Obese Type 2 diabetic patients

Table 10.7 Clinically relevant metabolic effects of thiazolidinediones

Glycemic effects
Increased uptake and insulin-mediated utilization of glucose
Glucose-lowering action without hypoglycemia
Non-glycemic effects
Lipids
Conversion of small, dense LDL particles in large and sparse
Increase of HDL cholesterol
Lower triglycerides if they are increased (>200 mg/dl)
Increase adipogenesis
Decrease of free fatty acids in plasma
Vascular
Ameliorate endothelial dysfunction?
Improve vascular resistance reducing a mean of 4 mm Hg in systolic and diastolic blood pressures
Ameliorate the procoagulant state decreasing the PAI-1 and fibrinogen concentrations
Decrease inflammation process measured by CRP
Decrease the thickness of the carotid intima-media
Reduce albuminuria
Pancreatic beta cells
Reduces the rate of loss of secretory function in animals

10.2.5 Alpha-glucosidase Inhibitors

Two oral antidiabetic drugs, **alpha-glucosidase inhibitors** and lipase inhibitors, lower blood glucose modifying the intestinal absorption of carbohydrates and fat, respectively .

The alpha-glucosidase inhibitors, acarbose, miglitol, and voglibose, have been studied extensively in Europe and Japan; two of them, **acarbose** and miglitol, are available in the United States. They inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharide in a dose-dependent fashion slowing the absorption of glucose. This action decreased postprandial blood glucose concentrations. Acarbose has a potential beneficial effect in postprandial hyperglycemia in both Type 1 and Type 2 diabetes patients. In older patients with type 2 diabetes, acarbose may also increase insulin sensitivity (Meneilly et al. 2000). These drugs also modify the secretion of gastrointestinal incretins.

10.2.5.1 Mechanisms of Action

Inhibitors competitively block alpha-glucosidase located in the brush border of the small intestine cells, enzymes for hydrolyzing essentials disaccharides,

oligosaccharides, and polysaccharides to monosaccharides. Under normal circumstances, the carbohydrates are absorbed quickly in the first portion of the small intestine. Therefore, these drugs delay the absorption of carbohydrates along the entire small intestine.

10.2.5.2 Doses, Associations, and Efficacy

Efficacy—Alpha-glucosidase inhibitors are less potent than most of the antidiabetic drugs lowering HbA1c by 0.4–0.9 % (Van de Laar et al. 2005).

Dosing—Acarbose is available as 50 and 100 mg tablets, which should be taken with the first bite of each meal beginning with 50 mg three times daily. Flatulence, diarrhea, and abdominal discomfort are dose related and will almost always resolve if the dose is decreased. Few people tolerate more than 300 mg daily. One of the main advantages is that they do not produce hypoglycemia.

10.2.5.3 Side Effects and Contraindications

Although alpha-glucosidase inhibitors have been studied as monotherapy for the initial treatment of diabetes and even prediabetes, most of the guidelines do not consider using them as a first-line therapy because of reduced efficacy, expense, and poor tolerance.

The formal contraindications to treatment with the inhibitors of alpha-glucosidase are intestinal malabsorption syndromes, inflammatory bowel disease, intestinal obstruction, and liver failure. They are also contraindicated in severe renal failure, pregnancy and lactation, as well as in children less than 12 years.

10.2.6 GLP-1 Receptor Antagonist

10.2.6.1 Mechanism of Action

The two main incretin hormones, GIP and GLP-1, are released predominantly from **L and K cells** (in the proximal and distal intestine) following nutrient ingestion promoting insulin secretion, glucagon release inhibition, delaying gastric emptying, and enhancing satiety (resulting in weight control) with GLP-1 being much more effective than GIP (Van Genugten et al. 2013).

Incretin mimetics or enhancers are one of the latest groups of drugs available for the treatment of T2DM—incretin therapy. Given the novel role of incretin therapy in terms of reducing postprandial hyperglycemia, and the favorable effect on weight with the reduced incidence of hypoglycemia, the used of them as alternative options in T2DM was explored [28].

Table 10.8 Effects of incretin therapy in the treatment of T2DM

(a) Glucose-dependent stimulation of insulin secretion
(b) Glucose-dependent suppression of glucagon secretion
(c) Reduced gastrointestinal motility
(d) Increased satiety
(e) Increased beta-cell mass with inhibition of beta-cell apoptosis
(f) Improvement of beta-cell function

Some evidence alludes to incretins potentially increasing beta cell mass and altering disease progression, so it might be helpful to introduce these agents earlier in the treatment algorithm.

Incretin acts primarily by increasing the physiological effects mediated via the hormone GLP-1, which is secreted along with GIP by intestinal cells when food is ingested, probably via the neural and endocrine signals associated with feeding. GLP-1 and GIP have multiple actions that enhance beta-cell response in a glucose-dependent fashion. In T2DM, the incretin response is diminished (Nauck et al. 1986).

Two strategies can restore the GLP-1 signal: (1) inhibiting the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades GLP-1 in vivo resulting in increased concentrations of endogenous GLP-1 called incretin enhancers or (2) using parenteral administration of GLP-1 mimetics or GLP-1 RAs (GLP-1 Receptor Agonists) that are DPP4 resistant (Druker 2006).

10.2.6.2 GLP-1 Mimetics

Currently four GLP-1 RAs are available.

The insulinotropic and extra-pancreatic effects of GLP-1 RAs have been described. In relation to glucose metabolism, GLP-1 increases insulin secretion and suppresses glucagon secretion; both mechanisms manifest only in the setting of hyperglycemia. In addition, GLP-1 induces satiety and has an effect on weight (Table 10.8) (Owens et al. 2013).

10.2.6.3 Pharmacological Profile of GLP-1

Pharmacology of GLP-1 can be appreciated in Table 10.9.

1. Prandial GLP-1 (Exenatide and Lixisenatide)

Exenatide is a synthetic form of exendin-4, a 39 amino-acid peptide isolate from the salivary secretions of the Gila monster with a 50 % homology with GLP-1 and is a potent agonist of the human GLP-1 receptor. Exenatide has a half-life of 2 h, so two injections daily are necessary. Different studies demonstrated that exenatide in

Table 10.9 Classification of GLP-1 RA according to pharmacological profile

Prandial GLP-1 RA	Exenatide
	Lixisenatide
Non-prandial GLP-1 RA	Extended release exenatide
	Liraglutide
	Albiglutide
	Semaglutide

Table 10.10 Comparison of pharmacological profile of GLP-1

	Prandial	Non-prandial
GLP-1 RA	EXENATIDE LIXISENATIDE	LIRAGLUTIDE EXENATIDE—LAR
Half-life	2–5 h	12 h-many days
Effect on fasting glucose	Modest reduction	High reduction
Effect on post-prandial glucose	High reduction	Modest reduction
Gastric emptying	High impact	No effect

combination with metformin, a DPP4 inhibitor, or rosiglitazone decreased post-prandial glycemia, and the most significant decrease was with rosiglitazone. When it was compared with glimepiride or glibenclamide, the decrease was almost the same. Another study compared exenatide with insulin glargine or biphasic insulin aspart, HbA1c was lower by both insulins, fasting plasma glycemia was lower with insulin glargine, and post-prandial glycemia improved with exenatide plus metformin and TZD (DeFronzo et al. 2008, 2010; Derosa et al. 2010, 2011) (Table 10.10).

Lixisenatide is a 44 amino-acid exendin-4 analog with an extended c-terminus. The half time of lixisenatide is 2.8 h, but the binding affinity for the GLP-1 receptor is fourfold greater than native GLP-1 that allows once daily injection. The Phase III GETGOAL program comprised 11 randomized studies that evaluated the efficacy and tolerability of lixisenatide 20 μg daily prandial in individuals with T2DM. Lixisenatide produces significant improvements in HbA1c, FPG, and PPG compared with insulin glargine or oral agents (Ahren et al. 2013; Riddle et al. 2013; Bolli et al. 2014; Fonseca et al. 2012; Pinget et al. 2013; Ratner et al. 2011; Lorenz et al. 2013; Kapitza et al. 2013).

2. Non-prandial GLP-1: Extended Release Exenatide, Liraglutide, Albiglutide, and Semaglutide

These are molecules that rely on different mechanisms to delay their absorption from the subcutaneous tissue and extend their duration of action (Table 10.10).

2a. ***Extended release exenatide*** is a formulation that encapsulates microspheres made of biodegradable polymer that allows once weekly administration. The Phase III clinical development programme of exenatide once weekly involved a series of trials known as the DURATION trials. Safety and efficacy of Exenatide once weekly were compared with exenatide twice daily, pioglitazone or sitagliptin, metformin, liraglutide, and insulin glargine (DURATION 1–6),

respectively (Bergenstal et al. 2010; Russell-Jones et al. 2012; Buse et al. 2012; Diamant et al. 2010; Raskin et al. 2005; Blevins et al. 2011). Extended release exenatide was superior in lowering PPG, had a low incidence of hypoglycemia but a greater incidence of gastrointestinal adverse events. The sustained elevated plasma concentrations of exenatide once weekly formulation induced tachyphylaxis with a progressive inhibition of gastric emptying, a key factor related with the reduction of PPG (Nauck et al. 2011).

2b. ***Liraglutide*** is an analog of human GLP-1with 97 % sequence homology, which contains a C_{16} palmitoyl fatty acid side chain that allows forming of heptamers when injected subcutaneously, and binding with albumin delays its absorption. It reaches the maximum concentration at 9–12 h after dosing and plasma levels remains stable for up to 13 h after injection. The LEAD studies were six randomized trials that assessed the safety and efficacy of liraglutide (0.6–1.8 mg) once daily alone or in combination with oral agents. In all of them liraglutide demonstrated a reduction of HbA1c, FPG, PPG, and weight loss (Buse et al. 2009); Nauck et al. 2009; Russell-Jones et al. 2009; Zinman et al. 2009; Garber et al. 2009; Marre et al. 2009).

2c. ***Albiglutide*** is a dimer of GLP-1 that is fused with human albumin that shares 97 % homology with native GLP-1. It has a half-life of 6–7 days giving the possibility of once weekly administration. The Phase III HARMONY program is investigating the safety and efficacy of albiglutide, once weekly. Results are available for HbA1c; it was significantly reduced, but PPG data is not available (Pratley et al. 2014).

2d. ***Semaglutide*** is a monoacylated human GLP-1 analog. The mode of action is identical to liraglutide but with a longer half-life of 6–7 days; it also allows once weekly administration. The phase III study SUSTAIN is still ongoing (Nauck et al. 2012).

10.2.6.4 Additional Benefits Beyond Glucose Lowering

GLP-1 and Cardiovascular Disease

Hypertension is a common and serious complication in type 2 diabetic patients and in combination with poorly controlled diabetes doubles the risk of death from CVD and total mortality. The effect of GLP-1 RA on blood pressure has been described. The majority of clinical trials with GLP-1 RA have demonstrated a significant reduction of systolic and diastolic blood pressure, some of them independent of weight loss. The mechanism is still not clear, but four theories have been described: all of them have in common the relaxation of the arteries by GLP-1 RA through the receptor of GLP-1 or without the activation of the receptor (Golpon et al. 2001; Nystrom et al. 2005; Nathanson et al. 2009; Yu et al. 2003).

On vascular endothelium GLP-1 RAs have shown to inhibit monocyte/macrophage accumulation in the arterial wall, inhibit the expression of inflammatory markers as TNFα, reduce adhesion molecules such as VCAM-1, and promote

vascular relaxants such as nitric oxide. The net result seems to be amelioration of endothelial function and plaque stabilization, which should eventually translate into direct protective effects of GLP-1 on the progression of atherosclerosis (Gupta 2012).

Dyslipidemia plays a critical role in the development of macrovascular disease. The effects of GPL-1 RA on dyslipidemia promote reduction of **apolipoprotein B-48** (ApoB-48) production and triglycerides absorption, and this effect could be independent of the delay of gastric emptying. GLP-1 infusions inhibited the postprandial elevation of triglycerides, Apo B-48, and free fatty acids (Seino and Yabe 2013).

Clinical Relevance of GLP-1 Analogs in Obesity

The effects of the GLP-1 RAs, liraglutide and exenatide, twice daily and once weekly on body weight have been demonstrated. Overall, the weight reductions were significant for GLP-1 RAs (the maximum weight loss from baseline induced by exenatide in a 24-week RCT was 3.1 kg and 3.6 kg in a 52-week RCT). In head-to-head comparison studies, GLP-1 RAs were shown to be superior to DPP-4 inhibitors with respect to weight loss. In general, the GLP-1 RAs, exenatide, exenatide, and liraglutide, once daily seem comparable concerning body weight reduction, confirmed by two head-to-head comparison trials in which liraglutide induced weight loss similar to exenatide (liraglutide −3.24 kg vs. exenatide −2.87 kg, non-significant (NS) and exenatide (liraglutide −3.58 kg vs. exenatide −2.68 kg, NS) (Astrup et al. 2009; Buse et al. 2010).

Reduced food intake may be a consequence of gastric distension due to delayed gastric emptying, thus inducing satiety, but may also be mediated by neuronal and CNS actions of GLP-1, as stated previously. To date, there are only few studies addressing the central effects of endogenous and exogenous GLP-1 in humans. A relationship between postprandial GLP-1 levels and the activation of brain regions involved in CNS appetite regulating centers was shown.

Many trials have shown that weight reduction by GPL-1 RA was associated with a favorable cardiovascular risk profile (Kim et al. 2009; Klonoff et al. 2008).

Clinical Relevance of GLP-1 Plus Insulin

There is evidence to sustain that FPG and PPG are independent predictors of cardiovascular disease; hence, the rationale to combine **insulin and GLP-1 RA** is related with the effect of insulin on hyperglycemia with the risk to induce hypoglycemia and weight gain. By contrast, GLP-1 is reliant on residual beta-cell function to normalize the blood glucose to complement their other actions on gastric emptying and insulin sensitivity via weight loss. So, the rationale of adding incretins to basal insulin is to counder balance the associated weight gain and

Table 10.11 Advantages of introducing incretin therapy before insulin

Potentially delay the need of insulin
Low risk of hypoglycemia
Weight loss

reduction or neutrality of hypoglycemia provoked by insulin (Yoon et al. 2009; Buse et al. 2011; Fonseca et al. 2007; Arnolds et al. 2010) (Table 10.11).

The different pharmacological profiles of GLP-1 RA contribute to different impacts on FPG or PPG levels suggesting that the selection of a GLP-1 RA should be guided by the predominant dysglycemic state of the patients. Patients for whom FPG is the primary treatment goal, long-acting non-prandial GLP-1 RAs may be the best option, whereas short-acting prandial GLP-1 RAs have a stronger reducing effect on post-prandial glucose levels because of the delay in gastric emptying (Monnier et al. 2003).

Where patient weight control is an issue, long-acting non-prandial GLP-1 RAs have a marginally greater effect on weight loss than short-acting prandial GLP-1 RAs.

10.2.6.5 Doses, Associations, and Efficacy

Storage: GLP-1 should be refrigerated between 2 and 8°C (36–46 F) and protected from light. After the first use, it may be stored at room temperature and should not be frozen or used if frozen. The pen should be discarded 30 days after its first use.

Application: Subcutaneously, each dose should be injected in the thigh, abdomen, or the upper arm.

Doses

Exenatide

Multiple dose prefilled pen: 1.2 ml—5 mcg per dose (60 doses) or 2.4 ml—10 mcg per dose (60 doses). The initial dose of exenatide is 5 mcg twice daily, 60 min before breakfast or dinner. Exenatide should not be administered after a meal. The dose can be increased to 10 mcg twice daily after 1 month of therapy.

Exenatide should not be indicated with glomerular filtration rate <30 ml/m/1.73 m^2.

Liraglutide

The initial dose is 0.6 mcg once a day for a week. The dose can be increased gradually in a week to 1.2 mcg and to 1.8 mcg per day.

Liraglutide should not be indicated with glomerular filtration rate <60 ml/m/1.73 m^2.

Lixisenatide

The usual starting dose of lixisenatide is 10 mcg (green pen) once a day for 14 days. After this the dose will be increased to 20 mcg (purple pen) once a day (Table 10.12).

Table 10.12 Doses of GLP-1 RA

GLP-1 RA	Doses (mcg)
Liraglutide	0.6/1.2/1.8
Exenatide	5/10
Lixisenatide	10/20

Lixisenatide should not be indicated with glomerular filtration rate <30 ml/m/1.73 m^2 and used with caution with GFR between 30 and 59 ml/m/1.73 m^2.

Association: GLP-1 could be associated with metformin, sulfonylureas, meglitinides, thiazolidinedionas, and basal insulin.

Efficacy: GLP-1 reduced HbA1c between 8.0 and 1.8 %.

10.2.6.6 Effects and Contraindications

Side effects: The most common side effects are nausea and occasionally vomiting, both diminish over time. Pancreatitis cases have been reported, but it is important to remark that pancreatitis in diabetic patients has a threefold increased risk compared with individuals without diabetes.

Thyroid cancer of C cell has shown an increased risk in rodents but not in humans or monkeys. However, based on that data, FDA recommended one of the contraindications for use in the family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN2).

Contraindication: Do not use in patients with a personal or family history of **medullary thyroid carcinoma** or in patients with MEN 2.

10.2.7 Dipeptidylpeptidase-4 Inhibitors

10.2.7.1 Mechanism of Action

DPP-4 inhibitors block DPP-4, an enzyme that degrades endogenous GLP-1. The rationale for the strategy of inhibiting DPP-4 in the treatment of type 2 diabetes is to prevent the inactivation of GLP-1, and therefore to enhance and prolong the action of the endogenously released incretin hormone. DPP-4 inhibitors are orally active and increase insulin secretion and reduce glucagon secretion, thereby lowering glucose levels (Holst and Deacon 1998). Until today five DPP-4 inhibitors are available (Table 10.13).

They do not appear to significantly decrease gastric emptying or promote weight loss; they are body weight neutral. Differences between GLP-1 and DPP4 inhibitors are important to evaluate at the time to indicate the appropriate one according to patient's necessities (Table 10.14).

Table 10.13 Features of DPP-4 inhibitors

DPP-4 Inhibitor	Administration (oral)	Clearance	Weight loss	GI side effects[a]
Sitagliptin	100 mg once a day[b]	Renal	Neutral	Neutral
Vildagliptin	100 mg twice a day[b]	Renal	Neutral	Neutral
Saxagliptin	5 mg once a day[b]	Renal	Neutral	Neutral
Linagliptin	5 mg once a day	Extrarenal	Neutral	Neutral
Alogliptin	25 mg once a day[b]	Renal	Neutral	Neutral

[a]GI gastrointestinal
[b]Doses should be adjusted to renal clearance

Table 10.14 Comparison between GLP-1 RA and DPP-4 inhibitors

	GLP-1 RA	DPP-4 inhibitors
Route of delivery	Parenteral	Oral
HbA1c reduction	0.8–1.8 %	0.5–1.1 %
Effect on weight	Induces weight loss	Weight neutral
Effect on gastric motility	Delaying gastric emptying	No effect
Gastrointestinal symptoms	Nausea–vomiting	Nausea (rare)
Hypoglycemia	Low incidence	Rare incidence
Immunogenicity	Potentially	No immunogenicity

The advantages of DPP-4 inhibitors over the GLP-1 analogs include their oral administration and the absence of side effects particularly nausea. Both have the advantage of reduced risk for hypoglycemia.

There have been concerns regarding the potential of classes, GPL-1 analogs and **DPP-4 inhibitors, to promote acute pancreatitis** including associated preneoplastic lesions, and potentially pancreatic cancer (Perfetti et al. 2000; Koehler et al. 2009; Gier et al. 2012; Butler et al. 2013). Analyses of the topic have made it clear that obese, type 2 diabetic subjects are more prone to developing acute pancreatitis than non-diabetic population. Until today, based on the available knowledge, incretin-based medications can be considered effective and safe (Nauck 2013).

10.2.7.2 Additional Benefits Beyond Glucose Lowering

Cardiovascular Function

DPP-4 has demonstrated significant reduction of SBP and DBP in patients with mild-to-moderate hypertension with type 2 diabetes independent of changes in body weight (Ussher and Drucker 2012).

In the development of atherosclerosis, DPP-4 inhibitors play a role on the proinflammatory cells, reducing macrophages and collagen in the plaque,

diminishing the plaque area (Shah et al. 2011). It was demonstrated in rats a decreased infarct size, a reduction of myocardial fibrosis, and improved LV relaxation, indicative of improved diastolic function in heart failure (Huisamen et al. 2011).

Recently, the results of cardiovascular safety trials of type 2 diabetes drugs, EXAMINE trial with alogliptin and SAVOR-TIMI 53 trial with saxagliptin, were reported. These two studies found no effect on the risk of fatal and non-fatal cardiac events and no increases in the risk of pancreatitis or pancreatic cancer. The studies did not demonstrate any cardiovascular protective benefits of DPP-4 inhibitors, but there were few limitations. First, the follow-up period was too short to evaluate the incidence of cardiovascular events because the effects of drugs fighting pro-atherosclerotic processes require more than 10 years. Second, the relatively small HbA1c-lowering effects on saxagliptin and alogliptin averaging only 0.3–0.4 % may influence the final results. Further sub-analysis and other ongoing trials need to be waited (White et al. 2013; Scirica et al. 2013).

Clinical Relevance of DPP4 Inhibitors in Obesity

Whereas DPP-4 inhibitors in general were weight neutral, however, small body weight reductions were observed for DPP-4 inhibitors when combined with metformin and/or compared with sulfonylurea agents or thiazolidinediones (Kostev et al. 2014).

10.2.7.3 Doses, Associations, and Efficacy

Doses of DPP-4 inhibitors available, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin, have been described in Table 10.13. Most of them, with the exception of linagliptin, should be adapted to creatinine

They could be used as monotherapy and could also be combined with metformin, sulfonylurea, TZD, SLGT2 Inhibitors, GLP-1, and insulin for the treatment of type 2 diabetes.

Efficacy reductions of HbA1c with DPP-4 inhibitors vary between 0.5 and 1.1 %.

10.2.7.4 Side Effects and Contraindications

Side Effects

Nasopharyngitis was one of the most common side effects. Mild Hypoglycemia is also one if it is used in combination with insulin or sulfonylurea. Gastrointestinal symptoms such as nausea, diarrhea, and constipation are rare.

Contraindications
DPP-4 inhibitors were contraindications in patients with type 1 diabetes, in pregnant or breastfeeding women, and in patients under the age of 18 or over the age 75.

Precaution
In patients who have or have had pancreatitis (inflammation of the pancreas) or any risk factors for pancreatitis such as gallstones (solid particles that form in the gall bladder), a history of alcoholism, or high triglyceride levels, DPP-4 should be avoided.

10.2.8 Sodium-Glucose Co-transporter Type 2 Inhibitors (SGLT-2 Inhibitors)

10.2.8.1 Mechanism of Action

The mechanism of action of this group of glucose-lowering drugs is unique in that they inhibit the renal reabsorption of glucose and induce glucosuria, thus decreasing glucose concentration independent from affecting insulin secretion. This positive effect occurs without the induction of hypoglycemia and because a specific mechanism of action is accompanied by weight loss and reduction in systolic blood pressure (SBP) (Rosenwasser et al. 2013).

The kidney contributes to glucose homeostasis by filtering and reabsorbing glucose back into the circulatory system. In non-diabetics, approximately 180 g of glucose is freely filtered per day, which is all reabsorbed in the proximal convoluted tubule. Two transporter families are involved with glucose reabsorption: glucose transporters (GLUTs) as passive transporters and sodium glucose co-transporters (SLGTs) as secondary active transporters. There are six types of SLGTs but two of them are well characterized as 1 and 2: SLGT-1—with low capacity, located in small intestine and in the renal proximal convoluted tubule and SLGT-2—with high capacity in the early proximal convoluted tubule, responsible for 90 % of glucose reabsorption. The remaining 10 % of glucose is reabsorbed by SLGT-1 (Rosenwasser et al. 2013).

The **SLGT-2 inhibitors** available are **dapagliflozin** and **canagliflozin; empagliflozin** will be available soon.

In terms of comparative studies of SLGT2 inhibitors with metformin, sulfonylureas, and DPP4, these new drugs have demonstrated reduction in hypoglycemia, weight loss, and reduction of BP. When it was compared with sitagliptin 100, FPG, HbA1c, and weight were lowered by SGLT-2. A significant weight reduction of 2–3 kg was noted.

Dapagliflozin 10 mg once daily was approved, as add on metformin, sulfonylurea and insulin (Hasan et al. 2014).

10.2.8.2 Additional Benefits Beyond Glucose Lowering

Clinical Relevance of SGLT-2 in Obesity

Body weight loss of about 1.09–5.05 kg has been reported across all studies with SLGT-2 inhibitors and is sustained long term as demonstrated by a 2-year study with dapagliflozin (Stenlof et al. 2013).

It is also important to remark that with all SGLT-2, the decrease in body weight was predominantly from fat mass rather than from lean mass. Additionally, the loss of fat was slightly more from visceral abdominal tissue than from subcutaneous fat, and waist circumference was also reduced by 1.52 cm. Caloric loss from glucosuria (200–300 cal per day), and not fluid loss through osmotic dieresis, is the major contributing factor to long-term reduction of body weight (Hasan et al. 2014).

Blood Pressure

A greater reduction on blood pressure was seen in systolic (1.66–6.9 mm Hg) than diastolic (0.88–3.5 mm Hg). The effect on blood pressure was not dose dependent and was not accompanied with changes in heart rate, hypotension, or syncope.

The antihypertensive effect was independent of HbA1c or body weight reduction (Hasan et al. 2014; Cefalu et al. 2013).

Lipids

There are inconsistencies about the effects of SLGT2 inhibitors on lipid profile. After 24 weeks of therapy with dapagliflozin, a small increase in high density lipoprotein (HDL) was noted (Ferrannini et al. 2010).

Uric Acid Reduction

Reduction of uric acid with SLGT2 inhibitors was significant, ranging from −5.9 to −17.8 % when used with OADs or as monotherapy, and −4.9 % in combination with insulin.

Even when the exact mechanism is unknown, decreases the uric acid might be of importance given mounting evidence of the relationship between **hyperuricemia and cardiovascular risk** (Hardy et al. 2011) (Table 10.15).

Table 10.15 SGLT-2 inhibitors: benefits and side effects

Benefits	Side effects
• Insulin-independent action	• Repeated urinary tract infections
• Associated with caloric loss (weight loss)	• Genital infections
• Complement action with other OA*	• Decreased blood pressure
• Can be used regardless of diabetes duration	• Hypoglycemia (if insulin or sulfonylureas is taken)

OA: Oral agents

10.2.8.3 Doses, Associations, and Efficacy (Dapagliflozin, Canagliflozin, and Empagliflozin)

Doses

Dapagliflozin Initial: 5 mg once a day taking with or without food. May increase to 10 mg a day in patients tolerating 5 mg/day who have a GFR $\geq$60 ml/min/1.73 m^2 and require additional glycemic control.

Canagliflozin is a once-daily oral medication indicated for adults with type 2 diabetes mellitus to improve glucose control in conjunction with diet and exercise. The recommended starting dose is 100 mg daily taken 30 min prior to the first meal of the day. Doses can be increased to 300 mg orally per day in those individuals who need further glucose management. No adjustment of dosage is recommended in mild renal impairment (GFR >60 ml/min/1.73 m^2). The dosage of canagliflozin is limited to 100 mg per day in patients with a GFR of 45–60 ml/min/1.73 m^2 and is not recommended in severe renal impairment of <45 ml/min/m^2.

Empagliflozin 10 mg once a day taking with or without food may increase to 25 mg a day

Association: indicated as monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin.

Efficacy: reduction of HbA1c between 0.5 and 0.8 %.

10.2.8.4 Side Effects and Contraindications

Side effects: The adverse events were genital infections and benign urinary infections. Mild hypoglycemia is possible if taken with sulfonylureas or insulin. Lowering blood pressure was noted.

Contraindications: SGLT-2 were contraindications in patients with type 1 diabetes, in pregnant or breastfeeding women, and in patients under the age of 18 or over the age 75. Also if they were on pioglitazone or loop diuretics.

10.3 Conclusions

Fortunately, new guidelines for the treatment of type 2 diabetes changed quickly from 2006 to the newer ones, introducing the concept for a patient-centered approach, and the need to achieve composite goals as well. More **intensive approaches (HbA1c <6–6.5 %)** should be considered in pregnancy and in highly motivated, compliant young patients with adequate resources, low risk of hypoglycemia, short duration of the disease, long-life expectancy, and the absence of microvascular disease and CVD comorbidities (Inzucchi et al. 2012). On the other hand, **less intensive treatments (HbA1c >7.5–8 %)** should be offered to older patients, less motivated, non-compliant, with inadequate resources, high risk of hypoglycemia, long duration of the disease, shorter life expectancy, advanced microvascular complications and the presence of CVD, and multiple or severe coexisting conditions (Ismail-Beigi 2011) (Figs. 10.3 and 10.4).

We must tailor our therapeutic goals for each patient in the following way: first, determining the HbA1c target together with the other therapeutic targets (hypertension, lipids, weight, etc.); second, building a personalized treatment with combined goals (glycemic, blood pressure, lipids, and weight); and third, avoiding side effects (hypoglycemia, weight increase, etc.) and elevated costs (Litwak 2013).

Following this approach, the highly prevalent phenotype subgroup of obese T2DM should be treated, encouraging changes in their lifestyle, considering complementary drugs in order to achieve glycemic control, and inducing weight loss avoiding hypoglycemia. We can observe more convincing ways to treat **obese type 2 DM** patients. GLP-1 receptor agonists appear to be a very reasonable option, associated not only with metformin but also with TZD and even SUs, reducing HbA1c and weight or at least avoiding weight increase. DPP4-I remains as a neutral medication related with weight increase. GLP-1 receptor agonists should be a very attractive option before starting with basal insulin in obese T2DM and associated

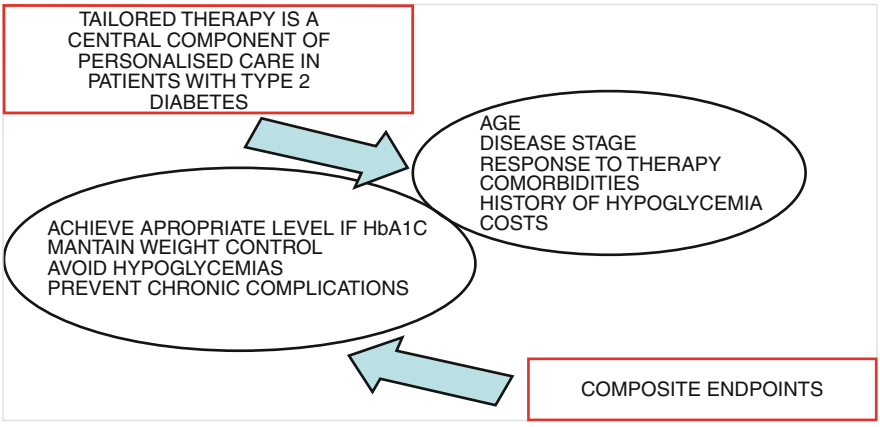

Fig. 10.3 Tailored therapy and composite end points

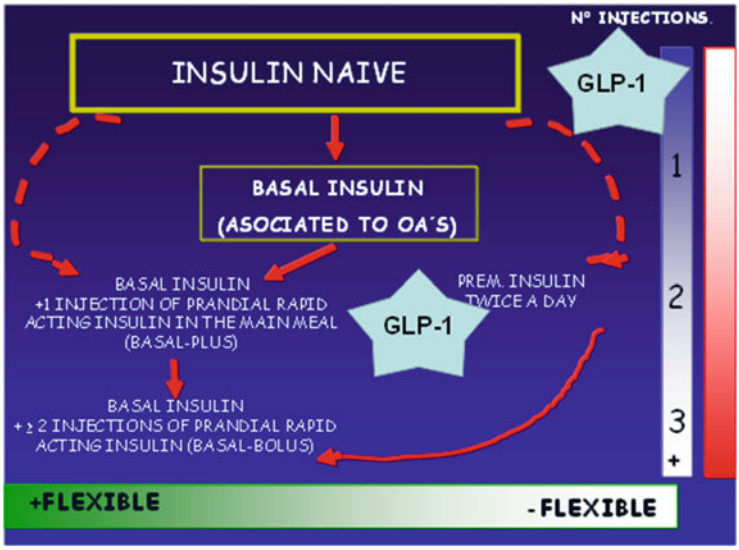

Fig. 10.4 ADA/EASD guidelines for insulin treatment. GLP-1: Glucagon-like peptide receptor agonists can be used in Obese Type 2 patients before starting basal insulin and in patients on basal insulin before starting with basal plus or basal bolus therapy

with basal insulin before starting with basal plus or basal bolus regimens (Tables 10.16 and 10.17).

The chance to better characterize diabetic patients, in the near future, by genetic information will probably allow us to know a very wide range of diabetic patient's subgroups. Nevertheless, one of the most frequent phenotypes is and will probably be the obese type 2 patient (Tuomi et al. 2014). Better pathophysiological approaches to these patients should be considered. There are clear indications to use in these patients metformin, DPP4 inhibitors, GLP-1 analogs/agonists, acarbose, and SGLT2 inhibitors as first-line drugs. "Incretin" therapy and the use of sodium-glucose co-transporter type 2 inhibitors, the latest drugs introduced for

Table 10.16 Risks of major antidiabetic agents

Side effect	Renal	Digestive	Heart failure	Cardiovascular	Bone
Metformin	Avoid renal failure	Moderate troubles	⇨	⇧	⇨
DPP4 inhibitors	Adjustment required	⇨	⇨	⇨	⇨
GLP-1 RAs	Exenatide	Moderate troubles	⇨	⇨	⇨
Thiazolidinediones	Fluid gain	⇨	Moderate troubles	⇨	Bone loss
Insulin	Hypoglycemia	⇨	⇨	?	⇨

Modified from

Table 10.17 Type 2 diabetes treatment guidelines

Drug	Efficacy	Hypoglycemia	Body weight	Side effects	Costs	Comments
Metformin (Met) (initial monotherapy)	⇧	⇩	⇨	Digestive symptoms, acidosis	⇩	After 3 months, two drugs may be needed
Metformin + Sulfonylurea	⇧	⇨	⇧	Hypoglycemia	⇩	[a]
Met + Thiazolidinedione	⇧	⇩	⇧	Edema/others	⇧	[a]
Met + DPP4 inhibitor	⇨	⇩	⇨	Uncommon	⇧	[a]
Met + GLP1 receptor agonist	⇧	⇩	⇩	Digestive	⇧	[a]
Met + insulin (basal)	⇧⇧	⇧⇧	⇧	Hypoglycemia	⇨	[a]

[a]If after another 3 months the 2-drug protocol does not meet HbA1c targets, a 3-drug option may be selected (Metformin + sulfonylurea, or metformin + thiazolidinedione, or metformin + DPP4 inhibitor, or metformin + GLP1 receptor agonist, or metformin + insulin, plus a third agent). In case within another 3–6 months the 3-drug approach fails, a multiple dose insulin strategy should be followed, plus 1–2 of the previous agents
Modified from the ADA/EASD, Inzucchi et al. (2012)

type 2 diabetes management, have a high impact on weight loss even when DPP-4 Inhibitors are neutral, making both groups eligible for obese diabetic patients. Early combinations together with changes in lifestyle would improve the outcome of this subgroup reaching combined goals like the decrease in HbA1c plus weight lost, avoiding hypoglycemia, and in many cases decreasing systolic blood pressure. Sulfonylureas, glinides, thiazolidinediones, and insulin will probably remain as a second choice.

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Chapter 11
Peripheral Signals and Food Intake Control

Hugo Mendieta Zerón and Julio César Téllez López

Abstract The food intake and satiety signals are regulated by a complex metabolic net that includes nervous system and several hormones. The metabolic signals derived in the periphery determines the food intake and energy expenditure. At the end of this route, eating signals are integrated at the Central Nervous System (CNS), being the arcuate nucleus a critical partner in this regulation. Central and peripheral hunger-satiety modulators are released to promote or inhibit food intake. Of the first group, ghrelin, mainly secreted by the oxyntic X/A cells of the stomach, exerts its effects through the growth hormone secretagogue receptor 1a (GHS-R1a), stimulating food intake. This hormone is the only known peripheral orexigenic peptide. Among the satiety signals, gut hormones such as cholecystokinin (CCK), glucose-dependent insulino-tropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) are secreted depending on the type of meal and the proportions of the macronutrients. Meanwhile, the enteric nervous system (ENS) controls most of the functions of the gastrointestinal tract. When the bolus enters the stomach and the small intestine, sensory stretch receptors are activated, which, through an action potential in the receiver, transmitted via the vagus nerve to the nucleus of the solitary tract, causes relay to the ventromedial nucleous (VMN) to generate the satiety response. Furthermore, one can identify immediate and log-lasting satiety signals. In this brief assay we show the principal mechanisms of the satiety signals, and some of them have more than one mechanism and/or time of action.

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11.1 Introduction

The central nervous system (CNS) integrates signals that promote or inhibit eating in order to maintain nutrient homeostasis. It is well known that metabolic signals derived in the periphery act in well-defined hypothalamic and brainstem neuronal circuits to control energy homeostasis. As such, the regulation of both food intake and energy expenditure is coordinated by peripheral signals that transmit information regarding nutritional and metabolic status of the individual that must reach the CNS neuronal circuits. The arcuate nucleus of the hypothalamus has become recognized as a critical center in this integrated circuitry. Although there is considerable anatomical evidence that the blood–brain barrier (BBB) protects the arcuate, neurons in this region have been repeatedly suggested to directly sense many circulating signals which do not readily diffuse across this barrier (Kohno and Yada 2012).

Central and peripheral hunger modulators are released in case of acute energy depletion, so as to promote food intake (Lowe and Butryn 2007). Ingested food, in turn, stimulates the release of central and peripheral satiety signals, inhibiting, at the same time, the secretion of hunger mediators (Murphy and Bloom 2006), restoring as immediate effect, the energy balance of the organism (Druce et al. 2004; Schwartz et al. 2000).

Obese patients experience less activation of higher brain centers in association with a meal. Altered satiety signaling primarily emanating from the gastrointestinal tract seems to lead to the development of obesity and type 2 diabetes (Hellström 2013). Even more, many gut hormones are directly involved in the regulation of islet hormone secretion and/or energy regulation (Irwin and Flatt 2013).

11.2 Hunger Signals

11.2.1 Ghrelin

Ghrelin is a peptidergic hormone of 28-amino acids, mainly secreted by oxyntic X/A cells of the stomach, the effects of which are exerted through the growth hormone secretagogue receptor 1a (GHS-R1a) (Kojima et al. 1999), mainly stimulating food intake (Romero-Pico et al. 2013). The secretion of this hormone increases during fasting and after food ingestion decreases until reaching basal levels, promoting and stopping eating, respectively.

Ghrelin is mainly expressed along with its receptor GHS-R1a in the hypothalamus, most abundantly in the arcuate nucleus (Olszewski et al. 2003). The central orexigenic effects of ghrelin are mediated by the neuropeptide Y (NPY) and agouti-related protein (AgRP) systems (Nogueiras et al. 2010). Recent studies have indicated a role for AMP-activated protein kinase (AMPK) as a mediator of ghrelin effects (Martínez de Morentin et al. 2014).

Ghrelin is the only known peripheral orexigenic peptide (Wren et al. 2001), and has been implicated in meal initiation (Cummings et al. 2002). Abnormal secretion of ghrelin has been associated with eating disorders (Monteleone et al. 2012). In addition to a central action, vagal afferents innervating the stomach express the ghrelin receptor indicating a possible peripheral mechanism (Le Roux et al. 2005).

11.3 Satiety Signals

11.3.1 General Overview

Gastrointestinal hormones modulate the glucose- and amino acids-induced secretions of insulin and glucagon, respectively. Serotonin (5HT) rise from the enterochromaffin cells during postprandial periods excites basal but inhibits excited β-cells. 5HT excites adrenal glands that release adrenaline (Ad) + dopamine (DA). Noradrenaline (NA) released from both sympathetic nerves and adrenal glands modulates the Ad release from the latter and excites α-cells. Dopamine released from adrenal glands and peripheral sympathetic nerves antagonizes Ad-induced hyperglycemia plus the NA-triggered glucagon secretion (Lechin et al. 2013).

After a meal, the time courses of gut hormone appearance in the bloodstream are broadly mirrored by the location of their respective secretory cell types along the gastrointestinal tract length. Thus, it is generally reported that as soon as nutrients enter the duodenum, the first hormones that appear in the bloodstream are cholecystokinin (CCK) and glucose-dependent insulinotropic polypeptide (GIP), whereas glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) release does not begin until the food has been shifted lower down the gastrointestinal tract (Pilichiewicz et al. 2007). This suggests the need for nutrients to make direct contact with individual enteroendocrine cells to trigger secretion. Yet, plasma GLP-1 and PYY levels can rise even before the jejunum contact to nutrients could be predicted.

The enteric nervous system (ENS) controls most of the functions of the digestive tract with a high degree of specialization and autonomy. Besides its sensory function, the vagus nerve is responsible for gastrointestinal secretory and motor activity. About 80–90 % of vagal fibers are afferent to the CNS, but these fibers are insufficient to provide a direct innervation of the large number of motor, sensory, and absorptive effectors, which are carried by the ENS (Feldman et al. 2014).

The ENS is organized in two plexes, the myenteric plexus located between the circular middle and the longitudinal outer layers, responsible for the generation of specific patterns of mobility, and the Meissner submucous plexus located between the circular middle and the mucosa layers, which coordinates the functions of secretion and absorption, blood flow, and muscularis mucosae contractility (Gil Hernández 2010). The ENS coordinates and transmits information from the sympathetic nervous system (SNS) and parasympathetic to the digestive tract.

The efferent fibers of the autonomic nervous system (ANS) carry information from the brain and spinal cord to the digestive tract, while afferent fibers transmit sensory information from chemoreceptors and interneurons that integrate the signals from the CNS and the ENS, to trigger the motor activity of gastrointestinal tract.

When the bolus enters the stomach and small intestine, sensory stretch receptors are activated, which generates an action potential in the receiver, which is then transmitted via the vagus nerve to the nucleus of the solitary tract, which in turn causes relay to the ventromedial nucleus (VMN) to generate the satiety response (González Hita et al. 2006).

11.3.2 Immediate Satiety Signals

The mechano-sensitivities and chemo-sensitivities of different vagal afferent neurons are now becoming clearer. The action of peptides released from enteroendocrine cells (EECs) may be local on vagal afferent fibers running close to their cell of origin or distal after delivery in the circulation. The nutrient status modulates these signaling mechanisms (Dockray 2013).

Generally, luminal chemicals influencing vagal afferent function do so by stimulating epithelial cells to release neurohumoral mediators, but glutamate, short-chain fatty acids, and bacterial products such as lipopolysaccharide (LPS) are able to cross or bypass the epithelium and act directly on afferent fibers (Steinert and Beglinger 2011). EECs secreting CCK, GLP-1, PYY, or 5HT act as specialized epithelial transducers of nutrient sensing in this system (Cluny et al. 2012).

Luminal glucose stimulates enterochromaffin (EC) cells that release 5HT, K-cells that release GIP, and L-cells that release GLP-1 and PYY. The principal mechanism of this action is the increment of pCaMKII; besides, there is also an activation of myenteric plexus and nodose ganglion neurons and of neurons in the nucleus tractus solitarius, the dorsal motor nucleus of the vagus, and the arcuate nucleus (Vincent et al. 2011). 5HT release from EC cells is a primary mediator of luminal glucose stimulation of intrinsic, afferent, and CNS neurons. In addition to the effects of luminal glucose on 5HT release from EC cells, evidence has also emerged that glucose influences the trafficking of 5HT3 receptors in vagal afferent neurons (Babic et al. 2012).

Cholecystokinin/CCK is typically known as a gut hormone secreted from the enteroendocrine I-cells in the small intestine in response to nutrient ingestion (Cummings and Overduin 2007), but it is also a neuropeptide localized at nerve terminals in the CNS and in the peripheral nervous system. The major physiological role of CCK is the regulation of energy balance through stimulation of short-term satiety, mediated through binding to CCK-1 receptors on vagal afferent neurons (Irwin et al. 2012; Dockray 2012). CCK also suppresses nutrient delivery to the small intestine by inhibition of food intake and gastric emptying. Moreover, CCK has also been shown to stimulate insulin secretion (O'Harte et al. 1998).

Recordings of different populations of vagal afferent and efferent nerve fibers serving the proximal and distal parts of the rat stomach and small intestine support the idea that CCK acts initially on intestinal afferent fibers, probably via a paracrine mechanism, to inhibit an excitatory vagal efferent pathway to the distal stomach; subsequently, there is stimulation of gastric vagal afferents, corresponding to a hormonal effect, that is coupled to stimulation of an inhibitory vagal efferent pathway to the proximal stomach (Okano-Matsumoto et al. 2011).

Vagal afferent neurons are a key target of CCK which stimulates expression in these neurons of cocaine- and amphetamine-regulated transcript protein (CARTp) and Y2 receptors and inhibits expression of melanin concentrating hormone and cannabinoid receptor-1 (CB1) receptors (Dockray 2012).

Food ingestion induces two peaks in GLP-1 secretion (Rask et al. 2001). The first even before nutrients can access the L-cells lower in the intestine, appearing within 15 min after meal initiation. Probably, this rapid response pertains to a neuroendocrine loop stimulated by the nutrient presence in the stomach or proximal intestine which leads to the release of GIP (Roberge and Brubaker 1993) and gastrin-releasing peptide (Reimer et al. 2001), which act through vagal pathways to stimulate L-cells to secrete GLP-1. The ENS may contribute to this early GLP-1 rise after a meal (Rocca and Brubaker 1999). The second phase is discussed below.

11.3.3 Long-lasting Satiety Signals

11.3.3.1 Cholecystokinin

Cholecystokinin (CCK) shares its active site and receptors with another gut hormone, namely gastrin (Rehfeld 2006). In the periphery, CCK primarily carries out its effects through the CCK receptor, showing a relative high affinity for the CCK receptor (CCK-A receptor) and a relative low affinity for the gastrin receptor (CCK-B receptor).

CCK stimulates gallbladder contraction and pancreatic enzyme secretion, and retards gastric emptying (Fried et al. 1991). Furthermore, the CCK receptor mediates the release of PYY and GLP-1, after lipid ingestion (Beglinger et al. 2010). Luminal fat and protein act on small intestinal I-cells to release CCK. Specifically, CCK is released by long-chain fatty acids and aromatic amino acids via GPR40 and calcium-sensing receptor (Dockray 2012).

11.3.3.2 Glucose-Dependent Insulinotropic Polypeptide

This incretin participates in the control of blood glucose levels in response to feeding by the augmentation of postprandial insulin secretion (Pederson and Brown 1976). Also, it has been demonstrated that the K-cell derived peptide

co-secreted with GIP, xenin-25, can significantly potentiate the insulinotropic action of GIP (Taylor et al. 2010).

The existence of a proximal–distal loop has been discussed in the scientific literature, without reaching a definitive conclusion. Also, a duodenum and distal gut hormonal link has also been proposed, with GIP being a potential candidate owing to its ability to stimulate GLP-1 release in rodents (Roberge and Brubaker 1993). However, in human subjects intravenous GIP infusion does not trigger GLP-1 secretion (Hansen and Holst 2002).

11.3.3.3 Glucagon-Like Peptide 1

GLP-1 is derived from the gene encoding proglucagon, which in the gastrointestinal tract and brain is post-translationally modified and cleaved into the biologically active forms, GLP-1 (7–36) amide (the major circulating bioactive species in humans) and GLP-1 (7–37) (Mojsov et al. 1986; Orskov et al. 1994).

GLP-1 has a second peak, larger than that controlled by the vagal pathways, and is thought to derive from direct nutrient contact with intestinal L-cells. Thus, direct hormonal and indirect neural mechanisms, both activated by nutrients within the gastrointestinal tract, have the ability to stimulate GLP-1.

This hormone has been identified as playing a prominent role in glucose homeostasis, gastrointestinal motility, and appetite (McIntyre et al. 2013; Umapathysivam et al. 2014). For example, gastric emptying is retarded by the acute administration of GLP-1 and its agonists, which explains the major mechanism underlying postprandial glycemic attenuation. However, after prolonged use, this effect is lost. Short-acting GLP-1 agonists may be superior to long-acting agonists when aiming specifically to reduce postprandial glycemic excursions in the treatment of type 2 diabetes (Umapathysivam et al. 2014).

Instillation of oil or protein hydrolysate into a spatially restricted segment of the mouse duodenum triggered GLP-1 release from a site distal to that exposed to nutrient, as demonstrated by selective blood sampling from different regions of the small intestine or by resection of the distal gut (Hira et al. 2009). Sectioning the vagus or applying pharmacological inhibitors suggested that the response depended on a neural loop, potentially involving gastrin-releasing peptide (Rocca and Brubaker 1999).

11.3.3.4 Insulin

Food ingestion stimulates insulin secretion not only via dietary macronutrient content (glucose, amino acids, and fatty acids), but also via incretin hormones like GIP and GLP-1 (Ghasemi et al. 2013). Overall secretion of insulin and insulin concentrations in systemic circulation are also proportional to body fat content. Insulin regulates the long-term feeding behavior and energy homeostasis (Havel 2001). Insulin entry across the BBB has been shown to be influenced by fasting,

food, refeeding, and composition of the diet (Strubbe et al. 1988; Kaiyala et al. 2000). Since insulin signaling in the brain limits food intake, insulin secretion over the long term functions as a negative feedback signal of recent energy intake and body adiposity (Morton et al. 2006).

11.3.3.5 Leptin

Leptin acting on its receptors (LepR aka ObRb) in the brain contributes significantly to the control of feeding (de Luca et al. 2005). After being released from the adipocytes, leptin is transported through the BBB to the CNS, where it activates, through other peptides, the autonomic nervous system; this effect results in a feeling of satiety. In the energy balance of the body leptin has a very important role by inhibiting the secretion of neurotransmitters, mostly neuropeptide Y (NPY), which is one of the strongest stimulators of the hunger center (and belongs therefore to orexigenic substances). Another action stimulated by leptin, which inhibits the appetite also, is the release of melanocyte stimulating hormone (MSH). Besides, leptin stimulates the cocaine- and amphetamine-regulated transcript (CART), hypothalamic neuropeptide with a characteristic anorexigenic action. Additionally, GLP-1 seems to play a role in the regulation of the metabolic effects of leptin.

A variety of factors such as corticosteroids, estrogens, insulin, and TNF-α potentiate the expression and secretion of leptin, while androgens, catecholamines, free fatty acids, growth hormone, and PPAR-γ agonists diminish them (Farooqi et al. 2007). These hormones as well as the concentration of ObRa and ObRe receptors' isoforms implicate leptin resistance and sensitivity (Munzberg 2010).

Leptin enhances butyrate uptake (Buyse et al. 2002), intestinal transport of fructose (Sakar et al. 2009) and oligopeptides (Buyse et al. 2002), and decreases galactose uptake (Barrenetxe et al. 2001) and glutamine transport. Glucose is the major end product of carbohydrate digestion, but it has not been dilucidated whether leptin can modulate glucose absorption.

11.3.3.6 Oxyntomodulin

Oxyntomodulin (OXM), processed from the same proglucagon product as GLP-1, is another intestinal L-cell-derived peptide secreted in response to feeding (Wren and Bloom 2007). It appears that the actions of OXM are mediated via binding to GLP-1 and glucagon receptors (Karra and Batterham 2010). Nonetheless, it appears that OXM induces catabolic effects that favor weight loss through activation of the glucagon receptor while modulating glucose homeostasis through agonism of the GLP-1 receptor. Moreover, administration of OXM inhibits food intake (Cohen et al. 2003) and causes weight loss (Wynne et al. 2005) in humans. However, OXM suffers an efficient enzymatic degradation (Druce et al. 2009).

11.3.3.7 Peptide-YY

Peptide YY (PYY) is a 36-amino acid peptide released by mucosal enteroendocrine L-cells (along with GLP-1 and OXM) in response to intraluminal nutrients (Adrian et al. 1985), with two main circulating forms, PYY(1–36) and PYY(3–36) (Grandt et al. 1994). All of the macronutrients stimulate the secretion of PYY (Pedersen-Bjergaard et al. 1996).

After secretion, PYY(1–36) is cleaved into the active form by DPP-IV (Mentlein et al. 1993) and acts specifically on Y2 receptors in the arcuate nucleus (ARC) and on vagal afferents expressing Y2 receptors (Koda et al. 2005), to suppress food intake. Circulating PYY is increased within 15 min following a meal and remains elevated for up to 6 h (Adrian et al. 1985), with a positive correlation between postprandial PYY levels and ratings of satiety in humans.

11.4 Type of Diet and Predominant Enteroendocrine Response

11.4.1 General Overview

It has been shown that solid foods have a stronger satiating effect than their liquid equivalent (Zhu et al. 2013). Thus, by modulating the consistency of the food one can modulate the glycemic response and satiety–hunger neuroendocrine signals.

In general, there is an agreement with the observation that postprandial insulin (Callahan et al. 2004), GLP-1 (Vilsboll et al. 2003a, b), PYY (Le Roux et al. 2006), and PP (Track et al. 1980) concentrations increase in proportion to meal size. Multivariate models have demonstrated that insulin, GLP-1, and PYY are sensitive to energy intake, whereas PP appears more sensitive to the mass of food consumed.

The combined effects of macro- and micronutrients on the peripheral signals that influence energy intake and appetite are undetermined (Berthoud 2004). Regardless, the observation that subjective appetite more closely approximated the total mass of food and water consumed rather than energy intake suggests that candidate gut hormone satiety signals should closely approximate the total mass of food and liquid consumed at a given meal.

Secretion of GLP-1, GIP, CCK, and PYY is triggered by the ingestion of carbohydrates, proteins, and lipids, with only relatively modest differences in nutrient responsiveness being reported between the I-, K-, and L-cells. GIP and GLP-1 release is particularly strongly stimulated by glucose and fat (Pilichiewicz et al. 2007), whereas CCK is released by fat and protein (Pilichiewicz et al. 2006).

11.4.2 Carbohydrates

Glucose is a robust trigger of GIP and GLP-1 release, but is less effective as a stimulus of CCK secretion in human subjects. In the experiments of Kuhre et al., fructose intake, in healthy humans, caused a rise in blood glucose and plasma insulin and GLP-1, although this rise is higher with isocaloric glucose. Remarkably, while glucose potently stimulated GIP release, fructose was without effect. Logically then, the pathways underlying fructose-stimulated GLP-1 release might be useful targets for type 2 diabetes mellitus and obesity drug development (Kuhre et al. 2014).

11.4.3 Lipids

Intestinal infusion of lipids results in slowed gastric emptying and transit time, the release of several gastrointestinal peptides including CCK, GLP-1, and PYY, and subsequent satiation. However, long-term intestinal adaptation to high-fat (HF) feeding leads to physiological alterations, which in turn can contribute to greater calorie intake compared to feeding an isocaloric diet but rich in carbohydrates (Paulino et al. 2008). Taken together, these results indicate that HF feeding in obese humans or in those prone to obesity can lead to overconsumption and excess weight gain through reductions in satiation signalings (Duca et al. 2013).

11.4.4 Proteins

Protein ingestion induces satiety and a high-protein (HP) diet heightens this feeling. Amino acid consumption is detected by multiple and redundant mechanisms originating from visceral (during digestion) and metabolic (inter-prandial period) sources, recorded both directly and indirectly (mainly vagus-mediated) by the CNS. Peripherally, the satiating effect of dietary proteins appears to be mediated by anorexigenic gut peptides, principally CCK, GLP-1, and PYY. In the CNS, HP diets trigger the activation of noradrenergic and adrenergic neurons in the nucleus of the solitary tract and melanocortin neurons in the arcuate nucleus.

Additionally, food intake might be modulated by the circulating levels of leucine. This amino acid is associated with neural mechanisms involving AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), energy sensors active in the control of energy intake, with an increasingly studied action in the hypothalamic arcuate nucleus. Likewise, HP diets inhibit the activation of GABAergic and opioid neurons in the nucleus accumbens, resulting in inhibition of food intake by reducing the hedonic response to food, explained partially because of their low palatability (Fromentin et al. 2012).

The effectiveness of protein as an enteroendocrine stimulus has been variously attributed to large and small peptides as well as amino acids, not only suggesting that luminal digestion may be important, but also that there may exist a range of sensors for protein products (Gribble 2012).

The supply of vital amino acids is tuned by adjusting food intake according to its dietary protein content. As has been probed in rats, oral L-arginine (Arg), L-lysine (Lys), and L-glutamic acid (Glu) induce reduction of food intake compared to all other 17 proteinogenic amino acids (Jordi et al. 2013). Other effects of those amino acids, mediated by the stimulus of neuronal activity in the area postrema and the nucleus of the solitary tract, are gastric secretion and/or emptying. Importantly, these peripheral mechanical vagal stimuli were dissociated from the amino acids' effect on food intake.

11.4.5 Fiber

A major determinant of energy density is dietary carbohydrate and specifically dietary fiber (Grunwald et al. 2001). In the recent years, fermentable dietary fibers have attracted more attention. Oligofructose is a non-digestible short-chain fructan derived from inulin and has recently been recognized as a dietary fiber (Cummings et al. 2009). Several studies have reported that oligofructose and an inulin/oligofructose mixture potently suppress food intake, reduce weight gain, and improve body composition in rodent models (Delmee et al. 2006). The appetite suppressing properties of oligofructose have been linked to an elevation of portal concentrations of PYY and GLP-1 and suppression of the orexigenic hormone, ghrelin (Cani et al. 2005).

11.5 Conclusions

Peripheral signals that participate in food intake control can produce their effect in a short immediate or late and long-lasting way. The conditions to have this behavior are a healthy ENS and an efficient gastrointestinal tract. The predominant effect will be the result of the different nervous and hormonal signals stimulated by the hunger state and the type of diet. Determining the most powerful factor in each case (hunger–satiety) will contribute to elucidate the best alternatives to drug designs and eating conduct interventions, in order to keep a metabolic homeostasis.

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Chapter 12
Appetite: Inhibiting Properties of Proteins

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Abstract Diets rich in proteins promote long-term body weight loss by increasing satiation with a greater effect than carbohydrates and fats. L-glutamate that imparts umami or savory taste is thought to be a signal for protein consumption and may promote the satiating effect of proteins. The ingestion of proteins results in the release of anorexigenic gut neuropeptides such as cholecystokinin, glucagon peptide 1, and peptide YY that transmit satiety signals to the brain steam via vagal afferent pathways. Gut neuropeptides come from enteroendocrine cells disseminated throughout the alimentary canal. They express chemosensing receptors in the apical membrane that can detect the presence of peptone and single amino acids in the luminal content. High-protein diets convey stronger AA-satiating signals to the brainstem and arcuate nucleus. They also reduce hedonic responses in the reward system. This chapter reviews the gustatory perception of single amino acids in the mouth and their distribution of AA sensors in the gastrointestinal tract including a short overview on their contribution in the integration of protein-satiety signals in the brain.

Abbreviations

5-HT	Serotonin
AAs	Amino acids
AMP-APK	AMP-activated protein kinase signaling
ARC	Arcuate nucleus
BW	Body weight
CaSR	Extracellular calcium-sensing receptor
CCK	Cholecystokinin
DAAs	Dispensable amino acids
DEE	Diet-induced energy expenditure

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EC	Enterochromaffin cells
FFM	Fat free mass
GCN2	General control non-repressed 2
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GMP	Guanosine-5′-monophosphate
GPCR	G-protein-coupled receptor
GPR92	G-protein-coupled receptor 92
GPRC6A	GPCR family C subtype 6A
IAAs	Indispensable amino acids
IMP	Inosine-5′-monophosphate
mGluRs	Metabotropic glutamate receptors
MSG	Monosodium glutamate
mTOR	Mammalian target of rapamycin
NPY	Neuropeptide Y
NST	Nucleus of the solitary tract
POMC	Peptide pro-opiomelanocortin
PYY	Peptide YY
T1Rs	Taste receptor type 1
TRCs	Taste receptor cells

12.1 Introduction

The most effective dietary strategy to lose body weight (BW) in obesity is to attain negative energy balance by energy restriction. But energy restricted regimens promote the desire to eat and reduce the feeling of fullness, which is a risk of overconsumption and regaining of the lost BW (Martens et al. 2013; Soenen et al. 2013). The long-term maintenance of BW after weight loss implicates to maintain both continuous satiety and a sufficient level of basal energy expenditure allowing energy balance (Westerterp-Plantenga et al. 2009, 2012). For this purpose, much work has been dedicated in studying the impact of micro- and macronutrients composition on feeding behavior and energy metabolism, and dietary proteins were more particularly studied. Cumulative evidence substantiates that high-protein meals promote BW loss and that diets with a high content of protein support a greater BW loss and BW maintenance in ad libitum than a low content of protein (Weigle et al. 2005). Protein is an indispensable component of the diet with a mean requirement of 0.66 g/kg of BW/day as derived from nitrogen balance studies (WHO/FAO/UNU 2007; Rand et al. 2003). Protein supply conserves nitrogen balance and is a source of amino acids (AAs) which are precursors for body protein synthesis and also have unique metabolic properties as a result of their involvement in energy nutrient metabolism (Martens and Westerterp-Plantenga 2014; Azzout-Marniche et al. 2014; Tomé 2004; Westerterp-Plantenga et al. 2006; Veldhorst et al. 2012). AAs are the building blocks of proteins, substrates for the Krebs cycle

and the synthesis of many active nitrogenous compounds such as nucleic acids, NO, glutathione, polyamines, taurine, and numerous neurotransmitters, and precursors of gluconeogenesis. When not bound to proteins, AAs impart taste by themselves and are involved in cell signaling (Kawai et al. 2012; Wu 2013; Tomé et al. 2009) by binding to taste G-protein-coupled receptors (GPCRs) that function as nutrient sensors in the gastrointestinal (GI) tract (Depoortere 2014; Steinert and Beglinger 2011; Tomé et al. 2009). The chemical signals that single AAs convey can control GI functions, food intake, and metabolism. If satiety refers to the processes that regulate the interval between meals and satiation to the ones that lead to the cessation of a meal, it seems that high-protein diets are satiating and individuals eat less of the relatively high-protein diets when given the option to eat as much as they want (Weigle et al. 2005). In fact, the satiating hierarchy of the three macronutrients seems to follow the same priority in which the body metabolizes them, proteins, carbohydrates, and fats, with proteins being the most gratifying and fats the least satisfying (Keller 2011; Westerterp-Plantenga et al. 2009; Veldhorst et al. 2008). This chapter will review the latest understanding in protein intake detection mechanisms through the ability of free AAs for generating oral (gustation) and post-oral (chemosensing) signals along the alimentary canal that seem to suppress feeding through humoral and vagus nerve pathways. There are potentially three mechanisms that may control food intake: (1) peripheral AA sensing, (2) post-ingestive effects, and (3) brain satiety networks. These three mechanisms may have different relevance temporarily in regulating overall food intake. We will focus on chemical sensing of AAs in gustatory and gastrointestinal system and its effect on brain satiety circuits.

12.2 Metabolic Effects of High-Protein Diets and Specific Appetite for Protein

The synthesis of proteins and other nitrogenous molecules are necessary for sustaining life. The main function of dietary protein is to provide nitrogen and indispensable amino acids to maintain the body protein pool and FFM by stimulating protein synthesis and inhibiting protein breakdown. Proteins are a source of essential amino acids, which are of critical significance to preserve homeostasis (Wu 2013). Nine of the twenty AAs have a carbon skeleton that cannot be synthesized de novo in animal tissues and they are usually limited in low-quality plant protein diets. These amino acids are traditionally considered nutritionally essential and have been classified as indispensable (IAAs), while AAs that can be produced de novo in animal cells are thought to be nonessential nutritionally and therefore dispensable (DAAs). Different dietary sources of protein vary on protein content, AA composition, protein digestibility, protein digestion rate, and the ability to induce protein synthesis and therefore different proteins may have diverse effects on body composition. Animal proteins are usually considered to have higher

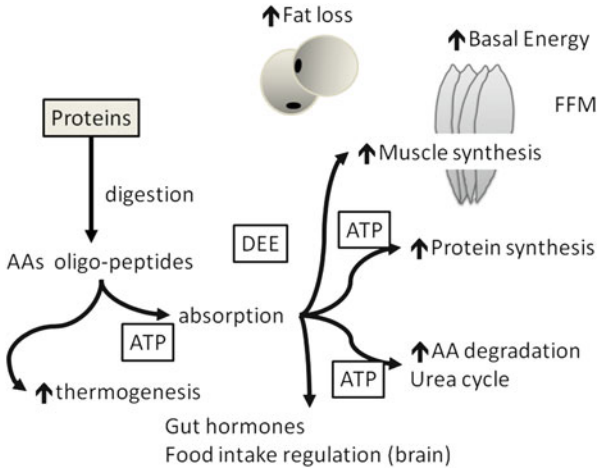

Fig. 12.1 Effect of dietary proteins on metabolism. The digestion, absorption, and metabolism of proteins cause high-energy expenditure in the form of thermogenesis and ATP utilization, either for the synthesis of new proteins or for the degradation of AA via the urea cycle. Proteins also help maintain a high basal metabolic rate by supporting muscle mass while increasing the loss of fat storage under negative energy balance. Finally, the signaling of protein intake through regulatory gut hormones controls food intake and the sensation of satiety. *FFA* fat free mass

content in indispensable amino acid and higher bioavailability and are considered to have a higher quality to support protein requirement (Tomé 2012, 2013).

Proteins are also believed to have higher diet-induced energy expenditure than carbohydrates or fat, DEE being the energy spent after a meal for the absorption and initial metabolic steps of nutrients (Westerterp-Plantenga et al. 2009). Either protein or urea synthesis requires energy in the form of ATP (Bendtsen et al. 2013; Gilbert et al. 2011) (Fig. 12.1). High-protein diets also induce the expression of the uncoupling protein (UCI-1) in brown adipose tissue of mice, which is a main regulator of energy expenditure in rodents (Ropelle et al. 2008). However, it is not clear whether the effect of proteins on energy balance is common to all proteins or diverges depending on the type of protein (Bendtsen et al. 2013; Gilbert et al. 2011).

Protein and particularly IAA deficiency is not compatible with survival and protein intake is tightly controlled. Protein consumption in animals and humans appears to be more tightly controlled than the intake of carbohydrates and fats (Griffioen-Roose et al. 2012). Spontaneously, animals select diets having significantly high amount of protein with a proportionate IAA profile and when given a choice among the three macronutrients they often prefer a diet with relatively high-protein content (40 % energy as protein) (Tomé 2004; Gietzen and Rogers 2006). In contrast, animals avoid single IAA-deficient diets (Koehnle et al. 2003), diets with a very low protein (<6 % of energy as protein) to avoid adverse effects from IAA imbalance, although they tend to ingest more of diets that are reasonably below the requirement (5–8 % of energy from protein) compared to regular diets with

10–15 % protein as energy. Higher intake from moderately low-protein diets appears to compensate for the supply of required nitrogen and IAAs and cover protein needs, and food choice is more likely involved in the capacity to reach protein sufficiency (Griffioen-Roose et al. 2014). This could however partly explain the need to consume less of diets with higher protein content as in this case protein control is no more involved in the control of food intake that is only driven by the sensing of energy sufficiency.

12.3 Peripheral Oral and Post-Oral AA Sensing

Foods contain a certain amount of proteins, peptides, and AAs that interact with taste receptors on the tongue. The same GPCRs are found in the alimentary canal (Finger and Kinnamon 2011). The taste of most L-AAs is either sweet (DAAs) or bitter (IAAs), with the exception of glutamic acid and aspartic acid that are sour in the acidic or umami in the ionic form at lower pH (Bassoli et al. 2014; Kawai et al. 2012). Although single AAs are not the most abundant food constituents and vary according to food preparation, they provide complex taste qualities that can modify the flavor of foods. Fermentation, aging, or maturation of foods increases the digestibility of proteins by releasing protein-bound AAs. Soups are also rich in single AAs coming from the extraction of AAs of meats and vegetables (Ninomiya et al. 2010). Humans have an innate attraction for sweet and savory tastes, but flavor preference, which also involves aroma and texture together with taste, is learned as a Pavlovian conditioning response from the post-oral nutritional consequence of food (Sclafani and Ackroff 2012; Teff 2011). A stronger AA taste stimulus may reinforce the satiating feeling of proteins. However, the sensory traits for protein intake regulation are not well understood yet. It has been hypothesized that savory or umami taste, the taste for L-glutamate, acts as a signal for AA ingestion (Griffioen-Roose et al. 2014; Sclafani and Ackroff 2012). The nutritional status (long-term protein intake) may influence the development of specific appetites. A recent study (Griffioen-Roose et al. 2014) found that individuals with a low-protein nutritional status had a higher liking for savory foods than those with a high-protein status. Thus, taste preference and brain reward responses may change with protein status to ensure proper ingestion and restore the body nutritional condition.

Oral and post-oral detection of umami taste involves the GPCR taste receptor type 1 (the heterodimer T1R1/T1R3) (Finger and Kinnamon 2011). L-glutamate is the main agonist for the human T1R1/T1R3, whereas 5′-ribonucleotides such as inosine-5′-monophosphate (IMP) and guanosine-5′-monophosphate (GMP) that enhance umami taste sensitivity function as allosteric modulators (Zhang et al. 2008). This mechanism is known as umami taste synergism. Other receptors also suggested as candidates for umami taste are the splice variants of metabotropic glutamate receptors mGluR4 and mGluR1 (Bachmanov et al. 2014; San Gabriel et al. 2009a) (Table 12.1). Additional GPCRs that are part of the AA signaling pathway are the extracellular calcium-sensing receptor (CaSR), the GPCR family C subtype 6A (GPRC6A), and the G-protein-coupled receptor 92 (GPR92)

Table 12.1 Distribution of AA taste receptors in the oral cavity and the stomach with their predominant functions

Tissue	Cell type	AA receptor GPCRs	Stimulant	Function
Taste buds				
Oral cavity	TRCs	T1R1/T1R3	L-Glutamate	Umami
			L-Aspartate	
			IMP, GMP	
		CaSR	Glutathione	Taste modifier
			Gamma-glutamyl	
			peptides	
		GPRC6A	L-Alanine	Unknown
			L-Arginine, Glycine	
			L-Lysine, L-Serine	
			L-Methionine	
		T1R2/T1R3	Glycine	Sweet
		T2Rs	L-Tryptophan	Bitter
			L-Phenylalanine	
		mGluRs	L-Glutamate	Umami
		GPR92	Peptides	Umami (?)
Stomach	Parietal	CaSR	L-histidine	↑Acid
			L-Phenylalanine	Secretion
			L-Tryptophan	Pepsinogen activation
		mGluRs	L-Glutamate	
	Chief cells	mGluR1	L-Glutamate	↑ Pepsinogen protein digestion
	EC	? (indirectly)	L-Glutamate	5-HT release
	G cells	CasR	As parietal cells	↑Gastrin
		GPR6A	As in taste	
		GPR92	Peptone	
	P/D1 cells	T1R3	L-Glutamate (?)	↓Ghrelin
	D cells	CaSR	As parietal cells	Somatostatin release
		GPRC6A	As taste cells	
		mGluRs	L-Glutamate	

TRC taste receptor cells, gastric secretion of acid by parietal cells increases with the hormone gastrin, chief cells produce pepsinogen to digest proteins, G-cells release gastrin, and D-cells release somatostatin. ECs are enterochromaffin cells that secrete serotonin (5-HT) and activate vagal afferents

(Depoortere 2014; Haid et al. 2013; San Gabriel et al. 2009b). GPR92 binds to protein hydrolysates (peptone) and it is suggested to participate in umami taste perception as well (Haid et al. 2013).

In the stomach where protein digestion starts, single AAs can regulate gastric secretion by modulating gastrin and somatostatin release (Haid et al. 2011). L-glutamate also potentiates gastric secretion via the vagus nerve after binding to glutamate receptors (T1R1/T1R3 and mGluRs) located in gastric glands (Khropycheva et al. 2011; Nakamura et al. 2011; San Gabriel et al. 2007; Uneyama et al. 2006). As a result, single AAs from the diet not only add flavor but may also increase protein digestion efficiency. Proteins are also able to suppress the release of ghrelin, the only GI hormone known to increase appetite (Foster-Schubert et al. 2008). Ghrelin-producing cells from murine stomach have no contact with the liminal content, but show T1R3 immunoreactivity (Hass et al. 2010). Circulatory AAs may suppress ghrelin release through T1R3 after absorption. To our knowledge, this has not been confirmed in humans.

These AA and oligopeptide receptors of the alimentary canal initiate the signals for the satiation mechanism.

12.4 Intestinal AA Sensing Signals Satiety in the Brain

The sensing of AAs in the intestine takes place in enteroendocrine cells (Fig. 12.2). The binding of single AAs or oligopeptides with their corresponding receptor triggers the release of regulatory gut hormones such as gastrin, somatostatin, serotonin (5-hydroxytryptamine, 5-HT) (enterochromaffin cells, EC), and ghrelin from stomach (Table 12.1), cholecystokinin (CCK) from duodenum (I-cells), and glucagon-like peptide 1 (GLP-1) and peptide tyrosine-tyrosine (PYY) from ileum and colon (L-cells) (Moran and Dailey 2011) (Table 12.2). These regulatory peptides act mainly locally on receptors at the end of nearby vagal afferents where they are found in higher concentration, but gut peptides can also function in an endocrine way through systemic circulation. Proteins are particularly effective in inducing CCK release and GLP-1 in humans. Protein hydrolysates appear to stimulate enteroendocrine function more potently than single AAs (Rasoamanana et al. 2012). Moreover, the umami seasoning monosodium L-glutamate (MSG) may be involved in the release of GLP-2 (Bauchart-Thevret et al. 2013; Wang et al. 2011). It is proposed that MSG enhances protein satiety acting as a signal for the satiating properties of protein (Masic and Yeomans 2014a, b; Ventura et al. 2012). In a protein-rich context MSG may enhance the effects of proteins.

Gut peptides are key elements in the transmission of the protein-induced signals of satiety to the nucleus of the solitary tract (NST) in the brainstem through the vagus nerve. The afferent vagal afferents send projections to the lamina propria underneath the lining of the GI track. At the end of these projections there are receptors for 5-HT, CCK, GLP-1, and PYY (Rasoamanana et al. 2012; Steinert and Beglinger 2011). The vagal afferents from the stomach mostly detect stretch

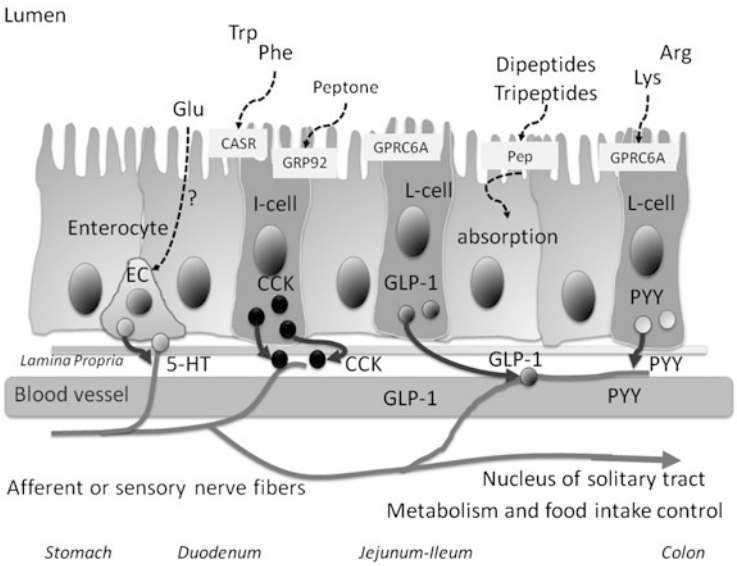

Fig. 12.2 Graphic overview of a section of the intestine with the expression of receptors that can sense the presence of AAs and oligopeptides in the luminal content. I- and L-cells represent the various types of endocrine cells that respond to luminal AAs with the release of gut hormones. *EC* Enterochromaffin cells, *Pep* peptide transporter, *CaSR* calcium-sensing receptor, *GPRC6A* G-protein-coupled receptor family C group 6 member A, *CCK* cholecystokinin, *GLP1* glucagon-like peptide-1, *PYY* peptide YY

Table 12.2 Distribution of AA taste receptors in the intestine and their digestive functions

Intestine	Cell type	AA receptor GPCRs	Stimulant	Function
Duodenum	I cell	CaSR	Aromatic AAs	CCK release (satiation motility)
		T1R1/T1R3	L-Glutamate	
			IMP, GMP	
		GPR92	Peptone	
Jejunum Ileum Colon	L cell	GRPC6A	Basic AAs	GLP-1
			Neutral AAs	GLP-2
				PYY (Satiation motility)
Jejunum Ileum	K cell	Unknown	AAs	GIP

I-, L-, and K-cells are enteroendocrine cells or specialized chemosensory cells dispersed along the epithelial lining of the intestine. I- and L-cells express AA taste receptors, are on direct contact with the intestinal content, and secrete satiating gut peptides like CCK, GLP-1, and PYY. Adapted from Nakamura et al. (2011) and Depoortere (2014)

depending of meal volume, but also seem to be selective for certain nutrients such as L-glutamate and IMP (San Gabriel and Uneyama 2013; Uneyama et al. 2006). Other AAs, glucose, or isotonic saline solutions do not have the ability to trigger vagal afferents from the gastric lumen. In the stomach, glutamate vagal stimulus seems to be mediated by the secretion of 5-HT and nitric oxide. The inhibition of either 5-HT or nitric oxide blocks the effect of luminal glutamate. However, vagal afferents in the intestine (celiac nerve) respond to all AAs as well as oligopeptides. Therefore, vagus nerve pathway transfers nutrient information to the brain as the main mechanism of gut–brain signaling by regulatory gut peptides. Dietary proteins may increase the NST sensitivity to CCK resulting in greater CCK-induced satiety and lower food intake (Journel et al. 2012). GI regulatory peptides can also act as hormones through the systemic circulation by reaching the arcuate nucleus (ARC) of the hypothalamus that is sensitive to protein intake and controls feeding.

The apical membrane of intestinal cells expresses diverse AA, di-, and tri-peptide transport systems able to concentrate AA inside enterocytes. High AA absorption after a high-protein meal activates mammalian target of rapamycin (mTOR) and inhibits general control non-repressed 2 (GCN2) and AMP-activated protein kinase signaling (AMP-APK) (Rasoamanana et al. 2012). mTOR triggers genes related with cell growth, whereas GCN2 and AMP-APK are markers for AA and energy deficiency. Branched chain AA and especially L-leucine are potent stimulus for mTOR.

ARC in the hypothalamus plays a key role in the integration of energy and food intake homeostasis. By balancing two parallel circuits, anabolic neurons (neuropeptide Y, NPY; and agouti-related protein neurons) and catabolic neurons (neurons producing peptide pro-opiomelanocortin, POMC), ARC conveys satiety signals to other centers of the brain (Journel et al. 2012). High-protein intake also upregulates the satiety network that leads to the secretion of the anorectic hormone PYY. AMP-APK and mTOR signaling have been found to be associated also to energy balance or intracellular AMP:ATP ratio in neurons from ARC. A high AMP:ATP ratio in the hypothalamus leads to an upregulation of AMP-APK and higher food intake, while a low ratio induces overexpression of mTOR resulting in a decline of food intake and BW loss (Cota et al. 2006). With protein intake, ATP increases in the hypothalamus, which leads to inhibition of the AMP-APK and activation of mTOR signaling. Since L-leucine is a key AA for mTOR pathway activation in the hypothalamus, this AA seems to play a key role in the satiety effect of high-protein diets (Ropelle et al. 2008). L-Leucine is able to suppress AMP-APK activation and NPY release, and increase POMC mRNA.

12.5 Reward System Modulation by Protein Intake

Journel and colleagues have recently reviewed the effect of dietary proteins on the reward pathway (2012). The mesolimbic reward system controls ingestive behavior independently from homeostatic mechanisms. The stimulation of the reward center

causes pleasure and enhances motivation for food. There are several factors that influence this network such as food flavor (taste, smell, texture, etc.) and energy and protein content. A high-protein meal appears to diminish the responses in the limbic system to food motivation and reward (Journel et al. 2012). Magnetic resonance technology has shown that the activity of the paraventricular nucleus and lateral hypothalamus diminishes in rats adapted to a high-protein diet. In rats, protein satiety gives a characteristic low signal in the amygdala, which is the part of the limbic system that combines memory with emotions and the sensory stimuli of food. The reward-driven eating behavior is reduced by high-protein diets. Neurotransmitters such as dopamine in the ventral tegmental area together with γ-aminobutyric acid in the nucleus accumbens as well as serotoninergic pathways are involved in the reward system. It is hypothesized that the accessibility of the precursors for serotonin and dopamine, the IAA tryptophan, tyrosine, and phenylalanine, which need to be provided by the diet, may control the concentration of these neurotransmitters in the reward system. High-protein ingestion leads to more available tryptophan, which may facilitate the synthesis of 5-HT in the brain. Certain proteins may have a greater effect on inducing 5-HT that is a key neurotransmitter in stress, mood, and feeding behavior. Tyrosine and phenylalanine concentration can affect the synthesis and release of dopamine as precursors of this neurotransmitter (Choi et al. 2011).

12.6 Conclusion

The loss of BW and its maintenance requires constant satiety, energy expenditure, and conservation of FFM while individuals continue in negative energy balance. Dietary proteins seem to bring greater BW and fat mass loss than dietary carbohydrates or fats under energy restriction (Krieger et al. 2006). Throughout food experience during lifetime, people learn to associate the sensory qualities or flavor-taste stimuli of foods with their post-oral outcome. In fact, food perception induces learned physiological conditioned responses in anticipation of ingestion, and this participates in a more efficient homeostasis. Traditionally, people are learned to prepare rich protein foods by culinary processes such as fermentation, aging, maturation, or boiling. These processes not only enhance the digestibility of proteins but also provide peptides and single AAs, which convey a rich combination of taste and aromas and complex and unique flavors. It is possible that a stronger flavor perception helps to establish stronger post-oral responses. Although there is no direct evidence to back up this hypothesis, recent studies seem to suggest that umami taste may be able to potentiate the satiating effect of proteins.

In the stomach and the intestine, di-, tripeptides, and single AAs convey satiety and metabolic signals to the NST via the activation of vagal afferents after the release of gut peptides, 5-HT, GLP-1, CCK, and PYY. AAs and peptides also regulate directly energy homeostasis through the modulation of mTOR, AMP-APK, and GCN2 in peripheral tissues and in the brain, ARC. At the end,

the hedonic or reward pathway in the brain that responds to the initial flavor stimuli together with the caloric contribution of the diet gets integrated with the hormonal homeostatic control and ingestive behavior. Although the integration of those pathways is not well understood yet, thanks to the progress in the past 14 years on the discovery of gustatory receptors we are learning in more detail the interaction of AAs with specific receptors in neuroendocrine cells of the GI tract and their physiological effect. For AAs the activation of the intestinal branch of the vagus nerve seems to be of most relevance to signal the satiating properties of proteins to the NST. But the activation of the gastric branch of the vagus nerve by glutamate deserves more research. AA absorption is also essential to convey energy and protein status. More studies on the link between the sensory properties of proteins and their satiating effect may help to support more efficiently BW management and control during dietary intervention.

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Chapter 13
Cell Therapy for Diabetes

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Abstract Diabetes mainly occurs in two forms, type I (juvenile diabetes) and type II (adult onset diabetes). Type II diabetes has been taking an epidemic toll on present day developing and developed countries. The reason is primarily attributed to high fat diet and sedentary lifestyle, both leading to obesity and insulin resistance. Also, diabetes is associated with various comorbidities, namely cardiovascular diseases, kidney failure, and retinopathy, that compromise the quality of life of an individual. Classical methods to treat diabetes using insulin injections, with or without oral administration of metformin and sulfonylurea groups of drugs, are met with limited success in mitigating the severity of the disease. Moreover, regular administration of insulin via subcutaneous route is cumbersome to the patient. Hence, cell therapies are a greatly sought-after alternative, which will fetch a permanent solution to cure diabetes. Islet transplantation has achieved limited amount of success, due to the shortage of the cadaveric pancreas. So, the proposed cell therapy alternative is based on functional β islet cells, derived from human pluripotent, mesenchymal, and adipose tissue-derived stem cells. Efficient protocols for in vitro differentiation of all kinds of stem cells, to obtain large quantities of functional β islet cells for transplantation, will provide and answer to address the global rise in diabetic cases. Also, clinical feasibilities and relative advantages of cell-based therapy for

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diabetes, over other interventions, will remain a major area of research in the near future, till successfully translated as a standard treatment for diabetic patients.

13.1 Introduction

Advancement of therapies is required to address the severity of any disease, till it is adequately controlled or eliminated from the human civilization. Mostly, in case of various metabolic diseases like diabetes and neurodegenerative disease, the limitations of drugs lie in only reducing the severity, and not in complete elimination of the disease. Hence, in order to circumvent such limitations, the concept of cell therapy/regenerative medicine was introduced in the field of biomedical science. Regenerative medicine is translational research and therapy encompassing stem cells, tissue engineering, and molecular biology. The precise concept deals with the replacement of the damaged or degenerated tissue/organs, with healthier tissues or organs, which would be able to restore the normal functioning of the organ.

A relatively new term "regenerative medicine" came into existence just a few years ago, and is attributed to William Heseltine (founder of Human Genome Sciences company) (Viola et al. 2003). However, it was referred in 1992 in an article on hospital administration, written by Leland Kaiser. One of the concluding paragraphs stated, "A new branch of medicine will develop, that attempts to change the course of chronic disease, and in many instances will regenerate tired and failing organ systems" (Kaiser 1992; Lysaght et al. 2008). In current times, cell therapy/regenerative medicine refer to a group of biomedical approaches to clinical therapies that may involve the use of stem cells (Riazi et al. 2009).

Apligraf®, an allogenic tissue engineered product, received its first US FDA approval in 1998. The autologous cell therapy product named Epicel®, originated from Green's laboratory, first unregulated by the FDA, was treated as a tissue graft. Both Apligraf® and Epicel® were used for the treatment of burns.

Besides, extensive research is ongoing to deliver cell therapy products for clinical trials in the areas of metabolic, inflammatory diseases and cancer. Furthermore, here is the list of some of the FDA approved cell therapy products into clinical trials: autologous cell therapy sources using bone marrow cells for treating long bone fractures and diabetic limb ischemia and cultured autologous skeletal muscle myoblasts for treating myocardial infarction and congestive heart failure. Allogeneic cell therapy sources involve fibroblasts for treating diabetic ulcers, cultured keratinocytes for treating burns, and microencapsulated islet cells for treating type I diabetes. Most importantly, autologous stem and non-stem cell-based therapies are worldwide rapidly growing therapeutic platforms, in the arena of regenerative medicine.

Autologous cell therapies are safer, as compared to allogenic and xeno transplants, and pose reduced risks associated with bio-incompatibility, immunological reactions, and disease transmission. Considerable success has been achieved in allogeneic cell therapies for treating prostate cancer, skin burns, wound healing, cosmetic surgeries, and pressure ulcers. Furthermore, autologous cell therapy-based treatments, for various incurable diseases like myocardial infarction, ischemic heart

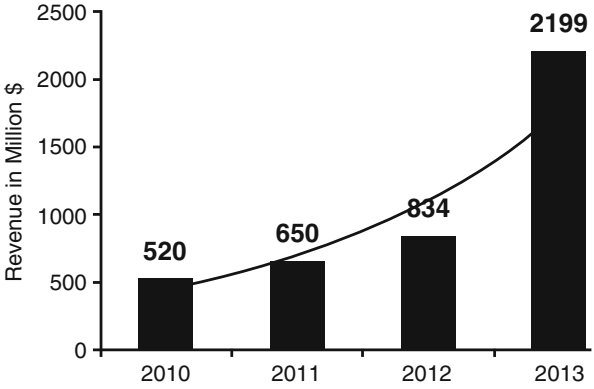

Fig. 13.1 Estimated market for autologous cell therapy (http://www.marketsandmarkets.com/PressReleases/stem-cells-market.asp)

failure, and diabetes, are rapidly emerging in North America. The market for autologous cell therapy products is estimated to show a steep rise, as depicted in the graph (Fig. 13.1).

Despite a humongous need for cell therapy for diabetes, only a small portion has been addressed, in terms of a consistent replenishment of damaged β cells. However, all the research work that have been carried out, till date, indicate relatively long-term graft survival rates, when compared to whole pancreas transplantation (Robertson et al. 2000). Long survival of the islet transplant graft is attributed to the better engraftment and immune response, as compared to whole pancreas transplantation.

Goals for obtaining an inexhaustible supply of functional β islet cells are achieved with varying degrees of success. Differentiation of human pluripotent (embryonic and induced pluripotent) cells, of respectively embryonic and adult origin, toward β cell lineage and direct reprogramming of the non-endocrine pancreatic cells, into functional insulin-producing cells, are the steps taken. Other cell types like conditioned lymphocytes, mononuclear cells, or a combination of cell types including hematopoietic, pluripotent, and multipotent ones are reportedly safe and feasible cell therapy options for diabetes (Jarajapu and Grant 2010).

Mesenchymal stem cells (MSCs), due to their property to secrete trophic factors, upon combination with other cell types, differentiated into functional β cells, and have thus provided added efficacy to cell therapy for diabetes (Jafarian et al. 2014).

13.2 Classical and Novel Approaches: Surgical and Non-surgical Approaches to Treat Diabetes and Respective Underlying Pathophysiology

With the worldwide epidemic of obesity, there has been epidemic of type II diabetes, which affects more than 370 million people globally (International Diabetes Federation Update 2012). Hence, treating insulin resistance is a major approach to control the epidemic of type II diabetes.

In order to maintain homeostasis, under insulin resistance conditions, β-cells initially increase the insulin output, thereby maintaining normal glucose tolerance. However, with further increase in insulin resistance, as in the case of obesity, the increased insulin output by the β-cells becomes insufficient to maintain normoglycemic conditions. Insufficient insulin production, under insulin resistance conditions, is often referred as β-cell dysfunction. β-cell dysfunction has a genetic as well as environmental component. The environmental component, in terms of diet and obesity, is playing havoc in causing type II diabetes. Research results have established an important correlation between hexoses and other carbohydrates, amino and fatty acids, insulin resistance, and β-cell dysfunction in modern times (LeRoith 2002).

Dietary imbalances in carbohydrates and fatty and amino acids have been proved to govern insulin resistance and β-cell dysfunction. Increased intakes of saturated dietary fat contribute to the development of obesity, insulin resistance, β-cell dysfunction, and glucose intolerance (Hu et al. 2001). Accordingly, modern strategies are being developed to maintain an optimum balance between the factors that govern β-cell dysfunction. Slowing down the β-cell dysfunction is one of the important strategies (Weir and Bonner-Weir 2004). Another one is to control type II diabetes via obesity reduction by bariatric surgery (Dixon et al. 2011). Finally, cell therapy is also resorted to cure in morbidly obese individuals suffering from type II diabetes.

Oral and injectable drugs aim to maintain the plasma concentrations of glucose at normoglycemic levels, thereby preventing diabetes-related complications. Examples of such drugs are sulfonylurea, biguanide, α-glucosidase inhibitors, and peroxisome proliferator-activated receptor γ (PPAR γ) agonists. Drugs like α-glucosidase inhibitors pose their effect by slowing the glucose absorption by the gastrointestinal tract (GI), thereby delaying the degradation of complex carbohydrates in the GI tract (van de Laar et al. 2005). One example of α-glucosidase inhibitors is pramlintide (Younk et al. 2011).

Various oral drugs available in contemporary times, and approved for the treatment of type II diabetes, are second-generation sulphonylureas, for example, glibenclamide (also known as glyburide) and glimepiride. Biguanide antidiabetics include metformin. Pioglitazone and rosiglitazone are PPAR γ agonists. α-glucosidase inhibitors are represented by acarbose, miglitol, and voglibose. One should also mention dipeptidyl peptidase (DPP4) inhibitors like algopiptin and linagliptin, sodium–glucose co-transporter 2 inhibitors like canagliflozin and dapagliflozin, and bile acid binding resins like colesevelam. Another oral drug named bromocriptine has been used as an antidiabetic, since it is believed to restore glucose metabolism via central nervous system by regulating the circadian rhythm (Weyer et al. 1999).

Earlier, insulin was the only injectable drug available for the treatment of diabetes. In current times, other drugs have been approved. They encompass islet amylin polypeptide analogues like pramlintide and glucagon-like peptide 1 (GLP1) receptor agonists like exenatide, liraglutide, and lixisenatide. Besides, there have been advancements in types of insulin used as injectables: rapid or short acting

insulin, for example, soluble or regular insulin, insulin aspart, insulin glulisine, insulin lispro, and insulin zinc amorphous; intermediate acting insulin, for example, isophane insulin/NPH insulin and insulin Zinc/Insulin lente; and long-lasting insulin, such as insulin zinc crystalline/insulin ultralente, insulin detemir, and insulin glargine (Kahn et al. 2014).

Therapies aiming at improvement of β-cell mass, or increasing β-cell secretory function, are either at research stage or in clinical trials. GPR40/free fatty acid receptor 1 (FFAR1) agonists are known to increase β-cell secretory function. TAK-875 is such an FFAR1/GPR40 agonist, which is in phase III clinical trial (Burant et al. 2012). Similarly, agonists of the receptor GPR119, located on β-cells and intestine, result in improved β-cell secretory function via release of incretin (Tolhurst et al. 2012). Betatrophin, a probable revolutionary compound, is a liver-derived protein first identified by Douglas Melton's group last year, resulting in increase of β-cell mass (Yi et al. 2013). Other approaches are decreasing the effect of glucagon, using glucagon receptor antagonists or glucagon antibodies (Gelling et al. 2003), reducing the hepatic production of glucose, by increasing the activation of glucokinase (Meininger et al. 2011), and increasing insulin action by inhibition of PTBIB (Ma et al. 2011).

Bariatric surgeries (laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass, and laparoscopic sleeve gastrectomy) are surgical interventions aiming at obesity reduction, yet these interventions have successfully attenuated type II diabetes (O'Brien et al. 2013; Courcoulas et al. 2014; Svane and Madsbad 2014). They have reportedly increased insulin sensitivity and gut hormone response, insulin secretion via improved β-cell mass, by tenfold increase in glucagon-like peptide 1 (GLP-1), and also reduced the mortality related to type II diabetes (Svane and Madsbad 2014). Also, they resulted in improved metabolism of patients (Raghow 2013). The downside are complications related to long-term nutritional deficiencies.

Cell-based therapies have different approaches, thus being fit for the treatment of type I diabetes, which results in autoimmune destruction of β-cells and requires intense attention. In contrast, type II diabetes can be managed by drugs and lifestyle changes. However, extreme cases of type II diabetes resulting from morbid obesity would also need cell therapy for diabetes.

Pancreas transplantation, islet transplantation, and β-cell transplantation involve surgical interventions (Chhabra and Brayman 2014), while intravenous injections of bone marrow mesenchymal stem cells, to mitigate diabetes, involve non-surgical procedures (Hao et al. 2013). Isolated islet transplantation is already less invasive than whole pancreas transplantation and hence could represent a safe, effective, and definitive treatment option for diabetes (Berney and Johnson 2010).

Isolated islet transplantations involve considerable improvements in the levels of glycated hemoglobin (HbA1c), reduced incidence of debilitating hypoglycemic episodes in transplanted individuals, and improved insulin sensitivity, glucose disposal, and free fatty acid clearance (Barton et al. 2012). Furthermore, preprocedural complications of islet transplantation have 20-fold lower risk of morbidity, reportedly as compared to whole pancreas transplantation (Barton et al. 2012). In a preclinical model of diabetic rats, tail vein infusions of MSC, a

less invasive method of administration, have been successfully used for the treatment of diabetes (Si et al. 2012). Taken together, cell therapy might prove to be the best approach to treat type I, and extreme cases of type II diabetes, as it is less invasive and more efficacious.

13.3 Cell Therapy for Diabetes: A Superior Holistic Approach for Continued Research and Treatment

In type I diabetes, β cells are mostly destroyed, and in type II diabetes β cell numbers may be reduced by 40–60 %. The proof-of-concept studies say that cellular transplants of pancreatic islets, which contain insulin-secreting β cells, can reverse the hyperglycemia of type I diabetes. There is now a need to find an adequate source of islet cells. Human and mouse pluripotent stem cells (human embryonic and human induced pluripotent) have been successfully differentiated into functional insulin-producing β-cells (Jiang et al. 2007a, b; Kroon et al. 2008; Bose et al. 2012; Jeon et al. 2012). From a research viewpoint, induced pluripotent stem cells (iPSCs) can also be generated from patients with diabetes to allow studies of the genomics and pathogenesis of the disease (Maehr et al. 2009).

Some alternative approaches for replacing β cells include finding ways for enhancing the replication of existing β cells, stimulating neogenesis (the formation of new islets in postnatal life), and reprogramming of pancreatic exocrine cells to insulin-producing cells. Stem-cell-based approaches could also be used for modulating the immune system in diabetes or to address the problems of obesity and insulin resistance in type II diabetes.

In accordance with the strategy of immune modulation, cord blood-derived multipotent stem cells have been used, to target insulin resistance in type II diabetic patients, and are already in phase I/II/clinical trials (Zhao et al. 2013). A list of all possible sources to obtain β-cells for cell therapy for diabetes include (1) insulin-secreting cell lines, (2) engineered non-β-cells for gene therapy, (3) β-cells or islets from other species as xenografts, (4) tissue stem cells from the pancreas, (5) bone marrow, (6) liver, (7) neural origin, and (8) pluripotent stem cells (PSCs), both embryonic and induced pluripotent (Jones et al. 2008).

In the case of type I diabetes, cell therapy is undoubtedly the ultimate solution. However, in case of type II diabetes, cell therapy can also be utilized to address the associated factors like metabolic improvement and restoration of insulin sensitivity. Indeed, cell therapy for type II diabetes does not mean pancreatic β-cell transplantation, under all situations. It can be conducted in the form of immune modulation via other kinds of stem cells, like bone marrow or cord blood MSCs. An elegant example to reverse type II diabetes is by using cord blood MSC to ameliorate insulin resistance (Zhao et al. 2013).

Use of immune/metabolism modulating stem cells can also give clues toward cases of insulin resistance that never progress toward a diabetic state. Immune

modulation of type I diabetes can also be beneficial for β-islet regeneration (Abdi et al. 2008). Furthermore, as reported by Abdi et al., mesenchymal stromal cells have the ability to promote immunity and could prevent autoimmune destruction of β-cells in type I diabetes.

Cell therapy could also be applied to treat diabetic complications, such as atherosclerosis and microvascular disease. Treating diabetes and handling associated comorbidities are equally important. In this scenario, cell therapy from iPS cells, mesenchymal, cord blood, and adipose-derived stem/non-stem cells are prospective candidates.

13.4 Various Kinds of Available or Feasible Cell Therapies for Diabetes in Clinics and Research

13.4.1 Human Cadaveric Whole Pancreas or Islet Transplantations as Cell Therapy for Diabetes

Transplantation of whole pancreas was the very first kind of cell therapy administered for type I diabetic patients. Whole pancreas poses comparatively fewer complications related to surgery and ensures a permanent solution for hyperglycemia. Islet transplantation, a less invasive procedure, encompasses transplantation of islets in the portal vein of the recipient's liver (White and Manas 2008; Merani and Shapiro 2006; Ricordi and Strom 2004). Islet isolation involves mechanical as well as enzymatic separation of islets from other tissues of the cadaveric pancreas. Islets have a different density than the acinar tissue, ensuring enrichment of an islet population following centrifugation. Indeed, automated methods for obtaining pure population of human islets have been in vogue since more than two decades (Ricordi et al. 1988).

Islets purified by density gradient centrifugation can be administered intraportally into the liver of the patient. Such islets have the capacity to home and revascularize in few weeks' time, thereby replenishing the islet cell pool of diabetic patients (Korsgren et al. 2008). Islet transplantation incorporates a true amalgamation of isolation method (Ricordi et al. 1988), and steroid free immunosuppression protocol, for long-term graft survival (Shapiro et al. 2000). However, initially the long-term graft survival was poorer than expected, and only 20 % of the patients exhibited insulin independence, 5 years later (Ryan et al. 2005). The limitations of survival were overcome, with the advent of novel T-cell depleting technologies, discovered recently (Bellin et al. 2008).

The deficient supply of cadaveric islets continues to hinder cell therapy for diabetes using human islets. Hence, the advent of clinical grade β-islets from stem cells is looked upon as a promising option for cell therapy to millions of patients, as opposed to hundreds in the case of cadaveric source.

13.4.2 Mesenchymal Stem Cells for Cell Therapy for Diabetes

Although mesodermal in origin, MSCs have the potential of multilineage differentiation (Pievani et al. 2014). The indicative markers for MSC are the presence of cluster of differentiation (CD) markers like CD73, CD105, and CD90 and an absence of hematopoietic stem cell markers like CD45, CD14, and CD34. MSCs can be isolated from various tissues like stroma of bone marrow, adipose tissue, and cord blood (Mosna et al. 2010).

Due to the easy availability of MSCs in large quantities, scientists have attempted to differentiate MSCs into functional insulin-producing β-cells, with varied degrees of success. Despite the multilineage potential of MSCs, mesodermal origin of MSCs makes them less efficient to differentiate into β-cells, of endodermal origin. Embryonic stem cells (ESC) can better differentiate into functional β-cells as compared to MSC (Jiang et al. 2007a, b; Kroon et al. 2008; Bose et al. 2012; Jeon et al. 2012). β-cell differentiation has been attempted from various types of MSC as bone marrow (Gabr et al. 2013; Karnieli et al. 2007), adipose tissue (Timper et al. 2006), umbilical cord blood (Prabakar et al. 2012), wharton jelly (Wu et al. 2009; Hu et al. 2013), dental pulp (Kanafi et al. 2013), placenta (Susman et al. 2010; Chang et al. 2007), and amnion mesenchymal stromal cells (Kadam et al. 2010a, b).

From a clinical viewpoint, postnatal MSCs like bone marrow, dental pulp, and adipose tissue MSCs can be used as autologous sources. Human extra-embryonic, tissue-derived peri-natal MSCs like amnion, placenta, Wharton jelly, and cord blood can be used as allogeneic sources to derive β-cells for transplantation (Bhonde et al. 2014). Although pluripotent stem cell-derived β-cells are easy to obtain, due to successful β-cell differentiation protocols, MSCs pose less or no ethical concerns, and no possibility of harmful effects of teratomas, unlike PSCs (Domínguez-Bendala et al. 2012; Davis et al. 2012).

In laboratory scale, all the aforementioned MSCs have been successfully differentiated into insulin-producing β-cells, which have also been tested on preclinical models of diabetes to ameliorate diabetes. Most importantly, autologous mesenchymal stem cells have been extremely successful, in clinics, from the safety point. In a case study 41 patients, all of whom received cell transplantation for cartilage repair of various joints, were followed for a period of up to 11 years and 5 months, with no adverse reactions (Wakitani et al. 2011).

To the best of our knowledge, there are no clinical trials which have used autologous bone marrow MSCs for replacing damaged β-cells. Interestingly, a recent report has harnessed the immunomodulatory property of MSCs to reduce the intensity of type I diabetes. MSCs injected through liver puncture in two patients resulted in the reduction of islet cell antibodies (ICA), glutamic acid decarboxylase (GAD), and insulin antibodies in 12 months, which, in turn, reduced the autoimmune destruction of islet cells in the patients (Mesples et al. 2013). Similarly, cord blood MSCs have also been harnessed, to improve the immune

modulation and insulin resistance of type II diabetic patients, and are in phase I/II/ clinical trials (Zhao et al. 2013).

13.4.3 Pluripotent Stem Cells for Cell Therapy for Diabetes

Although ample amount of success has taken place regarding the clinical transplantation of cadaveric islets into the liver, which could reverse diabetes (Halberstadt et al. 2013), the source of islets from the PSC source has yet to be in the clinics. Enhanced plasticity of PSCs has given greater hopes for the generation of β-cells. A large body of literature exists regarding differentiation of PSCs into β-cells. Various strategies/differentiation protocols for obtaining β-cells from PSCs were designed, primarily by mimicking in vivo pancreatic organogenesis (Jiang et al. 2007a, b; Kroon et al. 2008; Bose et al. 2012, 2014; Jeon et al. 2012).

Essentially they made use of various growth factors, in a stepwise manner, over the duration of 1 month or more. In addition to the growth factors, many protocols used small molecules for in vitro β-cell differentiation (Borowiak et al. 2009; Chen et al. 2009). The pitfalls are the presence of undifferentiated cell populations, and hence sorting for pure populations of differentiated β-cells or progenitor cells are a highly sought-after alternative (Fishman et al. 2012). Also, Fishman et al. successfully generated human ESC clones harboring GFP reporter constructs of Sox17, a definitive endoderm marker, and Pdx1, a pancreatic marker. Expression of GFP, in the ESC clones generated by Fishmann et al., helped obtaining pure populations of Sox17+/Pdx1+ pancreatic progenitor populations. The same strategy can be very useful for transplantation purposes. β-cells differentiated from human pluripotent stem cells (hPSCs) have been successfully tested on preclinical models of diabetes.

Per regulatory guidelines of most countries, any cell therapy product must be generated under good manufacturing practice (GMP) rules, in specifically licensed laboratories. Accordingly, the entire licensing process involves stringent quality control inspections and approval of raw materials, manufacturing, supply, and storage. In the case of hPSC-based cell therapy products, potential of tumorigenicity, inappropriate or incomplete differentiation, and potential of in vivo toxicities need to be evaluated on preclinical models before entering clinical trials. Also, in case of ESC therapy products, there are ethical concerns regarding the destruction of an embryo, while iPS cell therapy products are free from such ethical concerns.

Geron Corporation, a California-based company, received the first US FDA clearance on 2009, for a hESC-based cell therapy product, and initiated the first clinical trial. It was GRNOPC1, embryonic stem cell-derived oligodendrocyte progenitor cells, for treating patients with acute spinal cord injury. The trial was however discontinued in 2011, after treating four patients, because the company felt that the treatment was too expensive, and hence decided to channelize the funding for other projects (Lukovic et al. 2014).

Subsequently, Advanced Cell Technology entered into a Phase I/II trial, using GMP grade MA09 hESC line-derived retinal pigment epithelial (RPE) cells, for treating macular degeneration. Four months follow-up showed favorable results in two patients (Schwartz et al. 2012). Pluripotent stem cell-based clinical trials for diabetes have not yet been planned nor are they in the pipeline till date.

13.5 Details of Generation of Cell Therapy Products for Diabetes-Pluripotent Stem Cell Therapy: Mesenchymal Stem Cell Therapy

13.5.1 Details of Generation of Mesenchymal Stem Cell Therapy Products for Diabetes

Ethically acceptable with the possibilities of autologous source, generation of mesenchymal stem cell therapy products for diabetes should harness and maintain four basic properties of MSCs, such as (1) ability to migrate to the inflammation sites upon intravenous injections (2) ability to differentiate into functional β-islets (3) ability to secrete multiple bioactive molecules, which can inhibit inflammation, and heal the weak or dying β-cells (4) immunomodulatory functions of MSCs, along with lacking immunogenicity (Wang et al. 2012; Stagg and Galipeau 2013). Accordingly, large quantities of clinical grade MSCs can be generated under certified GMP conditions, from various sources like bone marrow, adipose tissue, and cord blood.

The scale-up of MSCs can be done under xeno free conditions. Hence, scaled up MSCs can directly be injected to the patients, in coherence with all the mentioned properties except for the second, which require additional steps of in vitro differentiation into functional β-islets, before transplantation. Furthermore, they can also be used as an adjuvant for better engraftment of transplanted β-islets from various sources like cadaveric and differentiated from human MSCs or PSCs (Rosengren et al. 2009).

Unaltered bone marrow MSCs injected into diabetic mice have also exhibited the potential of in vivo differentiation into functional β-islets (Iskovich et al. 2012). Hence, unaltered scaling up of human autologous bone marrow stem cells can be clinically useful, as they can differentiate in vivo into functional β-islets.

With regard to in vitro differentiation of β-islets prior to transplantation, the generation of cell therapy products requires a lot of culture manipulations. Such manipulations should follow various established protocols of β-islet differentiations from MSCs. It is important to scale-up the differentiation protocols by minimizing unwanted cell types, incomplete differentiations or differentiations, into possibly precancerous cells. In laboratory scale, protocols have a duration of approximately 2 months, and are spread over 2–3 steps. These involve 1,000-fold expansions of MSCs, transdifferentiation of MSCs first into endodermal cells, followed by β-cell

precursors in culture. Alternatively, the MSC can directly be subjected to culture conditions to obtain transplantable functional β-cell precursors.

A specific example of human bone marrow MSC involves a 2 months 5 days differentiation protocol (Tang et al. 2012). In this three-step protocol, first step involves culturing of human BM-MSCs in RPMI-1640 media containing bFGF, the second step involves treatment of BM-MSCs with bFGF and EGF, and the third step involves obtaining transplantable β-cell precursors using 5.5 mM glucose and 5 % FCS (Tang et al. 2012).

In case of adipose tissue-derived mesenchymal stem cells (AD-MSC), pancreatic organogenesis is mimicked (Chandra et al. 2009). AD-MSC differentiation protocol involves the use of cytokines, inducing definitive endoderm and pancreatic progenitors like activin A, GLP-1, and nicotinamide, respectively, in a stepwise fashion (Chandra et al. 2009). Similarly, dental pulp-derived MSCs also involve steps mimicking in vivo pancreatic organogenesis, and make use of cytokines along with activin A, Na-butyrate, GLP-1, and nicotinamide (Govindasamy et al. 2011). Also, differentiation schemes of perinatal MSCs, from umbilical cord and Wharton jelly, involve mimicking in vivo pancreatic organogenesis, and make use of definitive endoderm and pancreatic endoderm inducing cytokines including activin A, nicotinamide, exendin, GLP-1, and Na-butyrate (Gao et al. 2008; Tsai et al. 2012).

The donors should qualify in the screening tests designed by the regulatory bodies (Sensebé et al. 2011). Such stringency holds good for allogeneic donors, where one donor serves for multiple patients, awaiting to receive MSC-based cell therapy products. Screening tests for MSCs donors are similar to donors of other cell therapy products, and primarily involve health questionnaire and viral testing. Age is another important criterion. BM-MSCs from child donors are considered to be of high quality, owing to a higher concentration of colony forming unit fibroblast precursors (CFU-Fs) than from adults (Baxter et al. 2004). Also, increasing age of the donor for BM-MSCs adversely affect the proliferation and multipotency of MSCs (Stolzing et al. 2008).

BM is obtained from the donor's posterior superior iliac spine or crest, using an Illinois needle, or equivalent aspiration in a heparin-containing syringe (Bain 2001). Sample processing is done based on density gradient centrifugation, direct plating, or different enrichment strategies. Immunomagnetic beads-based enrichment of BM-MSCs are done on the basis of markers like STRO-1, CD49a, CD105, CD133, CD146, CD271, SSEA-4, antifebrin microbeads, aptamers, and aldehyde dehydrogenase activity (Guo et al. 2006; Gentry et al. 2007; Caplan 2007). However, the most common method to obtain clinical grade MSCs involve density gradient centrifugation of the bone marrow, followed by direct plating of the fractions on plastic cell culture dishes, to separate mesenchymal from hematopoietic cells.

A frequency of one MSC is obtained per million nucleated cells from adult bone marrow, while one MSC is obtained per 104 nucleated cells of umbilical cord blood (Gentry et al. 2007; Lu et al. 2006). Frequency of obtaining MSCs reportedly decreases tenfold from birth to teenage and a further tenfold from teenage to adulthood (Gentry et al. 2007; Lu et al. 2006; Caplan 2009). Similarly, high-

quality MSCs are obtained from adipose tissues, using centrifugation to discard adipocytes, followed by cell plating and extensive washings (Zuk et al. 2001), as manual methods, and automated systems like Celuton system, Cytori Therapeutics, San Diego, CA (Duckers et al. 2006). Umbilical cord blood-derived MSCs are obtained by standard process of gravity assisted collection, by cannulating one of the umbilical veins after delivery of the placenta, under aseptic conditions, and processing the cord blood for obtaining MSC (Bieback et al. 2004).

Other important parameters for obtaining clinical grade MSCs are MSC expansion media like α MEM or DMEM (Sekiya et al. 2002; Sotiropoulou et al. 2006). Fetal bovine serum (FBS) is an important component for MSC proliferation (Caterson et al. 2002). However, addition of FBS reportedly induces immunogenic properties to MSCs, thereby rendering them clinically inferior (Sundin et al. 2007). Accordingly, non-FBS human-derived products like basic FGF, TGFβ1, IGF, and PLT lysates are the preferred alternatives for clinical grade MSCs (Bieback et al. 2009).

Hypoxic conditions reportedly cause reduced oxidative damage to the MSCs, thereby maintaining their multipotentiality (Berniakovich and Giorgio 2013). Plating density from low ($1–5 \times 10^3$ per cm^2) to very low ($1–5 \times 10^1/cm^2$) is also conducive for maintaining multipotentiality of MSCs and hence should be used for maintaining clinical grade MSCs (Banfi et al. 2000).

Large scale MSCs need to be manufactured in cGMP compliant bioreactors (Chen et al. 2006; Gastens et al. 2007). Storage/cryopreservation comprises 10 % DMSO with electrolyte solution (plasmalyte A), and a protein source (human serum albumin), and freezing at the rate of 1 °C per minute. Recommended transport are dry shippers or liquid nitrogen (Hanna and Hubel 2009). Most important, all clinical grade MSCs should be tested for endotoxins, mycoplasma (Munson 1985), as well as functional potential like trilineage differentiation potential (Kim et al. 2009), immunomodulation (Bifari et al. 2008), and replicative senescence (Wagner et al. 2008).

13.5.2 Details of Generation of Pluripotent Stem Cell Therapy Products for Diabetes

Pluripotent stem cell-based therapies are one of the most promising areas of medicine, and many such therapies are now being developed by industrial and academic groups. Cell therapies based on adult stem cells have been in use for several decades. First successful bone marrow transplant was carried out in 1968 (Bach et al. 1968; De Koning et al. 1969). Although there are PSC products for diabetes in laboratory scale, none of the PSC-based products are in clinical trials. The general strategy for adult and all PSC therapies is the scale-up of undifferentiated cells, differentiation to a specific cell type, and delivery to the patient. Some of the regulatory issues surrounding this strategy arise from the fundamental

characteristics of PSC. Cells change over time both in vitro and in vivo, integrate and migrate after transplantation, and interact with host immune systems.

Cell products derived from PSCs present additional issues, like extensive replicative capacity and pluripotency. An advantage of PSC over MSC is the ability of PSC to replicate infinitely, in contrast to MSC, which has limited replicative ability, and thus gives rise to large quantities of cell yield. Such large quantities of cell yield from PSCs are advantageous for commercial cell therapy products. However, the ability of the cells to proliferate indefinitely will require the assessment of stability of the cells over time in vitro.

The pluripotency of the cells allows generation of a wide array of differentiated cell products, but also entails the possibility of teratoma formation, and the presence of unwanted cell types. For the safety of hESC/hiPSC (hPSC)-based cell therapies, the cells will require evaluation of the starting material, demonstration of a reproducible differentiation and cell processing, assessment of the identity of the final cell product, and characterization of in vivo properties, such as bio-distribution, tumorigenicity, toxicity, and immunogenicity.

Over the past decade, islet transplantation trials have demonstrated that patients with type I diabetes can be temporarily cured, by replenishing β cells and eliminating their dependency on insulin. The success of these trials is a proof that cell replacement therapy is a good option for treating diabetes. Due to scarcity or lack of donor islets, efforts are ongoing from many investigators in search for an alternative source of β cells, from human embryonic (hESCs) and iPSCs. Over the past few years significant research has been done in generating β-islets from hPSCs and as a result, it is now possible to generate insulin-producing cells from both hESCs and iPSCs.

Detailed steps of hPSC differentiation protocols always mimic in vivo pancreatic organogenesis. D'Amour et al. (2005) took a stepwise approach to set out to first differentiate hESCs toward definitive endoderm, a prerequisite for all pancreatic cell types. Also Shi et al. (2005) demonstrated the same approach to first differentiate the PSCs into definitive endoderm, followed by the differentiation into pancreatic β-islet cells, through the use of various growth factors in mouse cells. Later on, D'Amour et al. (2006) described a five-step and a four-step two-dimensional (or monolayer) hESC differentiation protocol that leads to efficient Pdx1 activation by day 12 and 15, respectively, and the impressive formation of up to 12 % insulin-containing cells.

Other protocols, which also mimicked in vivo pancreatic development, resulted in the formation of transplantable functional β-islet cells by day 18 (Madsen and Serup 2006) and day 25 (Jiang et al. 2007a, b).

The use of different model systems to understand early embryonic development had shown that nodal, a soluble molecule of the TGFβ/activin signaling family, was required for mesoderm and definitive endoderm formation during gastrulation. Higher levels of nodal were reported to promote endoderm specification (Conlon et al. 1994; Osada and Wright 1999; Lowe et al. 2001; Vincent et al. 2003). Based on these observations, D'Amour and colleagues implemented a protocol, in which hESCs were exposed to distinct soluble signaling factors. Activin A, another

member of the TGF-β signaling family, was used together with Wnt3a to generate cells expressing markers of definitive endoderm (D'Amour et al. 2005, 2006).

The approach of using embryonic signals to instruct hESCs to definitive endoderm, and subsequently to β-cells, was validated by several other groups using modifications of this procedure (Jiang et al. 2007a, b; Eshpeter et al. 2008; Mao et al. 2009). These cells generated by D'Amour et al. (2006) responded to a variety of insulin secretagogues, but only showed limited glucose responsiveness. Modified pancreatic differentiation by Kroon et al. (2008) resulted in insulin-producing cells from hESC, which were also in vivo responsive to glucose. More recently, Nostro et al. (2011) reported improved efficiency (25 %) of insulin-producing cells by stage-specific in vitro regulation of TGF-β family members.

Specificities of in vitro differentiation protocols from PSC are ensured by detailed studies of pancreatic organogenesis. For example, within the mouse embryonic foregut, pancreatic fate is first specified by the expression of the homeobox gene Pdx1 (pancreatic and duodenal homeobox-1) (Jonsson et al. 1994; Guz et al. 1995). Thus, activation of Pdx1 is considered a prerequisite for pancreatic differentiation in vitro, and should precede the progressive expression of more mature markers of the endocrine lineage, including Ngn3, Nkx2.2, Nkx6.1, MafA, and MafB (Jensen 2004). Moreover, MafA has been identified as the master regulator of glucose-stimulated insulin secretion, in functional β-islet cells (Hang and Stein 2011; Matsuoka et al. 2004; Zhang et al. 2005; Wang et al. 2007).

MafA transcription factor, which is expressed last among all β-islet transcription factors, has been involved in regulating β-cell function by activating the insulin gene promoter via Pdx1, which, in turn, positively regulates the essential β-cell genes such as Glut2, Pdx1, Nkx6.1, and Glp1 (glucagon-like peptide 1). Also, MafA and MafB have been implicated in functional maturation of pancreatic β-islet cells from hESC (Wang et al. 2007; Jonsson et al. 1994; Guz et al. 1995). Thus, activation of Pdx1 in β-islet differentiation in vitro strategies from ES cells were evolved, which mimicked β-cells organogenesis.

Use of small molecules like IDE1, IDE2, (-)-Indolactam V (ILV), and Stauprimide (Spd) are also encompassed in successful strategies for generation of functional pancreatic lineage from ESC (Borowiak et al. 2009; Chen et al. 2009). Moreover, such small molecules are less than 1,000 Dalton in weight and easy to synthesize in large quantities. They can be employed as agonists and antagonists of signaling pathways, promoting hPSC differentiation into β-cells. Other strategies successfully implemented for the generation of PSC-based stem cells involve the use of FACS sorting marker to isolate pancreatic progenitor cells (Fishman et al. 2012).

Important considerations regarding safe and clinical grade PSC-based therapy for diabetes involve the derivation of hESC and hiPSC. For the derivation of hESC, cGMP as well as feeder and xeno free conditions are preferred (Carpenter et al. 2009). For the derivation of hiPSC, dangers posed by lentiviral vectors must be considered, and hence, nonviral methods of gene delivery are a highly sought-after alternative (Carpenter et al. 2009). Another aspect of PSC-based stem cell therapy is product consistency, which involves aseptic environment, sterility, and traceability of the lot.

For ensuring the consistency parameter, sufficient quality check measures, in terms of adherence to the standardized protocols for cell expansion and differentiation, must be carried out (Carpenter et al. 2009). As the cells tend to lose their karyotype, and harbor certain genetic abnormalities under long-term culture conditions, quality checks regarding phenotype, karyotype, and imprinting status for PSCs and cell-based products should be mandated (Jung et al. 2012). Finally, starting material as well as the cell therapy products must be rigorously tested for tumorigenic potential along with toxicity and immunogenicity (Carpenter et al. 2009).

13.6 Clinical Translation of Islet Transplantation, in Modified Forms, as Cell Therapy for Diabetes

Clinical islet transplantation (CIT) represents the one of the best viable treatment for type I DM. However, concerns remain regarding the immune response, effective cell delivery and long-term survival of the free β-islets. Hence, modified methods of islet transplantations are highly sought-after alternative. Accordingly, in this section we provide transitory description of islet transplantation/cell therapy for diabetes in focus to islet encapsulation.

13.6.1 Islet Encapsulation Technology

To overcome the use of immunosuppression, islet encapsulation was proposed in this field. The first publication regarding cell encapsulation was noted in 1930s by Bisceglie et al. Different types of encapsulations for pancreatic islet cells are shown in Fig. 13.2.

The architectural ways for islet encapsulation fall in different categories, based on their size and implantation sites. Systematic representation of implant sites, for free islet and encapsulated islets, is highlighted in Fig. 13.3.

Various devices are used to hold the islets in their respective sites of transplantation: (1) Macro-devices: These devices hold islets within a major structure, and are further classified based on site of transplantation. (A) Extravascular diffusion devices: Most commonly implanted outside the vascular tissues such as the peritoneal cavity, omental pocket, or subcutaneous area. (B) Intravascular diffusion devices, which are placed in arterial vessels. (C) Intravascular ultrafiltration devices: They have a unique filter system, through which necessary nutrients/molecules can be delivered into a vein. (2) Micro-devices: They can incorporate single or small clusters of islets into spherical water-soluble polymers, such as alginate, or water-insoluble polymers such as polyhydroxyethyl methacrylate-methyl methacrylate. Despite their solubility in aqueous solutions, alginate-based

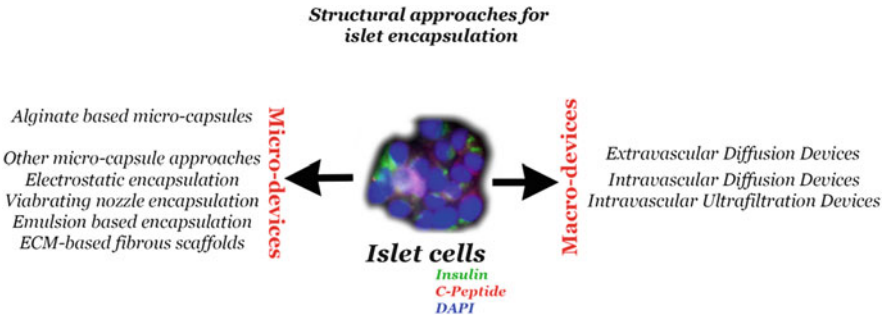

Fig. 13.2 Systematic representation of different methods for islet encapsulation

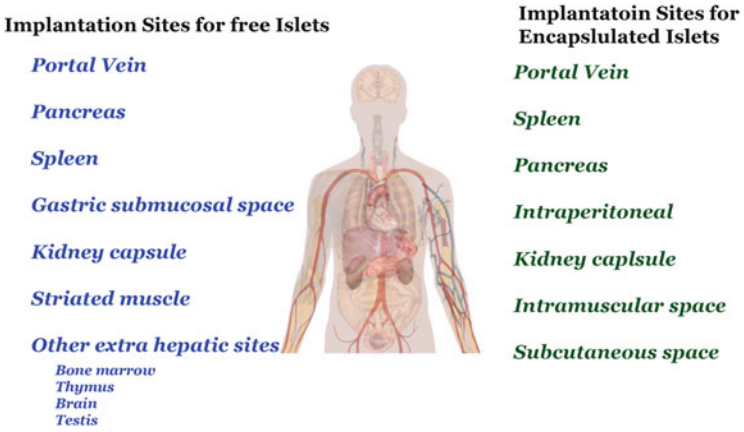

Fig. 13.3 Implant sites for free islet and encapsulated islets

capsules have been shown to be stable for several years in small and large animals, as well as in human (Soon-Shiong et al. 1994; De Vos et al. 1997a, b, 1999; Duvivier-Kali et al. 2001).

Among all microcapsules, the most widely implanted is the ionically crosslinked alginate-poly-amino-acid alginate (APA) encapsulation system. The major issues with islet encapsulation are: (A) Triggering inflammatory reaction that covers the capsule surface, which leads to fibrosis. (B) Clumping of capsules in transplantation sites, which results in starvation for oxygen. One study hypothesized that antigens shed from dead or dying cells are important in immune recognition (Sun 2008). To overcome the problem of maintenance of cell viability and function in islet transplantation, proper oxygen supply to encapsulated islets need to be assured (Colton 2014). The O_2 supply to encapsulated cells depends on many factors including: (A) Site of implantation and the oxygen portal pressure (PO_2). (B) Number and distribution of host blood vessels in the vicinity of the site. (C) Oxygen permeability of membrane capsule. (D) Oxygen consumption/exchange rate of the encapsulated tissues (Colton 2014).

Based on islet cell transplantation with encapsulation, the optimal site for transplantation of islets has not yet been defined. However, the successful outcome of encapsulated islets depends on parameters like implant site with an adequate microenvironment, vascularization, and nutritional support to maximize chances for the best engraftment of cells and to minimize morbidity. There are advantages and disadvantages with both micro- and macro-encapsulation. The added advantages should be used for allo and xenoislets without immunosuppression.

The thin wall and spherical shape of microencapsulation is optimal for cell viability and free diffusion of nutrients and insulin. Macro-encapsulation has good mechanical stability and cell viability, and also free diffusion of nutrients and insulin. During posttransplantation complications, macro-capsules are retrievable. The disadvantages of microencapsulations are mechanical and chemical fragility, with limited retrievability. For macro-encapsulation, the concerns are internal characteristics (i.e., diameter), which may potentially limit free diffusion of nutrients/insulin and cell viability. Multiple implants involving macro-encapsulation may produce significant tissue displacement/damage.

13.6.2 Current Challenges in Islets Encapsulation

Most important considerations for consistent clinical success include a source of functional cells, good biocompatibility, as well as mechanical and chemical stability. The most widely used material for microencapsulation is hydrogel alginate, and there is need for more reliable biomaterials. A membrane with suitable permeability cutoff values might provide immune protection to the implant, functional performance, biosafety, and long-term survival of the graft.

Another challenge involves the production of uniform capsules, with excellent repeatability and reproducibility, both within and between batches. To achieve reproducibility in terms of shape, size, and morphology, automated machines for microencapsulation are necessary. Despite the development of an ideal encapsulation, definition of the transplantation site along with survival and long-term function are significant obstacles, eventually requiring immunosuppressant or anti-rejections drugs. These in turn are associated with increased susceptibility to disease, infection, and cancer.

13.7 How Are Other Surgical Options Comparable with Cell Therapy Surgical Intervention for Diabetes

Cell therapies for diabetes involve more or less invasive procedures, like pancreas transplantation and β-islet transplantation, obtained from cadaveric, pluripotent, or MSC (Chhabra and Brayman 2014). β-islet transplantations are less invasive, via

the portal vein (Juszczak et al. 2009). Intravenous administration of mesenchymal stem cells is totally non-invasive, unlike bariatric and metabolic surgery for type II diabetes (Si et al. 2012). They can be administered to very old patients, without contraindications. However, long-term follow-up studies of islet transplantation need to be conducted, to assess the efficacy compared to bariatric/metabolic surgery, in the management of type II diabetes.

13.8 Conclusion

Cell therapy for diabetes can be more effective if administered at the early stages of the disease. However, in the current scenario, it only targets advanced cases of diabetes. More research needs to be done, to replenish β-cell precursors, or facilitate β-cell neogenesis (Fig. 13.4). Such kind of precursor cells can be administered to early stage diabetic patients.

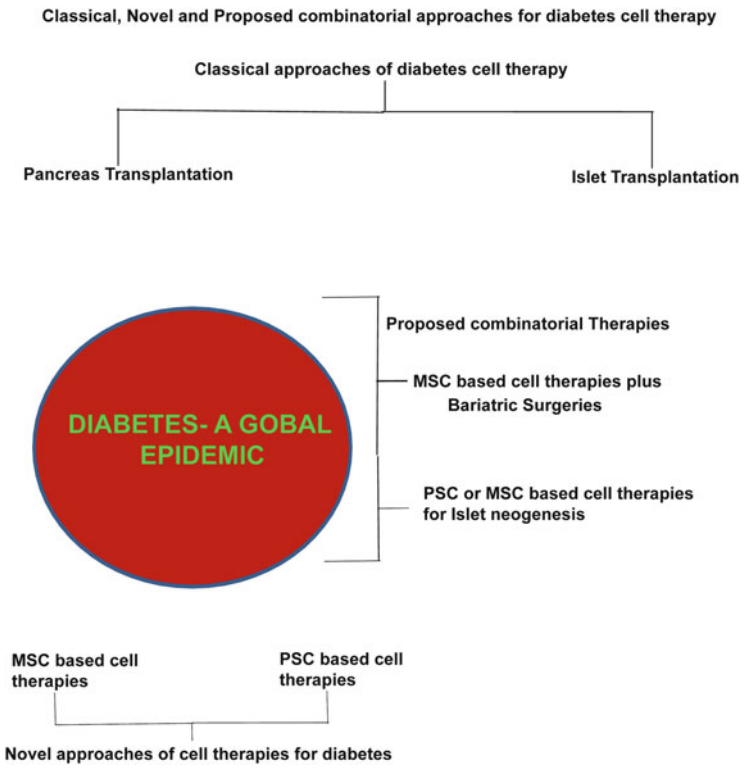

Fig. 13.4 Proposed model for combinatorial cell therapy for diabetes

Pluripotent stem cell therapy has revolutionized regenerative medicine in the present days. Cell therapy products from PSCs have been successful in ameliorating diabetes in small animal models. Unlike MSC, which are already in clinical trials for diabetes, fine-tuning of differentiation protocols needs to be done for obtaining large quantities of clinical grade β-cells from hPSC. Moreover, efficiency of differentiation of β-cells from hPSC is low, as compared to the efficiency of obtaining neurons from hPSC, thereby making the neuronal cells the first ones to be assayed in clinical trials. Efficient β-islet differentiation protocols, teratoma elimination, clinical grade cells, and testing of hPSC-based cells in large primate models should be stressed upon before entering clinical trials.

There are avenues to explore the combinatorial effects of existing anti-diabetic drugs, and cell-based therapy. Also bariatric/metabolic surgery could eventually be combined with the administration of MSC, owing to the ability of MSC to secrete bioactive molecules and immunomodulators, for control of resistant type II diabetes (Fig. 13.4). We propose a combinatorial approach to use cell therapy for diabetes along with existing options, with enormous research potential in the days to come.

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Chapter 14
Stem Cells Derived Insulin-Secreting Cells for Insulin-Dependent Diabetes Mellitus: Exploiting Laboratory Discoveries

Shruti Dave

Abstract The incidence of childhood diabetes—insulin-dependent diabetes (IDDM) continues to rise steadily, and the ever-increasing push toward more intensive management is limited by rising costs and the unremitting demand this form of therapy places on its recipients. Long-term management requires a multidisciplinary approach that includes physicians, nurses, dietitians, and selected specialists. Lack of care can be lethal and administration of insulin is essential for survival for IDDM patients. Since the identification of the autoimmune etiology of IDDM immunosuppressive agents has been proposed as a preventive treatment against the development of the disease, its nephrotoxicity and other adverse effects make it highly inappropriate for long-term use. While pancreas transplantation and islet cell transplantations also have their own limitations. Cell-based therapies mainly including insulin-secreting cells (ISC) represent a promising approach for treatment of IDDM. ISC can provide an abundant and reproducible source of beta-like cells material for transplantation. A number of highly differentiated ISC have been generated from stem cells which can produce remarkable amount of insulin and release it in response to physiological insulin secretagogues.

Abbreviations

AD-MSC	Adipose tissue-derived MSC
ADSC	Adipose-derived stromal cells
BM	Bone marrow
EMT	Epithelial–mesenchymal transition
ESC	Embryonic stem cell
GAD	Glutamic acid decarboxylase

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GFP	Green fluorescent protein
h-ASC	Human adipose-derived stem cells
HbA1c	Glycosylated hemoglobin
HGF	Hepatocyte growth factor
HSC	Hematopoietic stem cells
ICA	Islet-like cell aggregates
IDDM	Insulin-dependent diabetes mellitus
IPADSC	Insulin-producing ADSC
ISC	Insulin-secreting cells
MSC	Mesenchymal stem cells
NOD	Non-obese diabetic
PU-PVP-IPN	Polyurethane-poly vinyl pyrrolidone-interpenetrating network
SCF	Stem cell factor
SCID	Severe combined immunodeficiency
Tregs	Regulatory T-cells
UCB	Umbilical cord blood

14.1 Introduction

Banting and Best received the Nobel Prize in 1923, in a shortest time in history for their discovery of insulin in 1921–1922. Nearing a complete century since the discovery, it is right time to expect a change in the management strategies in insulin-dependent diabetes mellitus (IDDM). Although clinical research involving genetics, research in animal models, and human trials are under way aiming at a revolutionary breakthrough, human body is much more complicated and follows totally different rules of the game. Medical science can never be certain of the future unless there are answers to why, what, and how?

IDDM has been treatable since insulin became medically available in 1921 in the form of recombinant insulin preparations. However insulin therapy is a kind of a treatment modality but not a complete cure of the disease. In spite of taking these medications and stringent dietary and life style control, 30 % develop major organ problems and/or failure, along with disorders like neuropathy, retinopathy, vasculopathy, nephropathy, and others. It has been demonstrated that improved clinical management can make an enormous difference, but there is at present little evidence to suggest that its impact extends much beyond well-motivated patients, attending specialized centers. Meanwhile, the burden of long-term complications continues to rise, and it has been estimated that this increase will continue for at least 20 years, after an effective means of prevention becomes available (Green et al. 1996). IDDM, both the name and the notion emerged in the mid-1970s, when it became clear that this form of diabetes has an autoimmune basis, at least in the type 1 modality (Schatz et al. 2003).

Knowledge that the immune system may be involved raised therapeutic possibilities, because immunity had been successfully manipulated to our own advantage

(e.g., vaccines). In this case one way is to downregulate the immune system, subsequently preserving residual beta-cells. Efforts have been made to prevent this autoaggression with various therapies. The history of these attempts was reviewed by Skyler (1987). In the late 1970s, the use of immunosuppressive agents began to occur and in 1981, Eliot and colleagues treated newly diagnosed children with prednisone, with the aim of stopping pancreatic beta-cell destruction by the autoimmune process (Elliott et al. 1981). In those studies, some patients experienced short periods (<1 year), during which they were free from insulin treatment. But the chronic toxicity of immunosuppression and the loss of the metabolic benefits after the withdrawal of the immunosuppressive agents limited the routine use of these therapies (Couri and Voltarelli 2009). Also reported increased rate for carcinomas, non-Hodgkin's lymphoma, and many other adverse effects of immunosuppression for prevention and cure of IDDM questions their further safe use (Lipton et al. 1990).

The need for an essentially limitless supply, of a substitute for beta-cells of primary human islet of Langerhans, has led to a research on the suitability of stem or progenitor cells to generate insulin-secreting cells (ISC), in replacement therapies for diabetes. Other than downregulating the immune system for subsequently preserving residual beta-cells, another way is to offer a cell-based therapy, with differentiation of stem cells into functional insulin-secreting beta/beta-like cells, as the use of stem cells to treat IDDM has been proposed for many years.

14.2 Review

Scientific understanding of the cause of autoimmune IDDM began with the discovery of inflammatory insulitis by Von Meyenburg. Subsequently Gepts and others recognized that insulitis, an inflammatory lymphocyte infiltrate, was specifically associated with the islets of children with diabetes. The work of Doniach, Bottazzo, and Drexhage revealed that people with IDDM circulate antibodies, often present long before the disease onset, which target constituents of beta-cells and even insulin itself (Rossini 2004).

Autoimmune IDDM is not currently preventable. Beta-cells in particular are known to have a low proliferation rate, due to tight cell cycle control (Cozar-Castellano et al. 2006). Still, promising therapies are emerging, and it was been suggested that, in the future, IDDM may be prevented at the latent autoimmune stage, probably by a combination therapy of several methods (Bluestone et al. 2010).

14.3 Bridging the Crucial Step: Seeking a Functional Surrogate

Experimental replacement of beta-cells is being investigated in several research programs. Islet cell transplantation is expected to be less invasive than a pancreas transplant, which is currently the most commonly used approach in humans. In this procedure, islet cells are injected into the patient's body, where they take up residence and begin to produce insulin. The liver is expected to be the most reasonable choice, because it is more accessible than the pancreas, and islet cells seem to produce insulin well in that environment. The patient's body, however, will treat the new cells just as it would any other introduction of foreign tissue, unless a method is developed to produce them from the patient's own stem cells, or there is an identical twin available who can donate stem cells. Thus, patients now also need to undergo treatment involving immunosuppressants, which reduce immune system activity.

In an effort, researchers began to explore the possibilities of using cell-based therapies that would replace lost beta-cells. Within recent years, stem cell research has become a very important part of the scientific understanding of IDDM.

14.4 Why Stem Cells?

Cell-based therapy for IDDM encompasses all methods that involve creation or expansion of ISC in vitro, followed by their implantation in the patient. Building the ideal ISC faces challenges for use in cell therapy, as well as control of the autoimmune response to cells which express insulin, i.e., ISC. They must be reproducibly made to proliferate extensively and generate sufficient quantity of tissue; differentiate into desired cell type(s); survive in the recipient after transplant; integrate into surrounding tissue after transplant; function appropriately for the duration of the recipient's life and avoid harming the patient in any way. Thus cell therapy in actual sense involves "immunological resetting" involving stem cell rescue. The replacement cells must have the ability to synthesize, store, and release insulin in response to ambient glycemia. The proliferative capacity of these cells must be very tightly controlled to avoid the development of hyperinsulinemic hypoglycemia. To overcome transplant rejection, they should possess similar functional phenotype, but remain developmentally and immunologically distinct (Burns et al. 2004; Stainier 2006).

The origins of the field of stem cells can be traced back to the laboratory of Canadian scientists Ernest A. McCulloch and James Till at the Ontario Cancer Institute in Toronto, where two groundbreaking articles were published in 1963. McCulloch and Till, with Andy Becker and Lou Siminovitch, reported on the presence of self-renewing cells within the bone marrow (BM) of mice, and postulated that these cells were regenerative stem cells. This cell type was first

discovered in 1924 by the cell morphologist Alexander A. Maximo, who described a type of cell within the mesenchyme that develops into various types of blood cells. But Ernest A. McCulloch and James E. Till first revealed the clonal nature of marrow cells in 1963 (Becker et al. 1963; Siminovitch et al. 1963; Zhang et al. 1999).

Of course, we now know these cells to be HSC (hematopoietic stem cells), the first described adult stem cell. From the work of McCulloch and Till, the adult stem cell field gathered momentum in the late 1960s and early 1970s, as patients suffering from severe combined immunodeficiency (SCID) were treated using BM transplants or hematopoietic stem cells (HSC) concentrates (Dicke and van Bekkum 1973; Lin et al. 2000). The late 1960s saw the introduction of the bone marrow MSC (Friedenstein et al. 1968).

The isolation of human stem cells offers the promise of a remarkable array of novel therapeutics. Biologic therapies derived from such cells—through tissue regeneration and repair, as well as through the targeted delivery of genetic material—are expected to be effective in the treatment of a wide range of medical conditions. Transplanted human stem cells are dynamic biological entities that intimately interact with—and are influenced by—the physiology of the recipient. Before they are transplanted, cultured human stem cells are maintained under conditions that promote either the self-renewing expansion of undifferentiated progenitors or the acquisition of differentiated properties, indicative of the phenotype the cells will assume. After incompletely differentiated human stem cells are transplanted, additional fine-tuning occurs, as a consequence of instructions received from the cells' physiologic microenvironments within the recipient. The capabilities to self-renew and differentiate that are inherent to human stem cells point to their perceived therapeutic potential. Research has demonstrated that stem cells can be grown in the lab and could lead to a better availability of beta-cells. Thus stem cells are the promising tools addressing generation of beta-like cells/ISC as well as immunomodulation (Calafiore et al. 2014) (Fig. 14.1).

14.5 Early Attempts for In Vitro Beta-Cell Differentiation

Stimulation of beta-cell generation or generation of cells secreting insulin, for the treatment of IDDM, is attractive because it directly addresses the major functional deficiency underlying the disease. For IDDM therapy, it is not clear whether it will be desirable to produce only beta-cells—the islet cells that manufacture insulin—or whether other types of pancreatic islet cells are also necessary. Studies by Bernat Soria and colleagues indicate that isolated beta-cells—those cultured in the absence of the other types of islet cells—are less responsive to changes in glucose concentration, than intact islet clusters made up of all islet cell types. Islet cell clusters typically respond to higher-than-normal concentrations of glucose by releasing insulin in two phases: a quick release of high concentrations of insulin and a slower release of lower concentrations of insulin. In this manner the beta-cells can fine-

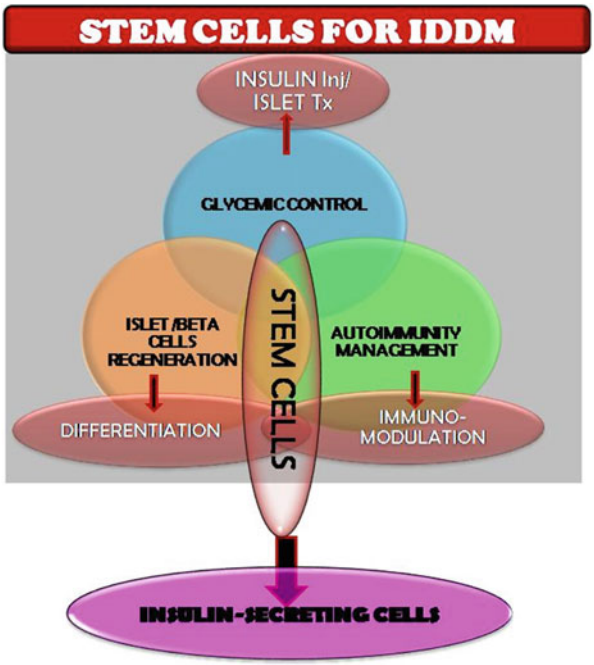

Fig. 14.1 Stem cells as a promising tool addressing generation of beta-like cells/insulin-secreting cells as well as immunomodulation

tune their response to glucose. Extremely high concentrations of glucose may require that more insulin be released quickly, while intermediate concentrations of glucose can be handled by a balance of quickly and slowly released insulin.

Isolated beta-cells, as well as islet clusters with lower-than-normal amounts of non-beta-cells, do not release insulin in this biphasic manner. Instead insulin is released in an all-or-nothing manner, with no fine-tuning for intermediate concentrations of glucose in the blood (Soria et al. 1996; Bosco and Meda 1997). Therefore, many researchers believe that it will be preferable to develop a system, in which stem or precursor cell types can be cultured to produce all the cells of the islet cluster. A list of different sources of stem cells and their advantages and disadvantages is mentioned here (Table 14.1).

14.6 Embryonic Stem Cells Experience

The discovery of methods to isolate and grow human-Embryonic Stem Cells (ESCs) in 1998 renewed the hopes of researchers, clinicians and diabetes patients and their families that a cure for IDDM and perhaps non-IDDM as well may be within striking distance. In theory, ESC could be cultivated and coaxed into developing the insulin-producing islet cells of the pancreas. With a ready supply of cultured stem cells at hand, the theory is that a line of ESC could be grown up as

Table 14.1 A list of the sources of stem cells. Their advantages and disadvantages

Stem cell type	Description	Advantages	Disadvantages
Embryonic	Cells from human blastocysts	Pluripotent	Requires embryo destruction
Fetal stem cells	Cells from gonads of aborted fetuses	Multipotent	Requires destruction of weeks old fetus
Umbilical cord stem cells	Cells from the umbilical cord blood of newborns	Multipotent/ pluripotent?	Low frequency of stem cells
Placenta-derived stem cells	Cells from the placenta of newborns	Multipotent/ pluripotent?	Low frequency (but higher than cord blood)
Adult stem cells	Cells from adult tissues	Multipotent	Very low frequency
Induced pluripotent stem (iPS) cells	Cells from adult tissues reprogrammed to pluripotency	Pluripotent	Not patentable

needed, for anyone requiring a transplant. The cells could be engineered to avoid immune rejection. Before transplantation, they could be placed into non-immunogenic material, so that they would not be rejected, and the patient would avoid the devastating effects of immunosuppressant drugs.

There is also some evidence that differentiated cells derived from ESCs might be less likely to cause immune rejection. Although having a replenishable supply of insulin-producing cells for transplant into humans may be a long way off, researchers have been making remarkable progress in their quest for it. While some researchers have pursued the ESC, others have focused on insulin-producing precursor cells that naturally occur in adult and fetal tissues.

In Spain it was reported using mouse ESCs that were engineered to allow to select for cells that were differentiating into insulin-producing cells (Soria et al. 2000). Bernat Soria and his colleagues added DNA containing part of the insulin gene to ESC from mice. The insulin gene was linked to another gene that rendered the mice resistant to an antibiotic drug. By growing the cells in the presence of an antibiotic, only those cells that were activating the insulin promoter were able to survive. The cells were cloned and then cultured under varying conditions. Cells cultured in the presence of low concentrations of glucose differentiated and were able to respond to changes in glucose concentration by increasing insulin secretion nearly sevenfold.

The researchers then implanted the cells into the spleens of diabetic mice and found that symptoms of diabetes were reversed. Manfred Ruediger of Cardion, Inc., in Erkrath, Germany, is using the approach developed by Soria and his colleagues to develop insulin-producing human cells derived from ESC. The non-insulin-producing cells will be killed off, and only insulin-producing cells should survive. This is important in ensuring that undifferentiated cells are not implanted that could give rise to tumors. However, some believe that it will be important to engineer systems in which all the components of a functioning pancreatic islet are allowed to develop.

Ron McKay and his colleagues described a series of experiments, in which they induced mouse ESC to differentiate into insulin-secreting structures, that resembled pancreatic islets (Lumelsky et al. 2001). McKay and his colleagues started with ESC and let them form embryoid bodies, and selected a population of cells from the embryoid bodies that expressed the neural marker nestin. Using a sophisticated five-stage culturing technique, they were able to induce the cells to form islet-like clusters that resembled those found in native pancreatic islets. The cells responded to normal glucose concentrations by secreting insulin, although insulin amounts were lower than those by normal islet cells. When the cells were injected into diabetic mice, they survived, although they did not reverse the symptoms of diabetes.

According to McKay, this system is unique in that the ESCs form a functioning pancreatic islet, complete with all the major cell types. The cells assemble into islet-like structures that contain another layer, which contains neurons, and were similar to intact islets from the pancreas. Several research groups are trying to apply McKay's results with mice, to induce human ESC to differentiate into insulin-producing islets. Melton, Nissim Benvinisty of the Hebrew University in Jerusalem, and Josef Itskovitz-Eldor of the Technion in Haifa, Israel, reported that human ESC could be manipulated in culture to express the *Pdx-1* gene, a gene that controls insulin transcription (Schuldiner et al. 2000; Melton 2006).

In these experiments, cultured human ESCs were allowed to spontaneously form embryoid bodies. The embryoid bodies were then treated with various growth factors, including nerve growth factor. They found that both untreated embryoid bodies and those treated with nerve growth factor expressed *Pdx-1*. ESC prior to formation of the aggregated embryoid bodies did not express *Pdx-1*. Because expression of the *Pdx-1* gene is associated with the formation of beta-islet cells, these results suggest that such cells may be one of the types that spontaneously differentiate in the embryoid bodies. They think that nerve growth factor may be one of the key signals, for inducing the differentiation of beta-islet cells, and can be exploited in the laboratory.

Complementing these findings is work done by Jon Odorico of the University of Wisconsin in Madison, using human ESC of the same source. In preliminary findings, he had shown that human ESC can differentiate and express the insulin gene. Itskovitz-Eldor and his Technion colleagues further characterized insulin-producing cells in embryoid bodies (Assady et al. 2001). They found that ESCs that were allowed to spontaneously form embryoid bodies contained a significant percentage of cells that express insulin. Based on the binding of antibodies to the insulin protein, Itskovitz-Eldor estimated that 1–3 % of the cells in embryoid bodies are insulin-producing beta-islet cells.

The researchers also found that cells in the embryoid bodies express *Glut-2* and islet-specific glucokinase, genes important for beta-cell function and insulin secretion. Although they did not measure a time-dependent response to glucose, they did find that cells cultured in the presence of glucose secrete insulin into the culture medium. They concluded that embryoid bodies contain a subset that appear to

function as beta-cells, and that the refining of culture conditions may soon yield a viable method for inducing the differentiation of beta-cells and, possibly, pancreatic islets.

14.6.1 Problem with ESC Research

According to many stem cell researchers, ESCs are the preferred stem cells for cell-based therapies. Although they tend be more versatile than adult stem cells, other sources have proven to be just as versatile (Kögler et al. 2004). The same properties that make ESC so versatile also make them unusable for therapy. Unless completely differentiated prior to use in patients, they will migrate throughout the body to produce tumors. Experiments performed in mice and rats have shown that spontaneous tumor formation is a persistent problem (Bjorklund et al. 2002; Carson et al. 2006).

Maintaining and growing ESC lines have also been problematic. Some of these lines may become mutated, making them unusable in patients (Draper et al. 2004; Cowan et al. 2004). The main problem with ESC research is tissue incompatibility (Phimister and Drazen 2004). In contrast to ESC technologies, adult stem cells have been used to treat some of the diseases, with the list growing every year. Pursuing this technology would eliminate the tissue rejection problems associated with ESC and the high cost associated with therapeutic cloning.

14.7 Fetal Tissue as Source for Islet Cells

Several groups are investigating the use of fetal tissue as a potential source of islet progenitor cells. For example, using mice, researchers have compared the insulin content of implants from several sources of stem cells—fresh human fetal pancreatic tissue, purified human islets, and cultured islet tissue (Beattie et al. 1997). They found that insulin content was initially higher in the fresh tissue and purified islets. However, with time, insulin concentration decreased in the whole tissue grafts, while it remained the same in the purified islet grafts. When cultured islets were implanted, however, their insulin content increased over the course of 3 months. The researchers concluded that precursor cells within the cultured islets were able to proliferate (continue to replicate) and differentiate (specialize) into functioning islet tissue, but that the purified islet cells (already differentiated) could not further proliferate when grafted. Importantly, the researchers found, however, that it was also difficult to expand cultures of fetal islet progenitor cells in culture.

Although precedents exist for the clinical use of human stem cells, there is considerable reluctance to proceed with clinical trials involving cells derived from embryonic and fetal sources. Alternative sources are listed here (Table 14.2).

Table 14.2 Alternative sources of stem cells for generation of beta/islet-like cells

Sources	Scientific studies (in vivo/in vitro study)
Embryonic stem cells	Generate embryoid bodies that contain cells with a B-cell-like phenotype with overexpression of PAX4, PDX1, or NKX6, during differentiation in human ESCs, while in case of Murine ESCs overexpression of insulin. Failure of study due to development of tumors in animal
Bone marrow-derived stem cells	BMSCs in regenerative processes in vivo remain the subject of study because infusion of bone marrow cells can restore chemically induced diabetes in mice. Notably, however, it has not been indisputably shown that BMSCs differentiate into beta-cells
Placenta-derived multipotent stem cells	Differentiation into insulin-positive cells which functionally secrete insulin in vitro Control blood glucose levels in vivo
Liver stem cells	When transplanted into immunodeficient diabetic mice, transduced with human telomerase (hTERT) and then PDX-1 produced cells with considerable amounts of stored and secreted insulin and maintained euglycemia for prolonged periods
Gastrointestinal adult stem cells	Transfected intestinal stem cells from the rat with genes encoding Pdx-1 and Isl-1, followed by exposure to the peptide betacellulin, which promotes pancreatic B-cell differentiation. The resultant cells made insulin and reduced glucose levels in vivo
Adipose tissue-derived stem cell	During the proliferation period, the cells expressed stem cell markers nesting, ABCG2, SCF, Thy-1, and Isl-1 together with induction of insulin, glucagon, and somatostatin

14.8 Adult Tissue as Source for Islet Cells

Adult stem cells such as BM and cord blood stem cells, which have been administered to many patients without adverse effects, are already recognized as being capable of differentiating into cells such as ISC. The production of insulin has already been demonstrated in animal models in which mesenchymal stem cells (MSC) were administered into mice. The use of adult stem cells to induce islet regeneration is also currently undergoing U.S. FDA approved clinical trials at the University of Miami. Additionally, results from numerous clinical studies involving the administration of BM stem cells by physicians outside of the U.S. have been very promising. One group in Argentina has reported that 85 % of type 2 diabetic patients who were treated with their own MSC were able to stop using insulin (Soria et al. 2005; Kaufman 2011; Leon-Quinto et al. 2004). Paracrine activity and capacity to reverse secondary complications are the other main characteristics of adult cells for their potential use (Leon-Quinto et al. 2004).

14.9 Pioneering Cell Therapy for IDDM

By the end of 2003, cell therapy for IDDM started being performed in humans, and reportedly the world's first study was performed at the University of São Paulo—Brazil (Voltarelli et al 2007, 2008). The basic inclusion criteria were age between 12 and 35 years and a diagnosis of IDDM less than 6 weeks prior to inclusion, confirmed by positive serum levels of anti-GAD antibodies.

In the first stage of the protocol, called mobilization, a small dose of cyclophosphamide was administered intravenously to mobilize HSC from the BM to the peripheral blood, followed by daily subcutaneous injections of the granulocyte colony stimulating factor to proliferate circulating stem cells; these cells were then collected and frozen.

Ten to fifteen days later, in second phase, called the conditioning regimen, high dose immunosuppression was used with intravenous cyclophosphamide 200 mg/kg plus intravenous rabbit anti-thymocyte globulin 4.5 mg/kg, with the aim of "turning off" the immune system, mainly the peripheral T-cells that retain immunologic memory. Later, they intravenously reinfused the previously collected HSC, which do not have immunologic memory, to regenerate a new immune system that will not attack pancreatic beta-cells. The procedure was called "immunologic resetting" and no beta-cells were regenerated, but those not yet destroyed were preserved. They included only newly diagnosed patients—that is, patients who still have residual beta-cell mass to be preserved.

Up to December 2008, they performed this procedure in 23 patients: 17 men and 6 women aged 13–31 with an average body mass index of 19.7 kg/m^2, glycemia level of 395.6 mg/dl, and glycosylated hemoglobin (HbA1c) level of 8.4 % at the time of diagnosis, and undergoing anti-glutamic acid decarboxylase (GAD) treatment ranging from 1.1 to 102 U/ml, and using an average dose of 0.4 UI/kg/day soon before starting the treatment.

All patients were recommended to be on a diet and to exercise regularly within a regimen of intensive insulin therapy and carbohydrate counting to try and achieve goals like: preprandial glycemia $<$120 mg/dL, postprandial glycemia $<$140 mg/dL, and HbA1c $<$7 %. Patients also received psychological guidance.

Of the 23 patients included, 20 remained free from insulin for some period. Of these, 12 have been continuously insulin-free since treatment, 8 became transiently insulin-free, and 3 maintained daily insulin doses. In the group of continuously insulin-free patients, most stopped daily insulin injections soon after stem cell infusion, and the mean period free from insulin was 31 months (ranging from 14 to 52 months). There was a significant reduction in HbA1c compared with pretreatment values, with all measures below 7 % during follow-up. In parallel, in this group of patients they observed important increases in mean C-peptide levels (0.8 nmol/L pretreatment vs. 2.9 nmol/L after 3 years; P $<$0.05).

Here three patients did not experience any period free from insulin. The limitations of the study, were risk of infections, elevated cost, need of an ultra-specialized

team, requirement for patients to have been diagnosed no later than 6 weeks prior to treatment, and so on (Couri and Voltarelli 2009).

In 2006, a Chinese group from the University of Naijing started a similar protocol, with the difference that the stem cell infusion was 50 % into the peripheral vein and 50 % straight into the pancreas, through arterial catheterization. Of the five patients initially treated less than 3 months after diagnosis, four became insulin-independent (two of them only transiently) and one had a 50 % decrease in insulin dose. All 11 patients who had been diagnosed over 3 months before treatment kept using insulin.

In 2008, researchers at the Medical School of Ribeirao Preto—USP started studies in humans with IDDM using MSC. The protocol included BM biopsy under general anesthesia in first-degree relatives for the collection of MSC. These cells were sent to a laboratory to be stimulated to proliferate for a month, and were later infused into the patient through a gelatinous solution of approximately 100 ml with no use of chemotherapy. Two patients have been included in this protocol but no follow-up data has been published (Couri and Voltarelli 2009).

Another form of cell therapy is that performed in Argentina, China, and United States, using stem cells from the patient's own BM (including a conglomerate of MSC and HSC), obtained in a bone marrow biopsy. While still under anesthesia, these cells are infused by arterial catheterization directly into the patient's pancreas. This therapy was performed in 22 IDDM patients and in 31 non-IDDM patients. But the authors did not publish complete data.

14.10 MSC-Based Therapies

MSC are multipotent non-hematopoietic progenitor cells that are being explored as a promising new treatment for tissue regeneration. MSC can be derived from adult BM, fat, and several fetal tissues. In vitro, MSC have the capacity to differentiate into multiple mesodermal and non-mesodermal cell lineages. MSC have been shown to provide cytokine and growth factor support for expansion of HSC and ESC (Majumdar et al. 2000; Haynesworth et al. 1996; Cheng et al. 2000, 2003).

One of the most remarkable and least understood findings is the ability of MSC to migrate to sites of tissue injury (Pittenger and Martin 2004; Bittira et al. 2003; Mackenzie and Flake 2001; Wu et al. 2003). Besides, MSC possess immunosuppressive effects, by modulating the immune function of the major cell populations, involved in alloantigen recognition and elimination. The intriguing biology of MSC makes them strong candidates for cell-based therapy against various human diseases. Generation of ISC from MSC represents an attractive alternative. MSC from pancreas, BM, adipose tissue, umbilical cord blood (UCB), and cord tissue have the potential to differentiate into ISC by genetic modification and/or defined culture conditions in vitro. On the other hand, MSC are able to serve as a cellular vehicle for the expression of human insulin gene. Moreover, protein transduction

technology could offer a novel approach for generating ISC from stem cells including MSC (Vija et al. 2009; Liu and Han 2008).

14.11 Pancreatic MSC to Treat Experimental Diabetes

There is evidence to suggest that pancreatic stem or progenitor cells reside within pancreatic duct cells, where they differentiate and migrate to form new islets during both organogenesis and regeneration. Pancreatic cells with the possibilities for generation of ISC are shown in Table 14.3. Ramiya et al. first described the generation of new islets from pancreatic duct epithelial cells in vitro, isolated from pre-diabetic adult non-obese diabetic (NOD) mice. These in vitro-grown islets contained alpha and delta cells, responded to in vitro glucose challenge and, once implanted into NOD mice, reversed IDDM (Ramiya et al. 2000).

Lu et al. demonstrated that transcription factor *Pdx-1* plays an important role in the differentiation of pancreatic stem cells into pseudo-islet cells. Moreover, with the use of hepatocyte growth factor (HGF), neonatal pig pancreatic duct-derived cell monolayers could be induced to form three-dimensional islet-like cells that synthesize and release pro-insulin and insulin. Therefore, pancreatic duct cells can be a source of pancreatic progenitor cells (Lü et al. 2007). However, it is worthwhile asking whether or not these progenitor cells are MSC. Seeberger et al. showed that pancreatic stem cells could differentiate into osteogenic, chondrogenic, and adipogenic lineages, and also express the transcription factors *Pdx-1*, *Pax-4*, and *Ngn-3*, suggesting that these progenitor cells are MSC that can transform into beta-cells (Seeberger et al. 2006).

Initially, Gershengorn et al. considered that pancreatic MSC could represent an abundant source of islet progenitors, and produce sufficient numbers of ISC for transplants, as fibroblast-like cells residing within the pancreas are multipotent and capable of reversible endoderm-to-mesoderm transitions, just like MSC (Gershengorn et al. 2004). Then the same researchers, as well as Atouf et al., concluded that mouse pancreatic beta-cells do not generate endocrine precursor cells by epithelial–mesenchymal transition (EMT) in vitro (Morton et al. 2007; Atouf et al. 2007).

Using recombinant-based genetic cell tracing, to determine the origin of proliferating fibroblast-like cells in mouse islet cultures in vitro, Chase et al. found that they do not undergo EMT, but represent MSC, like those isolated from BM (Chase et al. 2007).

Experimental approaches, using various phenotypic cell markers (such as nestin, *Ngn-3*, and c-Met), may improve the isolation of pancreatic progenitor cells. Timper et al. and Eberhardt et al. found that cells expressing nestin can be isolated from human and rodent pancreatic islets, and can be expanded in vitro (Timper et al. 2006; Eberhardt et al. 2006) . Nestin-positive islet cells display endocrine differentiating capacity, so this intra-cytoplasmic filament protein could correspond to a pancreatic stem or progenitor cell marker (Timper et al. 2006; Eberhardt

Table 14.3 Pancreatic cells for generation of islet cells

Candidate Cells	Possible mechanisms
Ductal cells	Ductal cells: less differentiated; progenitor stage: islet cells
β-cells	β-cells: less differentiated progenitor stage: islet cells OR β-cells: replication: increase β-cell mass
Other progenitor cells	Progenitor cells (phenotypically less defined): islet cells

et al. 2006; Chou et al. 2003) . Indeed, insulin, glucagon, *Pdx-1*/*Ipf-1* expression and low-level insulin secretion were detected in cultures of nestin-positive islet-derived stem or progenitor cells, suggesting that such cells can participate in the neogenesis of islet endocrine cells.

Stem or progenitor cells were independently isolated from pancreatic ducts and islets, in both developing and adult mice that, under specific differentiation conditions, were able to release insulin in a glucose-dependent manner (Seaberg et al. 2004). After differentiation, these cells expressed specific developmental pancreatic endocrine genes (such as *Ngn-3*, *Pax-4*, *Pax-6*, and *Pdx-1*). Some of these differentiated cells were nestin-positive and some were negative; yet, all cells had *Ngn-3*, a specific marker for pancreatic endocrine growth and development. The important role of the *Ngn-3* gene in islet-cell progenitor activation, and in expansion of the beta-cell mass, has been confirmed in a mouse model of injured pancreas (Xu et al. 2008). In that study, the authors showed that activation of *Ngn-3* gene expression increased beta-cell hyperplasia, whereas knockdown of *Ngn-3* impaired injury-induced beta-cell generation.

Moreover, the report shed light on a new population of *Ngn-3*-positive progenitor cells purified from adult mouse pancreas—specifically located in the duct lining. These cells were shown to differentiate into functional beta-cells in vitro, and after culture in embryonic pancreas explants. Suzuki et al. isolated pancreatic progenitor cells from neonatal and adult mice, using flow cytometry and clonal analysis, with the HGF receptor *c-Met* as a phenotypic marker. They determined that the interaction of *c-Met* and HGF is essential, for growth and differentiation of pancreatic stem or progenitor cells during development, and that it contributes to regeneration and homoeostasis of the pancreas in adults (Suzuki et al. 2004). While monolayer of human islet when expanded in culture in vitro was associated with loss of function and senescence (Beattie et al. 2002) (Table 14.3).

14.12 Umbilical Cord Blood Derived: MSC to Treat Experimental Diabetes

Human UCB-MSC are able to differentiate into functional ISC which, after administration in multiple low doses (50 mg/kg per 2 days) to the liver of STZ-induced diabetic mice, can normalize and stabilize glycemic levels (Chai et al. 2008). Ende

et al. also reported success with human-UCB-MSC, as a treatment for IDDM and non-IDDM in mouse models (Ende et al. 2004a, b). Human umbilical cord blood mononuclear-cell injections into the orbital plexus of obese B6.Y Lep(ob) mice, with spontaneous development of non-IDDM, improved blood glucose levels and survival rates, and led to normalization of glomerular hypertrophy and tubular dilatation (Ende et al. 2004a). Furthermore improved glycemic profiles, associated with histological improvement of insulitis, were obtained after intravenous administration of human UCB-MSC to 25 NOD IDDM mice with insulitis (Ende et al. 2004b). They concluded that UCB-MSC may represent a potential source of diabetic cell replacement, because of their availability, their low risk for immune rejection, and increased capacity for expansion.

14.13 Human UCB-MSC-Derived ISC to Treat Experimental Diabetes

Yan-Hua Hu et al. showed that MSC derived from human UCB have good research and application prospects in the treatment of diabetes. They induced UCB-MSC to ISC, by an inducing protocol with extracellular matrix gel. BALB/C nude mice were made hyperglycemic by intraperitoneal injection of streptozotocin. The diabetic mice were transplanted with 1×10^7 ISC under the renal capsule or with phosphate-buffered saline as a control.

After transplantation, the grafts were analyzed by immunocytochemistry for the expression of human insulin; the serum human insulin levels were measured; and blood glucose and body weight status were monitored. They noted that immunofluorescence showed that numerous ISC under the kidney capsule were insulin-positive. On day 14 after transplantation, the serum human insulin level of the treatment group ($n = 9$) averaged 0.44 ± 0.12 mU/L, which was higher than that of the control group ($n = 9$) that did not express insulin ($t = 10.842$, $P < 0.05$). The diabetic mice remained hyperglycemic, and kept losing body weight after ISC transplantation, and there was no significant difference in the control group. They found that ISC differentiated from UCB-MSC expressed human insulin after being transplanted into streptozotocin (STZ)-induced diabetic mice, but did not find a sustained correction of hyperglycemia and body weight loss.

They come to the conclusion that faulty functions of ISC in vivo were worthy of further research, for the differentiation of UCB-MSC into the beta-cell phenotype, and the improvement of the function of ISC in vivo (Lu et al. 2006; Kern et al. 2006; Pessina et al. 2004; Gluckman et al. 1989; Yan-Hua et al. 2009).

14.14 BM-Derived MSC to Treat Experimental Diabetes

Allogeneic or syngeneic BM-MSC transplantation, alone or in association with HSC, was performed on both STZ-induced diabetic mice and NOD models, with encouraging results in terms of improving glycemia and renal lesions (Wu et al. 2007; Lee et al. 2006).

In 2003, Ianus et al. reported, in a controversial and unconfirmed study, that BM-GFP (green fluorescent protein)-labeled murine cells, transplanted into lethally irradiated C57BL/6 mice, could be identified as representing 1.7–3 % of the recipient mice islet cells, and were able to express insulin, GLUT-2, and transcription factors typically found in beta-cells (Ianus et al. 2003). On the same year, Hess et al. showed that transplantation of either GFP-labeled whole marrow or GFP-labeled c-kit + BM murine cells, in STZ-induced diabetic NOD/SCID mice, enhanced islet regeneration, lowered blood sugar, and increased blood insulin levels (Hess et al. 2003).

These results were confirmed by Lee et al., in STZ-induced diabetic NOD/SCID mice that were repeatedly transplanted with human MSC, via intracardiac infusion. An increased production of endogenous beta-cells and higher levels of mouse circulating insulin were obtained, with improvement of hyperglycemia, and decreased inflammatory macrophage infiltrates in glomerular structures, compared with non-transplanted diabetic mice (Lee et al. 2006). In a model of murine STZ-induced diabetes, concomitant administration, via a single injection, of BM cells with syngeneic or semi-allogeneic MSC normalized blood glucose and serum insulin levels, and allowed regeneration of recipient-derived pancreatic ISC, due to the immunosuppressive effect of MSC on the beta-cell-specific T-lymphocyte response (Urbán et al. 2008). In addition, similar results were reported by Ezquer et al., in the same model of STZ-induced IDDM. Reversion of hyperglycemia and glycosuria was observed after injection of 0.5×10^6 MSC, with increased morphologically normal beta-pancreatic islets (Ezquer et al. 2008).

Allogeneic islet-like cells, differentiated from BM-MSC, have been transplanted in STZ-induced diabetic rats via the portal vein. Differentiated MSC were identified in the recipient animals' liver, and were able to produce islet hormones (insulin, C-peptide, glucagon, somatostatin, and islet amyloid polypeptide) and alleviate hyperglycemia (Wu et al. 2007).

Taken together, these in vitro and in vivo experiments demonstrate that the beneficial effects of MSC in IDDM may be related to both their immunosuppressant activity and subsequent protective effects on damaged tissue, and their capacity to differentiate into ISC.

14.15 BM-MSC-Derived ISC

ISC can be obtained from rat BM-MSC, using a high-glucose culture medium (Oh et al. 2004) or nicotinamide-enriched medium (Lee et al, 2006; Chen et al, 2004) to promote cell differentiation; the differentiated islet-like cells express insulin, at both mRNA and protein levels, and are able to control glucose levels in NOD rats (Wu et al. 2007; Jafarian et al. 2014).

It has also been shown possible to induce in vitro IPC differentiation of BM-MSC, isolated from IDDM ($n = 5$) and non-IDDM ($n = 5$) uncomplicated diabetic patients, through a specific 18-day, three-stage protocol (Sun et al. 2007). The protocol included using a combination of nicotinamide, activin-A, and betacellulin, in a high-glucose concentration (25 mmol/L) medium, to effectively promote BM-MSC differentiation. At the end of the culture period, the differentiated cells show a similar morphology to that of pancreatic islet-like cells, high expression levels of *Pdx-1*, insulin, and glucagon genes, and a positive response in terms of glucose dose-dependent insulin production (Sun et al. 2007).

To obtain beta-cell differentiation from 14 human BM-MSC donors, Karnieli et al. used a *Pdx-1* gene-transfer approach (Karnieli et al. 2007). *Pdx-1* is a major transcription factor for pancreatic development and the beta-cell gene expression profile. The researchers showed that 40–60 % of the *Pdx-1*-expressing MSC produced insulin, in response to increasing glucose concentrations. The transfected MSC, transplanted under the renal capsule of STZ-diabetic-SCID mice, were able to reduce glucose levels from above 300 to 200 mg/dL after 5 weeks. However, an abnormal response to the glucose tolerance test was noted 6–8 weeks after transplantation (Zuk et al. 2002).

14.16 Human Adipose Tissue-Derived MSC (h-ADMSC) to Treat Experimental IDDM

Only sporadic reports of generation and use of ADMSC, in trials to treat diabetes in animal models, have been noted so far.

Mahmoud Abu et al. checked if intraventricular injections of human adipose-derived stem cells/ADSC are effective in treating STZ-induced DM in nude rats. Twenty-two adult, male nude rats (strain Crl: NIH-Fox1RNU) were used to induce diabetes using STZ. Severity of the induced diabetic state was assessed by daily monitoring of body weight, clinical signs, and blood glucose levels. C-peptide was assessed before ADSC injection (T0) and at 3, 5, and 21 days after human-ADSC injection. STZ-induced diabetic rats were given two million freshly prepared human-ADSC intraventricularly, under echocardiography guidance, 10 days after STZ-injection.

Surviving rats were sacrificed 21 days after ADSC injection. Injection had no effect on the body weight of rats. Non-fasting serum glucose levels increased

significantly in both groups. In diabetic rats, C-peptide decreased significantly before ADSC injection and seemed to return to normal 21 days after ADSC administration. Results of this preliminary study suggested a beneficial effect of using human-ADSC for the treatment of STZ-induced diabetes in adult nude rats (Zuk et al. 2001; Shackelford et al. 1975; Clarke and Williams 1975; Zuk 2010; Abu-Abeeleh et al. 2010).

Lin et al. established IDDM in rats by intraperitoneal injection of STZ. One week after injection, blood glucose was in the range of 300–400 mg/dL. Ten of the STZ-treated rats were subsequently treated with *Pdx1*-transduced, ADSC-expressing *Pdx-1*, insulin-producing ADSC (IPADSC). Treatment was done by transplantation of two million rats IPADSC or injection of saline under renal capsule. These rats' fasting blood glucose levels and body weight were then monitored weekly for 7 weeks. Throughout the entire course IPADSC-treated rats had lower blood glucose levels than saline-treated rats ($P < 0.05$). Body weights of IPADSC-treated rats were also better than those of saline-treated rats, although the difference was not statistically significant ($P > 0.05$). At the end of the seventh week, all rats were examined for fur appearance and extent of cataract, tested for glucose tolerance, and then sacrificed for histological assessment. The results showed that rat ADSC produced increasing amounts of insulin, in response to increasing concentrations of glucose, and IPADSC-treated rats had higher levels of glucose tolerance. Histological examination of the kidneys showed the presence of transplanted cells, with formation of tissue-like structure, which also stained positive for insulin (Guiting et al. 2009).

Chandra et al. evaluated the physiological competence of human ADSC generated islet-like cell aggregates (ICA), to maintain glucose homeostasis in vivo, by transplantation of ICA in STZ-induced male Swiss albino diabetic mice, aged 8–10 weeks. On day-14th of maturation, ICA (1,000–1,200) encapsulated in calcium alginate were packed into biocompatible capsules of polyurethane-poly vinyl pyrrolidone-interpenetrating network (PU-PVP-IPN) and transplanted into the peritoneal cavity of diabetic mice ($n = 6$). By 2–3 weeks, mice transplanted with mature ICA showed reduction in blood glucose levels.

The mice maintained lowering of blood glucose (180–190 mg/dl) upto 8-week of follow-up. However, it was observed that normoglycemia was not restored. Transplantation of undifferentiated human adipose-derived stem cells (h-ASC) ($n = 6$) to STZ-induced diabetic mice also showed lowering of blood glucose (250 mg/dl) which was maintained but failed to restore normoglycemia within the stipulated time. To determine whether the ICA could regulate blood glucose levels independently of the endogenous pancreatic beta-cells, level of human as well as mouse C-peptide in blood serum of all experimental mice was measured. They found up to $1{,}155 \pm 165$ pM (3.49 ± 0.50 μg/l) of human C-peptide, in diabetic mice transplanted with day 14 ICA, on day 28 post-transplantation. Human C-peptide in mice transplanted with undifferentiated human-ASC (2×10^6), 28th days post-transplantation, measured $1{,}009 \pm 383$ pM (3.05 ± 1.16 μg/l).

The mouse C-peptide concentration was found to be very low to undetectable (~0.002 μg/l) in control diabetic mice. Also ICA retrieved from the transplanted

mice after 4-weeks showed good cellular aggregation and viability. The ICA and undifferentiated human-ASC showed insulin and C-peptide expression. So they found that mature ICA show hypoglycemic effect in experimental diabetic mice (Chandra et al. 2011).

To evaluate pancreatic repair, Kajiyama et al. used a mouse model of STZ-induced pancreatic damage resulting in hyperglycemia. STZ-treated mice transplanted with *Pdx-1*-transduced ASC showed significantly decreased blood glucose levels and increased survival, when compared with control mice. The transplanted stem cells became engrafted in the pancreas, wherein they expressed insulin and C-peptide, which is a marker of ISC. They found that stably engrafted *Pdx-1*-transduced ASC in the pancreas acquire a functional beta-cell phenotype and partially restore pancreatic function in vivo (Kajiyama et al. 2010).

14.17 In Vitro Generated ISC-Based Therapies in Humans: Our Experience

In vitro ISC were generated in 2007 at our center, using ADMSC (Dave et al. 2012, 2013a). In 2008 we published results using ISC with HSC to treat IDDM in 5 patients having disease duration of 0.6–10 years. Intra-portal administration of in vitro generated ISC and HSC were carried out. We decided to infuse the cells in portal circulation since liver is the most tolerogenic organ (Starzl 2001). Results showed 30–50 % decreased insulin requirements, with 4- to 26-fold increased serum C-peptide levels, with a mean follow-up of 2.9 months, without any untoward effects and without use of any immunosuppression (Trivedi et al. 2008).

In 2010 again we published results of insulin replacement therapy using these cells, in another 11 patients having disease duration of 1–24 years. Cells were administered intra-portally. In vitro generated ISC showed presence of pancreatic transcriptional factors *Pax-6, Isl-1,* and *Pdx-1* (by immunoflurescence assay) (Dave et al. 2014). Chemiluminescence assay detected secretion of glucose and C-peptide in response to glucose concentration in vitro. Over mean follow-up of 23 months, treated patients showed a decreased mean exogenous insulin requirement and Hb1AC, and raised serum C-peptide levels. They became free of diabetic ketoacidosis events, with weight gain on normal diet and physical activities, without any untoward effects, or use of any immunosuppression (Vanikar et al. 2010; Dave et al. 2013b,c).

14.18 Proposal for the Road Ahead

It seems that success evaded us till now, because of both unrealistic expectations and failed assumptions. Failure can, however, be highly educational. The experience gained from trials, when joined to other recent advances in knowledge, may provide useful clues and recommendations for the future.

The immune system is a formidable adversary, with an extensive range of weaponry at its disposal, and it is not easily diverted from its purpose, once fully mobilized against any particular set of antigens (Abdi et al. 2008; Hussain and Theise 2004; Mathis et al. 2001; Bach 2001). The literary analogy that springs to mind is that of the little Dutch boy, who prevented a flood by putting his finger in a hole in the dyke, and thus prevented it from enlarging. We may have been waving one finger ineffectually at a much larger breach in the defenses.

As we lack insight into the precise immune effector mechanisms, we believe it may be time to learn a lesson from successful therapeutic approaches. Combination or "cocktail" therapy for other disorders shows that multiple agents are often markedly superior to the use of a single drug/agent, and it stands to reason that the reversal of autoimmunity requires a similar approach. Indeed, the experience of Bosi et al. suggests that reactivation of autoimmunity, following islet transplantation, may be harder to treat than the alloimmune rejection process (Bosi et al. 2001; Holditch et al. 2014).

14.19 Protection of Transplanted Cells

Much progress has been made in recent years in developing new ways to prevent allograft rejection. These approaches are intended to replace prolonged immunosuppression, which compromises host immune defenses against infections and neoplasia. Cell encapsulation in polymer membranes has reached the stage of clinical trials, in patients with neural disorders. Intra-thymic transplantation of islets and BM has shown promise in induction of donor-specific tolerance (Posselt et al. 1990, 1992). In addition, a variety of immune effector molecules have been employed in attempts to manipulate donor cells genetically to resist immune attacks (Lau et al. 1996; Pearson et al. 1996).

Immuno-therapeutic approaches are also being investigated, including vaccination strategies with natural insulin epitopes. In recent years, increasing evidence has implicated $CD4^{+}CD25^{+}$ regulatory T cells (Treg) expressing the transcription factor Foxp3, in both the breakdown of self-tolerance and the restoration of immune homeostasis in IDDM. Tregs possess the ability of limiting effector responses, allowing the establishment of immunological tolerance. They also can be isolated and expanded using in vitro culture condition under a variety of culture conditions from peripheral blood for cell-based therapy (Sakaguchi et al. 2008). Thus in vitro generated Tregs can also be a useful tool for protection of transplanted islets or ISC.

14.20 Future Prospects

The work in recent years has demonstrated that transformed beta-cell lines or ISC can maintain the main differentiated functions of normal beta-cells, namely insulin biosynthesis and regulated secretion. The development of approaches to tightly regulate cell replication made it possible to use these cells in restoring and maintaining euglycemia in diabetic animals. Cell engineering with adenovirus genes that reduce cell immunogenicity, allowed successful transplantation across allogeneic barriers, without immunosuppression or immunoisolation. These genetic manipulations can be applied in the future to cultured human islets, to derive a universal donor human beta-cell line. Despite remaining challenges, genetically engineered beta-cells hold the promise of replacing insulin injections as an accurate, convenient, and safe way for long-term maintenance of euglycemia in IDDM patients (Orlando et al. 2014). Thus application of stem cells derived in vitro generated ISC in the cure for IDDM appears extremely promising, with bona fide hope for a permanent cure.

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